



TITLE:

An In Vitro Human Airway Model for Rapid Nasal Delivery Screening of Drug Formulations.

AUTHORS:

Patrick J. Hayden, Jennifer Bolmarcich, G. Robert Jackson Jr., Howard Cohen, Gina Stolper, Mitch Klausner. MatTek Corp.

ABSTRACT:

Purpose: Nasal delivery of protein and other high molecular weight drugs is an attractive option to injection or oral delivery. However, nasal delivery is limited by the maximum dose per spray and rapidity of clearance from the nasal cavity. These difficulties are best addressed early in formulation development prior to costly animal studies or clinical trials. The goal of the present study was to evaluate the EpiAirway™ organotypic tissue model as a pre-clinical screening tool for nasal drug delivery formulations.

Methods: Standard histological methods were utilized to characterize the structure of the EpiAirway tissue and transmission electron microscopy (TEM) was used to observe ultrastructural features of the tissue. Barrier properties of the tissue were monitored using trans-epithelial resistance (TER) and retention of tissue viability was confirmed using the MTT and LDH assays.

Results: H&E stained cross-sections show that the pseudo-stratified structure of the EpiAirway tissue closely resembles the human nasal epithelium. TEM micrographs reveal a highly differentiated tissue with numerous microvilli and cilia on the apical surface of the cultures as well as tight junctions between cells. TER measurements of control tissues average $>300 \text{ Ohm} \cdot \text{cm}^2$ confirming the presence of intact tight junctions. The addition of chitosan salts reduced TER values to $< 50 \text{ Ohm} \cdot \text{cm}^2$. These and other permeation enhancers reversibly decrease TER values and resulted in up to 360-fold increases in protein permeation across the airway epithelium with minimal toxicity (as determined by LDH and MTT assays). The increase in permeation correlates strongly with a decrease in resistance. This suggests that these enhancers act through the paracellular pathway, resulting in lowered resistance without changing cell viability or causing cell lysis. These enhancers thus represent promising formulation candidates for further animal or human clinical studies.

Conclusions: The EpiAirway model is a promising pre-clinical tool with great utility as a primary screen for the development of nasal drug delivery formulations.

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