Drug Distribution in Human Eye

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Introduction: Drug therapy of the posterior segment of an eye is very challenging due to the difficult accessibility. Modern drugs often are large molecules, such as peptides, antibodies or oligonucleotides which are administrated, e.g. by intravitreous injections which requires clinical conditions. Computer modeling can be helpful in designing new and less invasive routes of drug administration. In this work, Comsol Multiphysics 4.2a was used to create a 3D model to estimate drug clearance from vitreous humor. Factors affecting the distribution include mobility, partition and permeability coefficients between different parts of an eye (Figure 1).

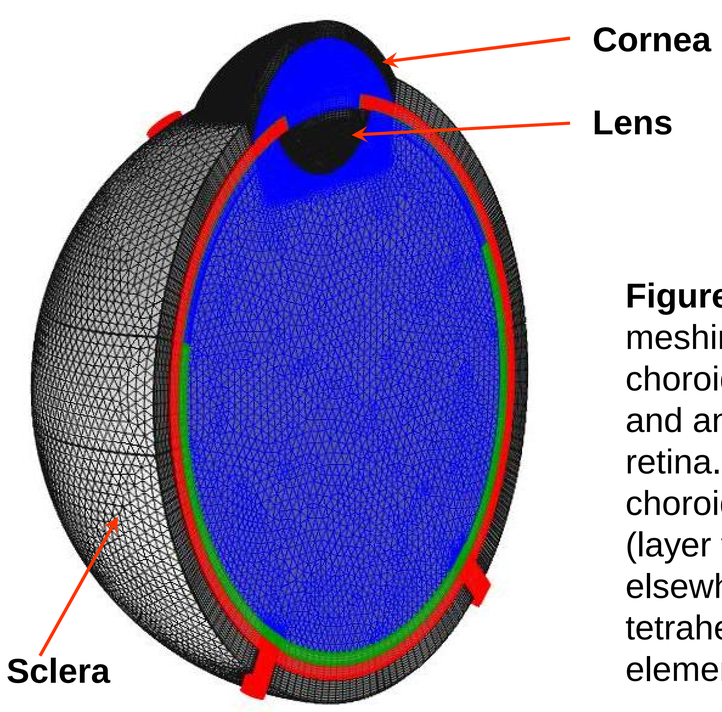

Figure 1. Geometry and meshing of an model eye: Red: choroid; Blue: vitreous humor and anterior chamber; Green: retina. Swept mesh in sclera, choroid, cornea and retina (layer thickness 0.1 mm), elsewhere mainly free tetrahedral. Total number of elements is ca. 2,000,000.

Computational methods. The model uses Navier-Stokes equation at steady-state and transient convective diffusion equation in the anterior chamber and choroid; blood flow into choroid was 1.0 ml/min and aqueous humor flow rate was 2.0 µl/min. Transient diffusion equation was applied in the remaining part of the eye. Uniform initial concentration distribution is assumed in vitreous humor, mimicking an intravitreous injection.

Boundary condition between any two phases (α and β):

$$\text{Flux} = \pm K_{\alpha/\beta}\left(P_{\alpha/\beta}c_\alpha - c_\beta\right)$$

$K_{\alpha/\beta}$ = permeability coefficient between phases α and β (cm/s)
$P_{\alpha/\beta}$ = partition coefficient between phases α and β; $P_{\alpha/\beta} = c_{\beta,eq}/c_{\alpha,eq}$

Table: Default values of the parameters of the model.

