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SIMPOSIO AFI

RIMINI 7 • 8 • 9
GIUGNO 2023



Associazione Farmaceutici Industria
Società Scientifica



UNIVERSITÀ DI PARMA

Polveri per inalazione

Ruggero Bettini

Dipartimento di Scienze degli Alimenti e del Farmaco

Università degli Studi di Parma



Somministrazione inalatoria (di polveri)

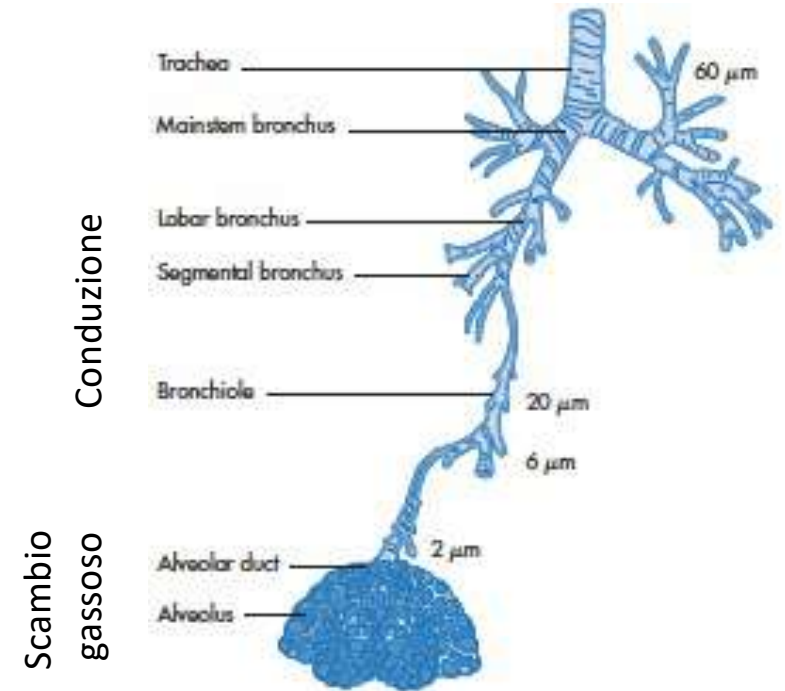
- Patologie delle vie aeree
 - Liberazione al sito d'azione
 - Rapido onset di azione
 - Riduzione del dosaggio vs per os
- Farmaci poco assorbiti per via orale o rapidamente metabolizzati (biologici)
- Minor attività metabolica vs orale



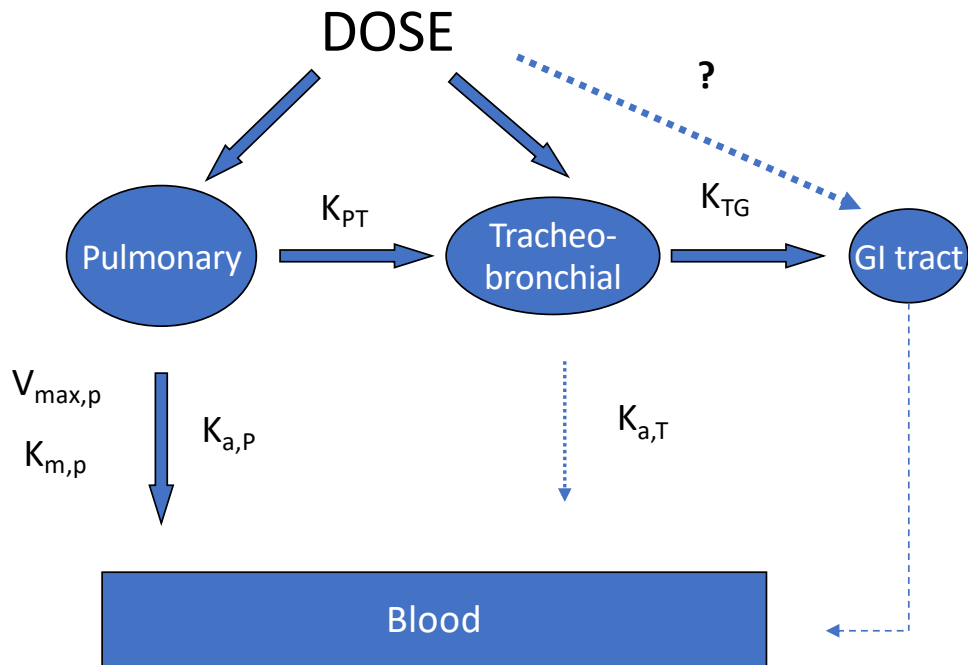
www.aptar.com

Albero respiratorio- non solo un tubo pieno d'aria

- Filtro aerodinamico efficiente
- Elevata immunocompetenza
 - Cellule con attività antigenica (macrofagi, cellule B e dendritiche)
 - Immunogenicità dei materiali (di superficie)
 - Dimensione (cattura macrofagica)
- Superficie 1 m² / kg body weight
- Ricca vascolarizzazione (scambio gassoso)
- Elevata permeabilità epiteliale



