Fibers and Polymers 2019, Vol.20, No.2, 229-235
DOI 10.1007/s12221-019-8829-8

ISSN 1229-9197 (print version)
ISSN 1875-0052 (electronic version)

Degradation and Drug-release Behavior of Polylactic Acid (PLA) Medical Suture Coating with Tea Polyphenol (TP) - Polycaprolactone (PCL)/ Polyglycolide (PGA)

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(Received September 5, 2018; Revised October 25, 2018; Accepted October 29, 2018)

Abstract: The drug-release time of suture should meet with the healing time of wound, so it is needed to control the drug-release performance of polylactic acid (PLA) suture. In this paper, two biodegradable polymers with different degradation rates, such as polycaprolactone (PCL) and polyglycolide (PGA), were applied to carry the drug of tea polyphenol (TP). The drug-loading finishing solution which is made of PCL/PGA carriers and TP, was coated on the PLA suture. The drug-release rate and time of PLA suture could be regulated by adjusting the proportion of PCL/PGA carriers. The results indicate that the surface of drug-loaded PLA suture becomes rough. There is no obvious chemical reaction among the drug, carriers and PLA suture, just physical adhesion. With the increasing of PCL in drug-carriers, the strength of suture gradually increases. At 70/30 of PCL/PGA, the fracture elongation of suture reaches the highest point. In process of degradation, the surface of drug-loaded PLA suture appears some holes after 25 weeks. The strength of sutures decreases gradually during degradation, and the effective strength time of sutures with various proportions of PCL/PGA is different. The drug-release rate of the suture is fast at early stage and slow at later stage and the higher the PGA proportion is, the faster the drug-release rate of the suture is.

Keywords: Polylactic acid, Suture, Drug release, Polycaprolactone, Polyglycolide

Introduction

The medical suture, made from polylactic acid (PLA), is derived from agriculture products. It has several attractive features, such as harmless, biocompatibility, biodegradability, and high strength [1-3]. Such a suture can degrade into CO_2 and H_2O during wound healing, which will avoid the pain caused by the unnecessary suture removal [4-6]. For this reason, PLA sutures achieved a wide application in modern surgery operations, especially operations for internal organs and some special sites, such as face and neck, circumcision, colostomy [7-9].

When the wound is sutured with surgical suture, a large number of oral anti-inflammatory and antibacterial drugs are generally required, to avoid wound infection, inflammation, rejection reaction, and so on [10-12]. However, a large number of oral drugs can damage normal tissues. In order to reduce the amount of oral drugs, it is necessary to make the drugs target the wound. It is an effective method to load the anti-inflammatory drug or other drugs on the surgical suture. The drug-loaded suture can directly release drug to the wound, and can reduce the damage to normal tissue [13-15].

When the drugs are loaded on the PLA suture, it is medically required that the original strength and flexibility of suture should not worsen too much, especially, the drug-release time of suture should meet with the healing time of different wounds. If the drug-release time is much longer than the wound healing time, the excessive drug will have a toxic effect in too-long application. If the drug-release time is much shorter than the wound healing time, the inadequate drug will not perform its anti-inflammatory function [16-18]. In view of the above, the drug-release time of suture needs to be regulated.

At present, Qin, Lee *et al*. added the drug to the inside of fiber, and then the drug-added fibers were made as a suture. But this method reduced the mechanical strength of fiber, and the drug-loading quantity is too small [19,20]. Xu, Wu *et al*. impregnated the suture into the solution of drug, so that the drug could enter into the suturing gap. However, this is only a simple method of loading drug, which can not control the drug-release and the loading-drug quantity [21,22]. Thimour-Bergstrom, Zhou *et al*. mixed the drug with a single degradable material to make the drug coating solution, and then the drug coating solution was coated on the surface of the suture. The drug could be released slowly with the degradation of the degradable material. So the release of drug relied on the degradation of single degradable material (e.g. polycaprolactone (PCL), polyglycolide (PGA), PLA and others), whose degradation rate was constant. Hence the drug-release couldn't be precisely regulated [23,24].

