Characterization of Dexamethasone-eluting PLGA Films Coated on Capsular Tension Ring to Prevent Posterior Capsule Opacification

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Abstract – The objectives of this study were to prepare PLGA film onto the surface of the capsular tension ring (CTR) for controlled drug release and investigate the influence of plasticizers, the test drug and measurement conditions on flexibility of the film. Film solutions were prepared by dissolving PLGA, plasticizer (triethyl citrate, TEC or polyethylene glycol, PEG), test drug (dexamethasone) in ethyl acetate then films were prepared by spray coating and evaporation method. Then, the flexibility of PLGA film was determined by elongation test. The addition of plasticizer, PEG or TEC to PLGA copolymer caused a depression of glass transition temperature (T_g) and the elasticity of PLGA films increased. The addition of dexamethasone to the PLGA/TEC matrix decreased the flexibility of film. Dimensional factors of the PLGA films such as width and thickness were significantly influenced on flexibility of films and film length and elongation speed had no considerable influence on elongation of films. In this study, sufficiently flexible and stable PLGA films capable of being coated onto CTR could be prepared. This PLGA films can be used as a platform for local drug delivery.

Keywords: PLGA film, Capsular tension ring, Flexibility, Plasticizer, Elongation test

INTRODUCTION

Posterior capsule opacification (PCO) is a major complication of cataract surgery occurring in 15 to 50% of the treated eyes following 3 to 5 years of the surgery (Bertelmann and Kojetinsky, 1995). It is caused by migration and proliferation of residual equatorial lens epithelial cells (LECs) to intraocular lens after cataract surgery resulting in significant visual impairment (Fernandez *et al.*, 2004).

The prevention of PCO is one of the big challenges in ophthalmic treatment because of the medical and financial implication and localized drug delivery to residual equatorial LECs is believed to be the optimal approach for the prevention of PCO. Several experimental studies using intraocular infusion of drugs such as colchicine, methotrexate, retinoic acid, 5-fluorouracil and dexamethasone have been performed in animal models to prevent

PCO (Ruiz *et al.*, 1995; Tetz *et al.*, 1995; Ismail *et al.*, 1996; Legler *et al.*, 1993; Power *et al.*, 1994).

CTR assists the cataract surgeon to have weak zonules and centers an intraocular lens. To prevent PCO, drug-eluting CTR has been developed as one of the PCO therapies (Apple *et al.*, 2000; Pandey *et al.*, 2002; Peng *et al.*, 2000a, 2000b). In this study, we designed poly(lactic-co-glycolic acid) (PLGA) films on CTR, horseshoe-shaped open ring with 0.1 - 0.3 mm thickness as a drug delivery platform. Film formulations based on an FDA approved biocompatible and biodegradable copolymer PLGA have been used for the controlled release of a number of different drugs (Dorta *et al.*, 2002; Gumusderelioglu *et al.*, 2000). Since PLGA film is brittle without any additives, the formation of physically stable PLGA films onto CTR having a big curvature seems to be very difficult. Thus, to deliver drugs from PLGA film formed on CTR for the prevention of PCO it is essential to produce flexible films capable of staying firmly on CTR.

It is well known that the addition of plasticizers such as polyethylene glycol (PEG) and triethyl citrate (TEC) causes a depression of glass transition temperature and

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thereby makes the film flexible (Kranz *et al.*, 2000; Webber *et al.*, 1998). Thus, the objectives of this study were to prepare of PLGA film with plasticizers to give flexibility and dexamethasone, a model drug, coated onto CTR and evaluate the physical properties of the PLGA film by investigating the influence of plasticizers, the test drug and measurement conditions on flexibility of the film. Film flexibility was evaluated by measuring the elongation properties of the PLGA films.

MATERIALS AND METHODS

Materials

PLGA with weight percentages of lactic acid to glycolic acid of 50:50 (molecular weight 57800 g/mol), polyethylene glycol (PEG) having molecular weight of 300 g/mol, and triethyl citrate (TEC) were obtained from Sigma-Aldrich Company (MO, USA). Dexamethasone was supplied by Tokyo Chemical Industry (Tokyo, Japan). All solvents were HPLC grade and obtained from Fisher Scientific (NJ, USA).

