Nano Innovation 2020
Rome, 15-18 September
Conference & Exhibition

The delivery of nanomedicines to the airways

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Rome, 18th September 2020

UNIVERSITÀ DI PARMA

BIOPHARMAnet TEC

Science fiction?

FT
FINANCIAL TIMES
Thursday, 3 March 2005

Roche launch AmpliChip - gene based Cytocrome P450 metabolism diagnostic kit

Roche CEO states:

"Star Trek medicine is still (!?) two decades away"

Personalized medicine

Medical nanorobots of tomorrow will…

"conquer human disease, ill health and aging"

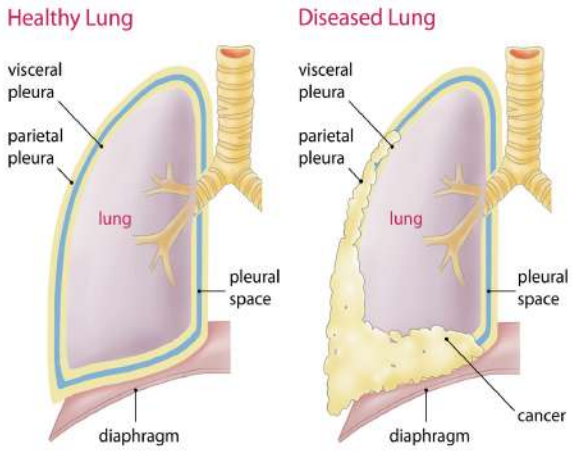
- Sensors
- CPU
- Homing device

Clinical uses for inhaled nanomedicines

Nanomedicines can contribute to treat severe diseases associated to the respiratory tract or can use the lung as a route for systemic treatment.

Localized diseases:

- **Asthma, COPD**
- **Infectious diseases (Pulmonary tuberculosis)**
- **Genetic disorders (Cystic fibrosis)**
- **Cancer**



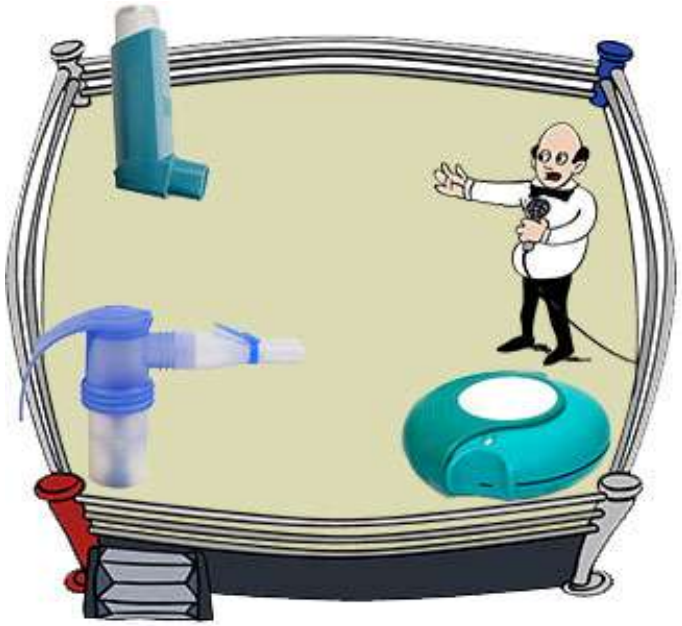
Systemic diseases:

- **Vaccination strategies**
- **High potency biotech drugs (peptides, proteins, nucleic acids)**

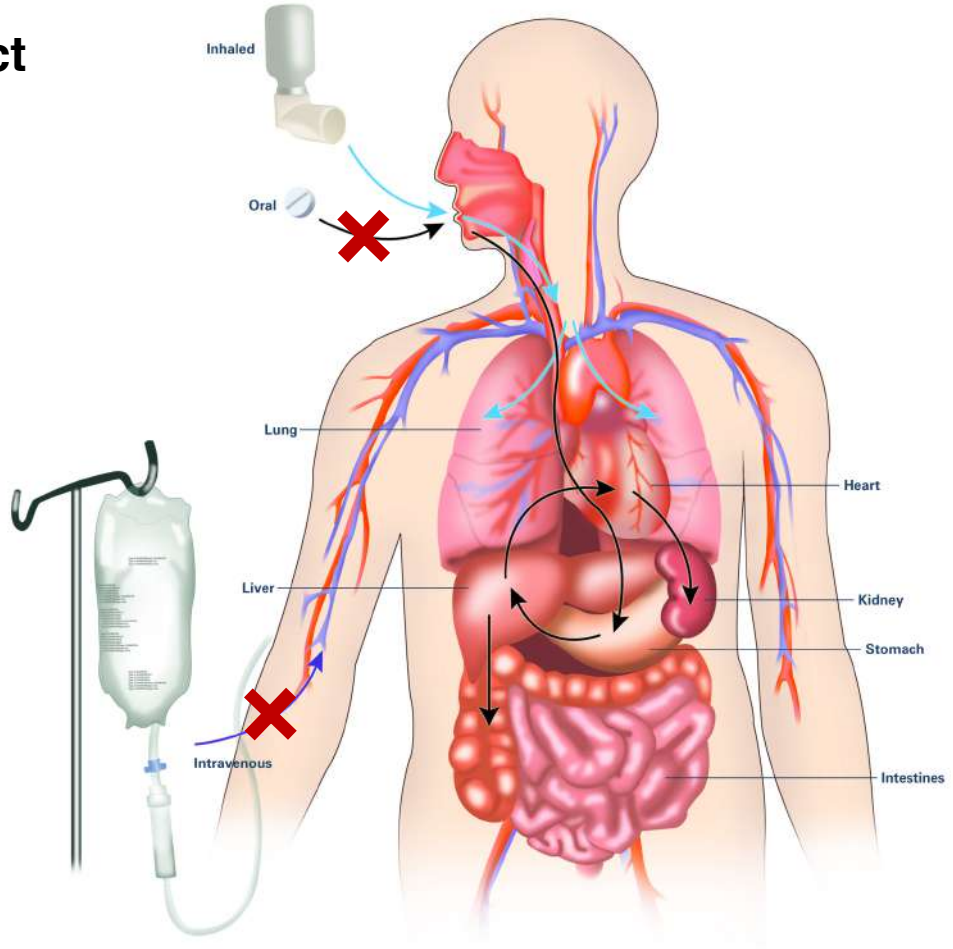
Opitz, I., 2014. Management of malignant pleural mesothelioma-The European experience. J Thorac Dis 6 Suppl 2, S238–52.

Nanoparticles: how to reach the lungs?

Pulmonary nanomedicines **direct** delivery in form of an aerosol.



http://www.inhalationreport.com/2010/07/21/inhalation-dosage-form-selection-mdi-vs-dpi-vs-nebulizer/

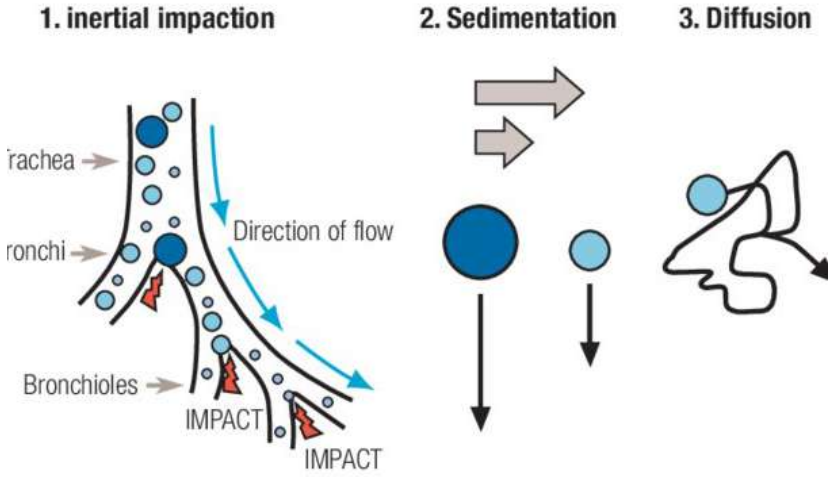


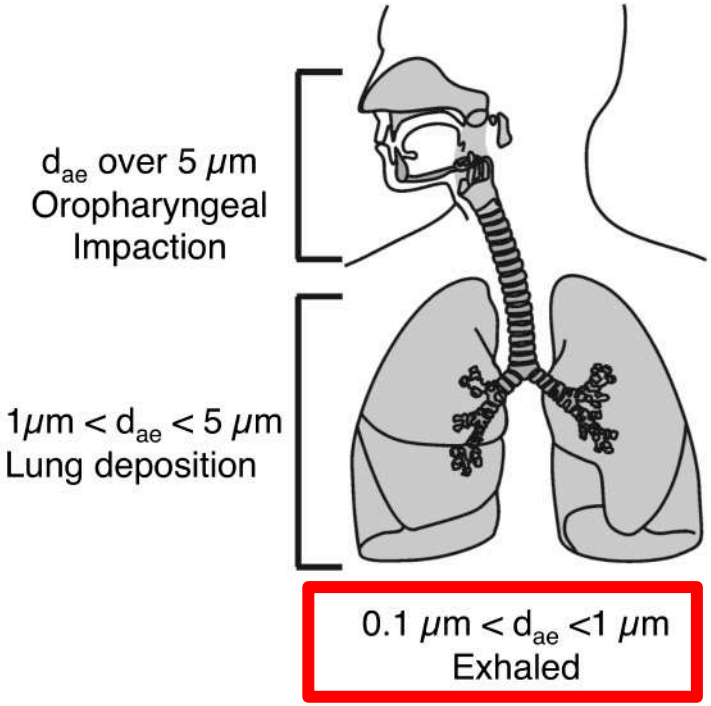
Delivering nanomaterials to the lung is not an easy task!

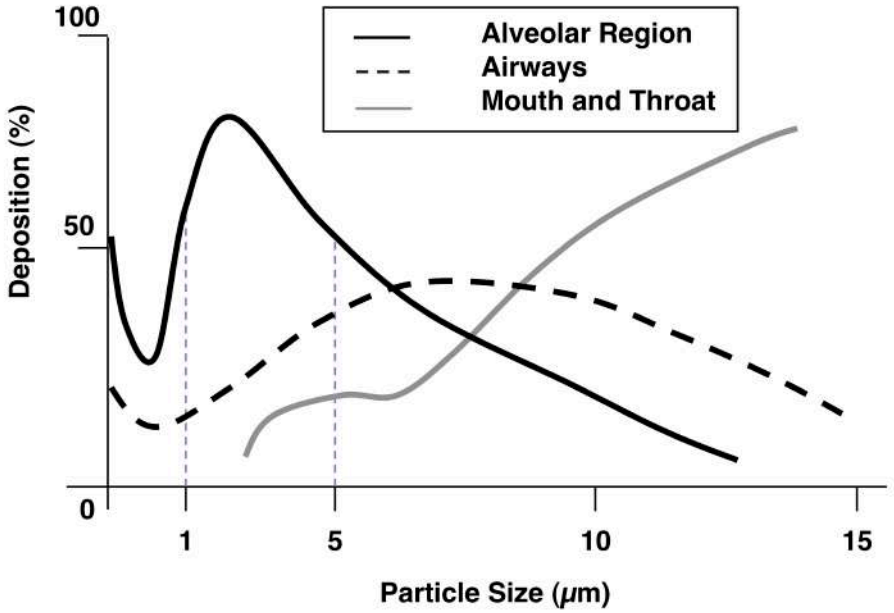
When size matters…

Nanomaterials are not meant

to deposit by impact or sedimentation.

