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Research paper

Dexamethasone-loaded poly(ε-caprolactone) intravitreal implants: A pilot study

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Abstract

Purpose: Poly(ε-caprolactone) (PCL) is a biodegradable and biocompatible polymer that presents a very low degradation rate, making it suitable for the development of long-term drug delivery systems. The objective of this pilot study is to evaluate the feasibility and characteristics of PCL devices in the prolonged and controlled intravitreous release of dexamethasone. *Methods:* The *in vitro* release of dexamethasone was investigated and the implant degradation was monitored by the percent of mass loss and by changes in the surface morphology. Differential scanning calorimetry was used to evaluate stability and interaction of the implant and the drug. The short-term tolerance of the implants was studied after intravitreous implantation in rabbit eye. *Results:* PCL implant allows for a controlled and prolonged delivery of dexamethasone since it releases 25% of the drug in 21 weeks. Its low degradation rate was confirmed by the mass loss and scanning electron microscopy studies. Preliminary observations show that PCL intravitreous implants are very well tolerated in the rabbit eye. *Conclusion:* This study demonstrates the PCL drug delivery systems allowed to a prolonged release of dexamethasone *in vitro*. The implants demonstrated a strikingly good intraocular short-term tolerance in rabbits eyes. The *in vitro* and preliminary *in vivo* studies tend to show that PCL implants could be of interest when long-term sustained intraocular delivery of corticosteroids is required.

Keywords: Poly(ε-caprolactone); Implant; Prolonged release; *In vitro* study; Short-term tolerance

1. Introduction

At a time when new active compounds are available for retinal diseases treatment, intraocular controlled drug delivery systems are essential to achieve an ideal pharmaceutical intervention. Polymeric drug delivery systems allow for a sustained and controlled release of the drug, thus optimizing its bioavailability and decreasing potential side effects. Particularly, biodegradable polymers have been extensively studied for ocular drug delivery systems as no surgical procedure is required to remove the empty device [1].

Pharmaceutical intervention for the treatment of diseases affecting the posterior segment tissues of the eye requires repeated intravitreous injection because effective levels of drugs in the vitreous and the retina cannot be achieved through conventional routes of administration [2]. Repeated intravitreous injection however has many drawbacks: (i) patient discomfort and compliance, (ii) cumulated risk of rare but severe complications such as endophthalmitis, retinal tears, hemorrhages and detachments, (iii) cataract, (iv) peak and valley drug levels, (v) toxic risk for ocular tissues when efficacy and toxicity threshold are close. Intraocular implants of biodegradable polymers overcome most of these drawbacks since they maintain stable long-term vitreous concentrations of drugs

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in the therapeutic range. Studies using biodegradable implants containing various agents have been reported [3–11] and dexamethasone biodegradable delivery systems have been developed to the prevention of inflammation after cataract surgery [12–14].

Posurdex (Allergan), a biodegradable polymer matrix prepared with poly-lactide-co-glycolide copolymer (PLGA), releases dexamethasone over approximately 5 weeks and clinical trials have been evaluating its usefulness in persistent macular edema associated with diabetes, retinal vein occlusions, uveitis, and post-cataract surgery. The Phase II clinical trial followed 306 patients who received one of the three treatments: a single implant with either a 350 or 700 μg dose of dexamethasone or observation without drug therapy. The results showed that the patients who had been implanted with the 700 μg dose had the greatest improvement in vision and most of these patients exhibited a three-line increase in visual acuity compared to the control group [15].

Within the biodegradable polymers, aliphatic polyesters, such as poly (ε-caprolactone) (PCL), are of particular interest as they allow for a long sustained and possibly modulated drug release rate [16]. PCL is a biodegradable and biocompatible semi-crystalline polymer having glass transition temperature of −60 °C and melting point ranging between 59 and 64 °C, depending upon its crystalline nature [17,18]. This polymer presents a very slow degradation rate, making it suitable for long-term delivery extending over a period of more than one year. Furthermore, it is biocompatible and very much used in the pharmaceutical and biomedical fields, respectively, as biomaterials (suture, ostheosynthesis material, artificial skin, support of cellular regeneration) or as prolonged drug delivery systems targeting specific tissues within the body [18]. PCL micro- or nanoparticles or solid implants have indeed been widely explored these last years for the administration of drugs by different routes and for the treatment of different diseases [18–23]. However, despite the potential of PCL, its utilization in ophthalmology, especially for the intraocular route, has been poorly explored.

The aim of this study was to develop and characterize biodegradable PCL implants, for intraocular prolonged and controlled release of dexamethasone. The *in vitro* release profile of dexamethasone was investigated and the implant degradation was monitored by the percent of mass loss and surface changes visualization using scanning electron microscopy. Differential scanning calorimetry was used to evaluate the stability and interaction of the implant and the drug.

Finally, the feasibility and short-term tolerance of PCL implants were evaluated in rabbit eye after intravitreous implantation.

2. Materials and methods

Dexamethasone alcohol (MW = 392.5; aqueous solubility at 37 °C = 1.0 mg/ml) and polymer poly(ε-caprolactone) (PCL; MW ~ 14,000; density = 1.145 g/ml at 25 °C) were purchased from Sigma–Aldrich Co. (France). Acetonitrile HPLC grade was purchased from EM Science, Merck KGaA (Germany). Ultrafiltrated water was obtained from Milli Q plus, Millipore (USA). All other chemicals were of analytical grade.

2.1. Preparation by compression of the implants containing poly(ε-caprolactone) and dexamethasone

Firstly, a 25% w/w concentration of the drug (dexamethasone) and the polymer [poly(ε-caprolactone)] was dissolved in a mixture of acetonitrile and distilled water (1:1). The formed solution was then placed in a freezer under −80 °C. Afterwards, the frozen solution was lyophilized (Christ Alpha 1-2 LD, Bioblock Scientific, France). Approximately 200 mg of the obtained powder was compressed in an evacuable KBr die (Shimadzu, Japan), using a hydraulic press SSP-10A (Shimadzu, Japan) at 10 ton/cm^2, during 10 min in the form of 13 mm diameter discs. The obtained discs were, next, cut in the size of implants of 4.0 mm of diameter. The implants were white to off-white in color, presented a rigid structure, and 1 mm in thickness (Fig. 1). The mean weight of the developed devices was 4.01 ± 0.20 mg, corresponding to approximately 1 mg of dexamethasone.

2.2. Content uniformity test for the dexamethasone-loaded PCL implants

For the determination of content uniformity of dexamethasone in the PCL implants, the procedure stated in the general chapter <905> uniformity of dosage units of the United States Pharmacopeia 29 [24] was followed.

Ten implants were selected and weighted. Each implant was dissolved in 100 ml of a mixture of acetonitrile and distilled water (1:1). The amount of dexamethasone was determined by high-performance liquid chromatography, according to the procedure described in the item 2.3.

The obtained values of the amount of dexamethasone in each implant (mg) were estimated and the results were expressed as the percent of the pre-indicated value (approximately 1.0 mg/ml). The relative standard deviation was also calculated.

Fig. 1. Macroscopical view of the developed implant.