Solvent screening

Selecting a solvent with an ability to solubilize PLGA and no interaction with CTR made of polymethyl methacrylate is important in the production of films onto CTR. A variety of organic solvents were screened for the solubilizing ability of PLGA based on the information reported (Table 1) (Brodbeck *et al.*, 1999; Ferruti *et al.*, 1995) and an interaction between solvents and CTR was evaluated by microscopic inspection.

Preparation of PLGA films onto CTR

Film compositions in solution were made by dissolving an appropriate amount of polymers (i.e., PLGA contain-

ing PEG or TEC) and dexamethasone in 1 ml of ethyl acetate to obtain a film former concentration of 1% w/v. The solutions were allowed to stand with stirring for approximately 1 h until visually clear. To form PLGA films onto CTR, the polymer solution was directly sprayed onto CTR from a distance of 5 cm using an airbrush (Model Spray-Work HG Super Fine Double Action Airbrush, Tamiya, Japan) and dried for 2 days at room temperature. When PLGA thin films were needed for the study of mechanical properties of the films, PLGA films were prepared by spraying the polymer solutions on a flat surface (1.0 × 1.0 cm) of silicone and evaporating the solvent.

Differential scanning calorimetry (DSC)

DSC was performed using a Mettler Toledo Star[®] calorimeter. Approximately 10 mg of PLGA films were placed in a crimped aluminum DSC pan. Then DSC curves of each film were obtained from the second heating run at a rate of 10 °C/min, after the first run of heating up to 100 °C and cooling to 0 °C at the same rate of 10 °C/min, under nitrogen atmosphere, in order to estimate the glass transition temperature.

Flexibility of PLGA films

The flexibility of films was evaluated through an elongation test. Square films of 1.0 cm × 1.0 cm with a thickness of 0.01 mm, were carefully placed between the two vertical grips. The thickness of the film was measured using a digital microscope VHX-100 (Kyence, UK). The movable grip was then driven upward with a speed of 10 mm/min until the rupture of the film. Percent elongation at break (ϵ) was calculated with the following equation:

$$\epsilon(\%) = \frac{L_R}{L_0} * 100$$

where L_R (mm) is the extension of the sample in the moment of rupture and L_0 (mm) is the original sample length. Each experiment was repeated five times.

Plasticizer effect on film flexibility

To examine the influence of increasing amounts of PEG or TEC in PLGA films on the flexibility of the films, the elongation properties of PLGA films containing 0.5, 1, 2, and 5% (w/w) of TEC or PEG were evaluated as previously described.

Drug effect on film flexibility

To test the influence of increasing amounts of dexamethasone in PLGA films on the flexibility of the films, the elongation properties of PLGA films containing 1, 2, and

Table I. Properties of organic PLGA solvents

	Boiling points (°C)	Solubility parameter MPa ^{1/2}
Methylene chloride	40	18.5
Ethyl acetate	77	17.6
Acetic acid	118	20.7
Dimethyl sulfoxide	189	24.5
N-methyl 2-Pyrrolidinone	202	23.1
Ethyl bebzoate	212	23.1
Triacetin	258	-
Benzyl benzoate	323	-

5% (w/w) of dexamethasone were evaluated as previously described.

Impact of film length, width, thickness and elongation speed on film flexibility

To examine the influence of the film length, width and thickness on the flexibility, PLGA films having different lengths (i.e., 1, 2, and 3 cm), different widths (0.5, 1 and 2 cm) and three different thicknesses (10, 20 and 30 μm) were prepared and measured for their elongation properties. And three different speeds of 5 mm/min, 10 mm/min and 20 mm/min were employed during the measurements to see how the elongation speeds influence the measurement results.

Mechanical stability of PLGA films formed onto CTR

As previously described, a polymer solution of 1% (w/v) in ethyl acetate was sprayed onto CTR from a distance of 5 cm using an air brush and dried for 2 days at room temperature. The PLGA films composed of PLGA : TEC: dexamethasone = 93 : 5 : 2. The surface morphology of the films was observed using a digital microscope (VHX-100, Kyence, UK) right after the CTR was stretched and bended ten times.

RESULTS AND DISCUSSION

Among the solvents screened (Table 1), the solvents with a low boiling point, for instance < 100, would be a good candidate because it will take little time for the solvent to be evaporated. In this regard, methylene chloride and ethyl acetate were selected as they have lower boiling points. Additionally, to check the interaction of CTR with these two solvents, it was immersed in ethyl acetate or methylene chloride and microscopically observed for any morphological changes of CTR. As a result of the immersion test, ethyl acetate was found to be a suitable solvent for the production of PLGA solutions.