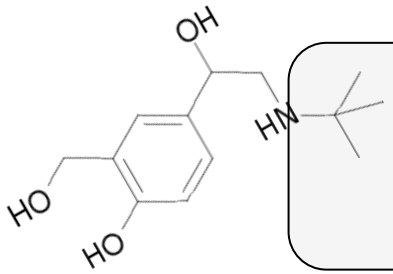




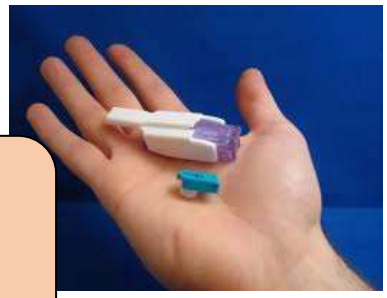


Pereira et al. Drug Deliv, 2016; 23(8): 2881–2896

Device-based delivery

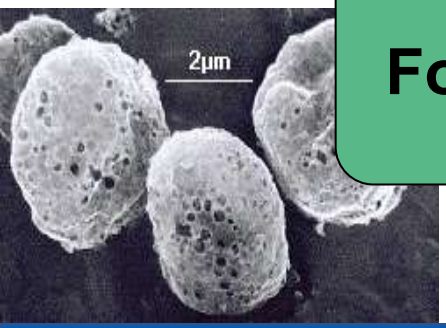


API



Device

Pulmonary administration

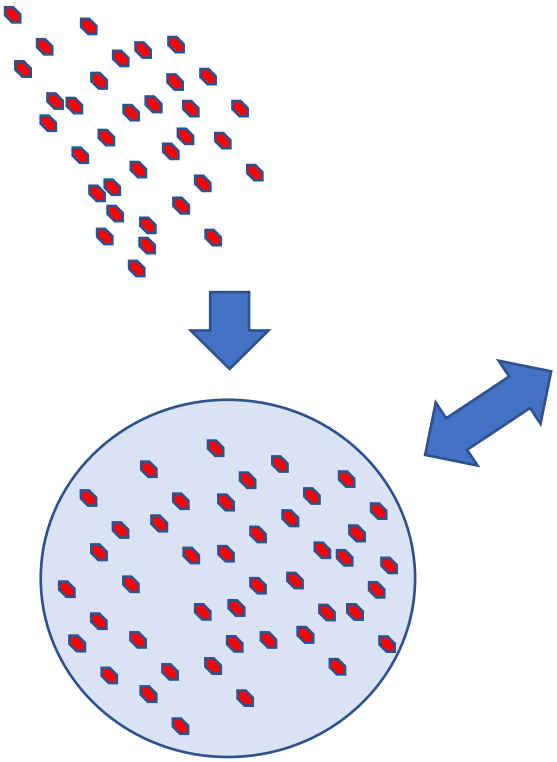


Formulation

Patient

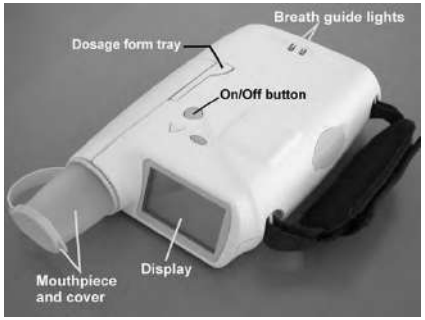
The art of aerosolizing nanoparticles

Nanomaterial



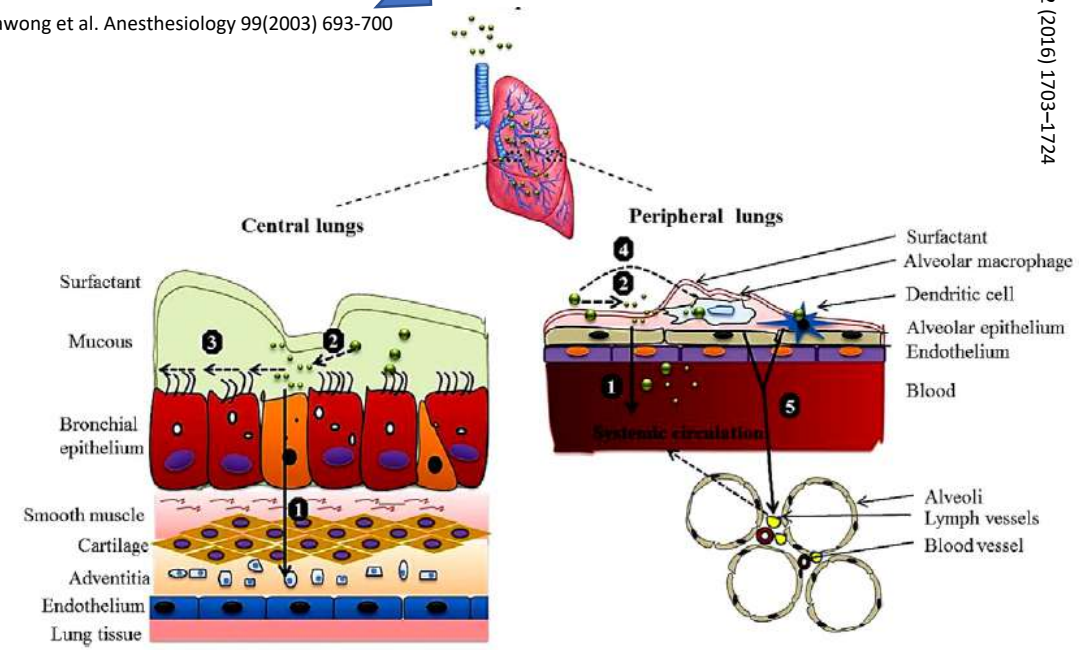
Micron-sized formulation
(droplets, particles, carrier)

Device



Thipphawong et al. Anesthesiology 99(2003) 693-700

Inhalation + Dispersion + Dissolution/Uptake

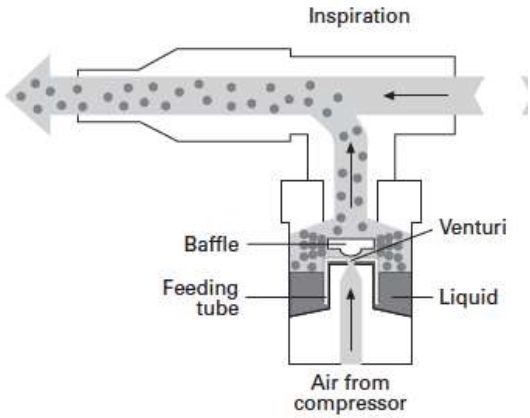


S. Haque et al Nanomedicine 12 (2016) 1703–1724

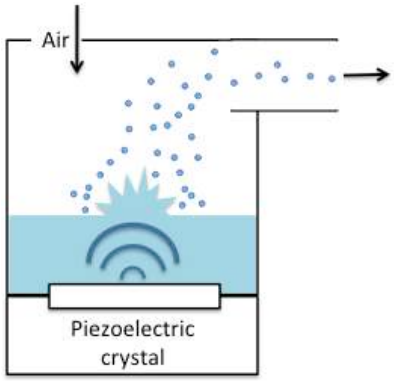
Nebulizers

Nebulizer technologies

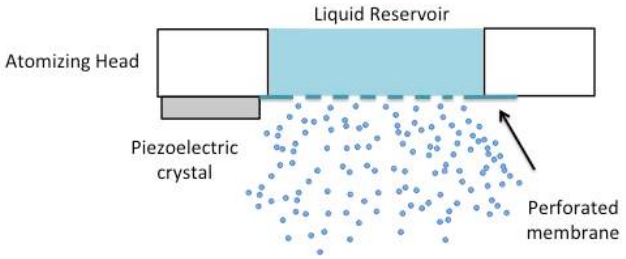
Air-jet



Ultrasounds



Vibrating mesh



O'Callaghan and Barry, Thorax 52 (1997) S31-S44

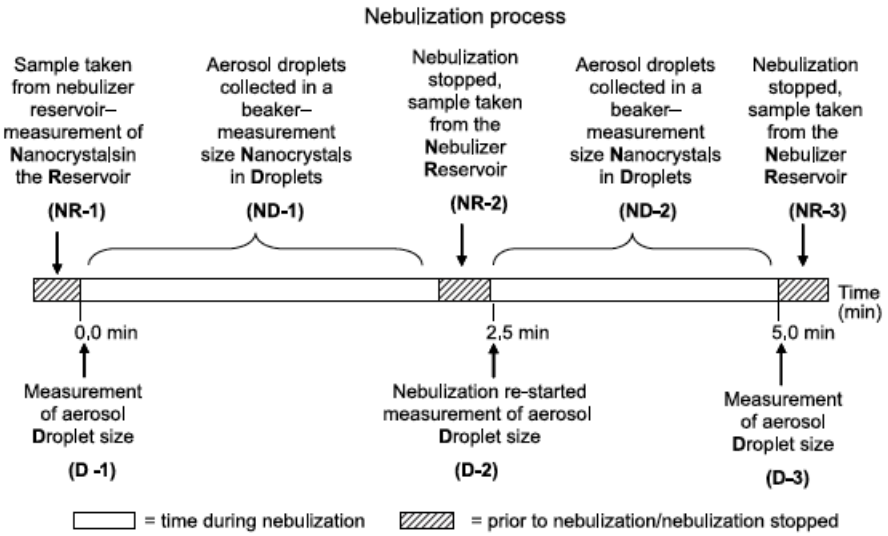
Particles not processed or modified.

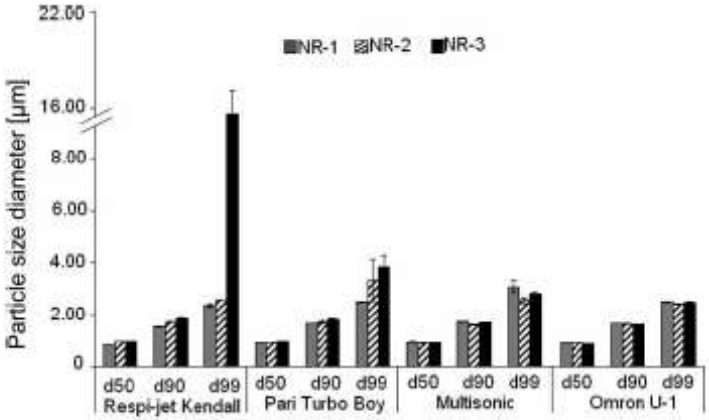
Nanoparticles seem especially adapt to improve delivery of drug suspensions that are not efficiently aerosolized with certain technologies.

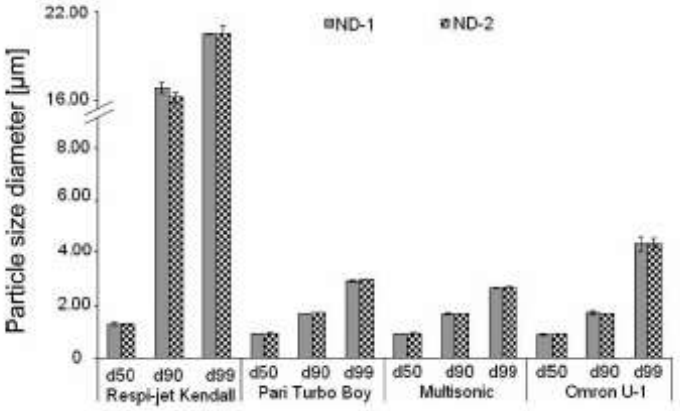
Nebulizers are not all the same…

Not all nebulizers techniques provide the same performances. Buparvaquone nanocrystals tested with different nebulizers show agglomeration.