In this paper, the drug was added into two biodegradable polymers (e.g. PCL and PGA) with different degradation rates, and then formed as the coating finishing liquid of drug-PCL/PGA. After that, the coating finishing liquid was coated on the surface of PLA surgical suture by the dip-padding method. The whole scheme is shown in Figure 1. The drugs will be released with the degradation of PCL and

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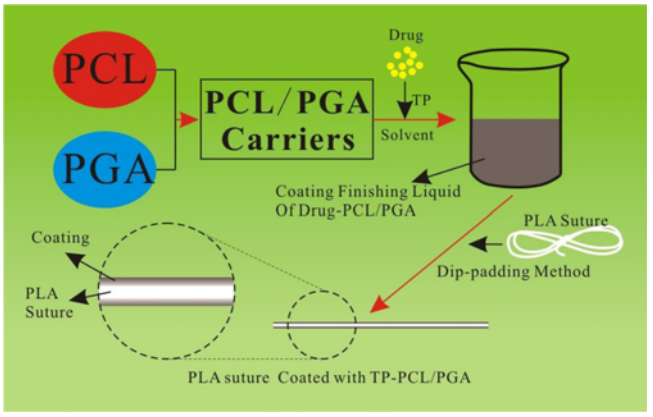

Figure 1. The whole scheme in this paper.

PGA carriers, so the degradation rate of PCL/PGA carriers affects the drug-release rate. We can regulate the ratio of PCL/PGA to control the degradation rate of carriers and the drug-release rate. The structure and properties of suture, such as the surface morphology, chemical structure, mechanical properties and degradation and drug-release behavior were studied.

Experimental

Materials

The drug carrier was made from polycaprolactone (PCL, $(C_6H_{10}O_2)_n$) with 48900 viscous molecular weight and polyglycolide (PGA, $(C_4H_4O_4)_n$) with 25000 viscous molecular weight, which were both provided by Natureworks Company (USA).

Tea polyphenols (TP) is a good representative of the natural anti-inflammatory drugs which are traditional Chinese medicines. TP can bring some positive effects, such as antimicrobial action, anti-inflammatory effect, improve immunity and so on, to the PLA sutures. TP used in this paper was provided by Shanghai Menghe Technology Company (China) and selected to load into PCL/PGA. TP was mainly contained three catechins: epigallocatechin (EGC), epigallocatechin gallate (EGCG) and epicatechin gallate (ECG).

The original polylactic acid (PLA) suture, produced by Zhejiang Gaoxin Company (China), was single ply yarn and 150D/72F.

The chemical reagents applied in this experiment frequently, such as ethyl acetate ($CH_3COOC_2H_5$), glycerol ($CH_2OHCHOHCH_2OH$), polysorbate-80 (tween-80) ($C_2H_{44}O_6(C_2H_4O)_n$), glucose ($C_6H_6O_6$), sodium chloride (NaCl), potassium chloride (KCl), calcium chloride (CaCl), magnesium chloride hexahydrate ($MgCl{\cdot}6H_2O$), epsom salt ($MgSO_4{\cdot}7H_2O$), sodium hydrogen phosphate (Na_2HPO_4), sodium bicarbonate (Na_2HCO_3), sodium hydroxide (NaOH), mono potassium phosphate (KH_2PO_4), ferrous tartrate solution ($C_4H_4FeO_6$) and distilled water (H_2O), were produced by Tianjin Beichen Fangzheng Reagent Company (China).

