ADVANCEMENTS IN OPHTHALMIC DRUG PRODUCT ASSESSMENT

The eye is an excellent target for topical drug delivery as a distinct organ with easy access. This can be achieved via injection or a transepithelial route (drops). From a patient perspective, drugs that can be delivered via application to the epithelium are often preferable to injection. However, due to the eye's structure and function, this route of delivery presents both unique challenges and opportunities.

The first challenge presented by the eye is that of clearance. Tear flow and blinking can clear formulation from the corneal surface within seconds, severely limiting the amount of drug that can be delivered. To mitigate this risk, a wide range of excipients (including but not limited to penetration enhancers and bio-adhesive agents) can be tested in various formulations.

Historically, early performance testing of ophthalmic formulations has been done in freshly harvested or frozen ex vivo eyes collected from animals (most commonly rabbits). This has proven to be a useful model for the development of ophthalmic drugs for decades but has its limitations in that it is non-human.

MedPharm has developed in vitro and ex vivo models to help characterize these formulations and increase their residency time under clearance in an efficient and cost-effective manner. This also reduces the reliance on relatively expensive in vivo animal studies at an early stage.

These tissues are not typically maintained in a physiologically stable state. This lack of physiologic stability can lead to loss of tight junctions, decreased barrier function, loss of glycocalyx, loss of efflux/influx pumps, and loss of enzymatic activity. Tight junctions and glycocalyx are primary components of barrier function in the eye, ensuring that the interior of the eye is isolated from the external environment. Efflux and

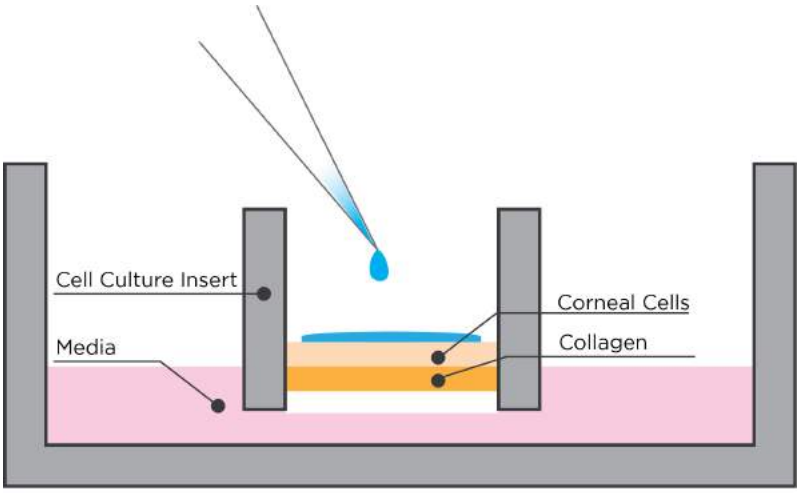

Diagram of a Transwell

influx pumps located in the cell of the corneal epithelium control the transport of ions, small molecules, water, and proteins in and out of the epithelial layer; these can work either with or against formulation activity, accelerating or slowing transport across the cornea. Enzymatic activity at the surface of the eye can break down portions of the formulation, both API and excipient.

To improve on the ex vivo model, MedPharm has developed methods to culture primary human corneal epithelial cells in an air-liquid interface system using the Transwell® tissue culture system. This allows for the development of a well-differentiated reconstructed human corneal epithelium (RhCE) with a distinct and separated apical and basolateral side. As this is a live, differentiated culture, physiologic barrier function is maintained. These constructs are useful for evaluating the performance of ophthalmic formulations for both penetration through the epithelium and adhesion to the apical layer under simulated clearance conditions.

In this system, formulations are applied to the apical side of the constructs in doses relevant to the expected per unit surface area dose of the drug in vivo. The formulation is exposed to clearance conditions, in which simulated tears are used to wash off the formulation at a determined rate. The fluid thus removed from the apical side can be assayed for drug concentration so that resistance to clearance can be assessed. During this wash-off process, media underneath the construct is collected at predetermined time points, and drug concentration is measured. **This allows for the simultaneous assessment of resistance to clearance and permeation of drug in the same system.**

These reconstructed tissues can also be cultured to simulate specific pathological conditions. This allows for the evaluation of relevant pharmacological activities at the corneal epithelium, such as dry eye and other forms of irritation.

RhCE's offer the key benefit of being a **cost-effective and readily available way of optimizing a product** by allowing the relatively rapid testing of multiple drugs and formulations. While there are models available for corneal tissue based on immortalized human corneal epithelial cells, these models can undergo significant metabolic changes through the transformation process needed to maintain long-term viability. These changes can result in a significant depletion in integrity as measured by trans-epithelial resistivity compared with primary cell cultures, which will significantly impact a drug's ability to permeate and penetrate the tissue.

Speak with a MedPharm expert about your project today.

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Breaking through boundaries