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Electrospun formulations of acyclovir, ciprofloxacin and cyanocobalamin for ocular drug delivery

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ABSTRACT

Two series of fibers containing the active ingredients acyclovir, ciprofloxacin and cyanocobalamin, and combinations of these drugs, were prepared by electrospinning. One set used the hydrophilic poly (vinylpyrrolidone) (PVP) as the filament-forming polymer, while the other used the slow-dissolving poly (ε-caprolactone) (PCL). The fibers were found to have cylindrical morphologies, although there was evidence for solvent occlusion with the PVP systems and for some drug particles in the PCL materials. The active ingredients were generally present in the amorphous physical form in the case of PVP, but evidence of crystallinity was observed with PCL. The existence of intermolecular interactions between the drugs and polymers was proven using simple molecular modeling calculations. Drug release from the various fibers was tested in a validated *in vitro* outflow model of the eye, and the fiber formulations found to be capable of extending drug release. We thus conclude that electrospun matrices such as those prepared in this work have potential for use as intravitreal implants.

1. Introduction

Cytomegalovirus (CMV) infections are a major clinical problem in patients with AIDS. Their main manifestation in AIDS patients is retinitis, which accounts for 20–30% of all cases (Pollard, 1996). Common symptoms of CMV retinitis include visual field defects with decreased acuity, the presence of floaters, and photophobia. Complications arise when retinitis is localized near the macula, which can lead to loss of vision and to hemorrhages replaced eventually by thin atrophic scar tissue and inflammation (Jouan and Katlama, 1999). Most ocular drugs when given by topical administration are rapidly cleared by the aqueous humor flowing into the anterior chamber and flushing the drug out via the trabecular meshwork, should they permeate the cornea. The drug will often therefore fail to reach reproducible therapeutic levels near the retina (Haghjou et al., 2013). Intravitreal (IVT) injection can provide adequate drug concentrations in the posterior segment. Unfortunately drugs in solution can rapidly clear within hours from the posterior cavity upon IVT injection. This reduces efficacy and frequent injections are required, which can lead to undesirable side effects and reduce patient compliance (Short, 2008).

To solve the general problem of fast ocular clearance times, new strategies are being investigated to deliver drugs as intravitreal implants specifically designed to prolong release. One example is Vitrasert® (Bausch & Lomb Inc., Rochester, NY, USA), a ganciclovir loaded intravitreal implant approved by the US Food and Drug Administration and administered for the treatment of CMV retinitis. The implant is primarily made of ethylene-vinyl acetate

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and polyvinyl alcohol, and the drug is released over a period of 6–8 months (Kuno and Fujii, 2011).

There are a number of drug candidates that can be used to treat ocular infections. Acyclovir (ACY) is an effective antiviral agent but is only slightly soluble in water. This limits its use in the eye since it is challenging to prepare a solution with sufficient solubility to exert a therapeutic effect. Ciprofloxacin (CIP) is widely used to prevent and cure bacterial infections, and thus can be used with ACY to provide broad-spectrum anti-pathogenic activity. It too has very poor water solubility. Cyanocobalamin (vitamin B12) has been reported to repair damage to the eye, and is used in some eye drops (*e.g.* Sante Beautéye (Santen Pharmaceutical Co., 2013)). A formulation containing all three ingredients, with solubility enhancement for ACY and CIP, would thus be a useful addition to the gamut of treatments for viral diseases of the eye.

Various strategies can be applied to increase the solubility and dissolution rate of poorly soluble drugs; one popular approach is to prepare amorphous dispersions of the active pharmaceutical ingredient (API) in a polymer matrix. The formation of such a solid solution or solid suspension removes the lattice energy barrier to dissolution, and the polymer carrier additionally helps to stabilize the amorphous form by preventing the API molecules from crystallizing. One method which has been widely explored to generate such pharmaceutical composites is electrospinning (Chakraborty et al., 2009; Williams et al., 2012). This approach is attractive in its simplicity. A co-dissolving solution of a polymer and an API is first prepared in a volatile solvent. This is then loaded into a syringe fitted with a metal needle (the spinneret). The polymer solution is ejected from the syringe towards a metal collector plate at a constant rate, controlled using a syringe pump. A high potential difference is applied between the spinneret (positive) and collector (grounded), causing rapid evaporation of the solvent and the formation of a non-woven mesh of polymer/API fibers, often with dimensions on the nanoscale.