Preparation of Drug-coating Finishing Liquid

4 g of PCL and PGA in different proportions were put in the 40 m*l* solvent of ethyl acetate ($CH_3COOC_2H_5$). They were stirred by a Magnetic Stirrer (ZNCL-TS500, Shanghai Xingchuang Instrument Co. Ltd. in China) under 800 r/min speed and 50 °C temperature for 30 min, and then the PCL and PGA were completely dissolved and then farmed as 40 m*l* PCL/PGA carrier solution. 1.5 g tea polyphenols (TP), 0.15 g glycerol ($CH_2OHCHOHCH_2OH$) and 0.03 g tween-80 ($C_2H_{44}O_6(C_2H_4O)_n$) were dissolved into 40 m*l* distilled water (H_2O), then farmed as 40 m*l* TP solution. 4 m*l* PCL/PGA carrier solution was added into the 40 m*l* TP solution, and then the mixed solutions were stirred by a magnetic stirrer at 1000 r/min for 30 min. After that, the mixed solutions were fully emulsified, and the drug was evenly dispersed, therefore the drug-coating finishing liquid of TP-PCL/PGA was prepared.

Dip-padding Process of Suture

The drug-coating finishing liquid of TP-PCL/PGA was put into immersion tank and remained the temperature at 50 °C. And then, the original PLA suture was dipped into the liquid and squeezed by roller, as shown in Figure 2. After that, the PLA suture was heated in a vacuum oven at 45 °C for 2 h. Finally, the PLA suture, coating with TP-PCL/PGA, was prepared.

Characterization Technique

The morphology of suture was investigated by scanning electron microscope (SEM, JEM2100F, Japan Electronics Corporation). The samples were sputtered by gold with an accelerating voltage of 5.0 kV. The mechanical properties of suture were tested by an Electronic Yarn Strength Meter (YG061), with 250 mm of clamping length and 250 mm/min of tensile speed. The chemical structure of suture was determined by a Fourier Infrared Spectrometer (TENSOR27, Germany) using the method of total reflection infrared spectrometry, with 4000-600 cm^{-1} of scanning range and 4 cm^{-1} of resolution.

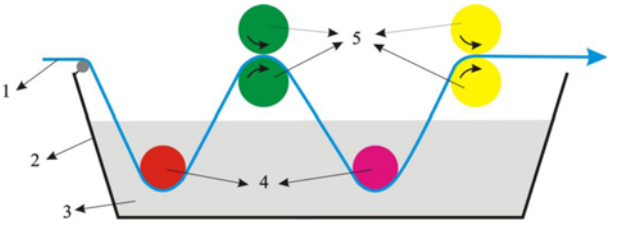

Figure 2. Process of dip-padding; (1) original PLA suture, (2) dip-padding tank, (3) coating finishing liquid of drug-PCL/PGA, (4) dipping rollers, and (5) rubber press rollers.

Degradation Test in Vitro

The degradation behavior of sutures was characterized through degradation test in vitro. The "Hanks" solution, which simulated the body fluid, was prepared according to the recipe of 1.0 g/*l* $C_6H_6O_6$, 8.0 g/*l* NaCl, 0.4 g/*l* KCl, 0.14 g/*l* CaCl, 0.1 g/*l* $MgCl{\cdot}6H_2O$, 0.06 g/*l* $MgSO_4{\cdot}7H_2O$, 0.06 g/*l* KH_2PO_4, 0.06 g/*l* Na_2HPO_4 and 0.35 g/*l* Na_2HCO_3 [25,26]. After that, the sutures were placed into the body simulation fluid of "Hanks" solution, and then they were put into a Thermostatic Water Bath (HH-8, Ningbo Textile Instrument Factory) at 37 °C which simulated the human body temperature. In the process of degradation test, the "Hanks" solution should be replaced regularly to simulate the body fluid circulation. The sutures will be degraded gradually in "Hanks" solution [27,28]. After a certain amount of time, the films were taken out and dried, and then the SEM and fracture strength of sutures during degradation were measured.

Drug Release Test in Vitro

0.1 g TP was dissolved in 100 m*l* distilled water. Afterwards, separately transfer 1 m*l*, 2 m*l*, 3 m*l*, 4 m*l*, 5 m*l* of such solution to 50 m*l* flasks and mixed with 9 m*l* distilled water and 10 m*l* ferrous tartrate solution (analytical pure), further dilute with phosphate buffered solution (pH=7.4, which was prepared by 1 *l* distilled water, 1.58 g NaOH and 6.8 g KH_2PO_4) to 50 m*l*. After standing for 15 min, their absorbance was investigated by ultraviolet spectrophotometer (UV-752, Youke apparatus Co., Ltd., Shanghai, China) at 540 nm. Based on the test results of absorbance (y) and TP concentration (x), the standard fitting line could be obtained as shown in Figure 3, and the fitting equation was y=1.93x+0.0047 (R^2=0.9957).