Droplets are in the range 3-5 μm for all nebulizers except for the Omron U-1 (8-10 μm)

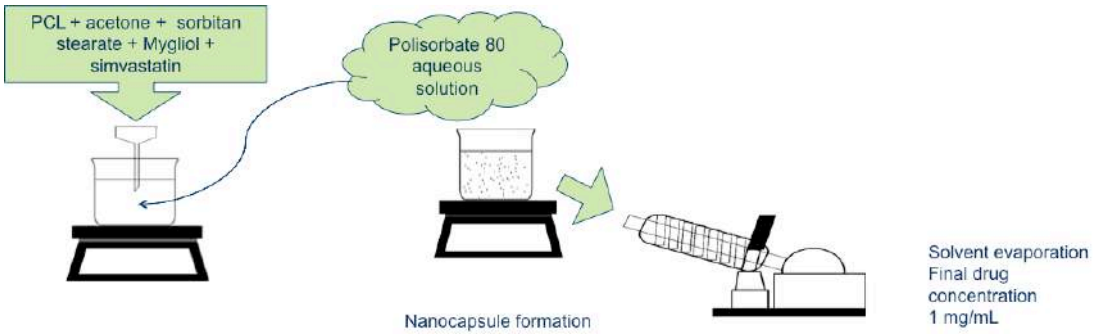


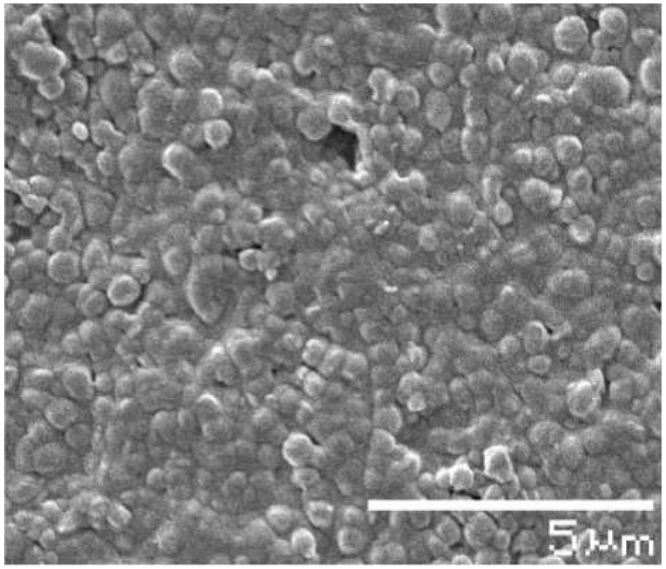




Hernandez-Trejo et al. J Drug Target 13(2005) 499–507

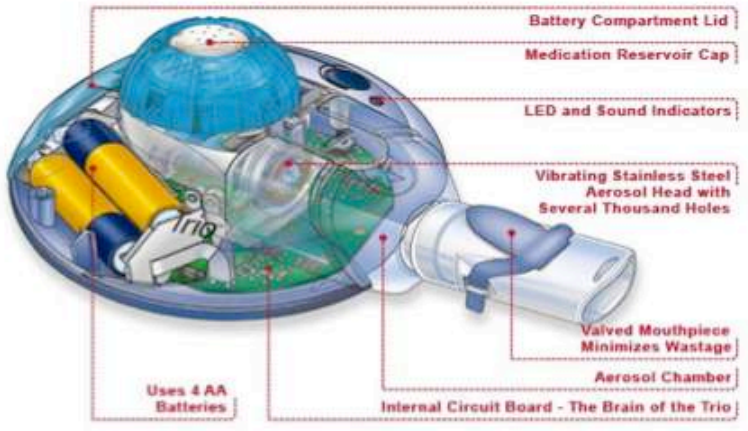
…nor nanoparticles

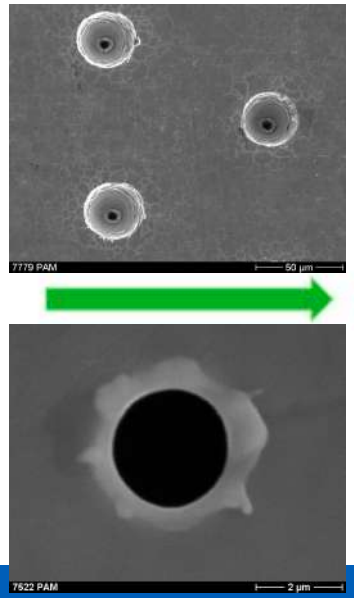


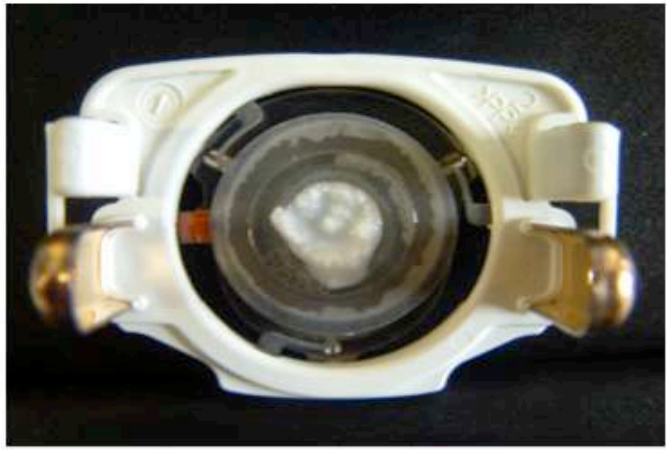


Mean particle size	205.5 ± 0.5 nm
Polydispersity index	0.11 ± 0.03
Zeta potential	-19.5 ± 0.13 mV
pH	6.06 ± 0.08
Encapsulation efficiency	99.18 ± 0.72%

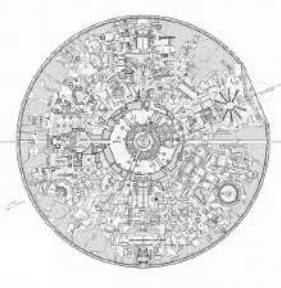
PARI e-Flow





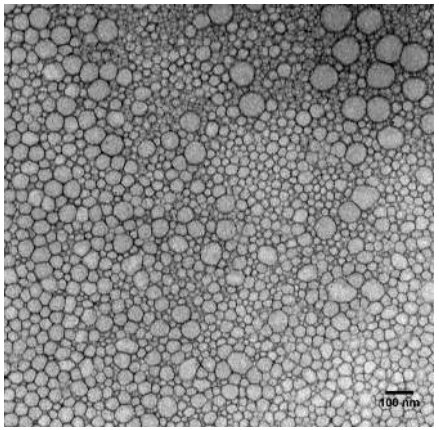


Design of nanoparticles is key



http://68.media.tumblr.com/b720e59d1925d25676311abd02067c01/tumblr_oie9lKXdBZ1qc4zz6o1_500.jpg

Coenzyme Q10 Solid Lipid Nanoparticles (40-60 nm)



European Journal of Pharmaceutical Sciences 113 (2018) 159–170

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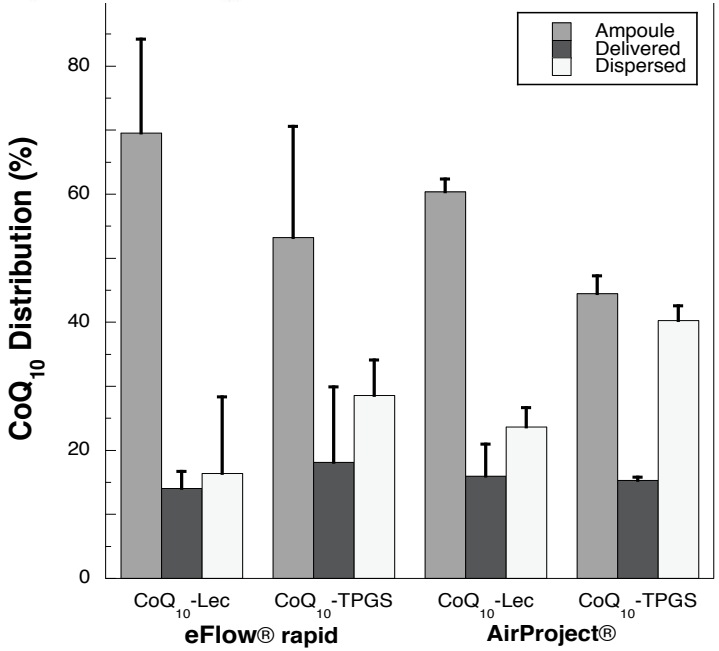
journal homepage: www.elsevier.com/locate/ejps

Nebulized coenzyme Q_{10} nanosuspensions: A versatile approach for pulmonary antioxidant therapy



