

Ocular and Systemic Distribution of ¹⁴C-Perfluorohexyloctane following Topical Ocular Administration to Rabbits

S. Krösser¹, E. Spencer², R. Grillenberger¹, C. Struble², K. Eickhoff¹

¹ Novaliq GmbH, Heidelberg, Germany, ² Covance Laboratories Inc., Madison, WI, United States.



Introduction

Dry eye disease (DED) is one of the most common pathological conditions of the eye, affecting millions of patients. DED is categorized as either aqueous-deficient or evaporative. Evaporative DED is mainly the result of increased evaporation of the tears, which can occur if the lipid layer of the tear film is disrupted. Meibomian Gland Dysfunction (MGD) is one of the main causes / accompanying syndromes of evaporative DED.

Perfluorohexyloctane, a semifluorinated alkane, which is now in Phase 2 clinical investigations in the US, is developed as an ocular treatment for the signs and symptoms of evaporative DED. Perfluorohexyloctane is an amphiphilic, physically and chemically inert, clear, colorless and laser stable liquid with the same refractive index as water. Due to its excellent spreading and film-forming properties it allows the lipid layer to restore and strengthen and thereby preventing excessive evaporation of the aqueous layer of the tear film. Herein, we present the ocular distribution and whole body disposition of radiolabeled Perfluorohexyloctane after topical ocular administration to rabbits.

Methods

Pigmented Dutch Belted rabbits received a topical ocular, bilateral dose of ¹⁴C-Perfluorohexyloctane at a targeted dose of 45.6 mg/eye.

Dosing regime	Samples collected
Single dose	<ul style="list-style-type: none"> Blood and ocular tissues, analyzed for radioactivity by Liquid Scintillation Counting (LSC) Blood and heads for quantitative autoradiography Blood and carcasses for whole-body autoradiography
Multiple dose	<ul style="list-style-type: none"> Blood and ocular tissues, analyzed for radioactivity by LSC

Table 1: Experimental study design

Results

After single and multiple topical ocular administration of ¹⁴C-Perfluorohexyloctane, exposure and distribution mostly occurred in the anterior segment of the eye, especially in tears, meibomian glands, conjunctiva and cornea (Figure 3). Interestingly, the high levels in tears were maintained for a minimum of 4 hours. In meibomian glands significant levels were seen up to 8 hours. Only minor distribution into the posterior ocular tissues was observed. These results were confirmed by quantitative whole head autoradiography (Figure 1). Low levels of radioactivity were detected in blood and plasma indicating that systemic adsorption was minimal after topical ocular administration of ¹⁴C-Perfluorohexyloctane (Table 2).

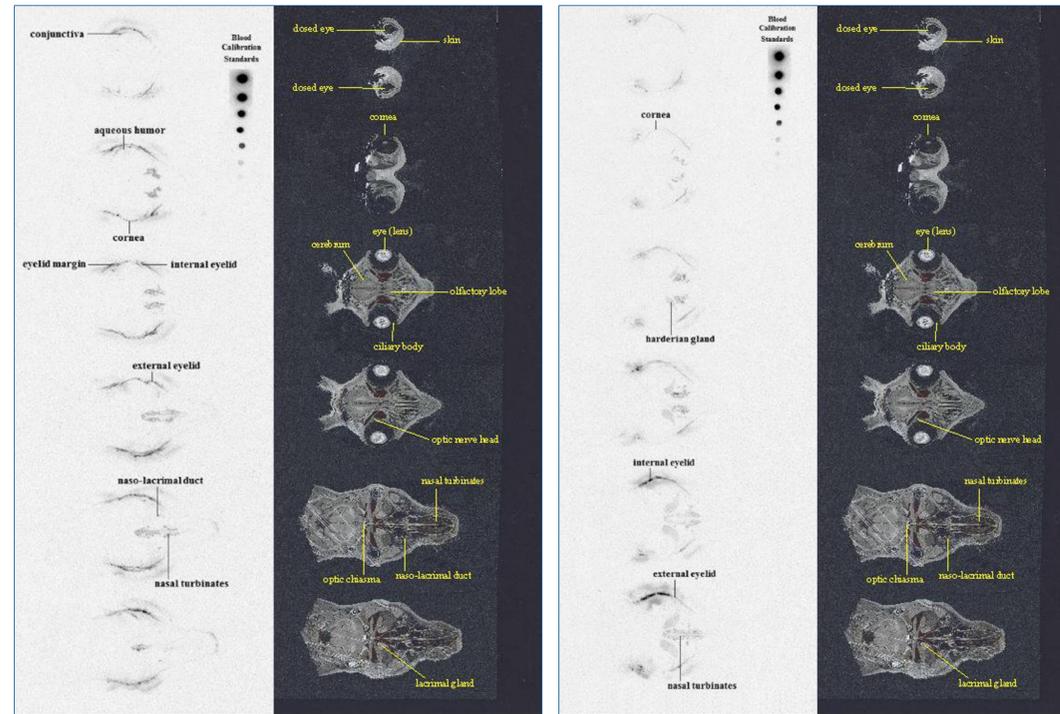


Figure 1: Autoradiography of the head 0.5 hours (left) and 24 hours (right) after single bilateral topical ocular administration of ¹⁴C-Perfluorohexyloctane