5 m of suture was put into 50 m*l* phosphate buffered solution in 37 °C thermostat water bath to release drug. At set intervals, 1 m*l* of this solution were taken out and observed its absorbance. Meanwhile, the volume of the solution remained the same, so a certain volume of solution was taken out, the same volume of pure phosphate buffered solution should be added [29]. According to the absorbance tests and standard fitting line in Figure 3, the concentration of drug in phosphate buffered solution at a specific time could be obtained. So the accumulative drug release rate could be calculated by the Formula (1).

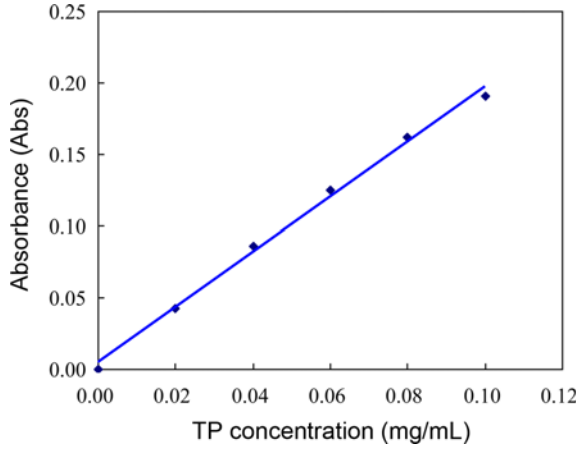

Figure 3. The standard fitting line for TP concentration to absorbance.

$$Q_t = \frac{m_t}{m_0} \times 100\% \quad (1)$$

where Q_t represented the accumulative release rate of TP at a specific time of t; m_t represented the amounts of TP released at a specific time of t; while m_0 represented the initial amounts of TP loaded on suture before drug release.

Results and Discussion

Surface Morphology of Drug-loaded PLA Suture

The surface morphology of sutures with different proportions of PCL/PGA was observed by SEM, as shown in Figure 4.

It can be seen from Figure 4(a) that the original PLA suture had no coating and the fibers in suture was smooth and loose. Figure 4(b)-(d) shows that the suture was coated with the drug-PCL/PGA on surface so the surface of suture was obviously rough. In addition, the coating material was filled into the gaps among fibers, and then the fibers in suture were stuck together. This indicated that the coating of drug-PCL/PGA made the fibers hold together, and improved the bundling of filaments in the suture. However, the coating led to the rough surface of the suture, which mean the stitching resistance of suture would increase.

The degradation and drug-release behavior of drug-coated sutures were tested via the experiments of drug-release and degradation. During the process of degradation, the surface morphology of suture with different proportions of PCL/PGA carriers will be changed, as shown in Figure 5.

Figure 5(a) and (b) shows that after 25 weeks of degradation, the surface of the original PLA suture just became rough but had no major defects. This indicated that the degradation rate of the original PLA suture was relatively slow. Figure 5(c) and (d) shows that after 25 weeks of degradation, the surface of drug-loaded suture, which was coating with 30/70 of PCL/PGA, appeared many holes. This indicated that the drug coating material on the surface of suture was degraded firstly in the process of degradation. The degrading rate of drug-PCL/PGA coating was very fast, and then many big holes appeared on the suture.

Chemical Structure of Drug-loaded PLA Suture

The infrared spectra of sutures with different proportions of PCL/PGA carriers are shown in Figure 6.

