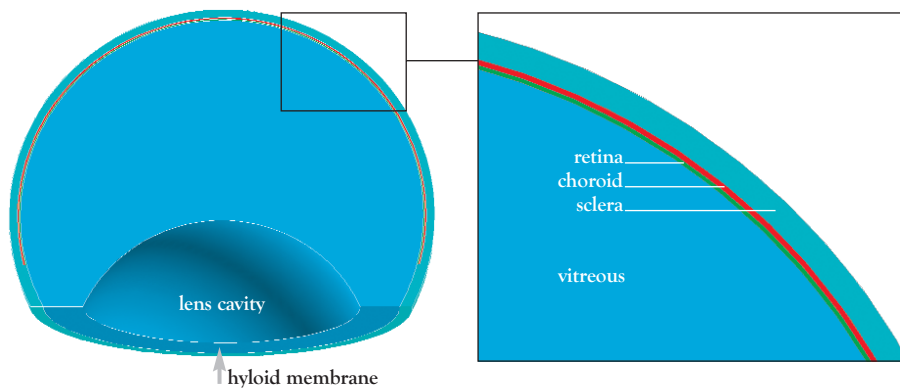


The geometry of the eye behind the lens cavity, showing the vitreous, retina, choroid, and sclera

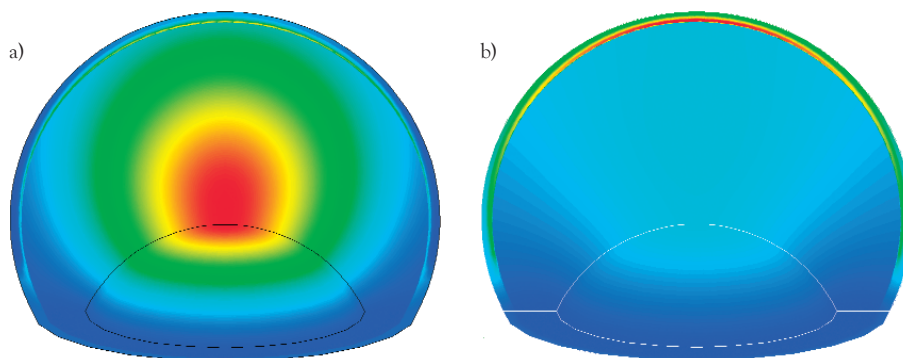


A Clear Vision for Drug Delivery

By Paul Missel, Larry Stevens, Jim Chastain, and Yoseph Yaacobi, Drug Delivery, Alcon Research, Ltd., Fort Worth, Texas, USA

IN THE MEDICAL FIELD, there is a growing interest in applying CFD to better understand the distribution and elimination of drugs in living systems. The eye presents a unique opportunity for this effort. Ocular physiology has been well studied and understood because of the tremendous importance of sight and the eye's accessibility to measurement. The eye possesses a high degree of azimuthal symmetry, which enables the comparison between simulated results and exact mathematical solutions for certain idealized problems [1]. Using realistic geometries and ocular properties, FIDAP simulations have recently been carried out to study a number of aspects relating to the spread of a drug administered to the eye.

Using GAMBIT, a geometrically accurate representation of the posterior segment of the eye – the interior portion behind and not including the lens – has been constructed. The posterior segment comprises most of a sphere, and has very thin shells near the exterior for the retina, choroid, and sclera. Inside is the vitreous, a gel consisting mainly of water. The retina contains light sensing cells and the neurons that transmit sensory signals. The choroid is a highly vascular tissue that provides nourishment to the retina and acts as the major sink for removal of many compounds from the eye. The sclera is a strong connective tissue that is, for the most part, avascular.



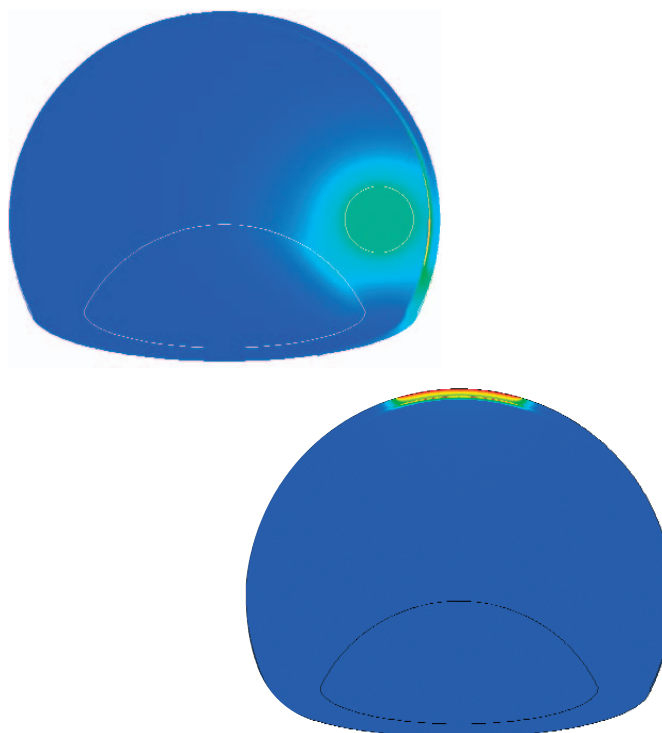
Simulations of concentration profile resulting some time after intravitreal injection of model compounds; a) 3.3 hours after central bolus injection of fluorescein, a rapidly diffusing compound effectively cleared by the choroid – the highest drug concentrations are found behind the lens, and b) 2.87 days after injection with a fluorescently labeled polymer, unable to be cleared by the choroid, and eliminated only by diffusion out the front of the eye. For the case on the right, the highest concentrations appear near the central retina

