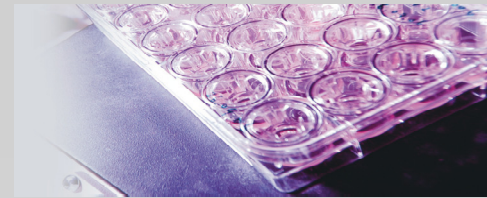




Epithelix

in vitro Solutions for Respiratory Diseases and Chemical Testing



An *in vitro* testing strategy for the development of novel inhaled therapeutics using Human 3D Airway Epithelium Model (MucilAir™)

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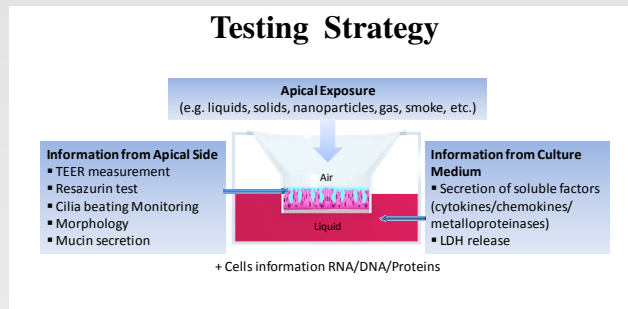
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In order to develop efficient tools and formulations for delivering drug to the lungs, *in vitro* cell models of the human airway epithelia would be invaluable. Epithelix has developed a novel *in vitro* cell model of the human airway epithelium named MucilAir™. MucilAir™ maintains the fully differentiated, morphologically and functionally, characteristics of the native tissues for more than one year (tight junctions, cilia beating, cytokine/chemokine/metalloproteinase release, ion transport and Cyp450s activity). Epithelia from several pathologies can be reconstructed (e.g. Asthma, Allergic Rhinitis, COPD, CF, etc.).

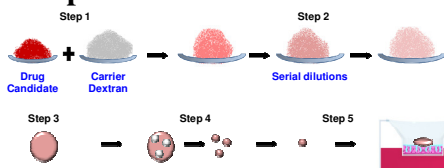
Due to its unique long shelf-life, this model is used for studying the human respiratory diseases, and for testing the long-term/chronic effects of drugs candidates on respiratory tract. Several applications of MucilAir™ relevant to Intranasal/intrabronchial drug delivery, evaluation of pro- or anti-inflammatory effect of drug candidates and formulations, acute, long-term and repeated dose inhalation toxicity testing, effect on cilia beating frequency and mucociliary clearance are presented.

The advantages of MucilAir™

- It is composed of **primary human respiratory cells**.
- It **mimics** the morphology and functions of the native human airway epithelium.
- It has a **unique shelf-life of 12 months**.
- Epithelia from **different pathologies** are available (asthma, COPD, CF, allergic rhinitis).
- It is **ready and easy to use**.

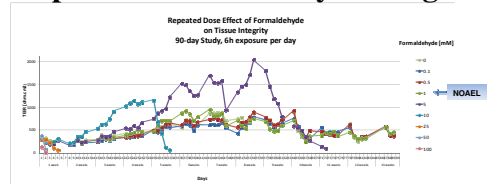


Solid Exposure: Dextran Tablets Preparation

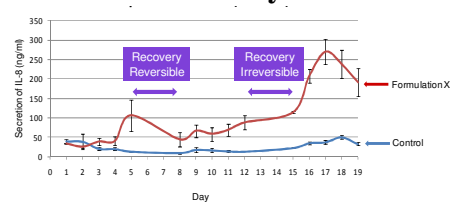


- 1- Dilute the drug candidate with the carrier at the targeted concentration and mix.
- 2- Make serial dilutions.
- 3- Compress the powder into a mold to obtain a large tablet.
- 4- Stamp out smaller tablets with a biopsy punch.
- 5- Apply on MucilAir™, incubate at 37°C for 24 hours and measure end-points.