Figure 6 shows that the suture with pure PCL (PCL/PGA=100/0) carrier had many characteristic peaks, including the expansion vibration peak of -CH at 2956 cm^{-1}, the

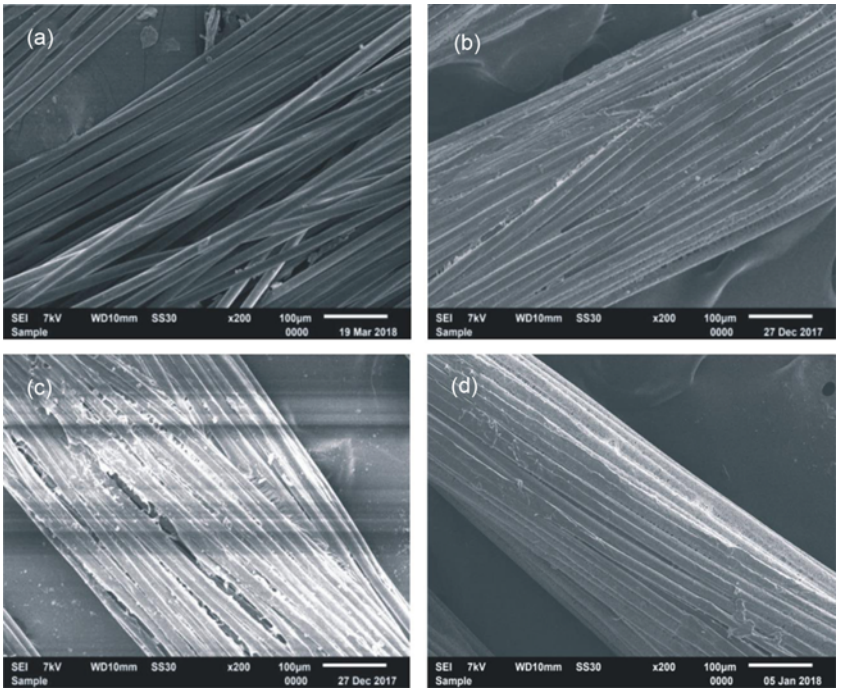

Figure 4. SEM images of sutures with different proportions of PCL/PGA; (a) original PLA suture, (b) PLA suture coating with 0/100 of PCL/PGA, (c) PLA suture coating with 50/50 of PCL/PGA, and (d) PLA suture coating with 100/0 of PCL/PGA.

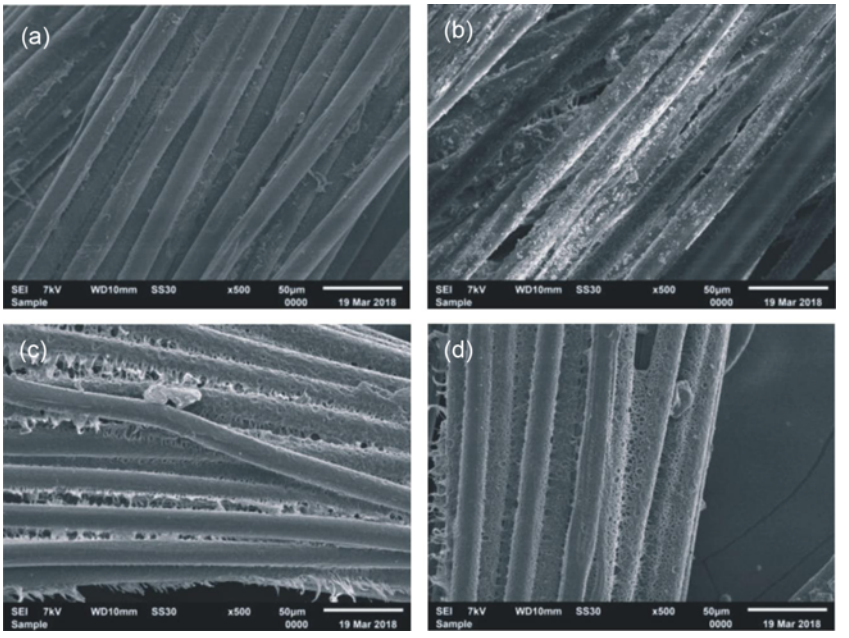

Figure 5. SEM of sutures; (a) original PLA suture; (b) original PLA suture degraded for 25 weeks, (c) PLA suture coating with 30/70 of PCL/PGA, and (d) PLA suture coating with 30/70 of PCL/PGA degraded for 25 weeks.