Chemically stable

Physically Stable

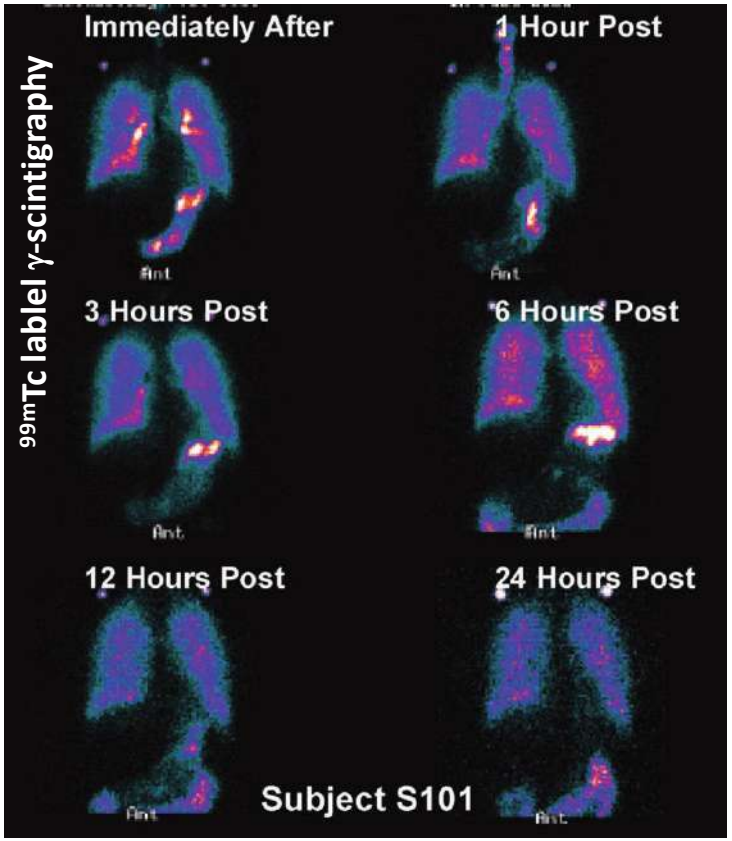
Nebulized with **any** type of device

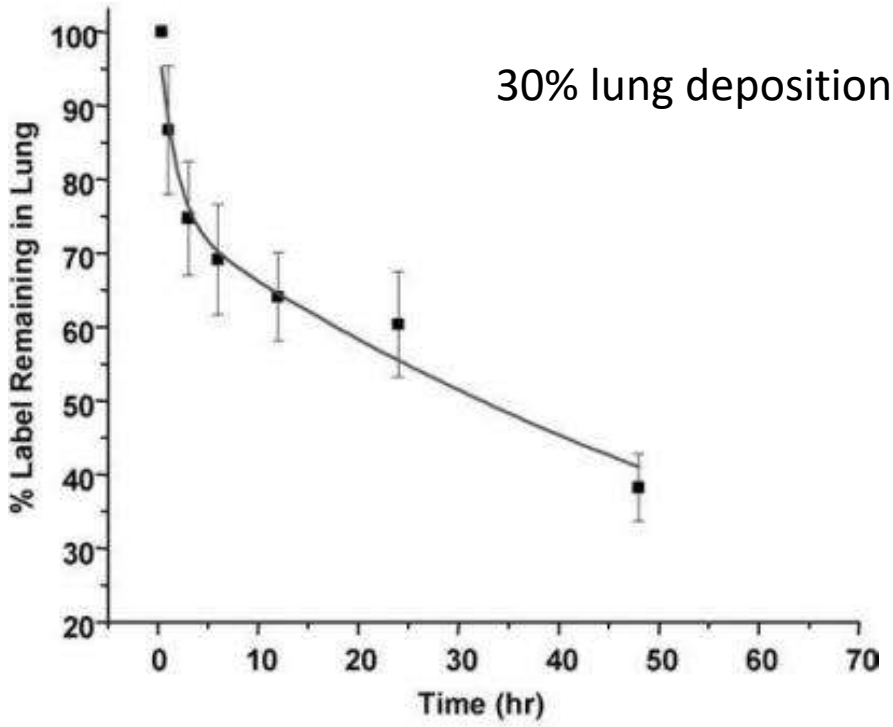
Respirable Fraction 55 – 70%
with Next Generation Impactor

Nebulization of Nanos in clinical trials

Antibiotic liposomal formulations for *P. aeruginosa* infections in cystic fibrosis patients.

Jet nebulizer (Pari LC STAR)





30% lung deposition

DPPC/Chol liposomes 0.3 µm
Amikacin 20 mg/ml

Weers et al. J Aerosol Med Pulm Drug Deliv 22 (2009) 131-138

Issues nebulizing nanosuspensions

High dependence of the treatment outcome are dependant on several parameters:

- **Nebulizing device choice**
- **Particles type, size and surface properties**
- **Stabilizers**

Furthermore, *long term stability and/or toxicity* of nanoparticles in suspensions present some problems: particle degradation, agglomeration, drug leaching could be expected.

Freeze-drying can be a solution however proper re-dispersion can be a challenge if the quantity of cryoprotectant and lyoprotectant is not sufficient (lactose, sucrose).

Pressurized Metered Dose Inhalers

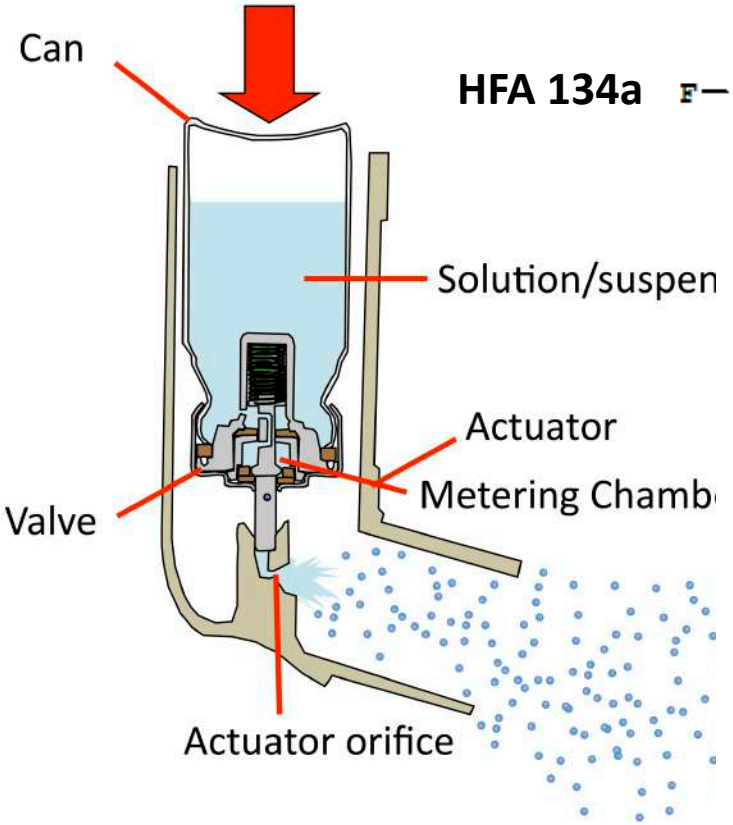
Portable, handheld and easily actuated pMDI are the **gold standard** in aerosol technologies. Several drugs that were solubilized by old CFC propellants are now in **suspension in HFA**.

Nanoparticles are expected to contribute to a better stability and delivery of suspensions in HFA.

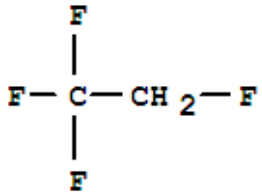
Due to their technical peculiarities however only recently have been used for the delivery of nanoparticles:

- Nanoparticles usually are produced to be aqueous dispersible
- The system is under pressure (liquefied propellant)
- The valve is dosing part of the suspension at each actuation
- The suspension is dried after actuation of the device

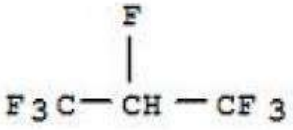
The pMDI device and technology

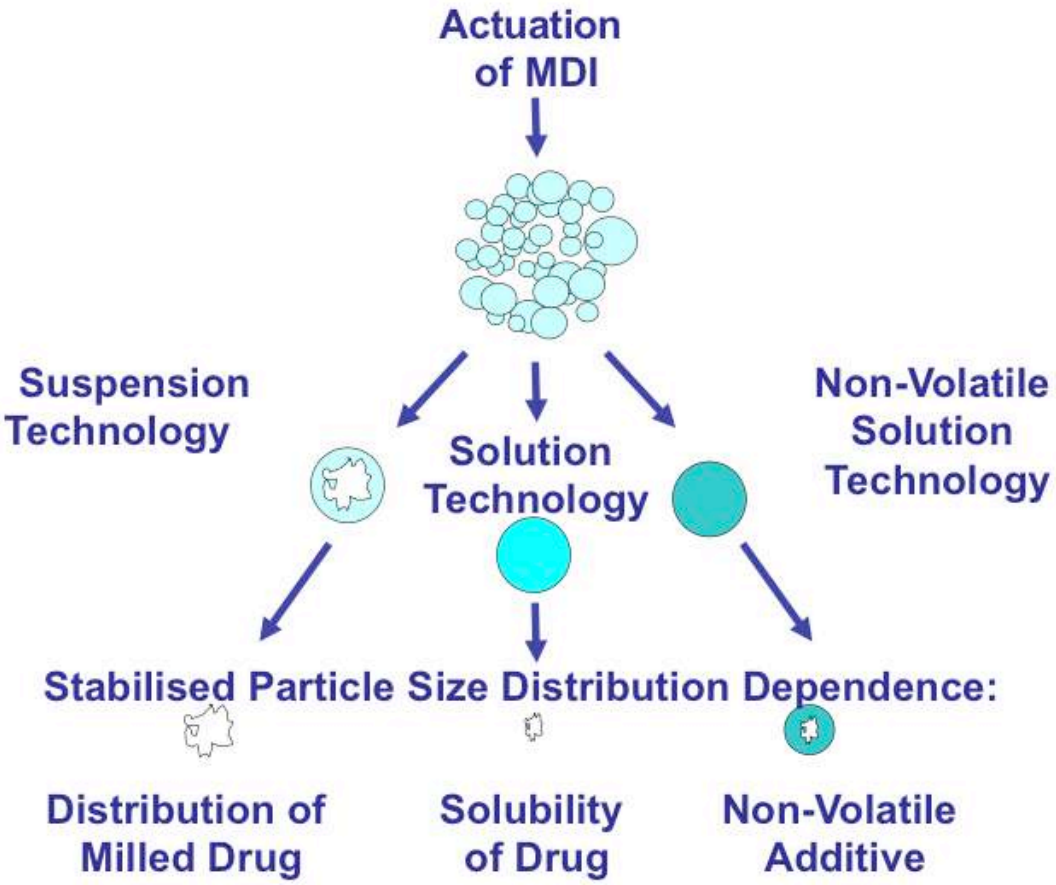


HFA 134a



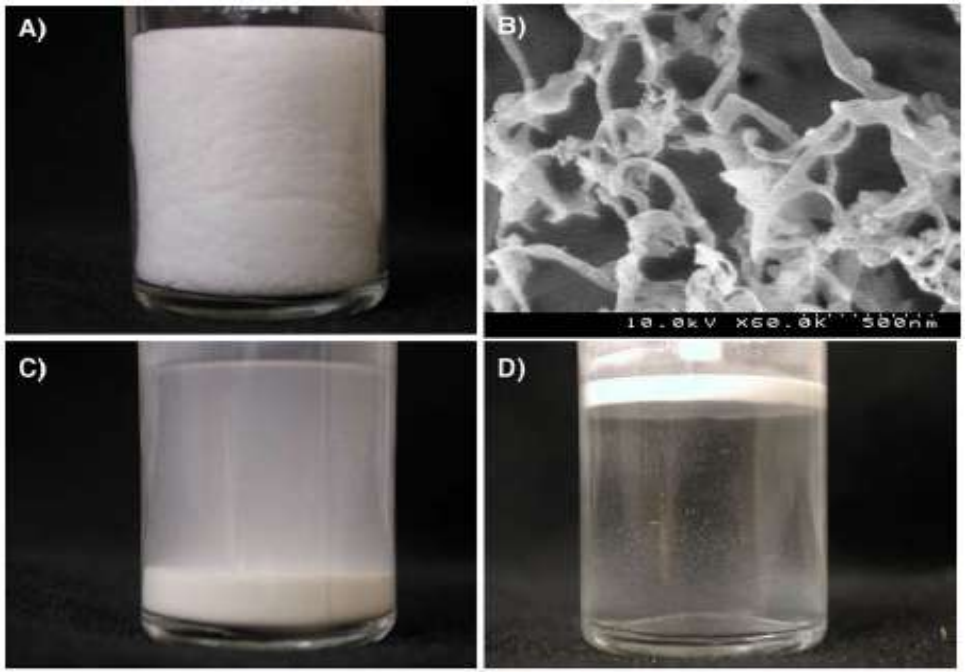
HFA 227





Stacked nanorods for pMDIs

Bovine serum albumin nanorods produced by thin film freezing (TFF). BSA wet milled or spray-dried could not provide an equally stable suspension in HFA.