Sample	ng Equivalents ¹⁴ C-F6H8/g						
	0.25 h	0.5 h	1 h	2 h	4 h	8 h	24 h
Blood	0	0	171	510	795	348	282
Plasma	0	0	196	611	973	434	360
Conjunctiva (bulbar)	5450	3680	3320	3050	1610	1340	1090
Conjunctiva (palpebral)	14200	5180	5700	4230	2500	1790	2270
Cornea	2040	8230	6110	3230	4480	6080	2730
Lacrimal gland (accessory)	577	0	255	1450	4280	2110	1500
Lacrimal gland (main)	1670	2770	641	1530	4130	2120	1810
Meibomian glands	294000	102000	57600	69200	29100	21100	14700
Tears	2390000	995000	444000	700000	207000	6660	1300

Table 2: Concentrations of radioactivity in blood, plasma, and tissues after single topical ocular administration of ¹⁴C-Perfluorohexyloctane

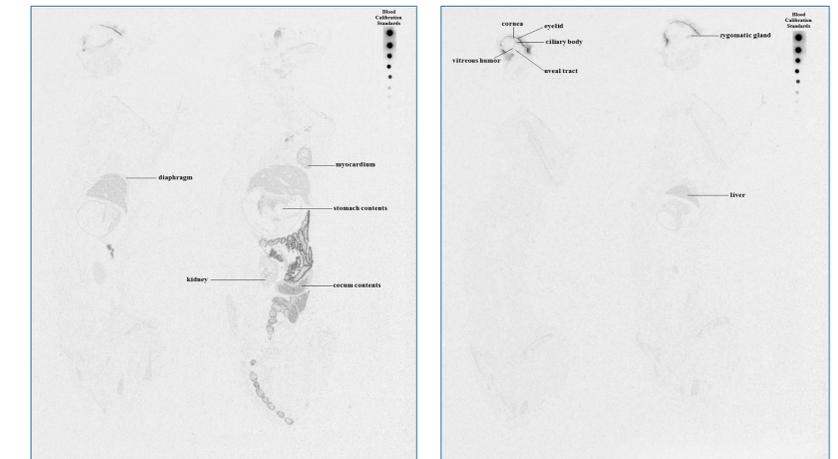


Figure 2: Whole body autoradiography 8 hours after single bilateral topical ocular administration of ¹⁴C-Perfluorohexyloctane

Autoradiography of the whole body indicated that apart from ocular tissues, radioactivity was primarily confined to the contents of the gastrointestinal (GI) tract suggesting that topical ocular Perfluorohexyloctane is eliminated with feces (Figure 2).

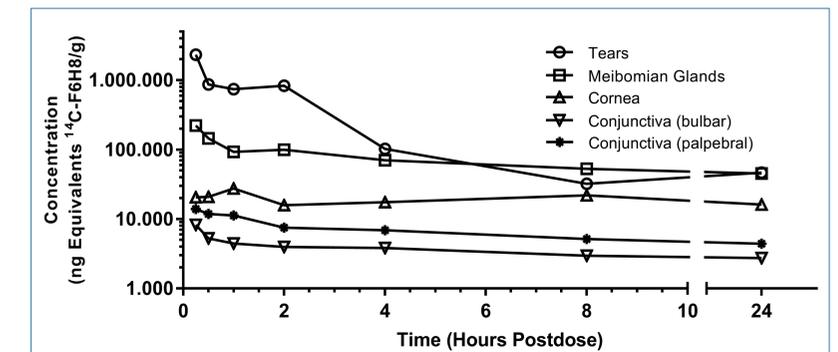


Figure 3: Concentrations of radioactivity in tears, meibomian glands, conjunctiva and cornea after multiple topical administration of ¹⁴C-Perfluorohexyloctane to Dutch Belted rabbits

Conclusion

Highest exposure and longest presence of ¹⁴C-Perfluorohexyloctane after topical ocular administration in rabbit was seen in anterior ocular tissues, especially tears and meibomian glands. In particular the high levels of Perfluorohexyloctane in the meibomian glands support its potential for treatment of MGD as it may solubilize the plugged meibom within the glands.