J Mater Sci: Mater Med (2007) 18:1623–1626
DOI 10.1007/s10856-007-3048-z

In vitro degradation and release profiles for Poly-dl-lactide film containing paracetamol

Shaobing Zhou · Bing Song · Xiaohong Li

Received: 28 February 2006 / Accepted: 5 May 2006 / Published online: 5 May 2007

Abstract The biodegradable film containing paracetamol with suitable dimensions was prepared by polymer solution-cast method. The study mainly investigated the in vitro degradation of the films without and with 7.0% and 14% paracetamol in the phosphate-buffer saline (PBS) of pH 7.4 at 37 °C. The results showed that the degradation rate for the film with same dimensions containing more drug was faster. The in vitro drug release profiles showed that paracetamol release from film matrix was almost sustained within one month. It suggested that the biodegradable film should be potential in preventing tissue adhesion and local inflammation on operating procedure.

Introduction

It is well known that tissue adhesion and local inflammation resulted from operation are an unsolved difficult-problem in the long history of surgery. Every year thousands of surgical cases of patients are all involved in preventing tissue adhesion and local inflammation all over the world. Now in China sodium hyalluronate and chitosan gel are mainly used on operating procedure to resolve the problem, but no good effect is obtained due to their purification. So in the paper we prepared a biodegradable film containing an antipyretic drug in order to resolve the problem. The film can act as a partition by covering surface of apparatus to prevent tissue adhesion. At the same time the drug sustained release from film matrix can resist local inflammation.

In recent years, biodegradable polymers, such as polylactide (PLA), polyglycolide (PGA), polylactide-co-glycolide (PLGA) and poly(ε-capralactone) (PCL) find increasing applications in the pharmaceutical industry as matrices for drug delivery systems [1] and in medicine as material for bone implants and bone fixation devices [2–4], surgical sutures [5], and anastomotic devices [6] owing to their excellent biodegradation and biocompatibility. The chemical and physical characteristics of synthetic PLA polymer can be controlled more easily by adjusting reaction additions than crude materials. Therefore, PLA was elected as matrix of the film in our experiment. Paracetamol (acetaminophen, *N*-(4-hydroxy-phenyl) acetamide) is a widely used as an analgesic and antipyretic drug, which is effective in relieving mild to moderate pain of a non-visceral origin. Its molecular formula is $C_8H_9NO_2$, and its structure is showed in Fig. 1. It was initially used as a prescription drug in the USA in 1951. Today it has been widely available without prescription in many countries. It can be dissolved with general organic solvent. In the study it was used as a model drug and mixed with PLA solution.

In this study, we prepared a series of biodegradable films containing paracetamol with different amount of drug by using solution-cast method. In vitro matrix degradation profiles of these films were characterized by measuring their weight loss, the intrinsic viscosity decrease and PBS medium pH decrease. In vitro paracetamol release profiles from the films were also investigated in the same instrument.

S. Zhou (✉) · B. Song · X. Li
School of Materials Science and Engineering, Key Laboratory of Advanced Technologies of Materials, Ministry of Education, Southwest Jiaotong University, Chengdu 610031, P.R. China
e-mail: shaobingzhou@hotmail.com

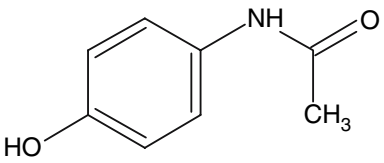

Fig. 1 Molecular structure of paracetamol

Experimental

Materials

Poly-dl-lactide was synthesized by ring-opening polymerization of cyclic lactide monomer as described previously [7]. Paracetamol was purchased from Kangquan pharmacy, Zhejiang, China. All other chemicals and solvents were of reagent grade or better.

Preparation of biodegradable film

Preweighed PLA, paracetamol and acetone solvent were placed in a beaker, and then the mixture became solution (4.0%, wt%) under stirring, finally the solution was cast in a mould. The mould was dried overnight at 30 °C to give a biodegradable film with 0.02 mm thickness.