Biofarmaceutica delle polveri inalatorie



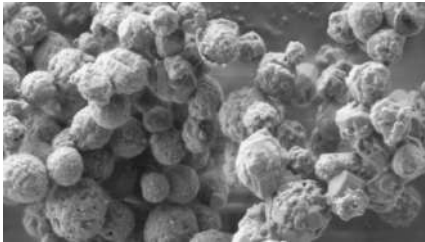
P. Byron RDD7, 2000, 41-48

BCS via Orale vs Inalatoria

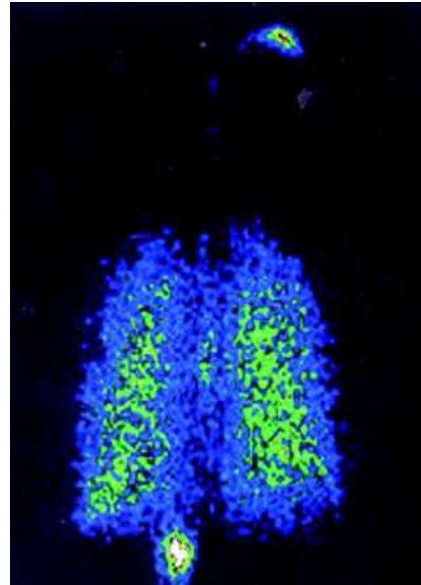
- Solubilità e velocità di dissoluzione
- Permeazione
- Stabilità nell'ambiente di rilascio
- Effetto di primo passaggio
- Tempo di transito/**deposizione**

Biodisponibilità nel/attraverso il polmone

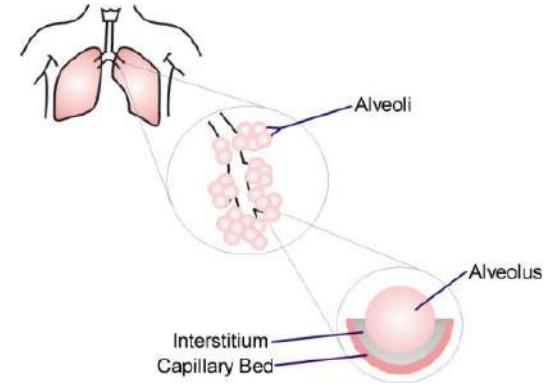
Tecnologia



Deposizione dell'aerosol



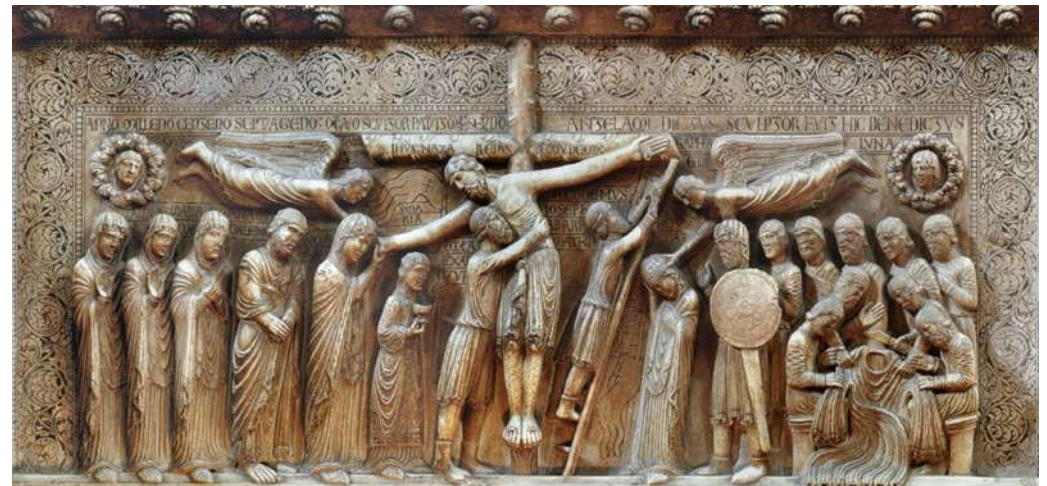
Assorbimento (dissoluzione/permeabilità)



$$\text{Biodisponibilità} = f_{\text{processo}} f_{\text{rilascio}} f_{\text{deposizione}} f_{\text{dissoluzione}} f_{\text{assorbimento}}$$

Fattori che influenzano la deposizione polmonare

- Velocità delle particelle
- Variabilità anatomica e stato patologico del paziente
(rimodellamento plastico)
- Manovre inspiratorie
- Diametro Aerodinamico



Benedetto Antelami, Deposizione dalla croce, 1178, Duomo di Parma

Dimensione particellare: meccanismi e zone di deposizione

Dimensione particellare

Impatto inerziale > 10 μm

Particelle con elevata velocità impattano contro parete piuttosto che seguire il flusso d'aria

$$\text{Probabilità di impatto} = \frac{V_t V \sin \theta}{g r}$$

Sedimentazione 0.5-3 μm

Segue la legge di Stokes

$$V_t = \frac{\rho g d^2}{18 \eta}$$

Diffusione < 0.5 μm

Spostamento secondo gradiente dal flusso d'aria alla parete

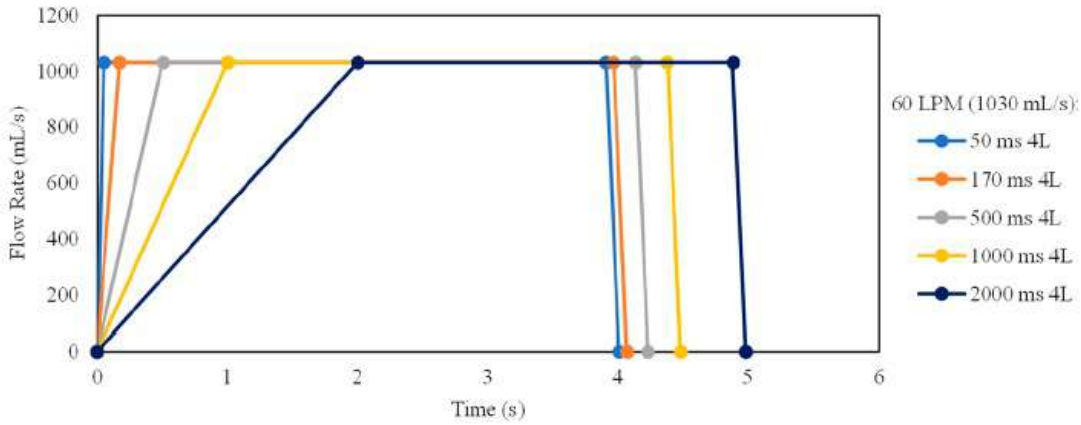
$$\text{Equazione di Stokes-Einsten } D = \frac{k_B T}{3\pi\eta d}$$

