Drugs and mucus | Deciphering the interaction mechanism using a biosimilar mucus model

2021 3Rs in transition From development to application
VIRTUAL CONGRESS - AUGUST 2021

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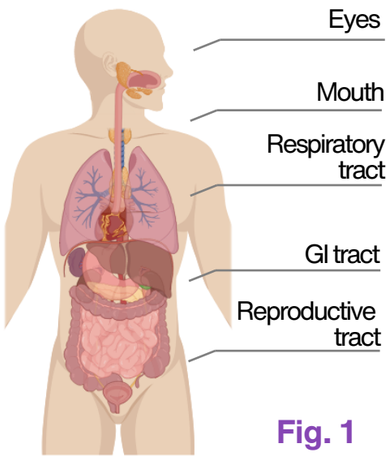


Fig. 1

Mucus distribution

The mucosal surfaces of the human body are constantly exposed to environmental threats. To counteract potential noxious agents, epithelia of the wet tissues are covered with a layer of mucus (Fig. 1)

Mucus is helping us staying healthy. It is a natural semipermeable network which barrier properties are mainly governed by mucins glycoproteins.

Mucus barriers

Mucus is a selective barrier against pathogens. However, it represents an obstacle even for drugs orally administered (Fig. 2).

Drugs may rest trapped into the mucus network.

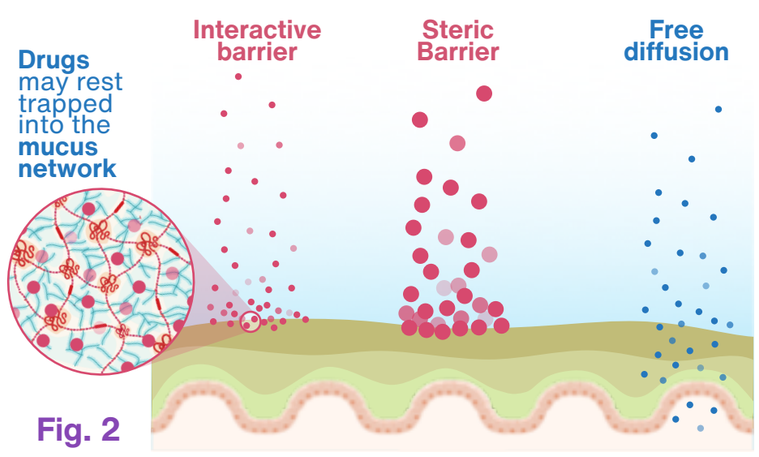


Fig. 2

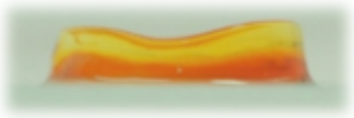
Up until now there are no standard protocols that model the passage of molecules through mucus.

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.

The viscoelastic property of cystic fibrosis (CF) mucus is achieved by taking advantage of the internal gelation of alginate in the presence of calcium ions.



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.

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. 3A). Another selection criteria was the homogeneous distribution within the molecular properties described by Lipinksi's rule of five (Fig. 3B).

