Assessment of Intravitreal Pharmacokinetics Using an *In Vitro* Phantom Model

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Purpose

Preclinical studies are an essential tool to help optimise the design of drug delivery systems. Unfortunately, there are presently no standardised models to evaluate intravitreally administered formulations, as a result it remains very difficult to predict their fate during the drug development process. Intraocular pharmacokinetics are primarily influenced by (1) vitreous liquefaction, (2) flow behaviour, and (3) saccade. Here, we developed an *in vitro* model and built in each of these three parameters to assess how they may affect intravitreal drug distribution and clearance.

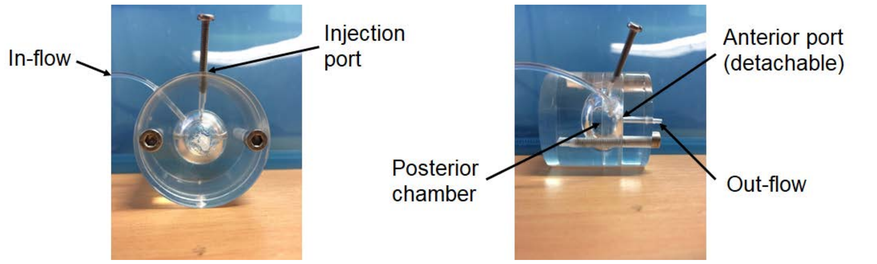
Methods

A poly(methyl methacrylate) mould was designed using dimensions of the human eye. Synthetic vitreous was prepared using various combinations of hyaluronic acid (HA) and agar to achieve a range of viscous properties. The model was (1) filled with varying viscosities of synthetic vitreous, placed in a rocking hybridisation oven at 37 °C and subjected to (2) 2 µl/min intraocular flow using an Ismatec pump and (3) saccade by setting the oven to 50 rpm. Sodium fluorescein was added into the model and its distribution around and clearance from the model were quantified. Diffusion and viscosity data from the model were further compared to that of *ex vivo* porcine eyes.

Results

Synthetic vitreous gels typically demonstrated greater viscosity than porcine vitreous. All prepared synthetic gels significantly slowed sodium fluorescein diffusion when compared to phosphate buffered saline (PBS). Simulated saccade only influenced dye migration in PBS but not in any tested gels. Surprisingly, in spite of the greater viscosity dye migration was consistently faster in synthetic vitreous than in the porcine eyeball. Applying intraocular flow to the system could override the influence of both vitreous viscosity and saccade, although the flow and saccade synergistically increased distribution in PBS and Vit Lo.

A



B

Parameter	Model eye	Equivalent human parameters
Casing material	Poly(methyl methacrylate)	Retina
Vitreous volume	4 ml	3.9-5 ml
Anterior chamber volume	Various iterations assessed	No reservoir (sink conditions due to anterior drainage)
In-flow	2 µl/min PBS into posterior chamber	Undefined (flow mechanisms proposed)
Posterior-anterior diffusion	Through hydrophilic PTFE membrane (0.45 µm pore size)	Trabecular meshwork (0.3-1 µm pore size)
Posterior-anterior diffusion area	113.1 mm² (1.131 cm²)	Undefined

C

Code	Concentration (mg/ml)	
	[HA]	[Agar]
Vit Hi	5	4
Vit Med	2.21	1.8
Vit Lo	0.7	0.95

D

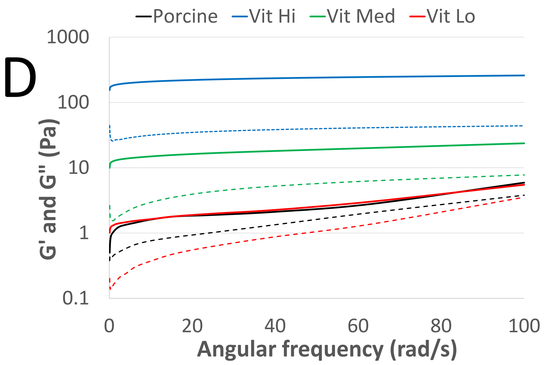


Figure 1 (A) Design of the model eye showing locations of in-flow, out-flow, injection port, anterior port and posterior chamber. In some cases, the anterior port of the system was replaced with larger reservoirs to achieve sink conditions. (B) Parameters of model eye with equivalent human ocular parameters listed. (C) Composition of synthetic vitreous gels identified in literature and used in the study. (D) Storage (solid) and loss (dashed) moduli of the gels in comparison to *ex vivo* porcine vitreous humour.