Upper airways

Middle airways

Alveolar region

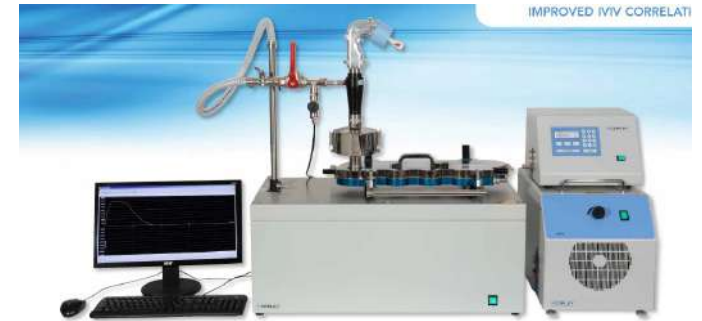
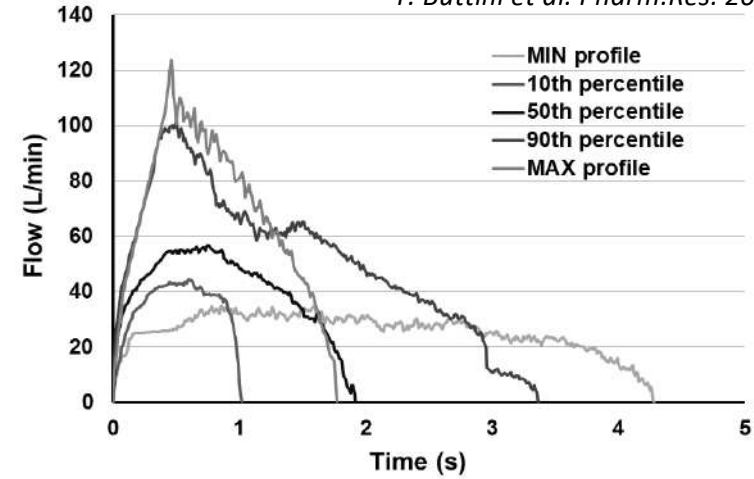
Profilo inspiratorio vero vs simulato



H.Gauani et al. Pharmaceutics 2023

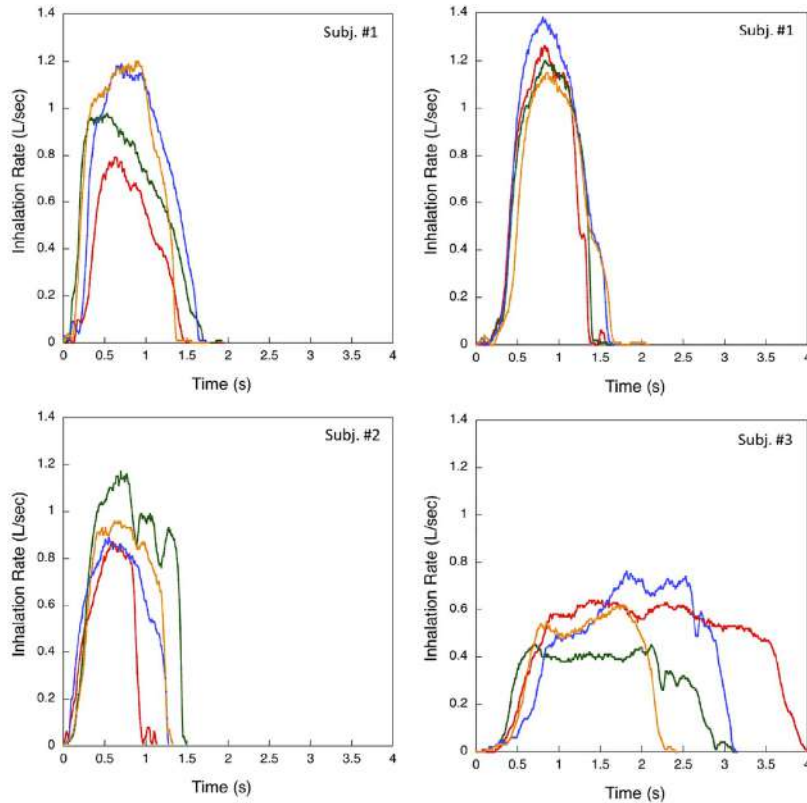
Inspiratory profiles of asthmatic patients through NEXTHaler®