expansion vibration peak of -C=O at 1730 cm^{-1} and the asymmetric expansion vibration peak of -C-O-C at 1168 cm^{-1}. The suture with pure PGA (PCL/PGA=0/100) carrier had many characteristic peaks, including the stretching vibration peak of -C=O at 1752 cm^{-1} and the bending vibration peak of $-CH_2$ at 1074 cm^{-1}. The suture with PCL/PGA mixed carriers had both characteristic peaks of pure PCL and that of pure PGA, and had no obvious new peak appeared. This indicated that there was no chemical reaction among the PLA suture, the PCL/PGA carriers and the TP drug. These

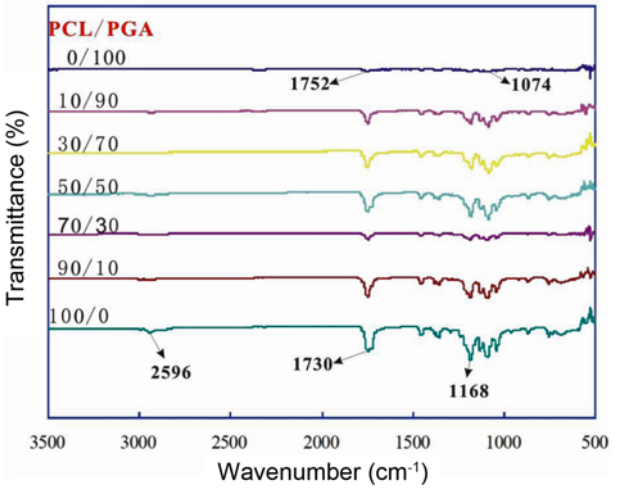

Figure 6. IR spectrum of sutures with different proportions of PCL/PGA carriers.

materials were just physically mixed and adhered together, which was very useful for ensuring the efficacy of TP drug.

Mechanical Properties of Drug-loaded PLA Suture

The different proportions of PCL/PGA carriers were coated on the surface of the original PLA suture. The mechanical property of drug-loaded PLA suture will be affected by the proportion of PCL/PGA, as shown in Figure 7.

Figure 7(a) shows that the proportion of PCL/PGA affected on the fracture strength of the suture. With increasing of PCL in the carriers, the fracture strength of suture increased gradually. This is because the pure PCL carrier had more excellent mechanical property than pure PGA carrier. Hence, as the proportion of PCL carrier coated on the suture increased, the strength of suture gradually increased. Figure 7(b) shows that with increasing of PCL in the carriers, the breaking elongation increased firstly and then decreased. When at 70/30 of PCL/PGA carriers, the suture had the maximum breaking elongation. This is because the breaking elongation depended on many factors, such as the flexibility of molecule, the intermolecular force, the slip among molecules and so on. When the PCL/PGA was at an appropriate ratio (e.g. 70/30), the molecules of PCL and PGA were easy to extend and slip under stress, so that the breaking elongation was very large.

In the process of degradation, the fracture strength of sutures with different PCL/PGA proportions will be changed, as shown in Figure 8.

Figure 8 shows that at 1 h of degradation, the initial intensity of original PLA suture was larger than that of these drug-loaded sutures. It may be because that in the dip-padding process, the suture would be damaged by mechanical action and solvent erosion, therefore, the initial intensity of these drug-loaded sutures were lower than that of original PLA suture.