Parameter	Value	Description
V_in	1.0[ml/min]	blood flow into choroid
r	0.7[mm]	choroid artery radius
rho	1030[kg/m^3]	blood density
eta	0.003[Pas]	blood viscosity
D_scl	9e-6[cm^2/s]	Diff. coeff. sclera
D_vh	9e-6[cm^2/s]	Diff. coeff. vitreous
D_ret	9e-6[cm^2/s]	Diff. coeff. retina
D_cho	9e-6[cm^2/s]	Diff. coeff. choroid
D_lens	9e-6[cm^2/s]	Diff. coeff. lens
D_ac	9e-6[cm^2/s]	Diff. coeff. anterior chamber
D_co	9e-6[cm^2/s]	Diff. coeff. cornea
K17	1e-5[cm/s]	Perm. coeff. sclera-choroid
K27	4e-5[cm/s]	Perm. coeff. RPE-choroid
K72	2e-5[cm/s]	Perm. coeff. choroid-RPE
K23	1e-5[cm/s]	Perm. coeff. retina-vitreous
K37	1e-5[cm/s]	Perm. coeff. choroid-vitreous
P23	10	Part. coeff. retina-vitreous
P17	1	Part. coeff. choroid-sclera
V_in_ac	2[ul/min]	aqueous humor flow rate
K39	1e-5[cm/s]	Perm. coeff. vh-lens
K38	1e-5[cm/s]	Perm. coeff. lens-ac, lens-cho, ac-cho, co-ac, co-scl

Results: The effect of varying parameter values on clearance of a probe molecule from vitreous humor was simulated.

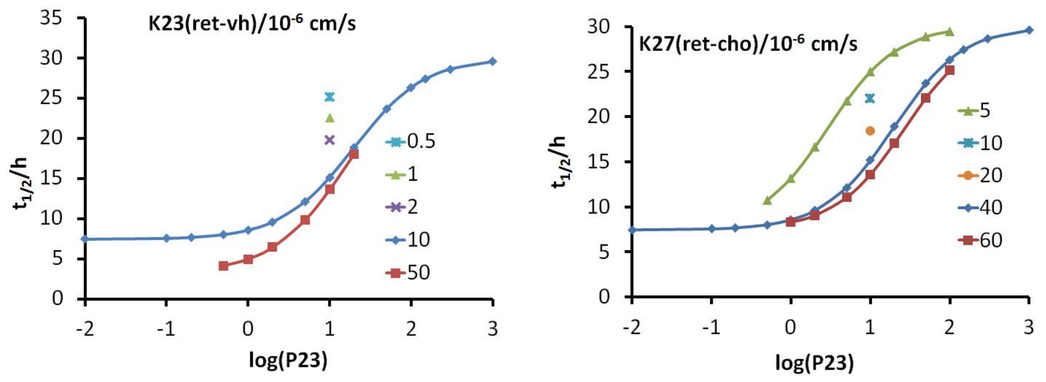

Figure 2. Effect of retina-vitreous humor partition coefficient on the half-life time with varying permeability coefficients.

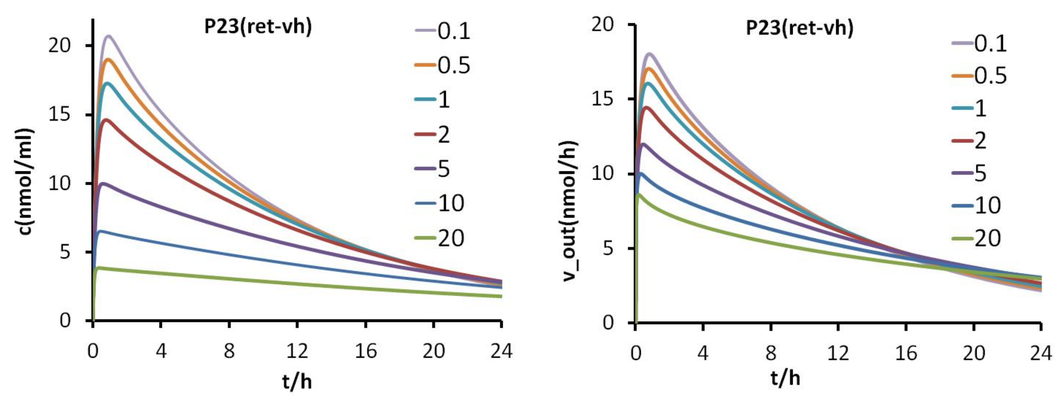

Figure 3. Effect of retina-vitreous humor partition coefficient on the average retina concentration (left) and outflow from choroid (right).