F. Buttini et al. Pharm.Res. 2016



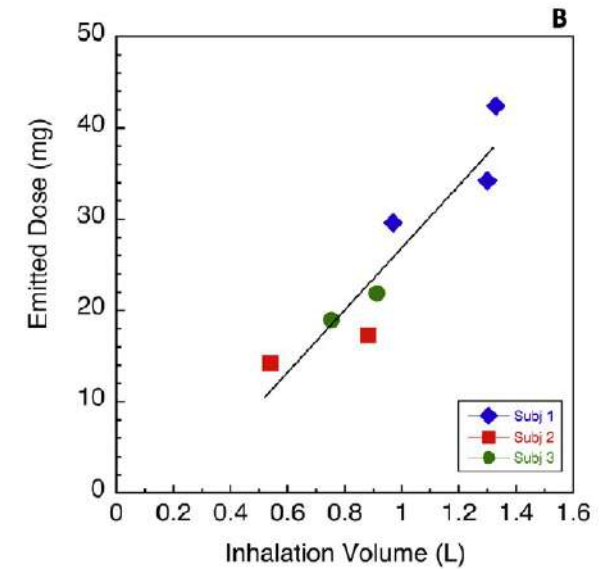
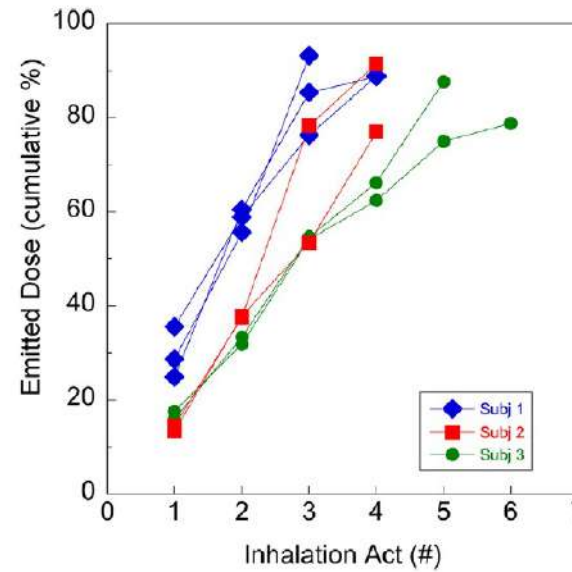
IVVC System for DPIs with Alberta Idealised Throat, Mixing Inlet, NGI and Breathing Simulator BRS 3000

Manovre inspiratorie



Dose administration maneuvers and patient care in tobramycin dry powder inhalation therapy

Francesca Buttini^{a,*}, Anna Giulia Balducci^{a,1}, Gaia Colombo^b, Fabio Sonvico^a,
Serena Montanari^{a,2}, Giovanna Pisi^c, Alessandra Rossi^a, Paolo Colombo^{a,d}, Ruggero Bettini^a



Proprietà aerodinamiche di una polvere

$$d_{ae} = d_v \sqrt{\frac{\rho}{\chi \rho_0}} \quad \text{particelle} \geq 0.5 \mu\text{m}$$

$\chi = \frac{\text{Resistenza alla caduta in aria della particella}}{\text{Resistenza alla caduta in aria della sfera di ugual volume}}$: fattore di forma (1 per la sfera)

ρ = densità **apparente della particella**

- Diametro
- Densità
- Morfologia
- Adesione/coesione
- Caratteristiche di superficie
- Solid-state chemistry (della superficie)

Miscele adesive

Ingegneria delle particelle

Miscele adesive e stato solido (Lattosio)

International Journal of Pharmaceutics 505 (2016) 383–393



Contents lists available at ScienceDirect
International Journal of Pharmaceutics

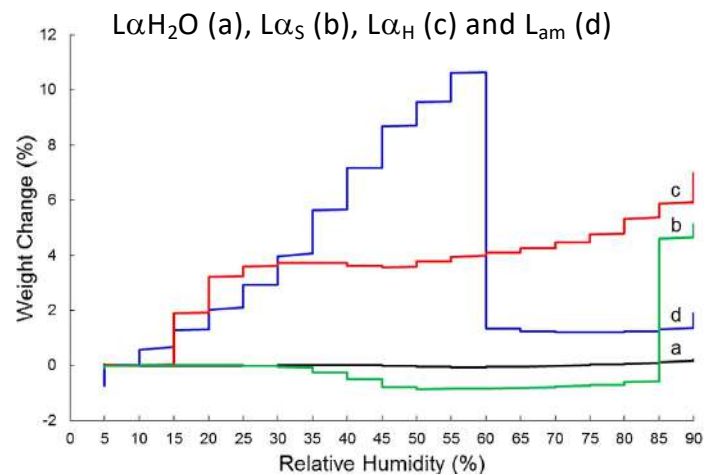
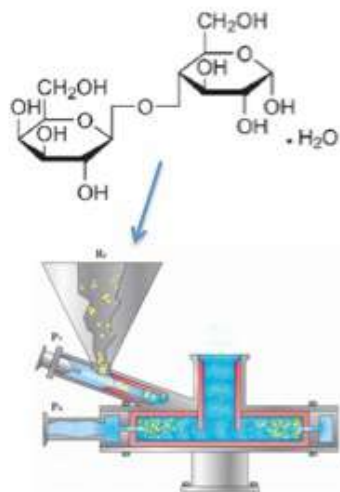
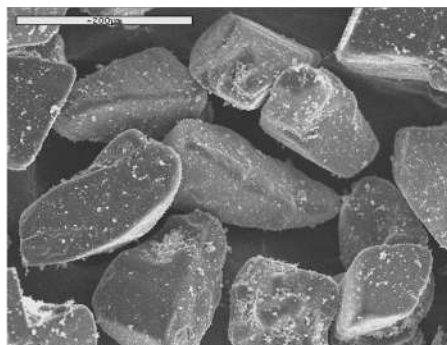
journal homepage: www.elsevier.com/locate/ijpharm



Quantitative determination of micronization-induced changes in the solid state of lactose