Engstrom et al. Pharm Res 26 (2008) 101-117

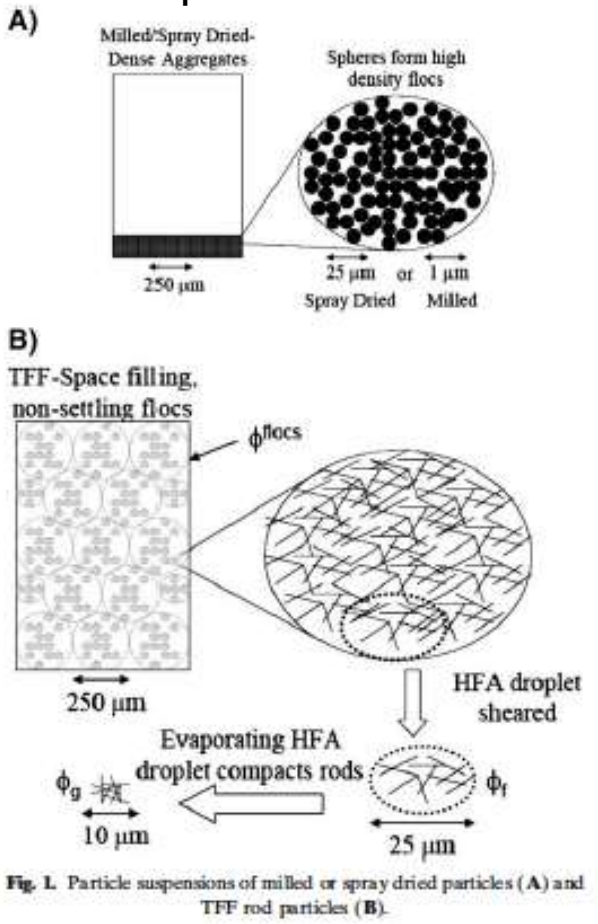


Fig. 1. Particle suspensions of milled or spray dried particles (A) and TFF rod particles (B).

FPF was found to be 47% for the TFF suspension

Insulin delivery via pMDI?

Insulin delivery to the lungs represent an alternative to current therapy of diabetes.

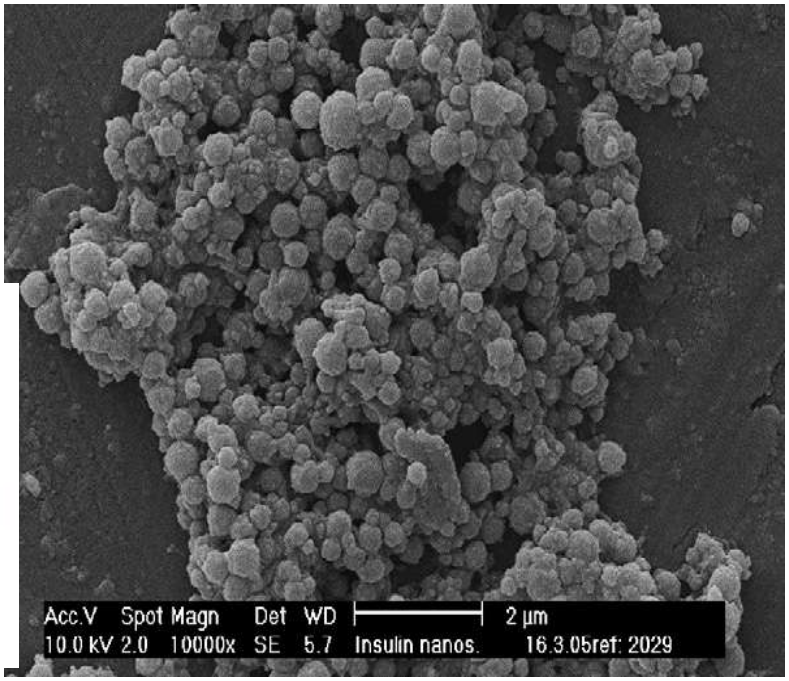
Also in this case nanoparticles are produced from a W/O (water in DCM) emulsion subsequently freeze-dried.

Insulin/Lactose Nps with lecithin and GMO as stabilizer

Freeze-dried nanoparticles were dispersed in essential oils before mixing with the propellant.

Table 2
Comparison of optimised pMDI formulations. Each result is the mean (±s.d.) of 3 preparations.

Property	GMO absent	GMO present
Nanoparticles hydrodynamic diameter (nm)	545.9 ± 12.7	346.7 ± 9.0
$FPF_{<1.7\,\mu m}$ (% (w/w) emitted dose)	20 ± 1.2	45 ± 3.5
Throat deposition (% (w/w) emitted dose)	74 ± 2.0	37.5 ± 4.5
Solid concentration (%, w/w)	1	1



Nyambura et al. Int J Pharm 375 (2009) 114-122

Dry Powder Inhalers

1. No need of a liquid vehicle to disperse the nanoparticles
2. Avoidance of problems of long term stability of nanosuspensions
3. Higher dosages delivered in comparison to MDI
4. Lower quantities of stabilizers/dispersant needed
5. Avoidance of mucociliary and in some cases phagocytic clearance

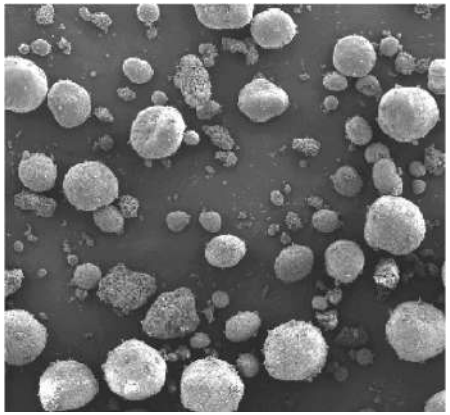
However nanoparticles present some **issues in handling, device filling and delivery to the airway** that can be overcome only by their incorporation in larger **micrometer sized structures**.

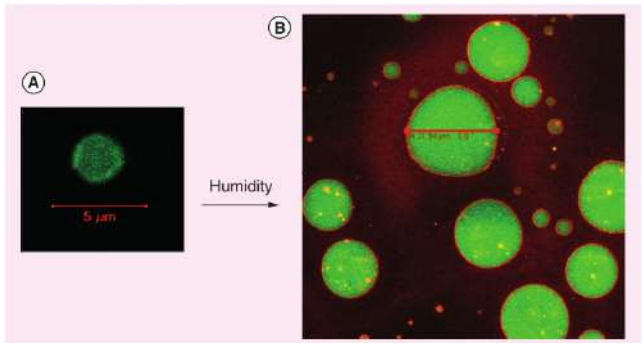
Effervescent nano-chemotherapy

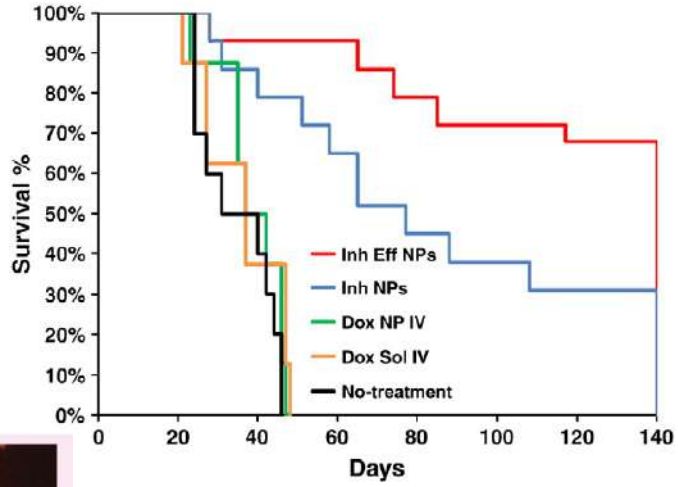
DOX-loaded PBCA nanoparticles were embedded in lactose particles containing sodium carbonate and citric acid obtained by spray-freeze drying.

The effervescence is used as nanoparticle active release mechanism at deposition.

L. Ely, W. Roa, W.H. Finlay, R. Lobenberg, Eur. J. Pharm. Biopharm. 65 (2007) 346–353.







Roa et al. J Control Rel 150 (2011) 49-55

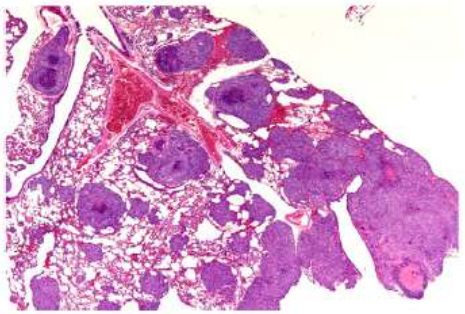


Fig. 2. Lung section of mouse from the non-treatment group. (20× magnification hematoxylin and eosin staining). Discrete tumor nodules are easily observed in the lung parenchyma.

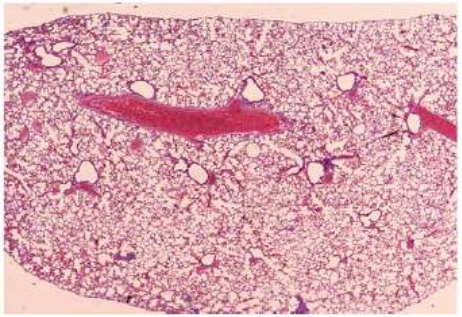
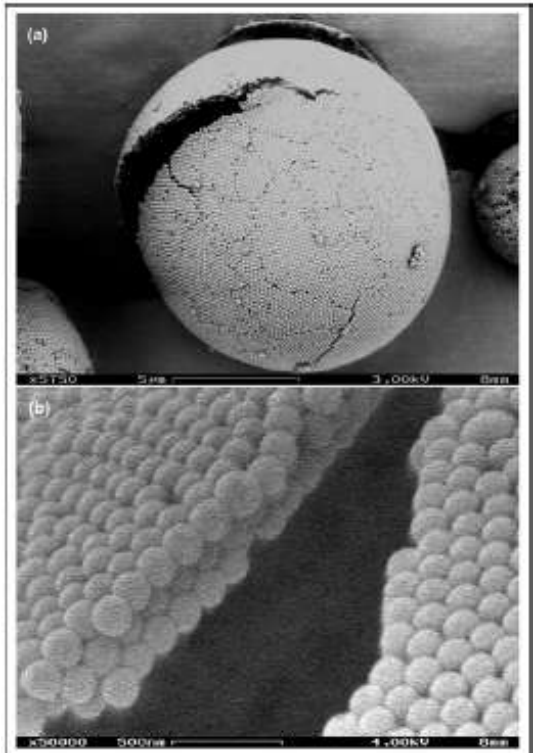


Fig. 6. Lung section of mouse treated with effervescent doxorubicin nanoparticle powder. (20× magnification, hematoxylin and eosin staining).

Porous nanoparticle-aggregate particles

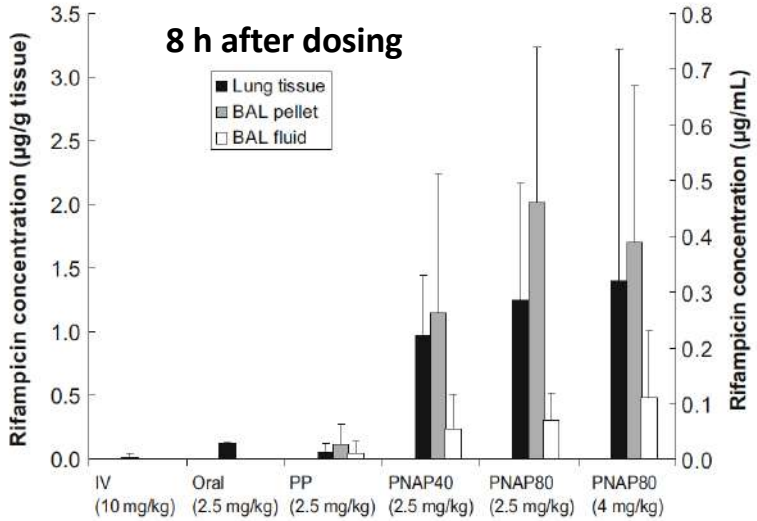
Directly from rifampicin loaded PLGA nanoparticles by spray drying, obtaining powders with a drug loading up to 10%.



