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Research Paper

New prostaglandin analog formulation for glaucoma treatment containing cyclodextrins for improved stability, solubility and ocular tolerance

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ABSTRACT

Latanoprost is a practically insoluble prostaglandin F2α analog considered a first-line agent for glaucoma treatment. From a pharmaceutical point of view, latanoprost is challenging to be formulated as an eye drop due to its poor water solubility and the presence of an ester bond that needs to be cleaved *in vivo* but maintained unchanged during storage. Cyclodextrins (CDs) are known to form complexes with hydrophobic drugs, influencing their stability, availability, solubility, and tolerance in a non-predictable manner. A variety of CDs including native α, β, and γCDs as well as substituted hydroxypropylβCD, hydroxypropylγCD, dimethylβCD, sulphatedβCD, and propylaminoβCD were screened and the most appropriate CD for the formulation of latanoprost for an ocular topical application was selected. Among the tested CDs, propylaminoβCD had the best trade-off between latanoprost stability and availability, which was confirmed by its complex constant value of 3129 M^{-1}. Phase-solubility and NMR investigations demonstrated that the propylaminoβCD effectively formed a complex involving the ester group of latanoprost providing protection to its ester bond, while ensuring proper latanoprost solubilization. Furthermore, *in vivo* experiments demonstrated that the latanoprost-propylaminoβCD formulation led to lower ocular irritation than the commercial latanoprost formulation used as a reference. The latanoprost-propylaminoβCD formulation was demonstrated to successfully address the main stability, solubility, and tolerance limitations of topical ocular latanoprost therapy for glaucoma.

1. Introduction

Glaucoma can be defined as a group of sight threatening conditions that involve damage to the optic nerve. This affects more than sixty million people worldwide and is the second leading cause of blindness [1–3]. Maintaining intraocular pressure (IOP) within physiological range prevents the development and progression of the disease. Not all glaucoma patients present an elevated IOP and chronic elevated IOP can easily go unnoticed until the first signs of vision loss evidence the optic neuropathy. After a glaucoma diagnosis, a lifelong treatment needs to be initiated as soon as possible to minimize further vision impairment.

Latanoprost is a prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analog, considered a first-line agent for glaucoma treatment and has drastically changed the management of glaucoma from a surgical approach to a local pharmacological treatment. Latanoprost was demonstrated to decrease the IOP in a highly efficient manner by enhancing the uveoscleral outflow, while inducing low systemic side effects [4,5]. Latanoprost design was based on the chemical structure of $PGF_{2\alpha}$, and is both a prodrug and an analog of $PGF_{2\alpha}$, as illustrated in Fig. 1. The naturally occurring $PGF_{2\alpha}$ was demonstrated to efficiently decrease the IOP after a topical ocular administration, but also induces unacceptable levels of ocular irritation and hyperemia [6]. Compared to $PGF_{2\alpha}$, latanoprost displays a higher ocular penetration and lower ocular irritation while achieving effective IOP reductions [5,7]. Once topically administered to the eye, latanoprost efficiently permeates the cornea, where it is enzymatically biotransformed; this leads to the release of the active latanoprost acid to the anterior chamber allowing the active to reach the iris-ciliary body where it achieves the therapeutic effect, as illustrated in Fig. 1B [8]. In contrast, the direct topical administration of latanoprost acid could be related to poor ocular penetration reported with PG analogs presenting low lipophilicity [7]. The

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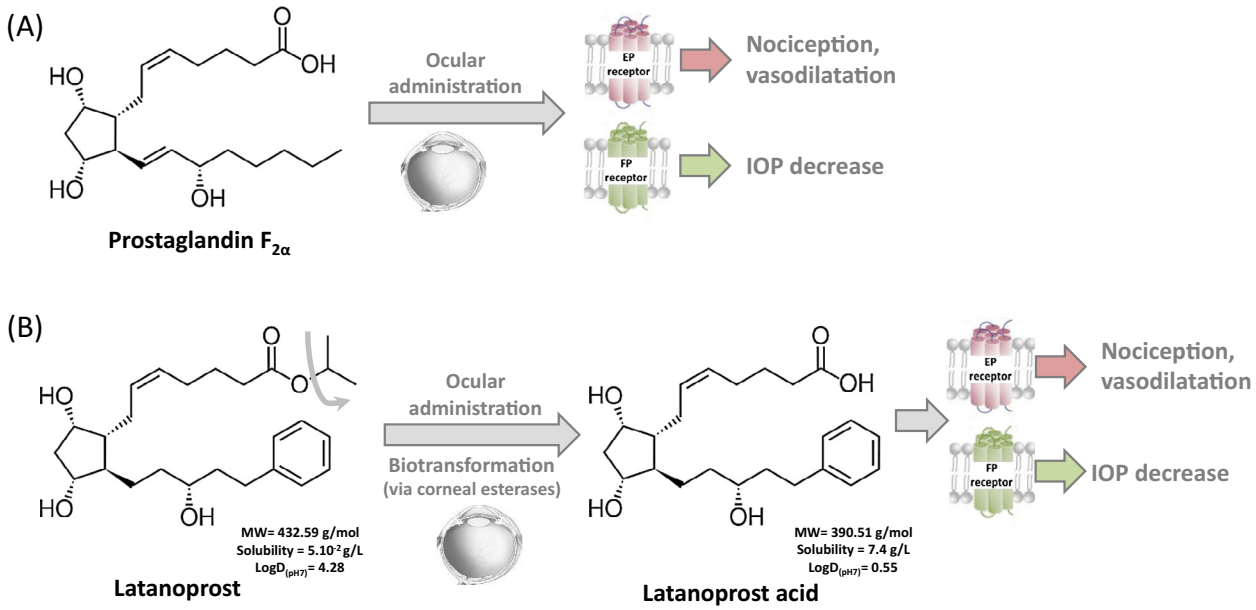