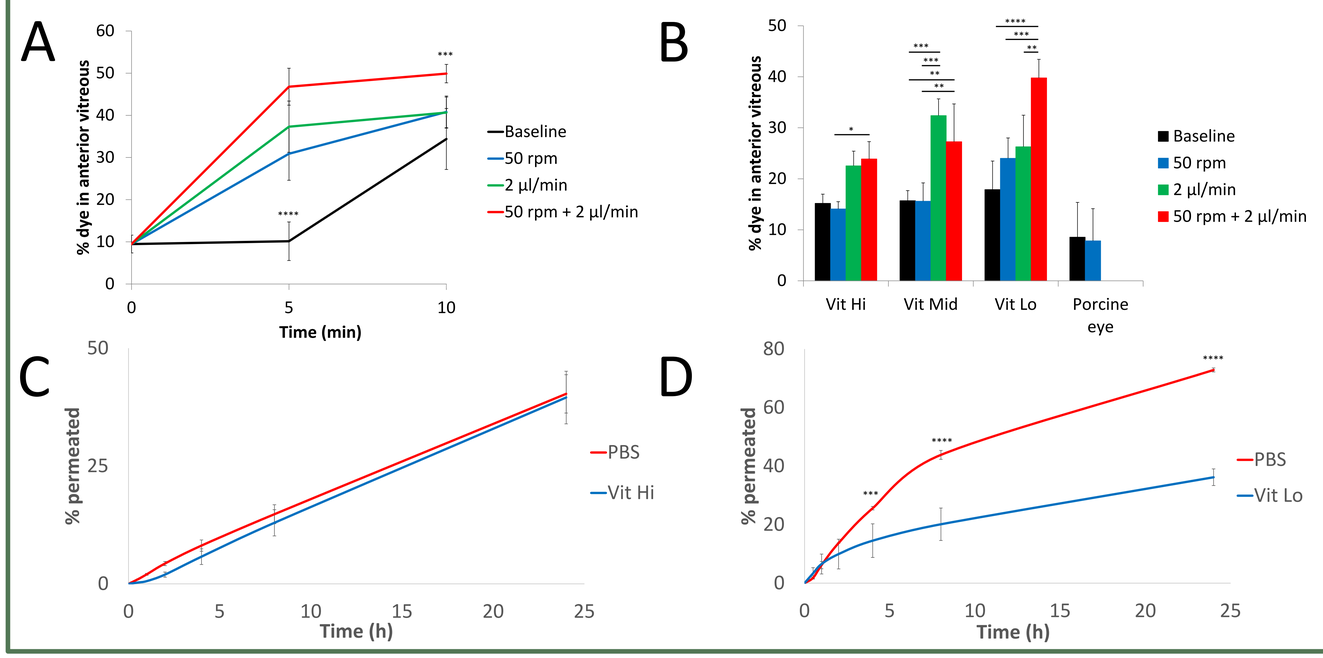


Figure 2 Impact of 50 rpm shaking and 2 µl/min flow on sodium fluorescein distribution (A) in PBS over 10 min and (B) in three synthetic vitreous humour preparations after 30 min. (C) Percentage clearance of fluorescein dye injected into PBS and the highest strength synthetic vitreous over 24 h upon application of 2 µl/min flow. (D) Percentage clearance of fluorescein dye injected into PBS and the lowest strength synthetic vitreous over 24 h via simple diffusion. In (A) and (B), aliquots were taken from the anterior and posterior half of the eye globe to determine distribution values. In (C), the 2 µl/min eluate that left the model through the anterior port was collected and sampled to quantify clearance. In (D), the anterior port was replaced by a 4 ml receptor chamber and the dye was allowed to diffuse from the posterior chamber to the receptor chamber through a hydrophilic PTFE membrane. Aliquots from the receptor chamber were collected and quantified.

Conclusions

Intraocular flow is the primary driving force for small hydrophilic dye migration around the phantom model, and is able to override the impact of both vitreous viscosity and saccade. Further studies will assess pharmacokinetics of larger molecules and nanoparticles using this model, and also compare model behaviour to obtained human data.