Tsapis et al. PNAS 99 (2002) 12001-12005

Nanoparticles aggregate showed a FPF around 40%

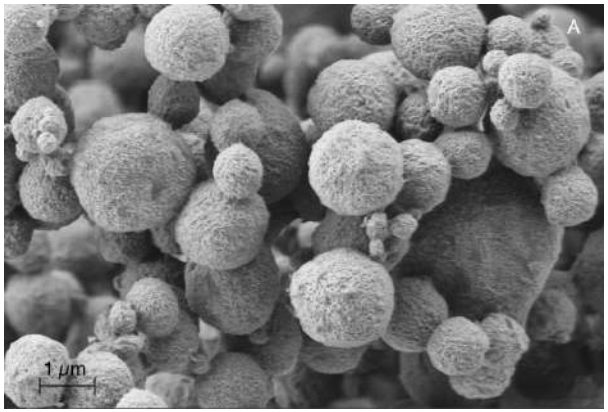
Administered to guinea pigs nanoparticles were compared to IV, oral or aerosolized rifampicin porous microparticles

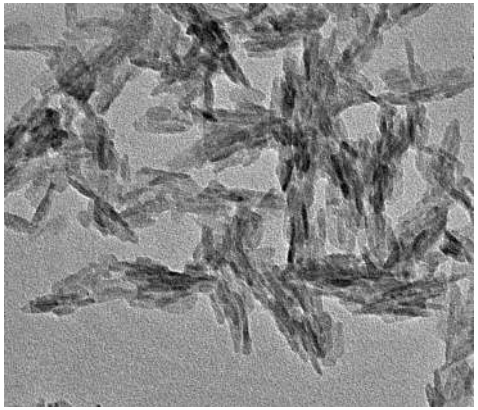


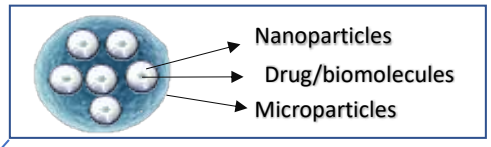
Sung et al. Pharm Res 26 (2009) 1847-1855

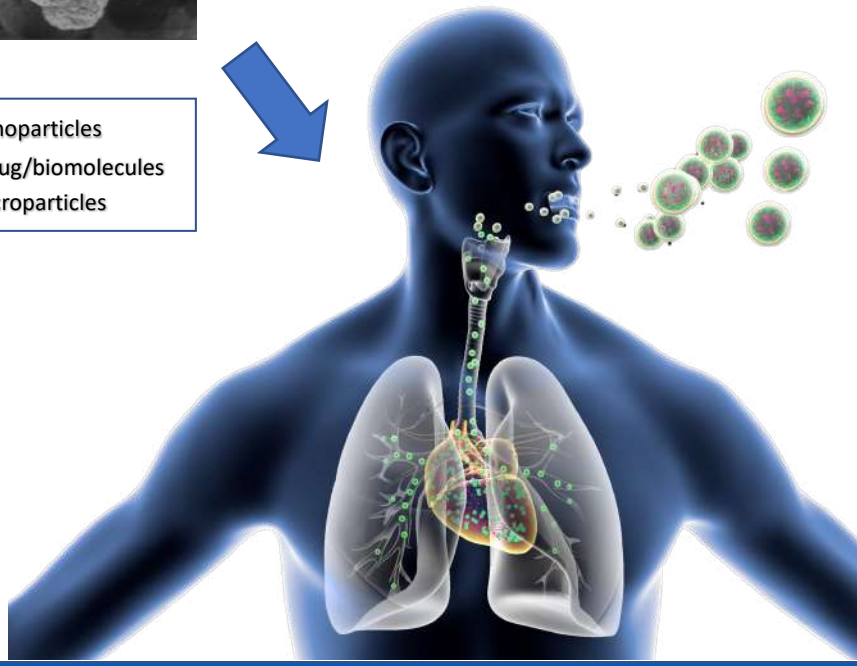
Cupido project

European Commission





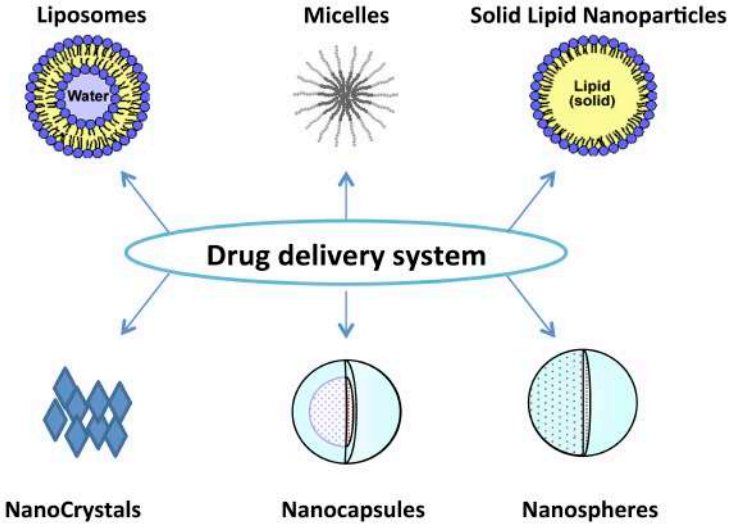


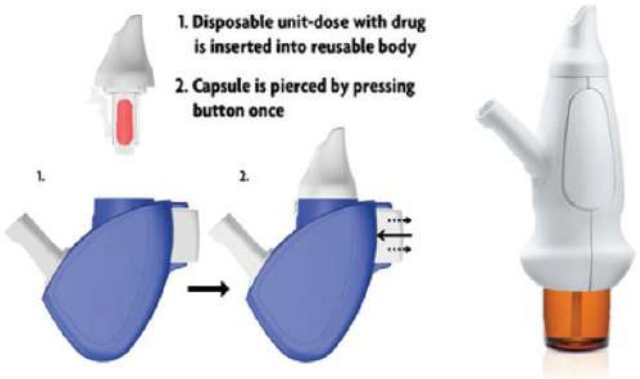


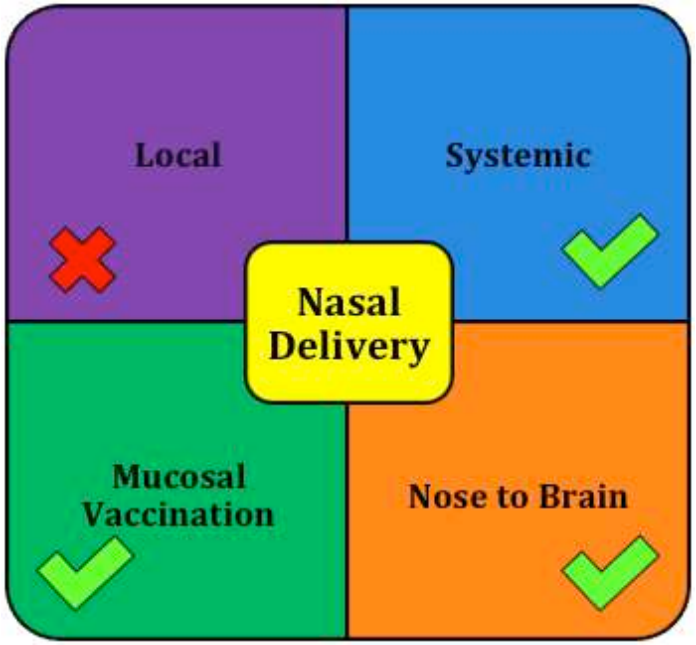
Conclusions about pulmonary delivery

- Nanotechnology appears as a tremendous opportunity to develop **new medicines** to be delivered to the lungs
- Technical **challenges** are connected to the delivery of nanosized materials
- **Polymers, stabilizers, diluents may not be approved for pulmonary use** and their safety should be demonstrated also in relation to nano-size related toxicology
- Delivery of **biopharmacetuicals** seems to be especially favoured

Nasal delivery of Nanoparticles







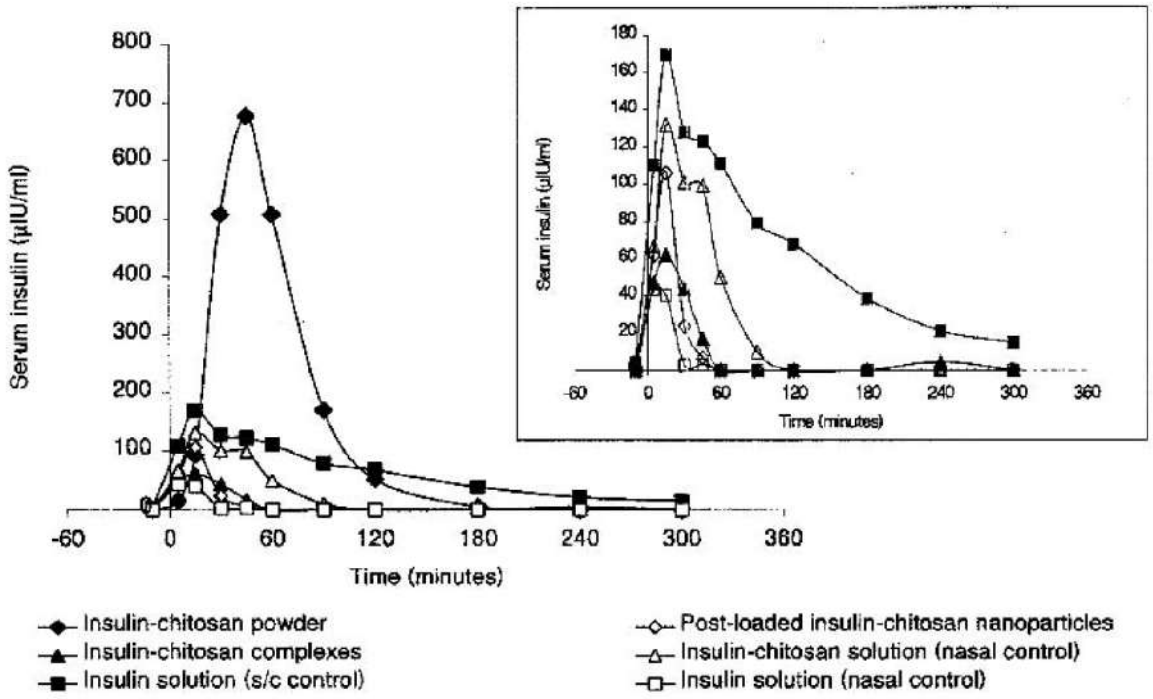
Djupesland Drug Deliv. and Transl. Res. (2013) 3:42–62

Djupesland Drug Deliv. and Transl. Res. (2013) 3:42–62

Do we really need nanoparticles?

