Nasal powder delivery – Characterisation of the influence of excipients on drug absorption

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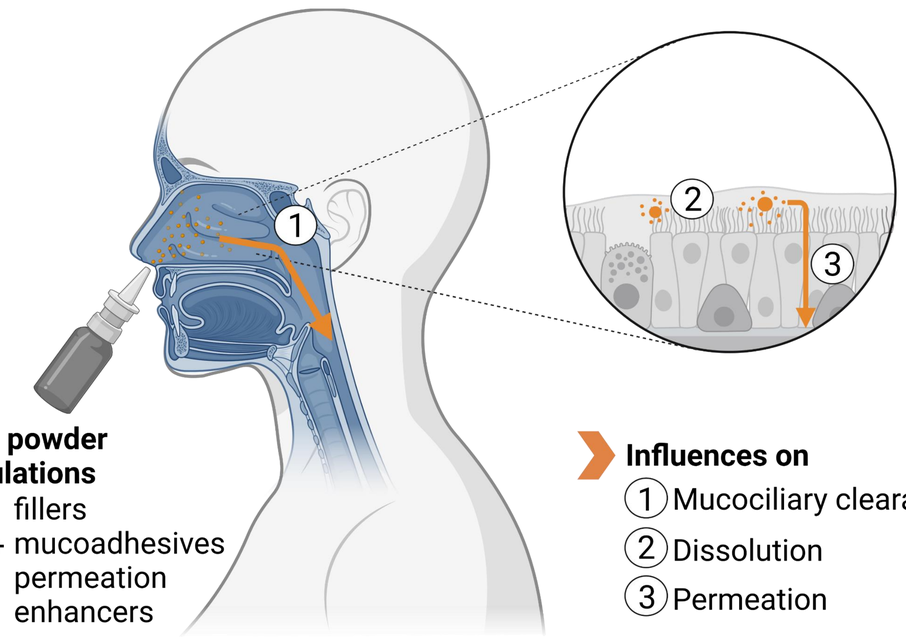
Introduction



Nasal powder formulations
drug + fillers, mucoadhesives, permeation enhancers

Influences on
1. Mucociliary clearance
2. Dissolution
3. Permeation

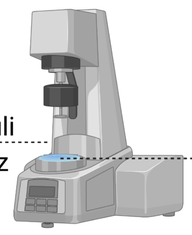
Easy access to a highly vascularised, relatively permeable mucosa via the nose offers high potential for systemic drug delivery. However, the natural mucociliary cleaning mechanism results in a short nasal residence time of drugs and thus poses a specific challenge. The formulation of nasal powders and the use of functional excipients are strategies to overcome this hurdle, but influence drug absorption multifactorially.

Therefore, the aim of this study was to distinguish influences of excipients on mucociliary clearance, dissolution and permeation, in order to enable a sound selection and thus the development of successful nasal products.

Characterisation methods

1 Influence on mucociliary clearance using oscillation rheology

Frequency dependent elastic and viscous moduli
Displayed frequency: 1 Hz

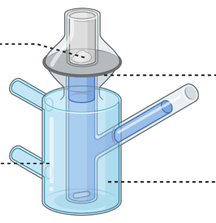


Dispersions of powders in simulated nasal fluid (SNF)
7.45 g/L NaCl
1.29 g/L KCl
0.32 g/L $CaCl_2$ x 2 H_2O
32 °C

2 Influence on drug dissolution using Franz diffusion cells

Donor
Powder on an air-liquid-interface

Acceptor
Simulated nasal fluid

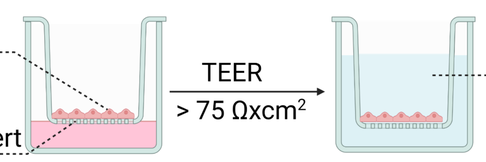


Membrane
Cellulose acetate (0.45 µm)

Temperature
32 °C

3 Influence on drug permeation using RPMI 2650 cells

RPMI 2650
Air-liquid-interface
Transwell insert
PETP (3 µm)



Test solultions
API + single excipients in HBSS + HEPES

Assessed excipients and model formulations

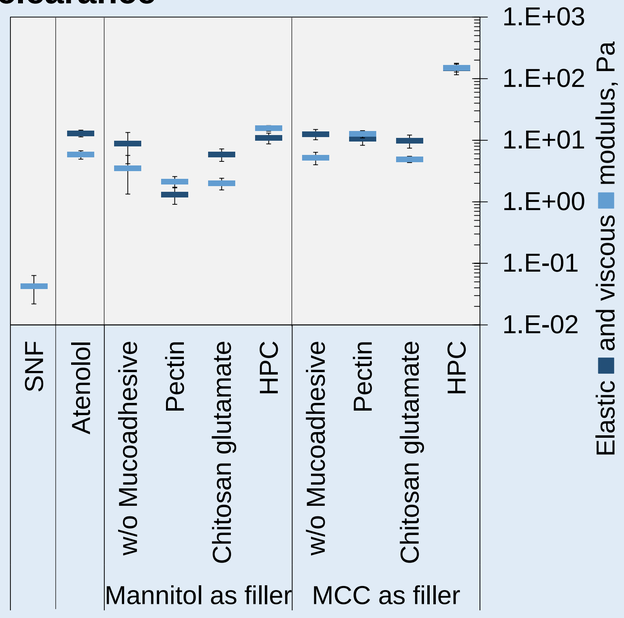
Function	Compound	Characteristics	Formulations		
			Control	w/o MA	With MA
API	Atenolol	Low and paracellular permeation marker	100%	40%	40%
Fillers	Mannitol	Water-soluble		60%	50%
	Microcrystalline cellulose (MCC)	Water-insoluble			
Muco-adhesives (MA)	Pectin	Anionic charge			10%
	Chitosan glutamate	Salt of positively charged chitosan			
	Hydroxypropyl cellulose (HPC)	Neutral			