Figure 8 also shows that the fracture strength of suture decreased gradually in the process of degradation and drug-release. The strength reduction rates of the sutures coated with drug-PCL/PGA were slower than that of original PLA suture, that is to say, the degradation rate of coated suture

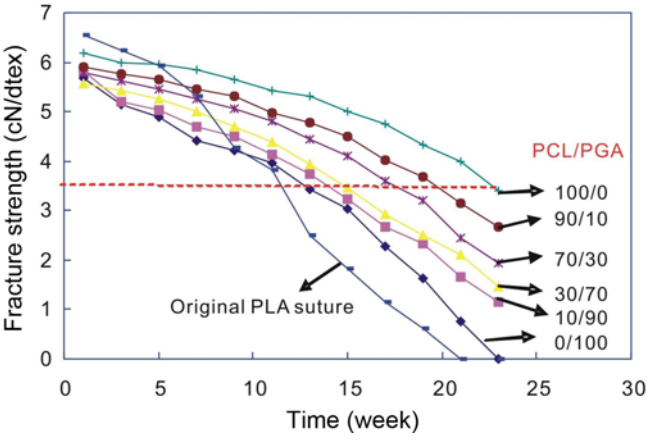

Figure 8. Fracture strength of sutures during degradation.

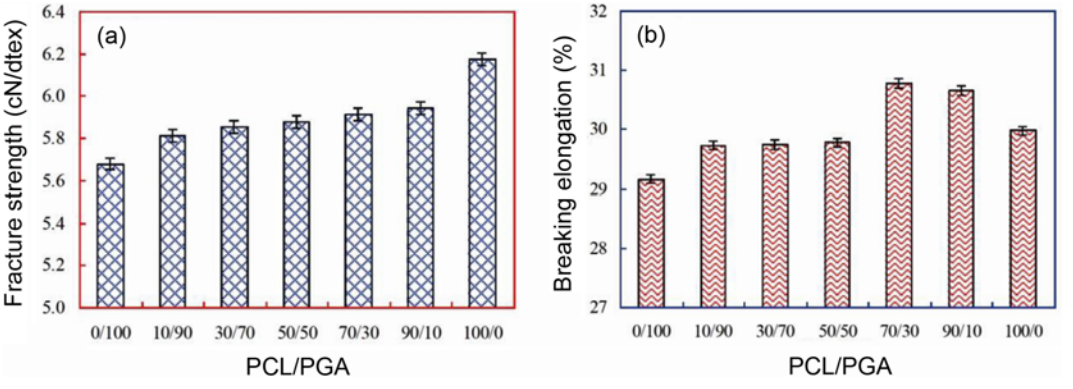

Figure 7. The mechanical property of drug-loaded PLA suture; (a) effect of the PCL/PGA proportion on the fracture strength of suture and (b) effect of the PCL/PGA proportion on the breaking elongation of suture.

Table 1. The effective strength-time of tightening wound for the suture

PCL/PGA	Original PLA suture	0/100	10/90	30/70	70/30	90/10	100/0
Effective strength-time/week	11.50	12.18	13.4	14.14	16.8	19.2	22.3

was slow. This is because after dip-padding process, a layer of drug-PCL/PGA was coated on the surface of suture. In the process of coated suture degradation from outside to inside, the coating of drug-PCL/PGA will be degraded firstly, and then the inner PLA suture will be degraded. Unlike the coated suture, the original PLA suture had no coating material, and will be directly degraded from suture-body itself. So the strength reduction rates of coated sutures were slower than that of original PLA suture.

When the strength of suture falls to a certain extent, the suture will lose the effect of tightening the wound, even will be broken under the wound tissue tension. Therefore, the suture should reach a certain standard of strength, to maintain the effectiveness of tightening wound. If the 3.6 cN/dtex of strength, which is generally required for skin injury suture, is designed as the standard of strength, the standard of strength (red dotted line in Figure 8) will be intersected with every strength-line in Figure 8, and the corresponding time of intersections (as shown in Table 1) is the effective strength-time of tightening wound for the suture. It can be seen from Table 1 that the more PCL in carriers, the longer effective strength-time for the suture.

Drug-release Property of Drug-loaded PLA Suture

In the process of suture degradation, the coating of drug-PCL/PGA was degraded gradually, meanwhile, the TP drug was be released from the carriers. The accumulated rate of drug-release, as shown in Figure 9, is applied to evaluate the drug-release property of drug-loaded PLA suture.

