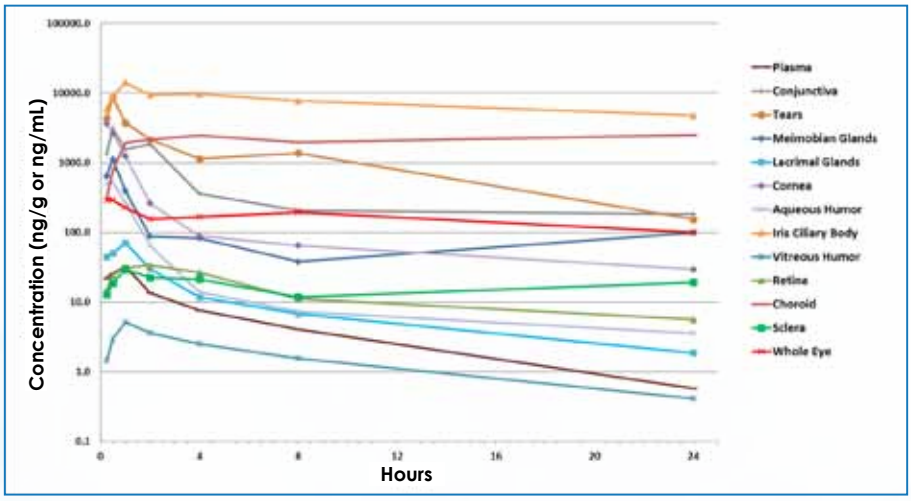
Ocular Pharmacokinetics

Pharmacokinetics is generally defined as the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body over a period of time. In the case of ocular pharmacokinetics, all of the above activities occur but the site of action may be either the meibomian glands, cornea, aqueous humor, vitreous humor, retina, and/or choroid depending on the ocular disease targeted. PharmOptima has extensive experience performing precise dissections and bioanalysis of ocular tissues from all preclinical species. As an example, below are two images of the meibomian glands from a study conducted with a potential dry-eye therapeutic, along with the concentration profiles of the ocular tissues collected and analyzed during one of the studies (Figure 1).

Rabbit Meibomian Gland

Rat Meibomian Glands

Figure 1: Plasma and Tissue Concentrations Following a 50µL Bilateral Topical Ocular Administration of a 0.25% Formulation



Determining the pharmacokinetic parameters in ocular tissues can be a major challenge because of the complex anatomy and dynamic physiological barrier of the eye. You can readily overcome these challenges by relying on PharmOptima's significant experience in conducting ocular pharmacokinetic studies.

Two common issues that impact ocular pharmacokinetic studies is the potential impact of the systemic contribution to the back of the eye tissues and melanin binding. Evidence of systemic contribution and melanin binding are presented in Figures 2 and 3.

See next page to continue.

Figure 2 demonstrates systemic delivery of compound to the back of the eye following intravenous administration, and evidence of melanin binding in the pigmented choroid as compared to retina.

Figure 2: Concentrations (ng/g or ng/mL) Following IV Dosing

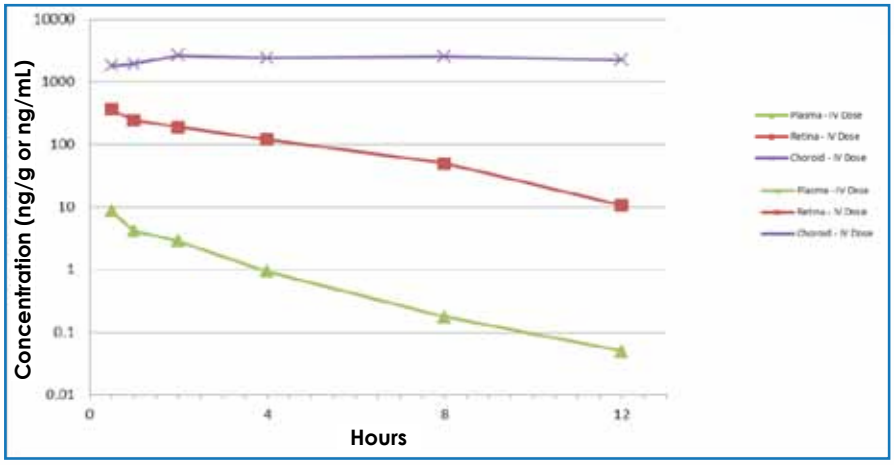
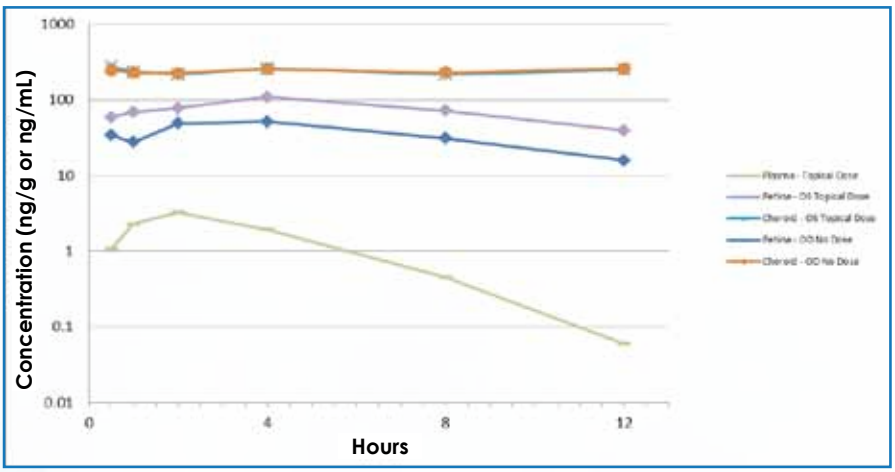


Figure 3 demonstrates the utility of a unilateral OS ocular topical dose with respect to systemic absorption and distribution to the back of the eye, as well as melanin binding in the pigmented choroid of the dosed and non-dosed eye as compared to retina.

Figure 3: Concentrations (ng/g or ng/mL) Following Ocular Topical to Eye



In vitro melanin binding studies are also available for screening a series of compounds or a definitive study for an individual compound. These studies can use rabbit or bovine choroids, melanin containing cephalopod ink, or synthetic melanin.

Following completion of your ocular pharmacokinetic study, PharmOptima will provide a complete study report with pharmacokinetic analysis (Phoenix WinNolin®).

Bilateral Ocular Topical	Plasma	Conjunctiva	Cornea	Aqueous Humor	Iris Ciliary Body	Retina	Choroid	Vitreous Humor	Submandibular Lymph Nodes
Tmax (hours)	0.5	0.5	0.5	2.0	4.0	4.0	4.0	8.0	0.5
Cmax (ng/g or ng/mL)	104	1,950	1,630	529	48,300	5,200	12,100	416	193
$t_{1/2}$ elimination(hours)	3.4	3.9	4.2	6.6	NC	4.1	NC	NC	4.3
$AUC_{0\text{-last}}$ (ng*h/g or ng*h/mL)	210	17,300	28,600	1,310	396,000	33,500	145,000	8,490	544
$AUC_{0\text{-inf}}$ (ng*h/g or ng*h/mL)	211	18,100	29,500	1,340	NC	34,300	NC	NC	553

NC: Not calculated