Pharmaceutical Nanotechnology

Nanoparticle-Based Topical Ophthalmic Formulations for Sustained Celecoxib Release

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ABSTRACT: Celecoxib-loaded NPs were prepared from biodegradable polymers such as poly-ε-caprolactone (PCL), poly(L-lactide) (PLA), and poly(D,L-lactide-*co*-glycolide) (PLGA) by spontaneous emulsification solvent diffusion method. Different concentrations of polymers, emulsifier, and cosurfactants were used for formulation optimization. Nanoparticles (NPs) were characterized regarding their particle size, PDI, zeta potential, shape, morphology, and drug content. Celecoxib-loaded NPs were incorporated into eye drops, *in situ* gelling system, and gel and characterized regarding their pH, viscosity, uniformity of drug content, *in vitro* release, and cytotoxicity. The results of optimized celecoxib-loaded PCL-, PLGA-, and PLA-NPs, respectively, are particle size 119 ± 4, 126.67 ± 7.08, and 135.33 ± 4.15 nm; zeta potential –22.43 ± 2.91, –25.46 ± 2.35, and –31.81 ± 2.54 mV; and encapsulation efficiency 93.44 ± 3.6%, 86.00 ± 1.67%, and 79.04 ± 2.6%. TEM analyses revealed that NPs have spherical shapes with dense core and distinct coat. Formulations possessed uniform drug content with pH and viscosity compatible with the eye. Formulations showed sustained release without any burst effect with the Higuchi non-Fickian diffusion mechanism. Cytotoxicity studies revealed that all formulations are nontoxic. Our formulations provide a great deal of flexibility to formulation scientist whereby sizes and zeta potentials of our NPs can be tuned to suit the need using scalable and robust methodologies. These formulations can thus serve as a potential drug delivery system for both anterior and posterior eye diseases. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:1036–1053, 2013

Keywords: poly-ε-caprolactone; poly(L-lactide); poly(D; L-lactide-*co*-glycolide); biocompatibility; ophthalmic; celecoxib; controlled release; nanoparticles; cytotoxicity

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDS) have been used topically to manage some ophthalmic problems such as to enhance mydriasis, reduce postoperative inflammation, and prevent and treat cystoid macular edema associated with cataract surgery. In addition, they can be used to decrease pain and photophobia after refractive surgery and to alleviate itching associated with allergic conjunctivitis.[1] More recently, it was suggested that NSAIDs are beneficial in the treatment of diabetic retinopathy,[2] age-related macular degeneration,[3] and ocular tumors.[4] Cyclooxygenases (COX) are a large family of enzymes that are mainly activated during an inflammatory response. Cyclooxygenase-1 (COX-1) is a constitutive enzyme, whereas COX-2 is an inducible enzyme that is expressed in inflammatory conditions and it is the predominant isoform implicated in eye diseases.[5] Celecoxib, an NSAID, exerts its action through a selective inhibition of the COX-2 enzyme.[6] It also has antivascular endothelial growth factor (anti-VEGF) effects, making it potentially useful in the treatment of proliferative diabetic retinopathy, neovascular age–related macular degeneration,[7] and some ocular tumors such as retinoblastoma[8] and metastatic uveal melanoma.[6]

The most common route of administration for celecoxib in treatment of ocular diseases is oral.[9] This route, however, has many drawbacks including that the amount of drug that reaches the eye is very low, thus requiring a high systemic dose for a long period of time, which may increase the risk of occurrence

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of drug side effects.[10] Several studies have been performed to overcome the drawbacks of the systemic administration of celecoxib. One such study prepared celecoxib in the form of periocular injectable microparticles for the treatment of diabetes-induced elevations in retinal prostaglandins, VEGF, and vascular leakage.[11] Another study evaluated subconjunctivally administered celecoxib-poly(D,L-lactide-*co*-glycolide) (PLGA) microparticles for sustained retinal drug delivery for treatment of diabetes-induced oxidative stress in a rat model.[12] A third study prepared the formulation of celecoxib in two injectable forms (i.e., celecoxib suspension in 0.5% carboxymethylcellulose and celecoxib-loaded poly(L-lactide) (PLA) nanoparticles) to study the effect of eye pigmentation on the transscleral drug delivery to the retina from both rapid release and sustained release formulations.[13] Although these studies showed increased delivery of celecoxib to the posterior segment of the eye, they all required invasive delivery methods. In our study, we sought to formulate celecoxib topical ophthalmic formulations to be administered noninvasively for treatment of both anterior and posterior eye diseases.