Figure 9 shows that in the process of degradation, the drug-release rates of sutures were very fast within 10 h. The release rates of sutures began to slow down after 10 h. This is because that the concentration of drug was very high in the early stage of drug-releasing, and easy to be permeated and dissociated from the PCL/PGA carriers, therefore, the drug-release rates of sutures were very fast in the early stage (within 10 h). In the later stage (after 10 h), with the slow degradation of PCL/PGA carriers, the drug was slowly released from the PCL/PGA carriers.

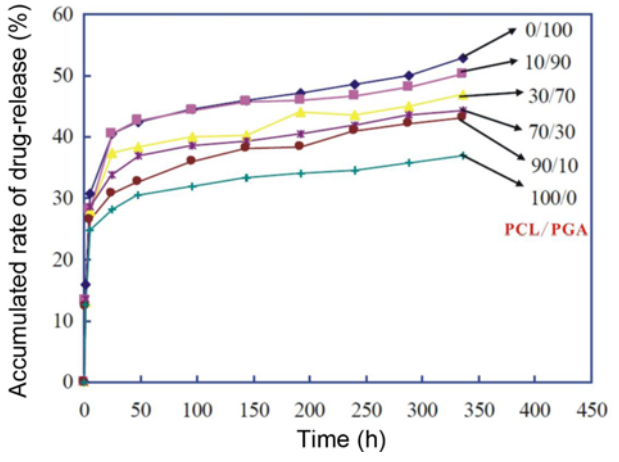

Figure 9. The accumulated rate of drug-release of sutures with different proportions of PCL/PGA carriers.

In addition, it can be seen from Figure 9 that the more PGA in the drug carriers, the larger accumulated rate of drug-release and the faster rate of drug-release for the suture. This is because that the degradation rate of PGA carrier was faster than that of PCL carrier. Therefore, the larger the proportion of PGA in the coating of suture was, the faster the degradation rate and drug-release rate would be.

Conclusion

The original PLA suture was smooth and loose. The surface of suture coated with the drug-PCL/PGA was obviously rough, and the fibers in the coated suture were stuck together. The drug coating material on the surface of suture, was degraded firstly in the process of degradation. The degrading rate of drug-PCL/PGA coating was very fast, and then many big holes appeared on the suture. There was no chemical reaction but physically mixture and adhesion, among the PLA suture, the PCL/PGA carriers and the TP drug. With increasing of PCL in the carriers, the fracture strength of suture increased gradually. When at 70/30 of PCL/PGA carriers, the suture had the maximum breaking elongation. The fracture strength of suture decreased gradually in the process of degradation and drug-release. The strength reduction rates of the sutures coated with drug-PCL/PGA were slower than that of original PLA suture. The suture with different PCL/PGA carriers had different effective strength-time of tightening wound. The drug-release rates of drug-loaded sutures were very fast within 10 h. The release rates of drug-loaded sutures began to slow down after 10 h. The proportion of PCL/PGA carriers was adjusted to control the drug-release performance of suture. This PLA medical suture can be used to stitch the wounds which have different healing time. The drug can be released slowly at an appropriate rate, and applied directly to the wound. Besides, this PLA suture loaded drug, can reduce the oral and injected dosage of drug.

Acknowledgement

This work was supported by the MOE (Ministry of

Education in China) Project of Humanities and Social Sciences (18YJC760051), 2017 Shanxi Philosophy and Social Science Project (201702), Program for the Philosophy and Social Sciences Research of Higher Learning Institutions of Shanxi (PSSR) (201803060), the Shanxi University Students Innovation and Entrepreneurship Training Program Project (2018099), the Students Innovation and Entrepreneurship Training Program Project of Taiyuan University of Technology (18049), the Scientific and Technological Innovation Programs of Higher Education Institutions in Shanxi, China (2015125) and the Youth Foundation of Taiyuan University of Technology, China (2015QN042). And Shuqiang Liu would also like to acknowledge financial support through International Visit Program of Taiyuan University of Technology.

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