In vitro degradation of biodegradable film

Preweighed films with dimensions of $100 \times 20 \times 0.02$ mm were placed in individual test tubes containing 15.0 mL of PBS (154 mM, pH 7.4). The tubes were kept in a thermostated shaking air bath (Hua Li Da Laboratory Equipment Company, China) that was maintained at 37 °C and 100 cycles/min. At predetermined intervals, the degradation medium was taken out from the tube containing films. Then, the films were rinsed with distilled water to remove residual buffer salts, and dried to constant weight in vacuum desiccator.

Estimation of in vitro degradation

The degree of degradation was estimated from the decrease of films mass loss, intrinsic viscosity and the pH of PBS. The determination of pH value of PBS, in which the in vitro degradation tests were performed, was carried out with a model PHS-3B pH meter (Shanghai scientific Instrument Co. China) equipped with a combined glass electrode. Mass loss was determined gravimetrically by comparing the dry weight remaining at a specific time with the initial weight. Samples of fresh film and films from the degradation experiments were dissolved in tetrahydrofuran (THF). The intrinsic viscosity was measured with an ubbelohde viscometer on solution of PLA in THF at 30 °C.

In vitro paracetamol release test

The in vitro paracetamol release profiles of the biodegradable films were determined as follows. The films with dimensions of $100 \times 20 \times 0.02$ mm containing different amount of drug were incubated into individual test tubes containing 15.0 mL of PBS (154 mM, pH 7.4). These tubes were allowed to store in the same air bath as mentioned in degradation test. At appropriate intervals, 1.0 mL of release medium was collected from the tube and 1.0 mL of fresh PBS was added back to the test tube. The release amount of paracetamol was measured with a Shimadzu UV-2550 spectrophotometer by comparing with its calibration curve. The UV-absorption spectrum of the paracetamol solution in PBS showed a characteristic absorption at 242.5 nm. The calibration curve of absorbance (OD) versus paracetamol concentration (%) was employed for studying the release of paracetamol from the biodegradable film matrix

Results and discussion

In our experiment, we obtained PLA films with and without paracetamol with PLA solution-cast method. Figure 2 showed the photos of only PLA film (a) and PLA film containing 7.0% paracetamol (wt%) (b) with same dimensions of $100 \times 20 \times 0.02$ mm taken with digital camera. The only PLA film (PF-0) was colourless and transparent like polyethylene film. However, the PLA films containing 7.0% paracetamol (PF-7) and 14.0% paracetamol (PF-14) were white and opaque. The dimensions of film can be easily controlled by adjusting polymer concentration.

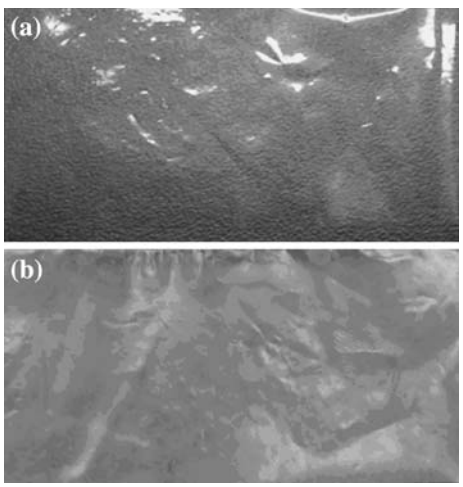

Fig. 2 The photo of PLA film (**a**) and PLA film containing 7.0% paracetamol (wt%) (**b**) taken with digital camera

In vitro investigation provides a convenient method to study the degradable characteristics of biodegradable polymers. Gravimetric studies of loss of these film masses during incubation under pH 7.4 of PBS at 37 °C are shown in Fig. 3. Taking one with another, all films mass decreased with increase of degradation time. However, the mass loss rate for these films is different. The mass loss rate for PF-14 is the fastest, while the rate for PF-0 is slowest. During the predetermined time (14 weeks), PF-0, PF-7 and PF-14 show 44.6%, 58.8% and 63.2% decrease in mass loss, respectively. We previously investigated in vitro degradation for the PLA and poly-d,l-lactide-poly (ethylene glycol) polymer in form of microspheres [8, 9]. In the experiment, the phenomena for in vitro degradation of these films were almost fit for our previous reports [8, 9]. The mass loss of films in the early stage may be resulted from lower molecular weight part of the copolymers dissolving into the degradation medium. In the later stage of degradation, the mass loss may be due to the hydrolysis of higher molecular polymer into oligomers. Polymer degradation is defined as the process of polymer chain cleavage. Degradation is triggered by water which hydrolyses the functional groups by which the monomers are usually connected [10].The more paracetamol with hydrophility was added in PLA film, the faster rate was obtained for water penetrating into the film matrix. Therefore, the degradation rate of the film with more paracetamol was faster.