Film solutions were prepared by dissolving PLGA, plasticizer (TEC or PEG) and dexamethasone in ethyl acetate. Then homogeneous PLGA film solutions were efficiently sprayed onto CTR using an airbrush and dried at room temperature.

The PLGA films showed a glass transition temperature (T_g) of 42.3 and were brittle in the absence of plasticizers. DSC scans for PLGA polymers with plasticizers showed a single T_g . The addition of PEG or TEC to PLGA copolymers caused a concentration dependent decrease in T_g values of the PLGA films (Figure 1). Indeed, the addition of increasing amounts of TEC or

PEG to PLGA up to 5% by weight produced a concentration dependent decrease in T_g of the blended polymer. These lowered T_g should lead to an increased film flexibility. PLGA films made from PLGA alone were fairly brittle when the elongation stress was applied. The addition of either PEG or TEC to the PLGA films resulted in an increase in the elasticity and flexibility of the films. The addition of increasing amounts of PEG or TEC to the PLGA films increased the elongation force as shown in Figure 2. This can greatly be attributed to the role of plasticizers which generally increase the flexibility of polymers.

The addition of dexamethasone at concentrations of 1, 2 and 5% (w/w) caused a concentration dependent decrease in the elasticity of these films as shown in Figure 3. The decrease in elasticity measurements caused by the addition of dexamethasone to the PLGA/TEC matrix may have been due to antiplasticization effect of drug and strong intermolecular interactions between the

Fig. 1. Effect of blending of TEC or PEG into PLGA films on the glass transition temperature (T_g): (●), TEC; (○), PEG (Mean $\pm$ S.D., $n=5$).

Fig. 2. Effect of plasticizer concentration on the elastic property of the PLGA films: (●), TEC; (○), PEG (Mean $\pm$ S.D., $n=5$).

Fig. 3. Effect of dexamethasone concentration on the elastic property of the PLGA films (Mean $\pm$ S.D., $n=5$).

drug and the polymer (Webber *et al.*, 1998).

For the evaluation of elongation properties of PLGA films, various dimensional factors of the PLGA films and measurement condition such as elongation speed were examined. The increase in film length and elongation speed had no considerable influence on elongation force as shown in Figure 4 and Figure 7, respectively. However, the width and thickness of film significantly influenced on elongation properties of the films and showed bigger differences in elongation properties than length or elongation speed as shown in Figure 5 and Figure 6, respectively. With the increment of film width and thickness, the elongation at break (%) was increased.

The polymer matrix should have good mechanical properties in terms of flexibility and long lasting adherence to the CTR surface at the required size when the device is deployed. Morphological features of PLGA films

Fig. 4. Effect of film length on the elastic property of the PLGA films (Mean $\pm$ S.D., $n=5$).

Fig. 5. Effect of film width on the elastic property of the PLGA films (Mean $\pm$ S.D., $n=5$).

coated onto the surface of CTR observed by optical microscopy. As can be seen in Figure 8, the plasticizer

Fig. 6. Effect of film thickness on the elastic property of the PLGA films (Mea $n\pm$ S.D., $n=5$).

Fig. 7. Effect of elongation speed on the elastic property of the PLGA films (Mean $\pm$ S.D., $n=5$).

Fig. 8. PLGA film coating on tension ring. (a) Coating free tension ring, (b) PLGA film with 5% TEC and 2% dexamethasone and (c) PLGA film with 2% dexamethasone.

containing films have good flexibility and were not changed in its morphology even after the mechanical stress of ten times of stretching and bending was applied.

In this study, CTR was coated with PLGA by spray coating and evaporation method. The addition of plasticizer, PEG or TEC to PLGA copolymer caused a depression of T_g sufficient to allow for the formation of flexible films at room temperature using PLGA polymer. The elasticity of PLGA films increased with the addition of either PEG or TEC as determined by elongation measurements, demonstrating the plasticizing effects of PEG and TEC. The decrease in elasticity measurements caused by the addition of increasing amounts of dexamethasone to the PLGA/TEC matrix may have been due to a stiffening effect. The increasing of film length and elongation speed had a slight influence on elongation. In conclusion, sufficiently flexible and stable PLGA films capable of being coated onto CTR could be prepared.

This PLGA films can be used as a drug delivery platform for the prevention of PCO.

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