A. Della Bella^a, M. Müller^b, L. Soldati^b, L. Elviri^a, R. Bettini^{a,*}

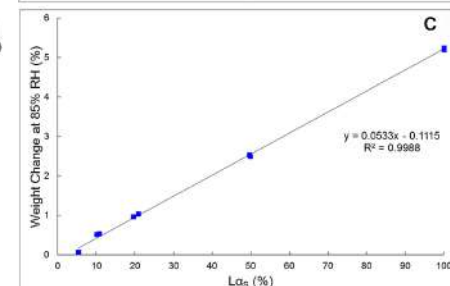
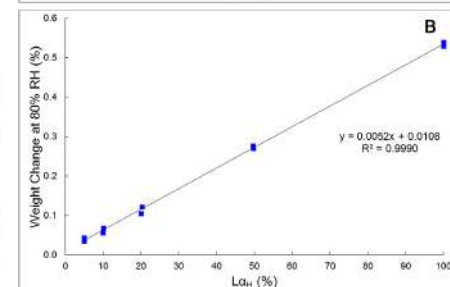
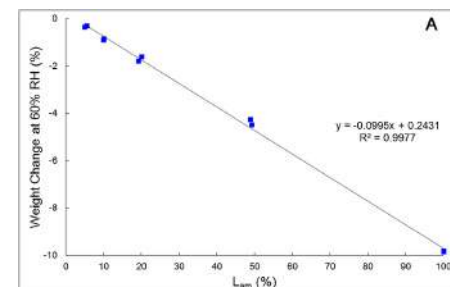
^aDepartment of Pharmacy, University of Parma, Parma, Italy
^bMicro-Sphere SA, Ponte Cremenega, Switzerland



$$y_{RH} = y_{RH}^{am} + y_{RH}^H + y_{RH}^S$$

↓
↓
↓

% amorphous % anhydrous α metastable % anhydrous α stable



LαH₂O = 74.8 %
 Lα_H = 23.0 %
 L_{am} = 2.2 %

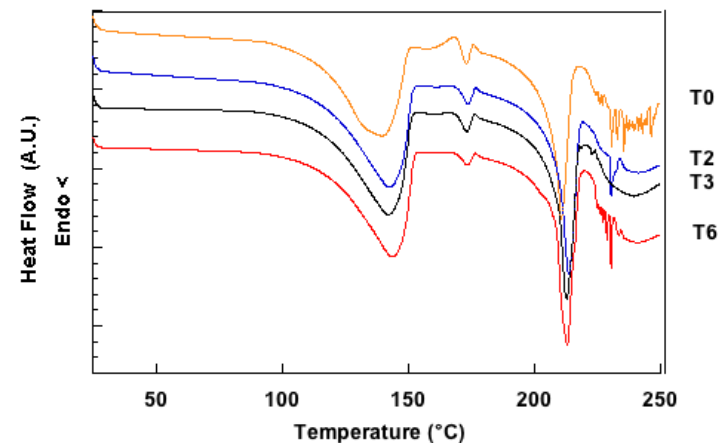
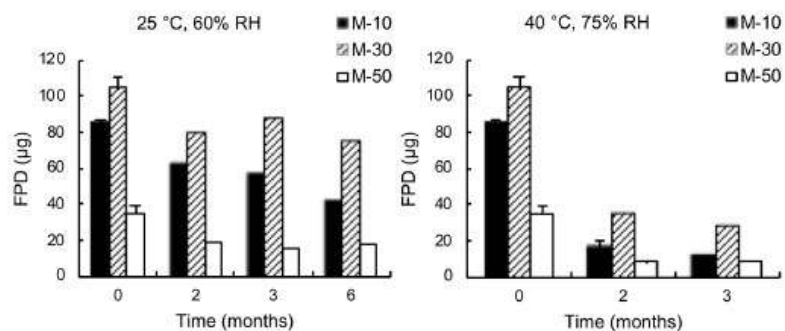
Article

Effect of Lactose Pseudopolymorphic Transition on the Aerosolization Performance of Drug/Carrier Mixtures

Andrea Della Bella ^{1,†}, Michele Müller ², Andrea Danani ³, Luciano Soldati ² and Ruggero Bettini ^{1,*}

Pharmaceutics **2019**, *11*, 576; doi:10.3390/pharmaceutics11110576

Mixture	ED (µg)	FPD (µg)	FPF (%)
M-SS	177.1 ± 3.4	26.8 ± 1.9	15.1 ± 0.8
M-10	178.7 ± 4.6	84.3 ± 2.6	47.2 ± 0.7
M-30	180.9 ± 9.7	103.4 ± 7.3	57.2 ± 2.5
M-50	102.8 ± 5.5	34.9 ± 4.6	33.9 ± 2.8



Mixture	ED (µg)	FPD (µg)	FPF (%)
H-SS	182.7 ± 11.6	76.2 ± 3.6	41.7 ± 1.9
S-SS	173.0 ± 2.7	54.4 ± 2.2	31.5 ± 0.9

Mixture	ED (µg)	FPD (µg)	FPF (%)
M-BUD	154.1 ± 4.3	27.9 ± 0.1	18.1 ± 0.5
S-BUD	149.6 ± 4.0	17.9 ± 1.3	12.0 ± 0.5

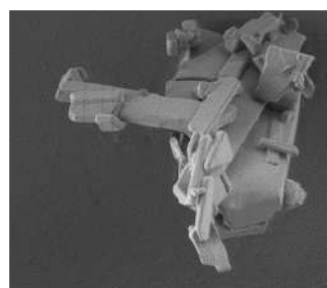
Miscele adesive (Mannitolo)