Repeated Dose Toxicity Testing



Pro-Inflammatory evaluation



Intranasal /intrabronchial permeation of drugs/formulations

Molecules	Papp (cm/s) A→R	Papp (cm/s) R→A	Asymmetry Ratio
Salicylic Acid	7.7 x 10 ⁻⁵	1.7 x 10 ⁻⁵	0.2
Nicotine	2.1 x 10 ⁻⁵	3.3 x 10 ⁻⁵	1.6
Ambroxol	1.3 x 10 ⁻⁵	1.9 x 10 ⁻⁵	1.5
Propranolol.HCl	1.2 x 10 ⁻⁵	1.6 x 10 ⁻⁵	1.3
Ibuprofen	1.1 x 10 ⁻⁵	1.9 x 10 ⁻⁵	1.7
Tripolidine.HCl	9.7 x 10 ⁻⁶	1.2 x 10 ⁻⁵	1.2
Quinidine	9.7 x 10 ⁻⁶	NC	NC
Tetracaine.HCl	8.0 x 10 ⁻⁶	1.1 x 10 ⁻⁵	1.3
Metoprolol	3.02x 10 ⁻⁶	NC	NC
Dopamine.HCl	3.0 x 10 ⁻⁶	2.5 x 10 ⁻⁶	0.8
Atenolol	2.2 x 10 ⁻⁶	6.7 x 10 ⁻⁶	3.0
Losartan	1.8 x 10 ⁻⁶	NC	NC

Batch	Age of the MucilAir™ (months)	TEER Before exp (Ω.cm²)	TEER After Exp (Ω.cm²)	Papp (cm/s) A→B
Nasal-MucilAir™				
Pol 41	13	554 ± 103	442 ± 33	3.97 10 ⁻⁵ ± 4.32 10 ⁻⁷
Pol 43	12	469 ± 9	355 ± 54	3.80 10 ⁻⁵ ± 2.06 10 ⁻⁸
Pol 49	9	615 ± 35	340 ± 14	3.02 10 ⁻⁵ ± 1.34 10 ⁻⁸
Pol 51	6	376 ± 65	256 ± 30	2.88 10 ⁻⁵ ± 2.41 10 ⁻⁸
Pol 52	6	396 ± 14	332 ± 40	1.68 10 ⁻⁵ ± 8.93 10 ⁻⁸
Pol 53	6	495 ± 23	439 ± 75	1.22 10 ⁻⁵ ± 5.37 10 ⁻⁷
Pol 55	2	589 ± 2	665 ± 35	2.23 10 ⁻⁵ ± 1.18 10 ⁻⁸
Pol 57	3	480 ± 35	294 ± 37	2.11 10 ⁻⁵ ± 9.49 10 ⁻⁸
Pol 58	2	413 ± 28	406 ± 14	2.20 10 ⁻⁵ ± 1.12 10 ⁻⁸
Pol 59	2	375 ± 2	338 ± 2	1.86 10 ⁻⁵ ± 9.52 10 ⁻⁸
Pol 60	1	619 ± 26	460 ± 44	2.01 10 ⁻⁵ ± 1.00 10 ⁻⁸
Mean Value (N=22)				2.45 10 ⁻⁵ ± 2.42 10 ⁻⁸
Bronchial-MucilAir™				
Bron 009	8	371 ± 72	310 ± 23	2.26 10 ⁻⁵ ± 1.12 10 ⁻⁸
Bron 011	8	152 ± 0	190 ± 0	1.82 10 ⁻⁵ ± 9.96 10 ⁻⁸
Bron 014	6	236 ± 91	233 ± 40	0.89 10 ⁻⁵ ± 2.71 10 ⁻⁷
Bron 015	5	152 ± 23	191 ± 14	0.93 10 ⁻⁵ ± 8.26 10 ⁻⁷
Bron 016	3	480 ± 49	406 ± 107	1.26 10 ⁻⁵ ± 3.54 10 ⁻⁸
Mean Value (N=10)				1.43 10 ⁻⁵ ± 2.83 10 ⁻⁸
TOTAL Nasal-MucilAir™ and Bronchial-MucilAir™				
Mean Value (N=32)				2.13 10 ⁻⁵ ± 2.05 10 ⁻⁸

(a)

(b)

Figure (a): Assessment of the drug permeability across MucilAir using 12 reference compounds.

Figure (b): Inter-Batch variability. A→B transport of Salicylic Acid (1 mM; pH 7; N=2) was measured on several batches of MucilAir from different donors. Cultures with ages from 1 to 13 months were compared. Interestingly slightly lower permeability constants of salicylic acid were obtained on Bronchial epithelium.

Conclusions

- 1: Taken together, MucilAir™ is a good, reliable *in vitro* cell model for studying respiratory absorption.
- 2: High reproducibility and small inter batch variability are observed.
- 3: Age of the culture of MucilAir™ has minor influence on permeability.
- 4: Standard Operating procedures are defined and available.

Acknowledgements



More Information