A physiologically accurate CFD model must include factors such as drug diffusivity, partitioning into tissue, drug clearance, and (when appropriate) hydraulic flow from intraocular pressure. For the most part, the last effect can be neglected for small, rapidly diffusing molecules common in most drugs of interest to ophthalmology [1]. Separate independent experiments are usually performed for measuring parameters such as tissue diffusion and partition coefficients.

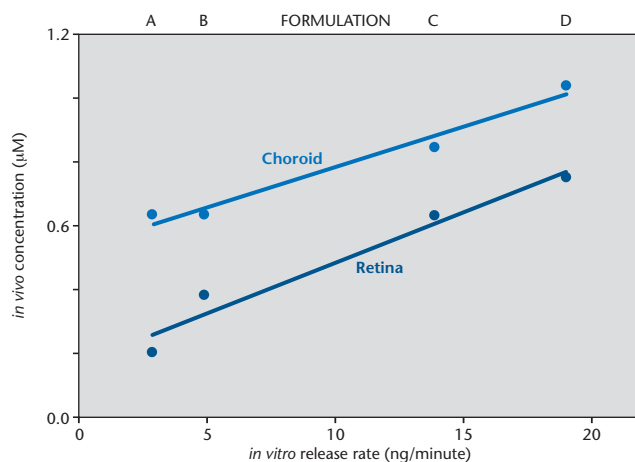
The CFD model was created to correspond to published experiments for which the ocular drug distribution has been obtained. In one such a study [2], the intravitreal distributions of two different fluorescen compounds were compared some time after a 15 microliter central bolus injection. The vitreous diffusivity was taken to be $6 \times 10^{-6} \text{ cm}^2/\text{s}$ for fluorescein, a small model drug compound, and a factor of ten smaller for a fluorescently labeled polymer. The scleral diffusivity was taken to be about 1/13th of that in the vitreous, and that in the retina and choroid was a factor of ten lower than that, consistent with *in vitro* transport experiments [3]. For both compounds, drug loss by diffusion through the front of the eye and eventual elimination through the mechanism of aqueous humor turnover was permitted. This loss was handled by a simple flux boundary condition of drug concentration applied on the annular boundary outside the lens. The magnitude of the flux boundary condition was calculated from the ratio of the aqueous humor production rate divided by the area of the hyloid annulus. No losses were permitted on the lens boundary. For fluorescein, drug loss by vascular clearance through the choroid was permitted as well. This loss was simulated using a special reaction in FIDAP.

The simulations reproduced the general features found in the experiments [2]. The fluorescein was effectively cleared by the choroid, and the fluorescently labeled polymer was not, resulting in two very different concentration profiles. After about 3 hours for the rapidly diffusing fluorescein, the highest drug concentrations were immediately behind the lens, and for the most part the concentration contours were parallel to the retina. After about 3 days for the more slowly diffusing polymer, the highest concentrations were at the rear of the retina, and the concentration contours were perpendicular to the retina.

Also simulated was the steady-state distribution resulting from two different modes of administration of a similar model compound: a spherical implant placed on one side of the vitreous, away from the optic path, and a drug tablet placed in direct contact with the exterior sclera in the juxtasccleral space directly behind the eye. Drug partition coefficients were assumed to be 1 for vitreous, 4 for both retina and choroid, and 2.2 for the sclera. This means that a four-fold multiplicative increase in drug concentration was expected between the vitreous and retina at the vitreous-retinal boundary. The steady-state concentration profiles achieved by the implants were very highly focused, with most of the drug near the implant in each case. These highly focused drug distribution profiles have been confirmed by experiments, and are a geometrical consequence of drug clearance by the choroidal shell.



