Systemic delivery of meloxicam nanoparticles via the nasal route

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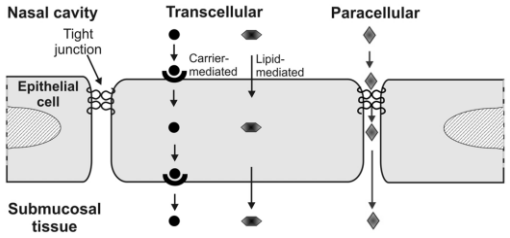
Intranasal delivery of drugs

- Local delivery: nasal allergy, congestion, infection
- Systemic delivery
  - Crisis treatment (rapid onset)
  - Long term treatment (daily administration)
  - Peptides and proteins (difficult to administer)
- Vaccine delivery: antigens, DNA vaccines
- Access to CNS: to reach local receptors, to circumvent the BBB
  - Horvát et al., 2009: 4.4 kDa dextran – paracellular marker
  - Sipos et al., 2010: β-amyloid 1-42 – biologically active peptide

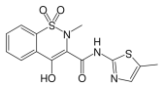
Horvát, S. et al., Eur.J.Pharm.Biopharm.,72: 252–259, 2009
Sipos, E. et al., Cell. Mol. Neurobiol., 30: 405–413, 2010

Transport across the epithelium

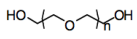


Pharmaceutical materials

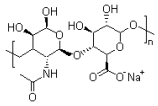
Model drug
- Non-steroidal anti-inflammatory and analgesic drug
  - Meloxicam (MEL)



Excipients
- Grinding additives
  - Polyvinyl-pirrolidon-C30 (PVP)
  - Polyethylene glikol 6000 (PEG)

- Mucoadhesive and viscosity increasing excipient
  - Sodium hyaluronate (HA)

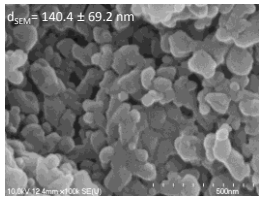


Preparation of MEL nanoparticles by co-grinding

Co-grinding: planetary monomill

Factorial experiment design
(COST=Change One Separate factor at a Time)

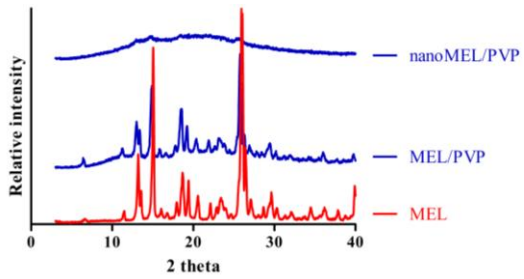
Optimised parameters:
- Grinding time: **2 hours**
- Rotation speed: **400 rpm**
- Excipient: **PVP-C30**
- MEL/excipient ratio: **1:1**



Cumulative collision energy transferred (kJ·g^{-1})					
		Meloxicam/ excipient weight ratio			
Rotation speed (rpm)	Collision frequency (s^{-1})	No additive	1 : 0.5	1 : 1	1 : 2
200	240	8.56	5.71	4.28	2.85
300	360	28.89	19.27	14.45	9.63
400	480	68.50	45.67	34.25	22.83

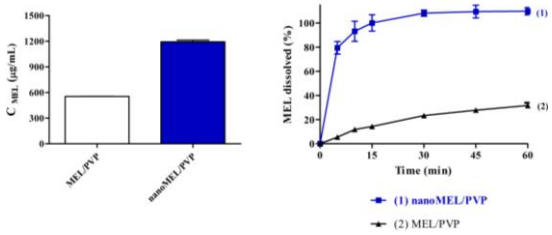
Kürti, L. et al., Powder Technol., 212: 210–217, 2011

XRPD analysis of meloxicam

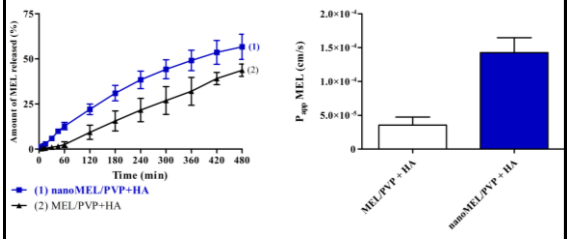


Kürti, L. et al., Powder Technol., 212: 210–217, 2011

In vitro experiments
Solubility, extent of dissolution
pH 7.4; 37°C

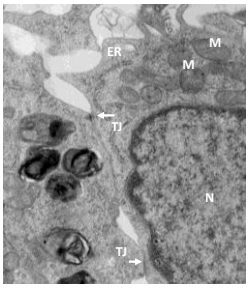


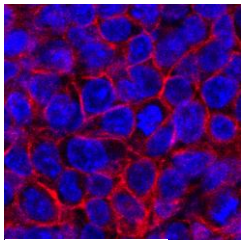
In vitro permeability
Lipophilic membrane
Franz diffusion cells
pH 7.4; 37°C