Article

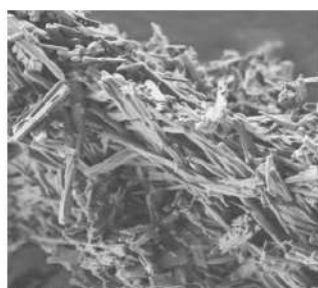
Mannitol Polymorphs as Carrier in DPIs Formulations: Isolation Characterization and Performance

Ayça Altay Benetti ^{1,2,†}, Annalisa Bianchera ^{1,4}, Francesca Buttini ¹, Laura Bertocchi ¹ and Ruggero Bettini ^{1,2,*}

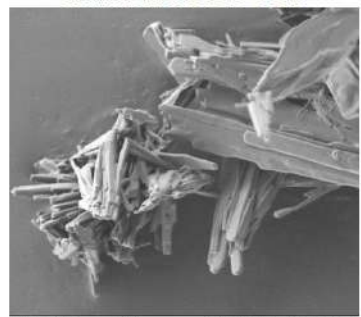
Pharmaceutics 2021, 13, 1113. <https://doi.org/10.3390/pharmaceutics13081113>



δ mannitol with 1% of PVP K30



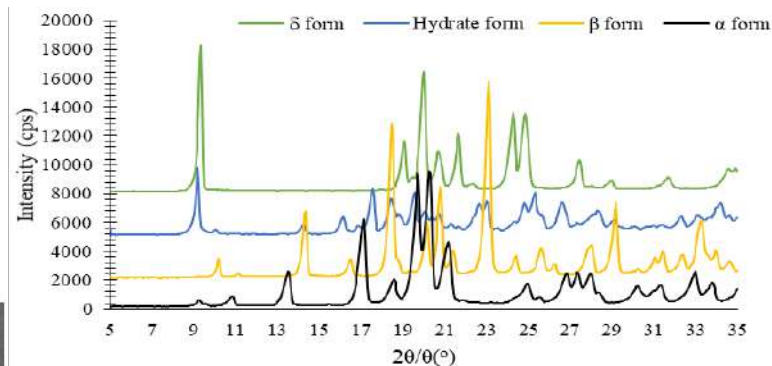
α mannitol with 2% of FVA



Mannitol hemi hydrate with 1% of CaCl₂



β mannitol



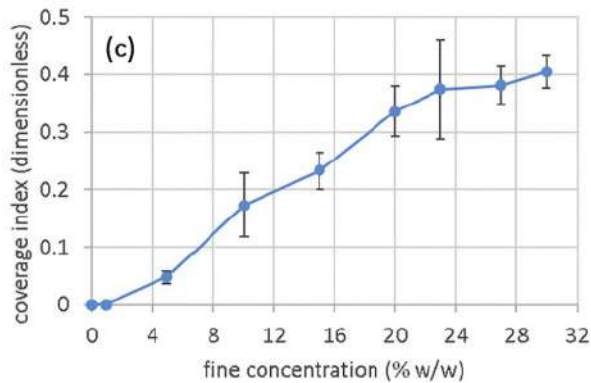
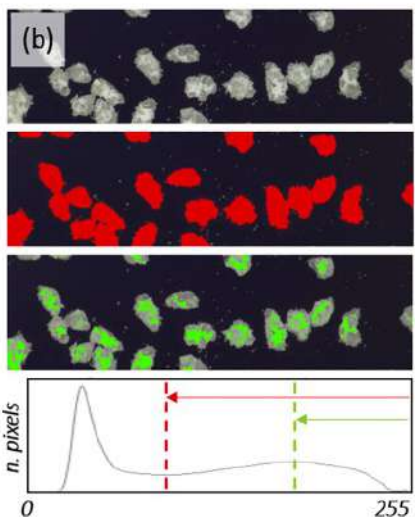
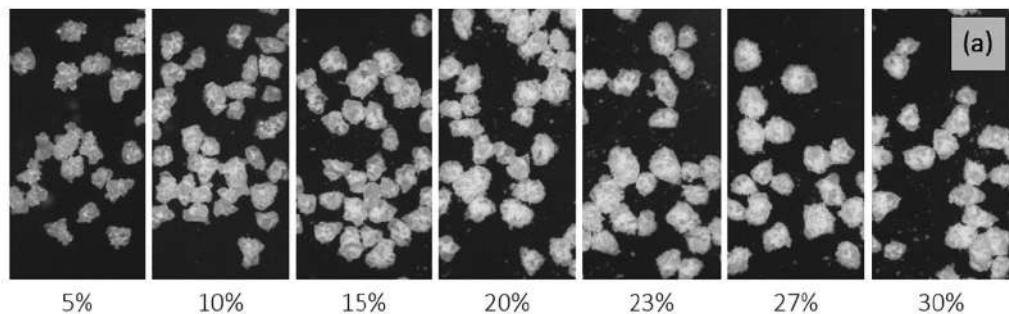
Carrier	Emitted Dose (%)	FPD (μg)	FPF (%)	MMAD (μm)
MM50	80.1 ± 12.7	10.0 ± 2.5	8.4 ± 1.7	3.6 ± 0.1
δ form	90.4 ± 18.5	16.0 ± 1.6	9.3 ± 2.4	4.1 ± 0.0
β form	97.6 ± 3.2	29.8 ± 1.9	13.9 ± 0.7	4.7 ± 0.5
α form	81.7 ± 9.0	21.8 ± 4.8	13.4 ± 4.3	4.1 ± 0.1