Electrospinning has been used to prepare numerous formulations with enhanced solubility/dissolution characteristics, and ACY, CIP and B12 have all been previously processed in this manner. Only a single publication relating to B12 electrospinning could be found in the literature, focused on preparing temperature-sensitive release systems based on poly(ethylene oxide) and poly(isopropylacrylamide) (Song et al., 2011). A number of reports of CIP spinning exist, focused primarily on would dressings (El-Shanshory et al., 2015; Unnithan et al., 2012), oral hygiene (Bottino et al., 2014) or urinary devices (Macocinschi et al., 2015): no studies have been reported targeted at ocular drug delivery.

Yu et al. have undertaken several investigations into ACY fibers, using both slow and fast dissolving polymers. Core/shell fibers of poly(vinyl pyrrolidone) (PVP) were prepared with a shell containing PVP, sodium dodecyl sulfate (as a permeation enhancer) and sucralose (a flavor enhancer), and a PVP/ACY core (Yu et al., 2011). These were designed for oral application, and found to release all the incorporated drug within 1 min. Analogous systems and results were obtained using electrospraying, a technique closely related to electrospinning which produces particles instead of fibers (Liu et al., 2014). Sustained release systems loaded with ACY have also been prepared with poly(acrylonitrile) as the carrier polymer (Chen and Yu, 2010; Yu et al., 2010).

All of the abovementioned systems were prepared with applications other than the ocular field in mind. In this work, we sought to develop electrospun systems to allow effective healing of viral eye infections. ACY, CIP and B12 (see Fig. 1) were first spun individually before combination formulations were

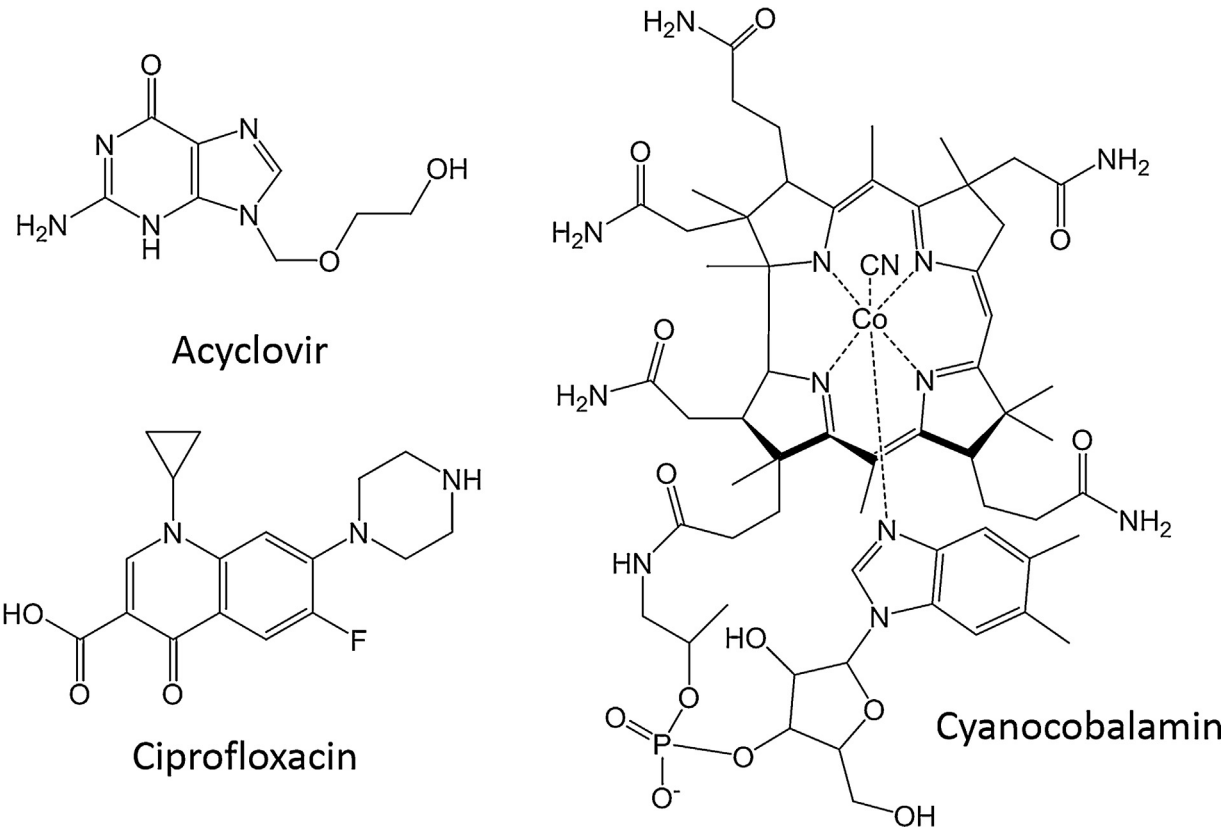

Fig. 1. The chemical structures of acyclovir, ciprofloxacin and cyanocobalamin.