P_{app}= permeability coefficient
1-h timepoint

In vitro cell culture model of nasal drug delivery based on RPMI 2650 cells



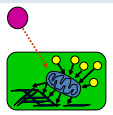


β-catenin immunostaining - red
cell nucleus staining - blue

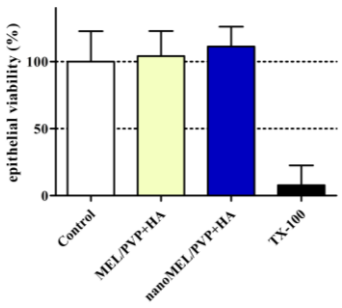
ER, endoplasmatic reticulum; M, mitochondrion; N, cell nucleus; TJ, tight junction

Kürti, L. et al., Toxicol. *In Vitro*, 26: 445–454, 2012
Kürti, L. et al., Cytotechnology DOI 10.1007/s10616-012-9493-7

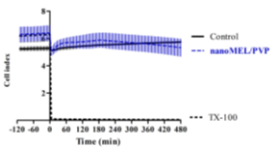
Effects of MEL nanoparticles on nasal epithelial cell viability
RPMI 2650 cells, 1-hour treatment

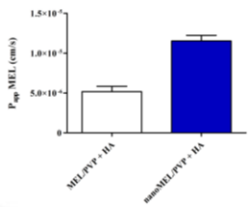


MTT test



Nanoparticles cross the nasal epithelial barrier
human RPMI 2650 cells





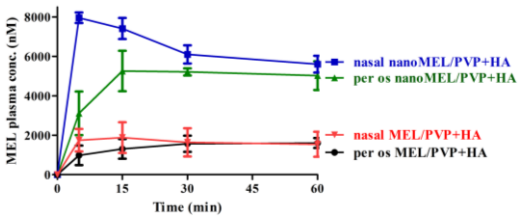
Cell microelectronic sensing

xCELLigence, Roche

P_{app}= permeability coefficient
1-h treatment

In vivo animal experiments
influence of formulation on nasal and oral delivery of MEL

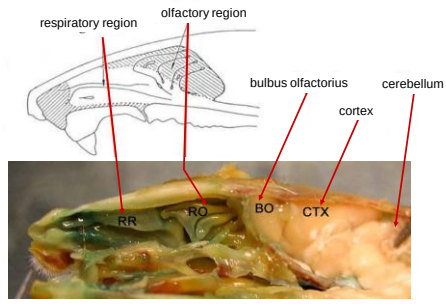
60 µg drug single dose/animal
male Sprague–Dawley rats
n=5



Pharmacokinetic parameters of intranasal meloxicam

	nasal MEL/PVP+HA	nasal nanoMEL/PVP+HA	p
k_a (1/min)	NA	NA	NA
k_e (1/min) ± SD	5.6×10^{-4} (± 3.6×10^{-4})	8.8×10^{-4} (± 7×10^{-4})	*ns*
t_{max} (min)	312.0 (± 107.3)	5.0 (± 0.0)	***
c_{max} (µM)	2.92 (± 0.96)	7.95 (± 0.23)	***
AUC 0-t (µmol*min/L)	3342.0 (± 1236.0)	4838.0 (± 384.4)	*
AUMC (µmol*min²/L)	3.24×10^7 (± 3.69×10^7)	7.17×10^6 (± 1.32×10^7)	*ns*
MRT (min)	2882 (± 2298)	1064 (± 98)	*ns*

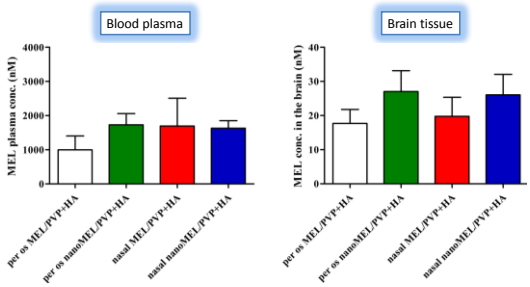
Permeability of cerebral blood vessels in rats



intravenous fluorescein and Evans blue dye

Wolburg, H. et al., Histochem.Cell Biol., 130: 127–140, 2008

Meloxicam in the blood and in the rat brain tissue 24 hours after drug administration



Summary

- Meloxicam nanoparticles have different physico-chemical properties compared to the pure active agent
- Nasal administration of pharmacons offers novel therapeutic opportunities
- *In vitro* screening methods are important in the selection of an optimal pharmaceutical composition for nasal delivery
- Pharmacokinetic profile of meloxicam altered due to the nanonization process and the nasal administration route
- Nanonization and intranasal administration are favourable combinations

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