SS

BUD

Carrier	Emitted Dose (%)	FPD (μg)	FPF (%)	MMAD (μm)
MM50	87.3 ± 2.0	36.2 ± 0.2	26.6 ± 1.3	1.6 ± 0.2
δ form	78.4 ± 3.5	26.3 ± 8.2	19.6 ± 3.2	2.9 ± 0.4
β form	71.3 ± 7.6	104.7 ± 7.2	58.1 ± 3.9	1.8 ± 0.1
α form	76.5 ± 8.6	84.0 ± 14.6	53.5 ± 5.1	1.8 ± 0.1

Drug loading e dose



Contents lists available at ScienceDirect

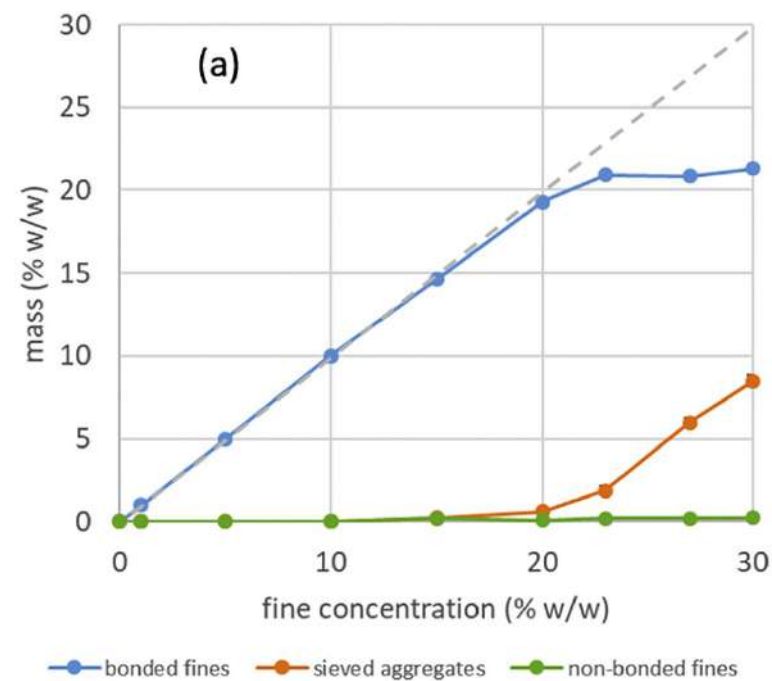
Powder Technology

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

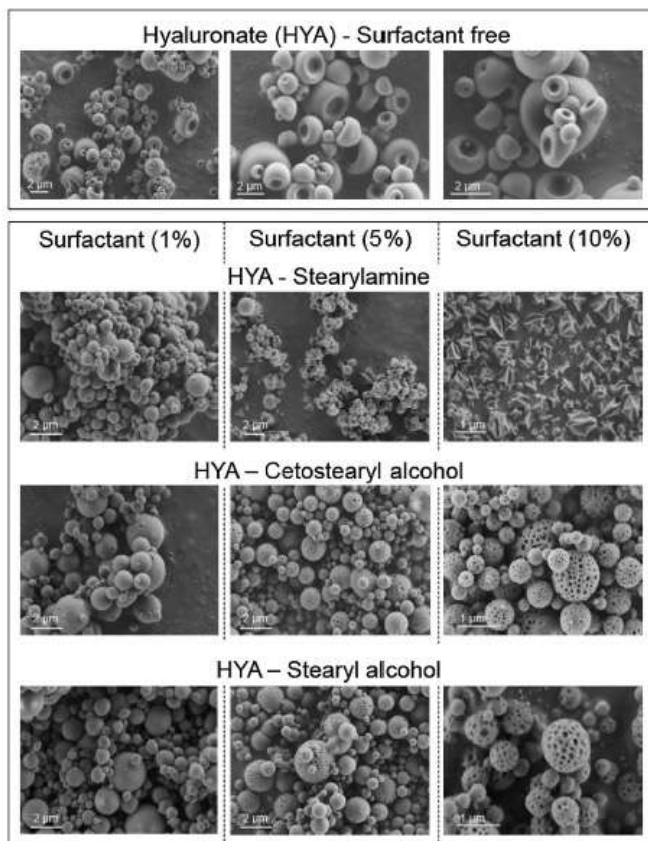


Quantifying the loading capacity of a carrier-based DPI formulation and its dependence on the blending process

Andrea Benassi^{a,*}, Ilaria Perazzi^b, Roberto Bosi^a, Ciro Cottini^a, Ruggero Bettini^b