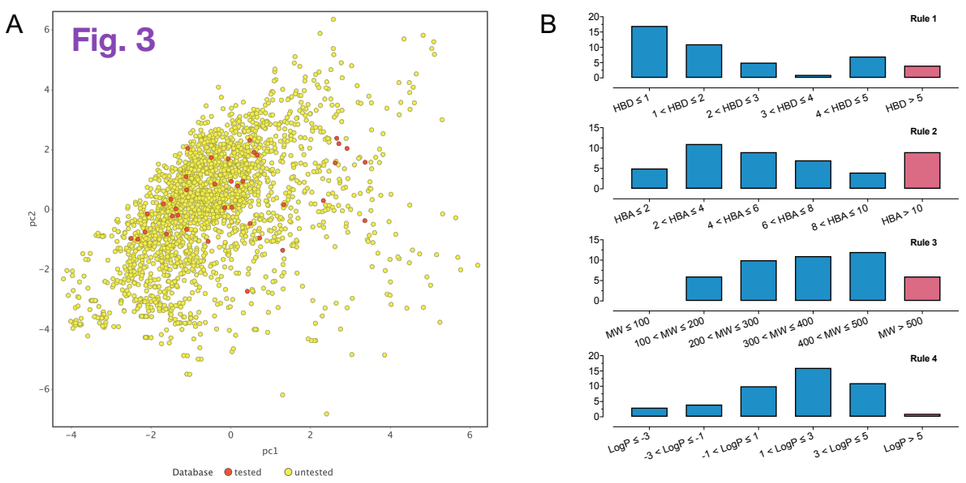


Fig. 3

Diffusion of drugs

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

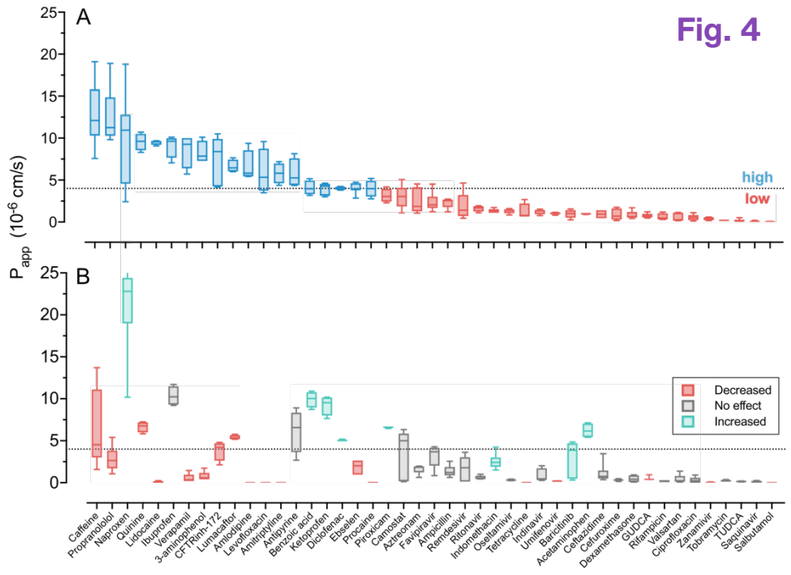
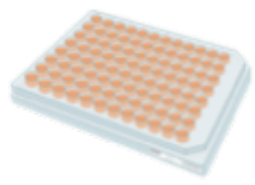


Fig. 4



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

Calcium-drug complexes are more permeable

The ion-pairing with Ca^{2+} can increase the passive diffusion of some negatively charged compounds through the PAMPA phospholipid membrane

About 18% of the tested compounds presented **higher permeability** in the presence of the mucus model (Fig. 5A). These drugs are relatively small molecules, lipophilic, medium-low polar and usually anions at pH 7.4.
We proved that **ion-pairing with Ca^{2+}** is the reason of the increased permeability (Fig. 5B). Calcium ions can form asymmetric complexes having large radius, and binding of calcium is highly selective.

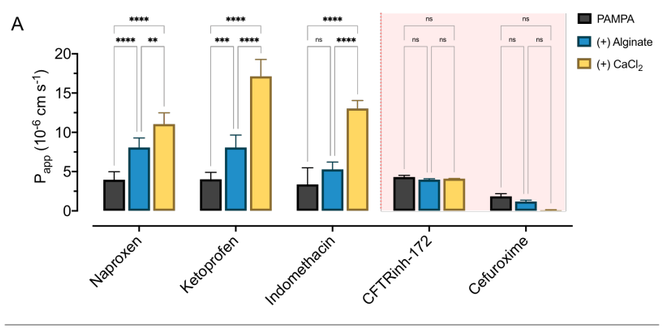
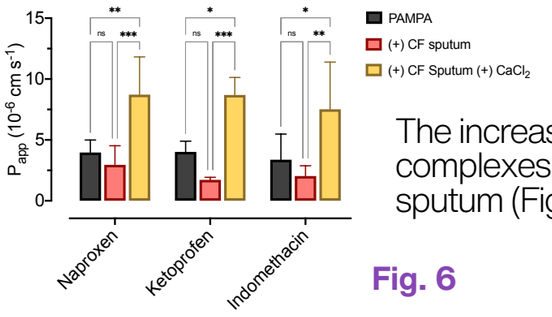


Fig. 5



The increased permeability of calcium-drug complexes is proved even through cystic fibrosis sputum (Fig. 6).

Fig. 6

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
- **Calcium-drug complexes** can increase passive diffusion of some anionic compounds.
- **The mucus model is fully tuneable.** The production method allow to incorporate other mucus components

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