The excipients were fractioned on a laboratory sieve shaker and a sieve fraction of 32-150 µm was used for the experiments. Model formulations were prepared by blending API and excipients in a Turbula blender.

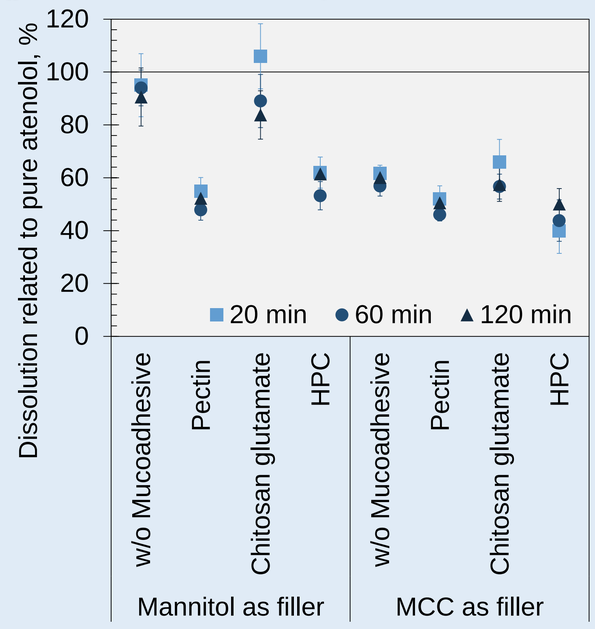
Results and discussion

1 Influence on mucociliary clearance

Undissolved drug particles increased the elasticity of SNF sufficiently to slow down mucociliary clearance (>2 Pa). However, this effect will decrease with progressing drug dissolution in the nose. The use of insoluble or swelling excipients can induce a longer lasting effect. An additional increase in elastic and viscous modulus compared to pure API was only observed with the formulation containing MCC and HPC.

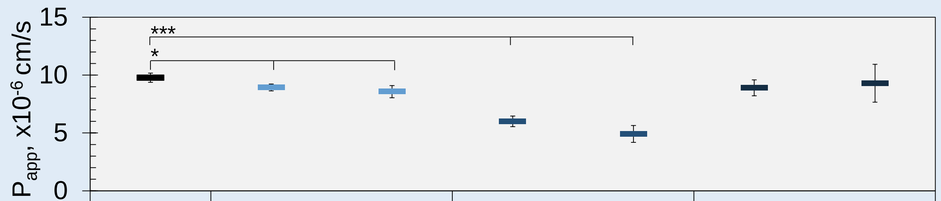


2 Influence on drug dissolution



Formulations containing mannitol with or w/o chitosan glutamate showed a similar dissolution profile as the pure API. All other formulations, containing insoluble or gelling excipients, decreased the dissolution rate similarly. Considering the results of the rheological assessments (1), the formulation containing MCC and HPC is expected to show the greatest benefit if a prolonged nasal residence time is required for drug permeation.

3 Influence on drug permeation



	Atenolol	Pectin 0.25%	Pectin 0.50%	Chitosan glutamate 0.25%	Chitosan glutamate 0.50%	HPC 0.25%	HPC 0.50%
TEER start, Ω*cm²	91 ± 2	91 ± 8	93 ± 3	92 ± 1	88 ± 8	92 ± 1	83 ± 5
TEER end, Ω*cm²	96 ± 2	93 ± 5	93 ± 6	69 ± 2	66 ± 5	90 ±3	80 ± 8
pH of drug solution	7.2	7.1	7.0	6.7	6.3	7.3	7.3

Pectin and chitosan glutamate reduced the permeability of atenolol. Chitosan glutamate however, reduced the TEER of the cell barrier, which supports the postulated function of chitosan to enhance permeation by opening tight junctions. The slight acidic reaction of chitosan glutamate may contribute to the yet reduced permeability. A higher portion of atenolol is in its ionised form at lower pH, which contributes less to permeation. The acidic reaction of chitosan glutamate may limit its use with drugs that are weak bases, as pH adjustment is difficult in powder formulations.

*Mean +/- standard deviation (n=3; pH: n=1 *=p<0.05; ***=p<0.001)*

Conclusion

The use of excipients in nasal powder formulations can specifically adjust drug absorption. The separate characterisation of processes that influence drug absorption is essential for a sound selection of functional excipients. The methods described in this work enable the detection of counteracting effects on absorption and thus, the selection of excipients with the most promising overall properties.

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