The intrinsic viscosity ([η]) of the films decreased continuously after being exposed to PBS at pH 7.4 at 37 °C. Figure 4 shows the decrease in intrinsic viscosity with degradation time. The result almost corresponds to the result of Fig. 3. The intrinsic viscosity decrease for all films proceeded in a fairly linear fashion versus incubation time. Similarly, the intrinsic viscosity of film with more paracetamol shows the decrease faster. The instant decrease in [η] suggests that polymers chain scission began as soon as the sample was exposed to PBS. Water permeated into film matrix resulting in random hydrolysis of ester bonds and the decrease of the viscosity.

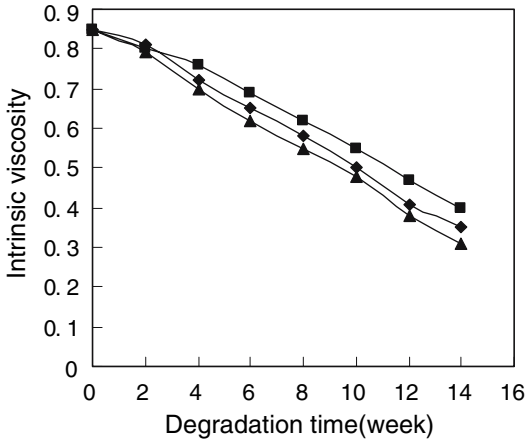

Fig. 4 The change of intrinsic viscosity of PF-0 (■), PF-7 (◆) and PF-14 (▲) incubated in PBS at 37 °C

Figure 5 displays the decrease of the media pH versus incubation time. The result has little difference from the results of Figs. 3 and 4. During the initial 4 weeks, the pH decrease profiles of these media were slow and have no difference. In the later incubation time, the degradation media for PF-0, PF-7, and PF-14 show approximately 14.0%, 22.0%, and 27.0% decrease in pH, respectively. The pH of PBS medium decrease may be that the degradation generated many oligomers and lactic acid products and so on.

The calibration curve of absorbance (OD) versus paracetamol concentration was obtained with a UV-2550 spectrophotometer as follows: $A = 0.08055C + 0.00000$ where A is absorbance and C is paracetamol concentration. The calibration curve has a very good correlation

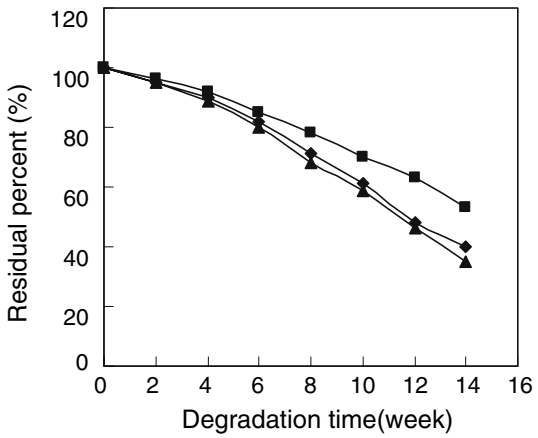

Fig. 3 The percent residual weight of PF-0 (■), PF-7 (◆) and PF-14 (▲) incubated in PBS at 37 °C

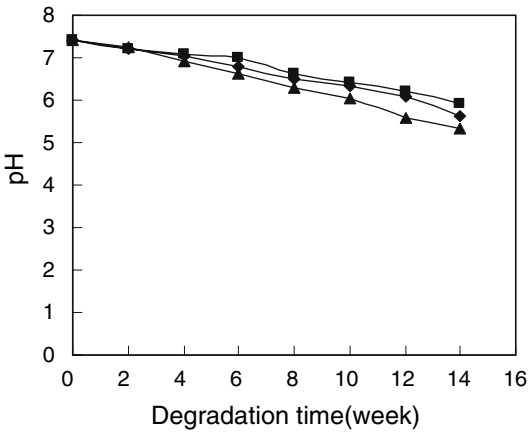

Fig. 5 The change of pH value degradation medium of PF-0 (■), PF-7 (◆) and PF-14 (▲) incubated in PBS at 37 °C