A major drawback of the conventional topical ophthalmic drug delivery system is rapid and extensive loss of drug caused by the drainage through the nasolachrymal duct and high tear fluid turnover.[14] Several studies have attempted to increase the corneal penetration of drugs using colloidal drug delivery systems, such as liposomes,[15] nanoparticles,[16] and nanocapsules,[17] which would in turn improve its therapeutic effect. Although these studies showed improved kinetics of drug release because of the presence of colloidal suspensions, they did not address the rapid drainage from the eye because they were in the form of a saline suspension. In our study, we incorporated our nanoparticles in three physically different vehicles that prevented its rapid drainage through the nasolacrimal duct.

In the present study, we report a modified spontaneous emulsification solvent diffusion method to prepare celecoxib-loaded nanoparticles (NPs) prepared from different synthetic biodegradable polymers, including poly-ε-caprolactone (PCL), PLA, and PLGA, for topical ophthalmic use. PCL, PLA, and PLGA are biodegradable and biocompatible polymers that are approved by U.S. FDA. Chemically, they are polyesters that are degraded by the cleavage of the ester bonds in the aqueous system, yielding nontoxic biocompatible degradation products.[18,19] We then incorporated the drug-loaded NPs in three different ophthalmic dosage forms including eye drops, a temperature triggered *in situ* gelling system, and a preformed gel. The current study was aimed at developing and optimizing sustained release biodegradable nanoparticulates formulations of celecoxib for topical ocular delivery.

MATERIALS AND METHODS

Materials

Celecoxib, PCL (average molecular weight 14,000 Da), PLA (molecular weight 152,000 Da), PLGA (lactide–glycolide 75:25; molecular weight 66,000–107,000 Da), hydroxypropylmethylcellulose (HPMC), methylcellulose (Methocel, MC), polyvinyl alcohol (PVA; molecular weight 31,000–50,000 Da), Triton X-100, methyl thiazol tetrazolium (MTT), sodium chloride, potassium chloride, sodium phosphate dibasic, potassium dihydrogen phosphate, absolute ethyl alcohol, acetone, and dichloromethane (DCM) were purchased from Sigma-Aldrich (St. Louis, Missouri). Soybean L-α-lecithin (98% phosphotidyl choline) was purchased from Calbiochem (San Diego, California). Poloxamer 188 (Pluronic F68; polyethylene-polypropylene glycol, a block copolymer of ethylene oxide and propylene oxide; average molecular weight 8400 Da) was purchased from Spectrum Chemical (New Brunswick, New Jersey). Dimethyl sulfoxide (DMSO) was purchased from ThermoScientific (Rockford, Illinois). Glacial acetic acid was purchased from Fisher Scientific (Fair Lawn, New Jersey). Eagle's minimal essential cell culture medium (EMEM) was purchased from ATCC (Manassas, Virginia). All chemicals utilized for preparing buffers are of the analytical grade. All materials were used as received without any further treatment.

Methods

Preparation of Plain and Celecoxib-Loaded Nanoparticles

Plain NPs were prepared using a spontaneous emulsification solvent diffusion technique[20] with some modifications. Tables 1–3 showed the formulation ingredients used for preparation of NPs for preliminary study and optimization. Briefly, two concentrations were used for each polymer 0.1% and 0.2% (w/v). The polymer was dissolved in DCM then lecithin was dissolved in the polymer solution in a concentration of 0.0%–2% (w/v), and finally acetone was added to the previous organic solution. Different NP stabilizers (i.e., cosurfactants) including poloxamer 188 or PVA were dissolved in different concentrations ranging from 0.2% to 3% (w/v) in deionized water (DIW). The organic solution was injected into the aqueous solution (under magnetic stirring, 900 rpm) with an injection flow rate of 0.8 mL/min using an infusion pump (Fisher Scientific) that connected to a syringe attached to a 25 gauge needle. The obtained emulsion was sonicated (Misonix S-4000; Qsonica, Newtown, Connecticut) at 100% amplitude for 10 min in an ice bath. The obtained NPs dispersion was stirred overnight at a moderate stirring rate (200 rpm) to