Fig. 1. Prostanoic receptor-mediated ocular effects after direct topical application of (A) prostaglandin $F_{2\alpha}$ and (B) latanoprost. The latanoprost biotransformation process and the physico-chemical characteristics of latanoprost and latanoprost acid are illustrated in (B). (IOP: intraocular pressure).

mechanisms behind the ocular effects of latanoprost acid were elucidated in previous studies, reporting that the therapeutic IOP reducing effect was linked to the stimulation of prostanoic receptors type F (FP receptors) present in the ciliary body and iris, while the ocular irritation was related to the stimulation of prostanoic receptors type E (EP receptors) present in the cornea and conjunctiva [5–7,9–14].

From a pharmaceutical point of view, the formulation of latanoprost for ocular topical administration with an appropriate stability, solubility, and tolerance can be challenging. First of all, *in vitro* stability of the formulation can be difficult to achieve since the ester bond of the latanoprost needs to be stable *in vitro*, but rapidly cleaved *in vivo* to produce the active latanoprost acid. An adequate equilibrium between *in vitro* stability and *in vivo* reactivity is difficult to reach. As a matter of fact, latanoprost was reported to be unstable under UV and thermal stresses [15–19]. Secondly, the solubility of latanoprost is challenging since it has a low solubility in water (water solubility of 50 mg/L) and a high lipophilicity ($Log D_{(pH7)}$ of 4.28) leading to a proven tendency to adsorb onto the surfaces of laboratory equipment and formulation containers [20–23]. These characteristics, together with the fact that latanoprost has a high potency and is formulated at a low concentration (0.005% w/v), can lead to a significant drug loss and result in a potential decrease in effective dosage and treatment efficacy. Finally, the tolerance of latanoprost is also a challenge since ocular irritation was reported after the topical ocular administration of PG analogs [5,7,9,24–27]. This ocular irritation can lead to compliance issues, which are known to be particularly problematic in life-long glaucoma management. The importance of the ocular irritation issue is supported by the fact that new formulations with lower PG analog concentrations are being developed to decrease the associated ocular irritation. This is the case for Lumigan® (Allergan, Irvine, USA), a bimatoprost eye drop formulation, which has recently been relaunched at 0.01% bimatoprost instead of the initial 0.03% bimatoprost formulation [28,29].

The use of cyclodextrins (CDs) in combination with latanoprost represents an interesting option to simultaneously address the stability, solubility, and tolerance issues related to latanoprost formulation for ocular therapies. Cyclodextrins are cylindrical oligosaccharides presenting a hydrophilic surface and a lipophilic cavity known to form complexes with poorly water-soluble drugs [30]. Such complexes present a number of interesting features for the formulation of latanoprost for ocular topical treatments since they can act as (i) stabilizers by preventing drug hydrolysis [31], (ii) solubilizers by creating water-soluble complexes with the drug [30,32–36], (iii) anti-irritants by shielding irritating drugs [37], and (iv) drug carriers by improving drug delivery to the eye [38]. In addition, CDs are considered as non-toxic due to their very low penetration through biological barriers [31,37,39]. However, the effect of CDs on drug properties is not predictable and not all CDs can be expected to have the desired effects on drug properties.

The aim of this study was to develop a new latanoprost formulation containing CDs to address current stability, availability, solubility, and tolerance issues related to the formulation of latanoprost for topical ocular administration. In a first step, a panel of CDs was screened to evaluate their impact on drug stability *in vitro* and on drug availability *ex vivo*. The latanoprost-CD combination displaying the best trade-off between stability, and availability was then selected for further characterization and investigation regarding the complex. Finally, the *in vivo* ocular tolerance of the latanoprost-CD formulation was investigated to evaluate the potential anti-irritating effect of the CD. The commercially available latanoprost 0.005% formulation (Xalatan®, Pfizer Inc., NY, USA) was used as reference for all the experiments.

2. Materials and methods

2.1. Materials

Latanoprost, deuterated latanoprost, latanoprost acid and deuterated latanoprost acid were purchased from Cayman chemicals (Michigan, USA). Xalatan was purchased from Pfizer (Zurich, Switzerland). Pharmaceutical grade native α, β, and γ cyclodextrins (αCD, βCD, γCD), hydroxypropyl-β-cyclodextrin (HPβCD), and hyd roxypropyl-γ-cyclodextrin (HPγCD) were a kind gift from ISP Global Technologies Deutschland GmbH (Cologne, Germany). Dimethyl-β-cyclodextrin (DMβCD), highly sulphated-β-cycl odextrin (HSβCD), and disodium-monohydrogenophosphate were obtained from Sigma–Aldrich (Buchs, Switzerland). The 6-monod eoxy-6-N-mono(3-hydroxy)propylamino-β-cyclodextrin (PAβCD)