"It can be concluded, that nanoparticle formulations do not improve the efficiency of the nasal administration of drugs (such as peptides and proteins) over and above that found for relevant solution or powder control systems of the same material." Illum, J Pharm Sci 96 (2006) 473-483

Insulin nasal delivery in sheep



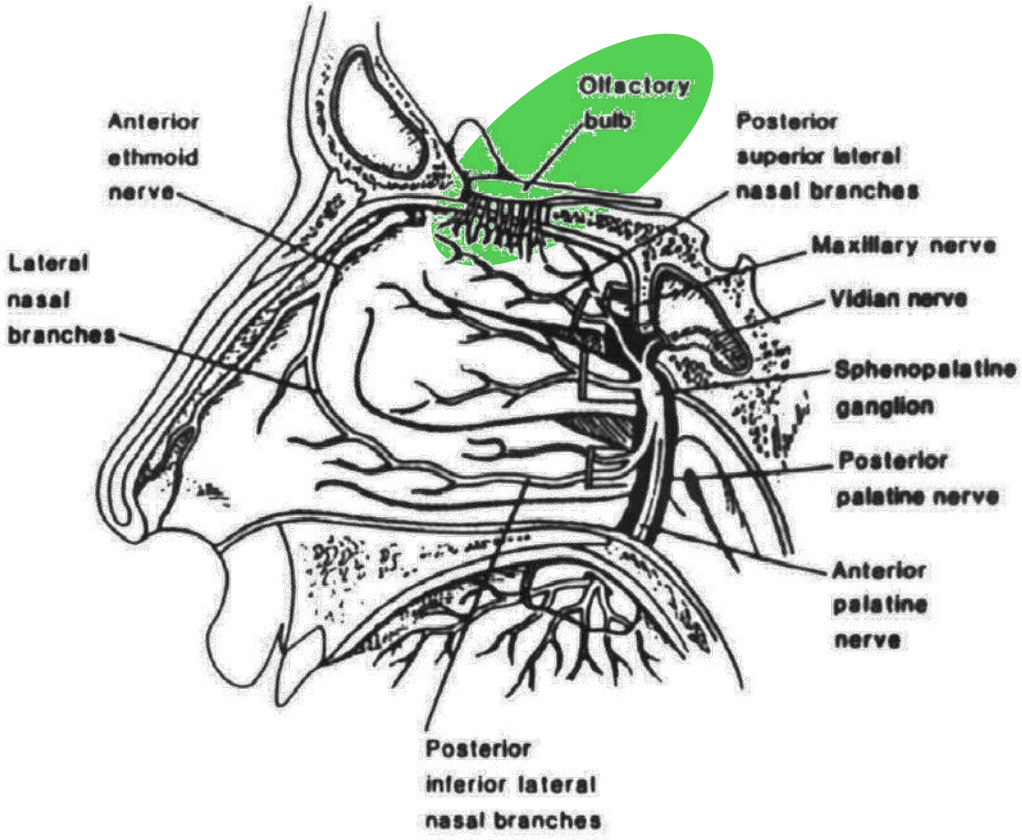
p

AUC (µIU/ml.min))	Frel (%)
6579.1[l,m,n,o,p]	100
491.7[l,q,jj]	0.5 ± 0.1[nn]
2575.0[m,r,kk]	3.6 ± 0.8[oo]
13286[n,q,r,s,t,jj,kk,ll,mm]	17.0 ± 6.6[nn,oo,pp,qq]
817.5[o,s,ii]	1.8 ± 0.9[pp]
1985.6[p,t,mm]	1.3 ± 0.8[qq]
$P < 0.0001$	N/A
$P < 0.0001$	$P < 0.0001$

ven as mean ± SD (n = 6).

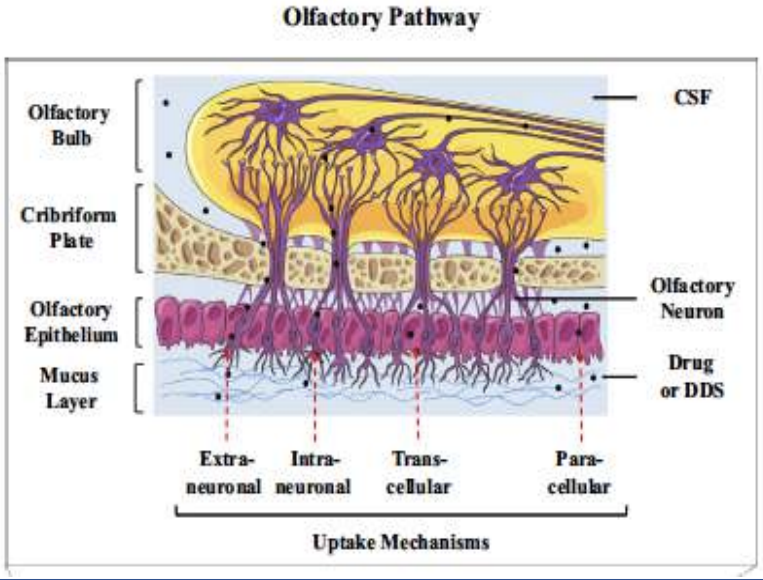
ative to SC data from the same animal.

Nose-to-brain delivery



Mistry et al. Int J Pharm 379 (2009) 146–157

- Access to CNS
- Bypass blood brain barrier
- Bypass periferic metabolism
- Ease of administration
- Favorable brain/blood ratio

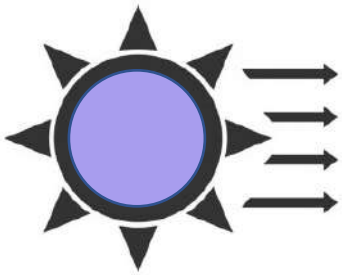


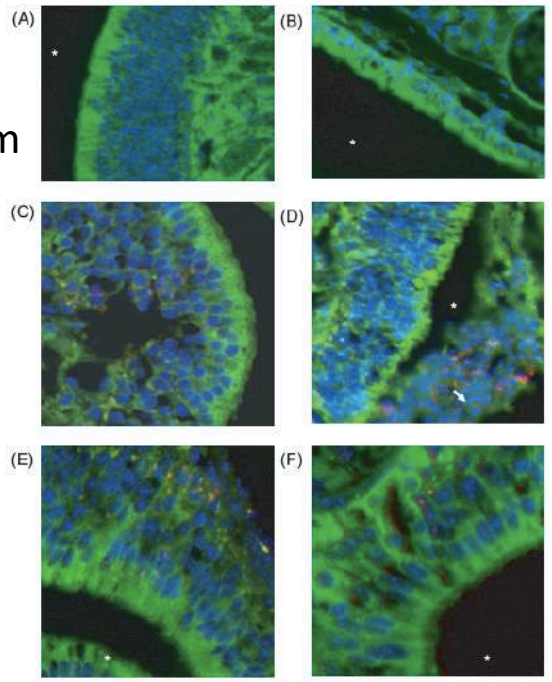
E. Samaridou, M.J. Alonso / Bioorganic & Medicinal Chemistry 26 (2018) 2888–2905

Which advantages?

(i) whole **particles are taken up**

(i) nanoparticles drug release





Olfactory Epithelium

Respiratory Epithelium

100 nm PS

100 nm Chitosan-PS

100 nm P80-PS

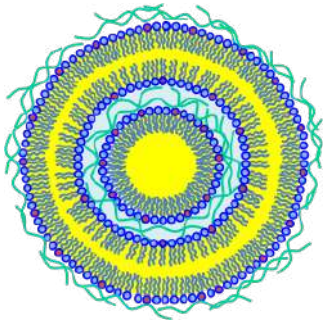
200 nm P80-PS

Mistry et al. J Drug Target (2009) 17(7): 543–552

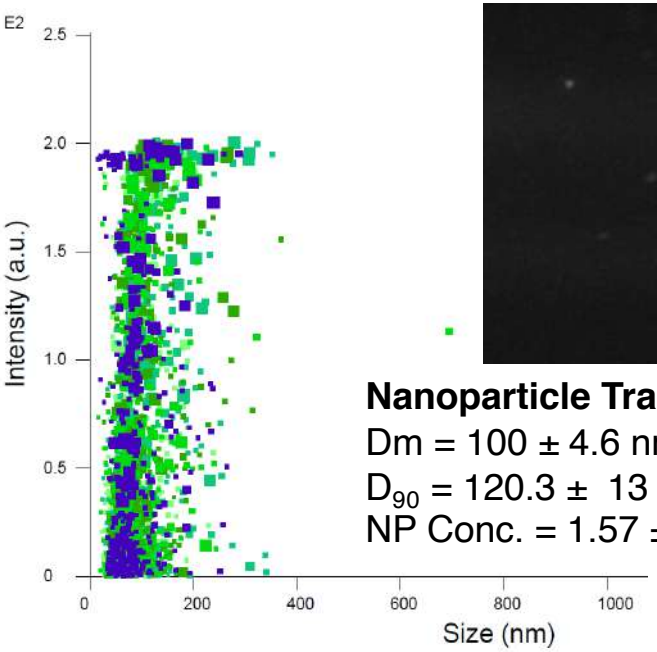
Particle size and surface properties of nanoparticles affect the uptake from the nasal epithelia

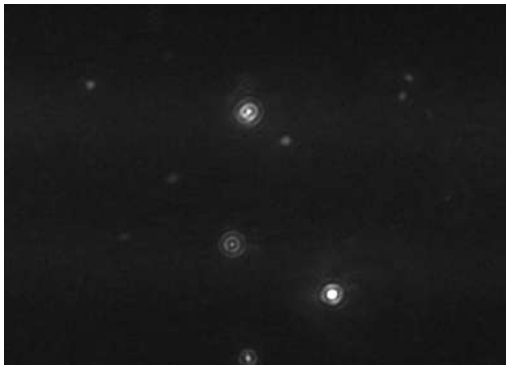
In any case, aspects related to the eventual damage to the tissue from nanoparticles uptake and accumulation have to be addressed

Simvastatin-loaded hybrid nanoparticles

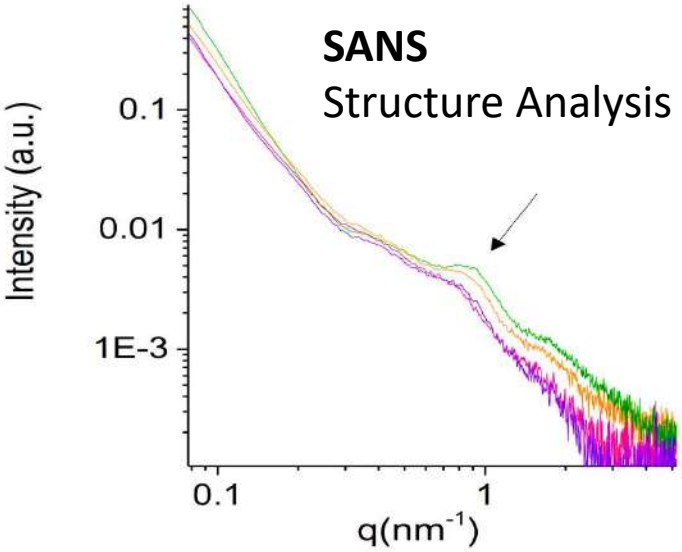


Oil core
Lecithin
Chitosan



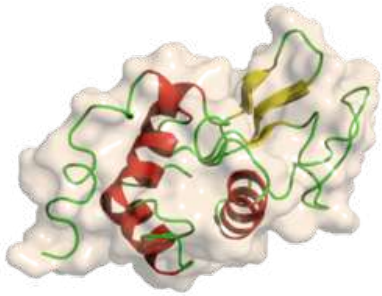


Nanoparticle Tracking Analysis
Dm = 100 ± 4.6 nm
D_{90} = 120.3 ± 13 nm
NP Conc. = 1.57 ± 0.20 10^{14} / ml