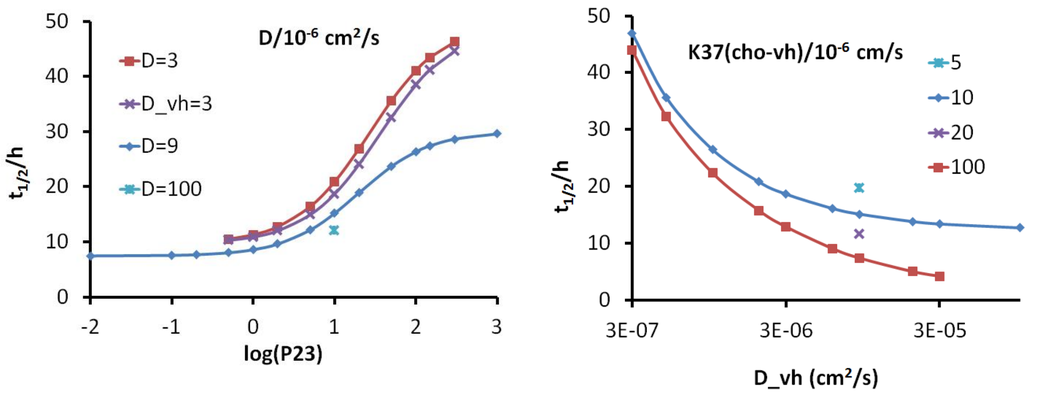

Figure 4. Effect of common (D) and vitreous diffusion coefficient (D_vh) on the half-life time with varying retina-vitreous partition coefficient (left) and vitreous humor-choroid permeability coefficient (right).

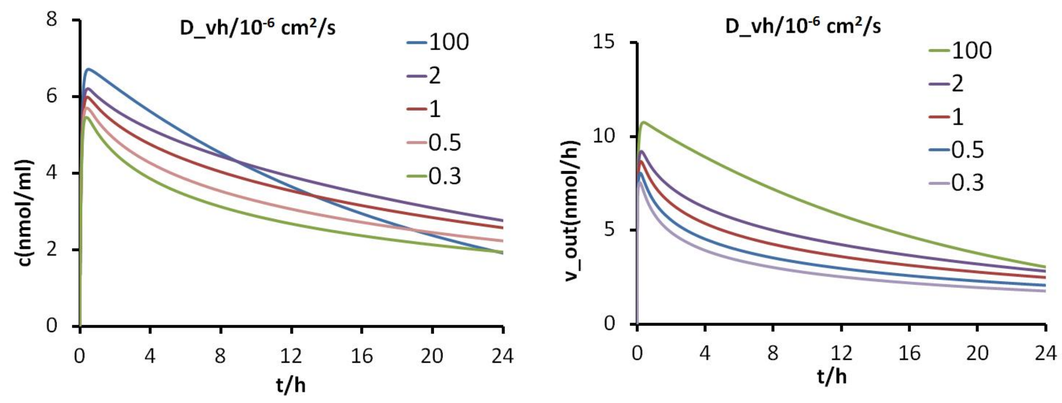

Figure 5. Effect of vitreous diffusion coefficient on the average retina concentration (left) and outflow from choroid (right).

Conclusions: The most significant factors affecting the clearance of a molecule from vitreous humor are its lipophilicity, reflected in the value of P23, and its diffusion coefficient in vitreous humor D_vh. Hydrophilic molecules transfer to the blood circulation in choroid, from which they are cleared along the convective flow. In this case, the permeability across vitreous humor-choroid boundary also has a significant role. The model is developed further by taking into account protein binding in the blood circulation. Also, quantitative structure-activity relationships (QSAR) can be used to estimate the parameter values needed in the model.

Meshing has a very high importance and affects the calculation time, convergence and accuracy of the mass balance.

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