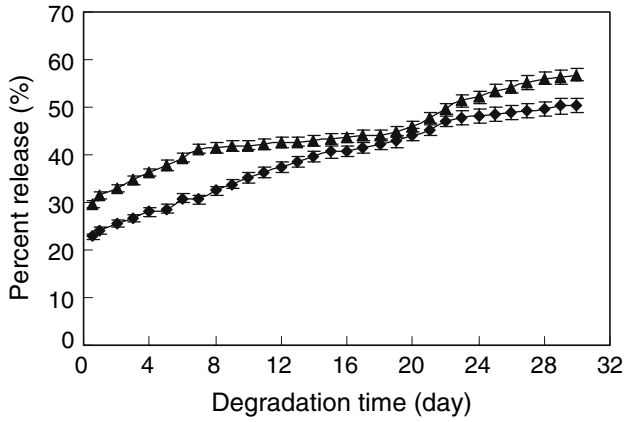

Fig. 6 Percent release of paracetamol from PF-7 (◆) and PF-14 (▲) incubated in PBS at 37 °C. Each point represents the mean of three individual samples of films

coefficient $r_2 = 0.99889$.We calculated the release concentration of paracetamol in PBS easily according to the formula. Figure 6 shows the percent release of paracetamol from PF-7 and PF-14 against incubation time. The release profiles of the two samples consist of a short burst release followed by a gradual release phase. The extent of burst release at the initial phase increased with paracetamol increase in the film. PF-7 shows about 22% burst release, while PF-14 shows 30% burst release during 12 h. In the following period, drug release from the two films was sustained. As seen in Fig. 6, PF-7 and PF-14 show 50% and 60% paracetamol release within 4 weeks, respectively.

It is known that the release for drug delivery system based on biodegradable polymer involves two different mechanisms, that is, diffusion of drug molecules and degradation of polymer matrix. The burst release of drug is associated with paracetamol molecules dispersing close to the film surface, which diffuse out in the initial incubation time. The gradual release of drug is owing to the swollen inner structure formed by contacting with the aqueous release medium, and drug diffusion through the swollen phase [8]. In the later degradation time, some micropores were formed on the surface and in the matrix of the film due to polymer degradation and drug diffusion out from the matrix of the film.

Conclusions

In the study, we obtained the degradation profiles of film matrix and drug release profiles mainly by in vitro test. It supplied us a reference to study biodegradable polymer and drug delivery system. It will be very important for us to investigate the effect of the biodegradable film preventing intestinal adhesion and obstruction for animals in vivo in the following period.

Acknowledgements This work was supported by Project 50303018 supported by National Natural Science Foundation of China and the Cultivation Fund of the Key Scientific and Technical Innovation Project, Ministry of Education of China.

References

1. U. EDLUND and A. -C. ALBERTSSON, *Advances in Polymer Science*, **157** (2000) 68–105
2. P. YLINEN, *J. Mater.Sci. Mater. Med.* **5** (1994) 522–528
3. G. O. HOFMANN, *Arch. Orthop. Trauma Surg.* **114** (1995) 123–132
4. O. M. BÖ STMAN, *Clin. Orthop. Rel. Res.* **329** (1996) 233–239
5. P. J. OSTHER, P. GJøDE, B. B. MORTENSEN, J. BARTHOLIN and F. GOTTRUP, *Br. J. Surg.* **82** (1995) 1080–1082
6. J. S. WOOD and D. B. FROST, *Am. Surg.* **59** (1993) 642–644
7. D. K. GILDING and A. M. REED, *Polymer* **20** (1979) 1459–1464
8. SHAOBING ZHOU, XIANMO DENG, XIAOHONG LI et al, *J. Cont. Rel.* **75** (2001) 27–36
9. SHAOBING ZHOU and XIANMO DENG, *Reactive funct. Poly.*, **51** (2002) 93–100
10. GÖPFERICH A. Degradation of Biodegradable Polymers. Biodegradable polymers-from monomer to the clinic. Sixth World Biomaterials Congress(USA) 2000