Understanding the mechanisms governing the interaction of drugs with mucus using a novel biosimilar mucus model

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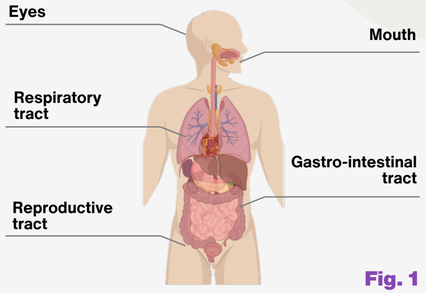


Fig. 1

Mucus distribution

Mucus covers all the wet tissues of the human body. Mucus is helping us staying healthy. It is a natural barrier (Fig 1).

Mucus barriers

Mucus is a selective barrier against pathogens however, it is an obstacle even for drugs orally administered.
Drugs may rest trapped into the mucus network (Fig 2).

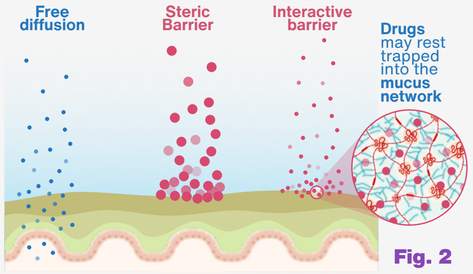


Fig. 2

The need

Up until now there are no standard protocols that model the passage of molecules through mucus.

Pharmaceutical companies need an *in vitro* screening mucus model in order to reduce the number of non effective drugs reaching preclinical trials.

Physico-chemical characteristics

The developed mucus model reproduces the physico-chemical properties of cystic fibrosis mucus.

Rheological parameters such as the elastic (G') and the viscous (G") modulus of the biosimilar mucus are as similar as possible to the pathological mucus.

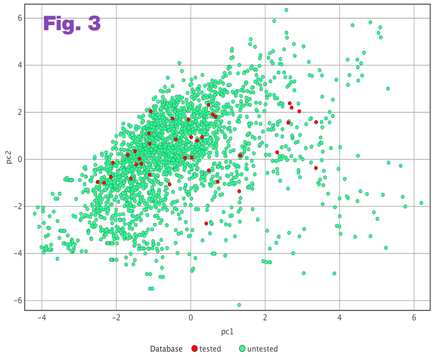


Fig. 3

Drugs selection

45 drugs have been selected among commercially available compounds.

The selected drugs are well distributed within the DrugBank database of approved drugs implying a wide coverage of chemical heterogeneity (Fig. 3).
Another selection criteria was the homogeneous distribution within the molecular properties described by Lipinksi's rule of five (data not reported).

Diffusion of drugs

The mucus model can be coupled to classic diffusion platforms (e.g. Transwell, PAMPA, PermeaPad) for high throughput analysis.

The diffusion across the mucus model of different drugs was studied by means of PAMPA and compared with the diffusion rates in absence of mucus (Fig. 4).

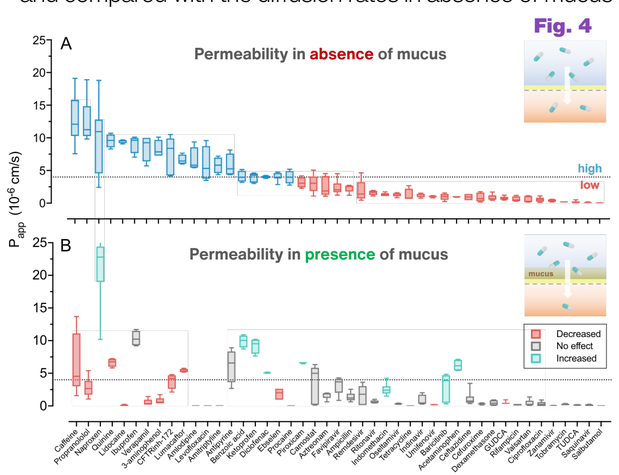
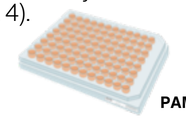


Fig. 4



PAMPA plate

Few anionic compounds presented **higher permeability** in the presence of the mucus model.
We proved that **ion-pairing with Ca^{2+}** is the reason of the increased permeability (Fig. 5)

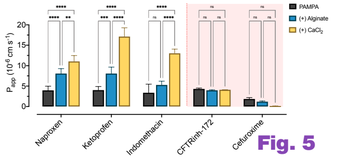


Fig. 5

Take home messages

- The **effect of mucus is difficult to predict** in pathological conditions and **the PAMPA system is a too simplistic model**
- A **fast screening** of highly retained compounds can be assessed with the mucus model
- Diffusion of some anionic drugs through mucus can be increased by formation of **calcium salts**
- **The mucus model is fully tuneable.** The production method allow to incorporate other mucus components

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