Steady-state drug distribution resulting from hypothetical implants delivered either as a spherical device interior to the vitreous (top left) or as a disc surface (tablet) in direct contact with the exterior sclera at the rear of the eye (lower right); the drug is localized near each device



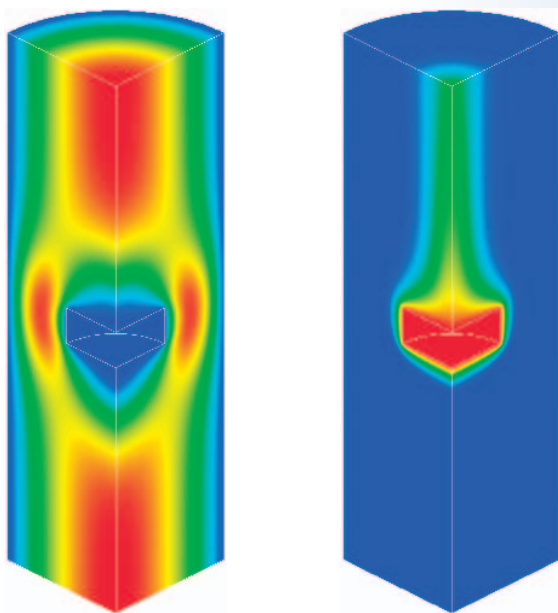
Correlation between *in vivo* measurements of the steady-state drug concentration achieved in ocular tissues immediately beneath the juxtasccleral device six weeks post-implantation and the *in vitro* dissolution rate measured from four formulations selected to provide a wide range of release rates; the fact that the lines are more or less straight demonstrates a high correlation between the *in vitro* release rate and the concentration delivered *in vivo* to ocular tissue, suggesting that changes in release rates measured in the *in vitro* test are predictive of meaningful changes in the rates of drug delivery to the eye *in vivo*

CFD simulations of the *in vitro* dissolution process have also been performed, and have proven useful in designing a reliable test to help optimize the dosage formulation. The test places the dosage form as a central obstruction in a cylindrical flow cell. The release medium flows at a very slow speed of about 0.1 ml/min, unusual for this type of test, but more physiologically appropriate for the extended release of a sparingly soluble compound. This choice of design enables the laminar flow velocity and the convective diffusion/dissolution process within this flow field to be simulated with extremely high accuracy. Moreover, the simulations are within a few percent of agreement with experimental results [4] for an idealized device, a tablet comprised mainly of a model compound. The CFD-optimized flow cell was also able to predict a very useful *in vivo/in vitro* correlation.

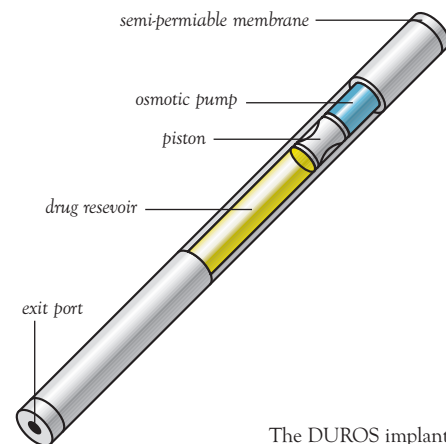
With appropriate modifications, CFD is proposed as a tool for simulating an arbitrary mode of ocular drug administration. Further simulation and development of the *in vitro* flow-through dissolution method are underway, in an attempt to bring a Quality by Design approach to the development, selection, and evaluation of ophthalmic drug delivery devices. ■

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Simulation of the dissolution process for a drug tablet suspended in a cylindrical flow cell



The DUROS implant

ALZA'S DUROS® IMPLANT, a titanium cylinder about the size of a matchstick, was designed for potent drugs requiring subcutaneous delivery to treat chronic conditions. It consists of a titanium cylinder equipped with a semi-permeable membrane, an osmotic engine, a piston, a formulation compartment, and a small restriction at the exit port where the formulation is discharged. While a commercial product called Viadur (for the treatment of prostate cancer) exits using this platform to deliver a solution formulation, development is underway for the delivery of suspension formulations using the DUROS implant.

A suspension formulation is comprised of a viscous liquid suspending agent, or vehicle, and small drug particles. Maintaining the suspension's physical stability for the lifetime of the implant, both for storage and during use, represents a challenge for the formulator, since the implant is designed to deliver the drug for up to one year. In order to help guide the choice of appropriate vehicles, models were developed for predicting the release rate variability as a result of suspension sedimentation. The modeling effort was divided into two parts. First, the suspension stability was predicted using a Stokes Law sedimentation model that accounts for hindered settling and the suspended particles' polydispersity. Second, a CFD flow model was used to simulate the pumping of the suspension after different degrees of segregation had occurred, and to predict the drug release rate as a function of time.