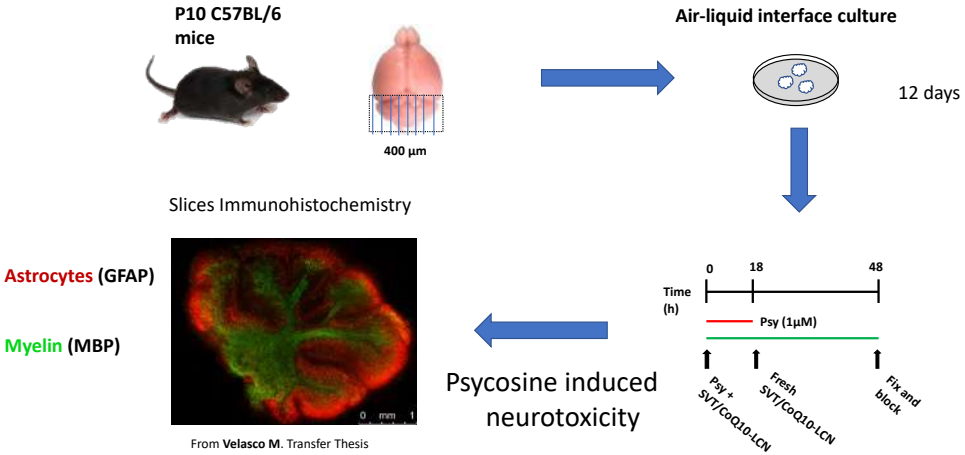
SANS
Structure Analysis

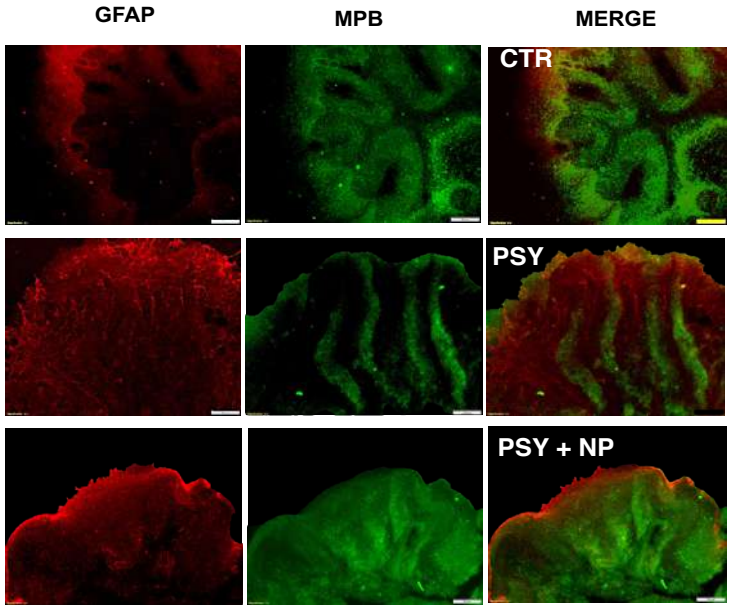
Simulated Nasal Fluid with
0.5% mucin and 0.5 mg/ml
lysozyme

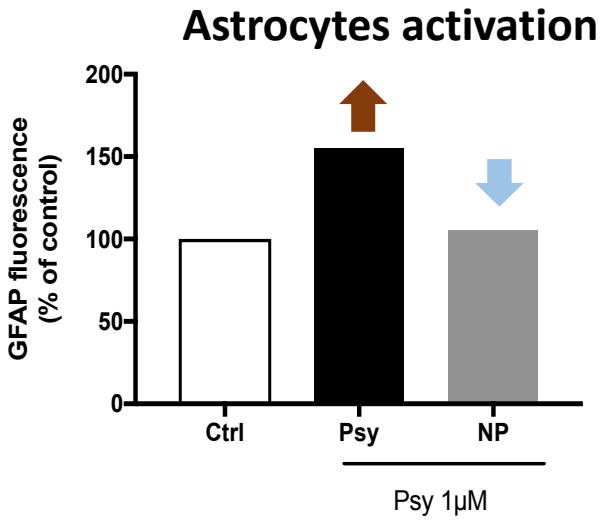


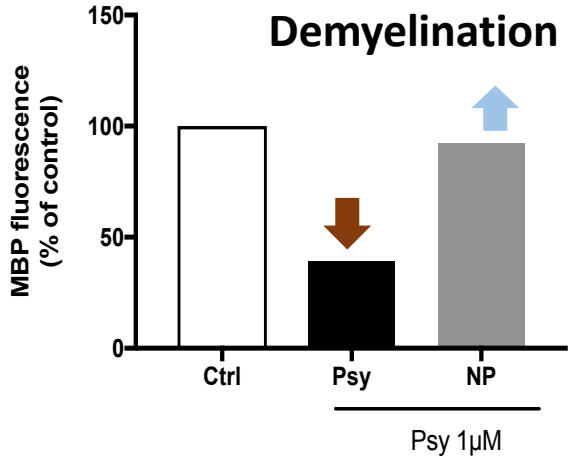
Model of neurodegenerative disease

Organotypic Cerebellar Slices Culture Immunocytochemistry









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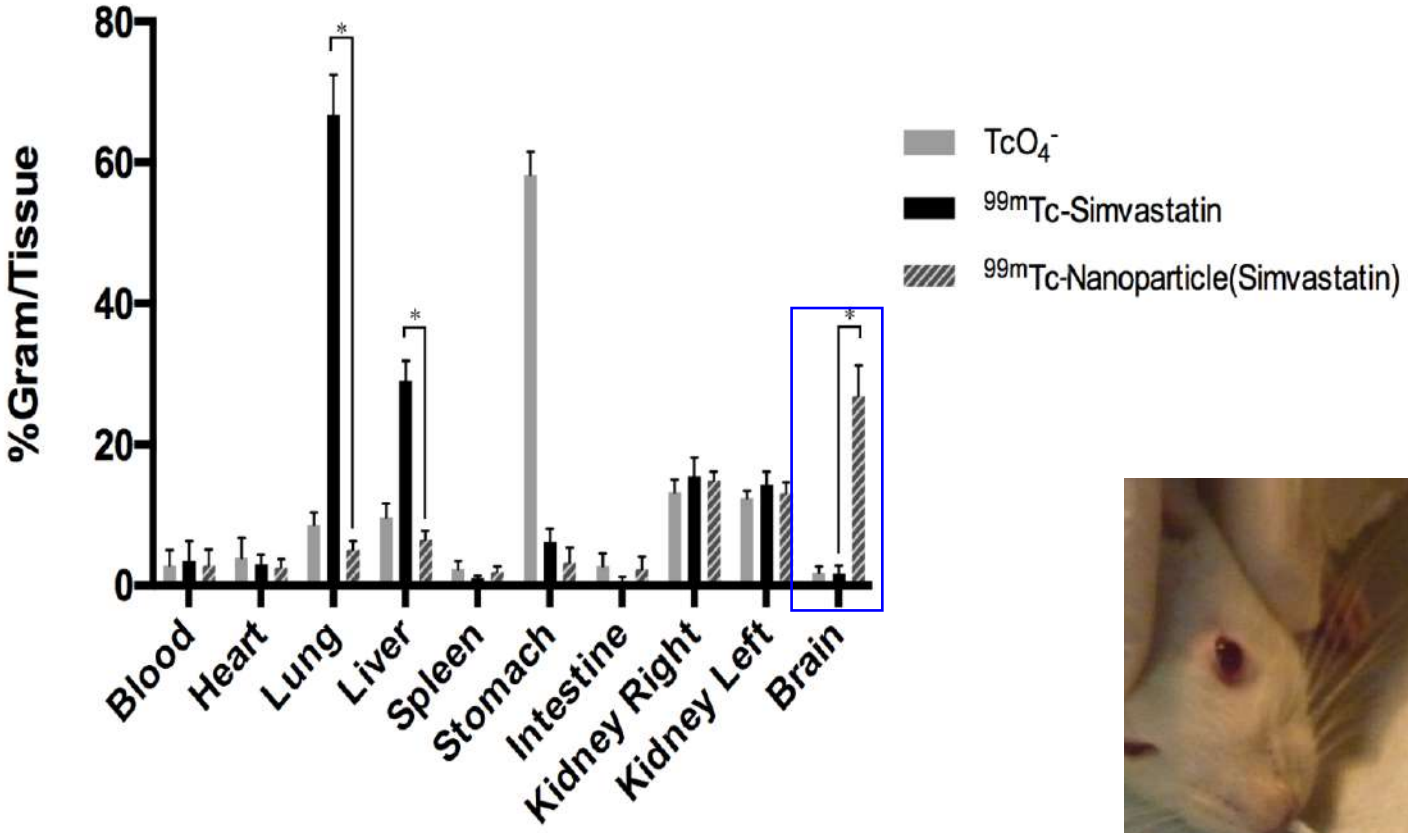
Gamma scintigraphy in rats

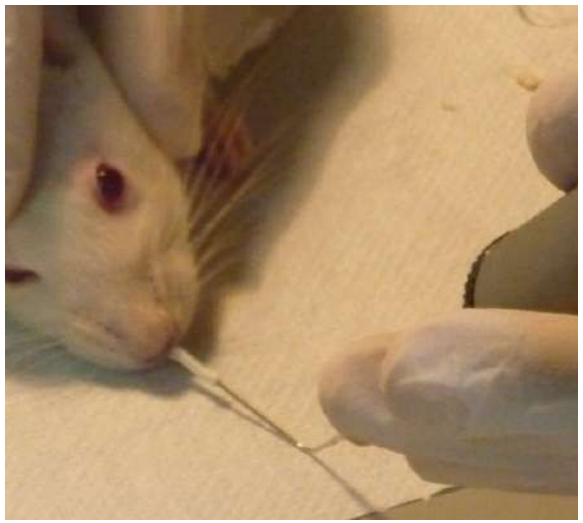
International Journal of Nanomedicine
Dovepress
ORIGINAL RESEARCH

The nasal delivery of nanoencapsulated statins – an approach for brain delivery

Clementino et al. International Journal of Nanomedicine 11 (2016) 6575–6590



Radioactivity biodistribution in Wistar rats 90 minutes after the nasal instillation of 20 uL (10 uL in each nostril) of 99mTc labeled simvastatin-loaded nanoparticles and simvastatin suspension expressed as percentage of the dose per gram of tissue.



Conclusions about nasal delivery

- Nanotechnology appears as a tool that could be included in **new medicines** for nasal delivery
- The administration presents a lower number of issues compared to pulmonary delivery
- **The real improvement provided by nanoparticles is being object of debate**
- The usefulness in vaccine delivery appears **demonstrated**
- Nose-to-brain appears the **holy grail of CNS therapy** but new molecules/nanoformulation/device combos have to be explored

Thank you!
Grazie! Merci! Danke!
谢谢
ありがとうございました

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