Semi-fluorinated alkanes for topical delivery of Cyclosporine A

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Purpose

Cyclosporine A (CsA) is an anti-inflammatory agent frequently used to treat ocular inflammatory conditions such as dry eye syndrome. However, the poor water solubility of CsA makes it difficult to formulate into an acceptable ocular dosage form. Semi-fluorinated alkanes (SFAs) are a novel class of inert, non-toxic and amphiphilic liquids that can dissolve several hydrophobic drugs to form clear solutions and have therefore been suggested as carriers for topical administration of hydrophobic drugs such as CsA.

OBJECTIVE

To compare the corneal bioavailability of CsA from SFA solutions with that from Restasis® and Ikervis® emulsions.

Methods

An *ex vivo* porcine eye model was used to study the penetration of a) Restasis® (0.05% CsA ophthalmic emulsion), b) Ikervis® (0.1% CsA ophthalmic emulsion), and c) 0.05% or 0.1% CsA in F4H5 (perfluorobutylpentane). The amount of drug penetrated per gram of cornea between 0.5 to 4 h after application was assayed by HPLC and statistically compared using a two-way ANOVA. Drug distribution in different layers of the cornea was also visualized by substituting CsA with a hydrophobic fluorescent dye and viewing corneal sections under a fluorescent microscope.

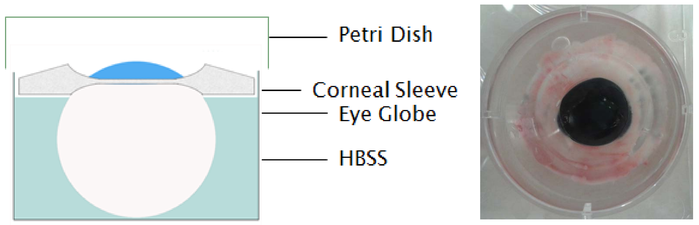

Figure 1: Set-up of the *ex vivo* porcine eye penetration model used to study corneal penetration of CsA and the hydrophobic fluorescent dye

Results

Significant improvements in corneal CsA permeability were obtained using F4H5 as the vehicle. The corneal CsA concentration after application of 0.05% CsA in F4H5 (C_{1h} = 5,844 ± 2,408 ng/g) was more than seven folds greater than from Restasis (C_{1h} = 761 ± 286 ng/g). Similarly, the corneal CsA concentration obtained after application of 0.1% CsA in F4H5 (C_{1h} = 12,556 ± 4752 ng/g) was more than four folds greater than from Ikervis (C_{1h} = 2,900 ± 341 ng/g).

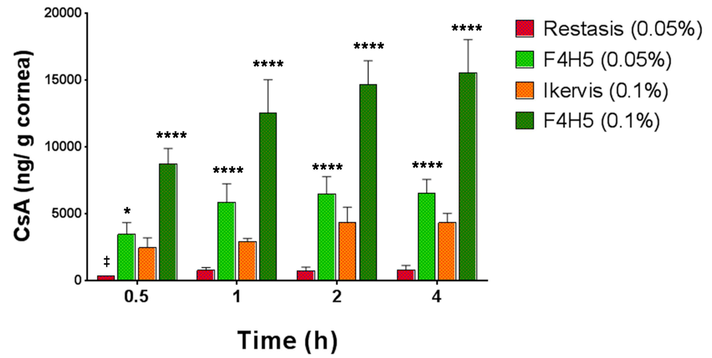

Figure 2: Corneal CsA concentration after application of test formulations; Statistical comparison was performed using Holm-Sidak's multiple comparison test (*: $p \leq 0.05$;****: $p \leq 0.0001$)
‡ values were below the limit of quantification (LOQ) for Restasis at 1h

Table 1: Effective permeability (P_{eff}), area under the curve (AUC) and relative bioavailability ($F_{Relative}$) after application of test formulations

Formulation (CsA conc.)	$P_{eff\ (0-1\ h)}$ ($cm.h^{-1}$)	$AUC_{(0-4\ h)}$ ($ng.h.g^{-1}$)	$F_{Relative}$ (Restasis/Ikervis)
Restasis® (0.05%)	0.5 x 10^{-3}	2,688	-
F4H5 (0.05%)	3.2 x 10^{-3}	22,395	**8.3**/ 1.6
Ikervis® (0.1%)	0.9 x 10^{-3}	14,214	-
F4H5 (0.1%)	3.3 x 10^{-3}	51,408	19.1/ **3.6**

Fluorescent micrographs revealed that the dye delivered by the F4H5 had significantly higher corneal permeability than when incorporated into the commercial formulation vehicles. The hydrophobic dye was primarily retained in superficial layers of the corneal epithelium when applied in Restasis or Ikervis; however, delivered by F4H5 the dye was able to penetrate all epithelial layers, while also diffusing deeper into the corneal stroma.

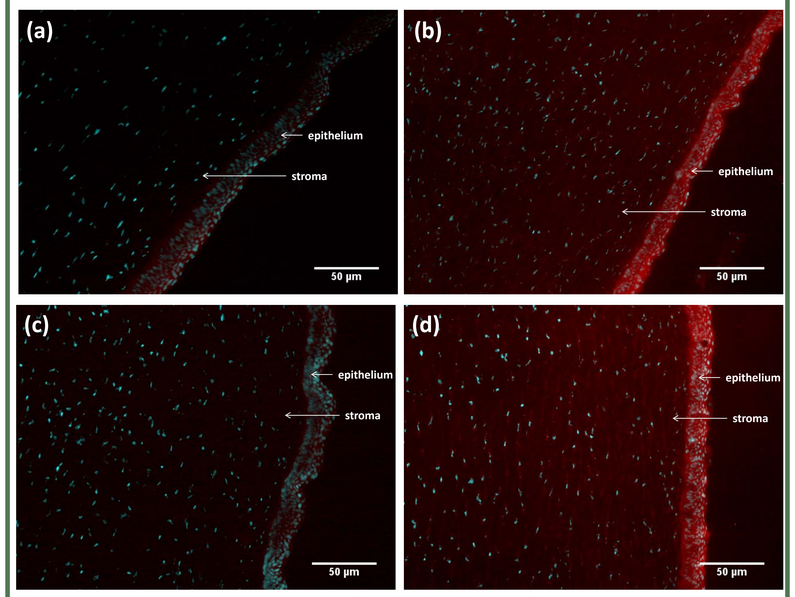

Figure 2. Corneal penetration of a hydrophobic fluorescent dye (red) delivered by (a) Restasis 0.05%, (b) F4H5 0.05%, (c) Ikervis 0.1% and (d) F4H5 0.1% . Corneal cells are stained with DAPI (blue).

Conclusion

This study demonstrated that SFAs, such as F4H5, can significantly enhance the corneal absorption and penetration of hydrophobic molecules. The bioavailability of CsA administered as a solution in F4H5 was several folds higher than from commercially available ophthalmic emulsions with dye diffusion seen across the entire cornea. Therefore, SFAs present a very promising vehicle for topical ocular CsA delivery.