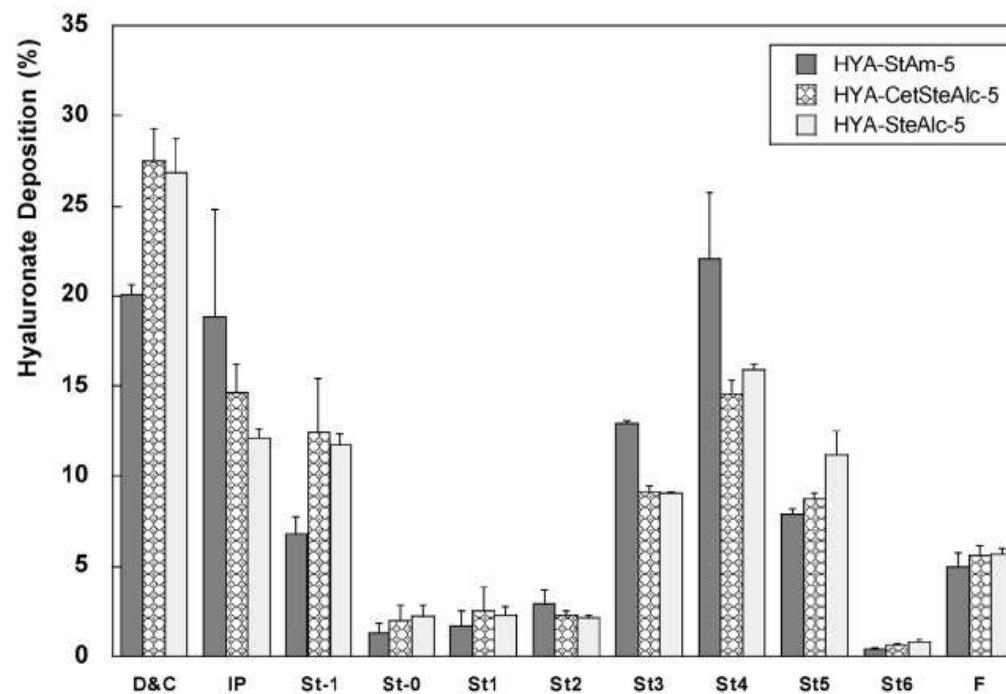
Particle engineering



Engineered sodium hyaluronate respirable dry powders for pulmonary drug delivery



Francesco Martinelli^a, Anna Giulia Balducci^{b,1}, Abhinav Kumar^c, Fabio Sonvico^a, Ben Forbes^c, Ruggero Bettini^a, Francesca Buttini^{a,c,*}



Delivery polmonare e malattie infettive

Infezioni polmonari

- Elevata concentrazione locale < frequenza di dosaggio
- Terapia non invasiva
- Ridotta distribuzione sistemica
- Targeting macrofagi alveolari

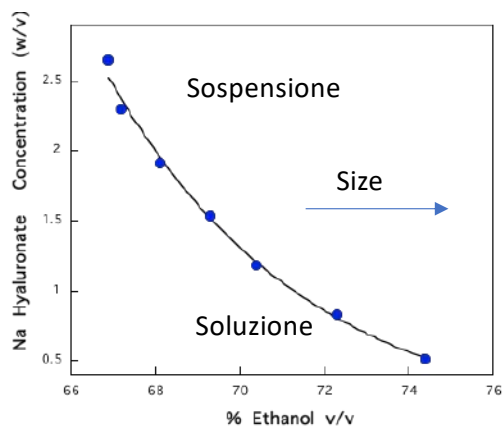
Vaccinazione

- Antigene/vaccino in grado di suscitare risposte immunitarie sia locali che sistemiche
- Particelle ingegnerizzate contenenti l'antigene un bulking agent e un immuno-adiuvante
- Caratteristiche anatomiche e fisiologiche favorevoli
- Nessuna necessità di catena del freddo per lo stoccaggio e il trasporto
- Somministrazione più semplice

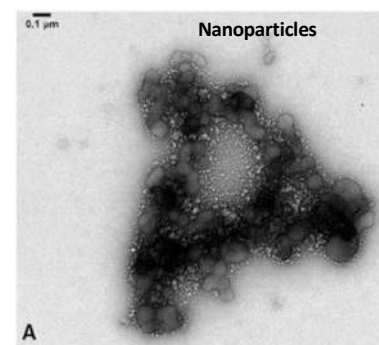
AMs target : Size e materiale

- Nanoparticles 200-500 nm
- HA → AM CD44 receptors
- Relatively low MW HA to improve inflammatory and immune response → AM capture
- Bacterial Efflux pump inhibitor

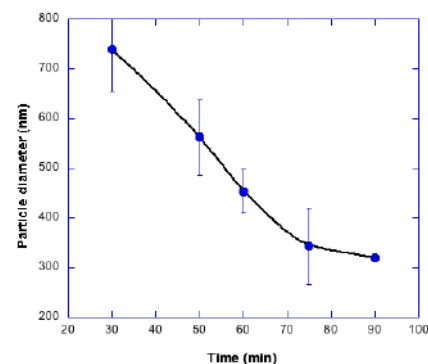
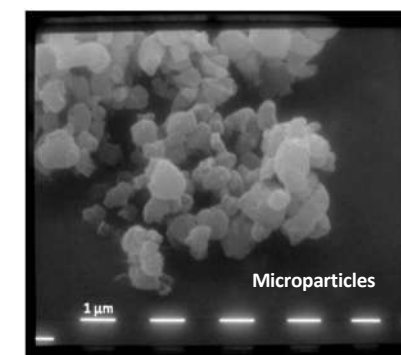
Nanoparticelle di HA per antisolvente (etanolo)



HYA LMW	35%
Isoniazide	18%
Rifampicina	35%
Verapamil HCl	12%



S.D.

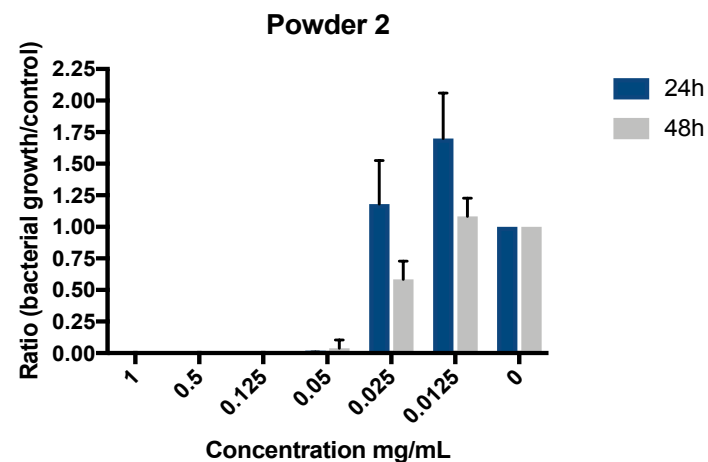
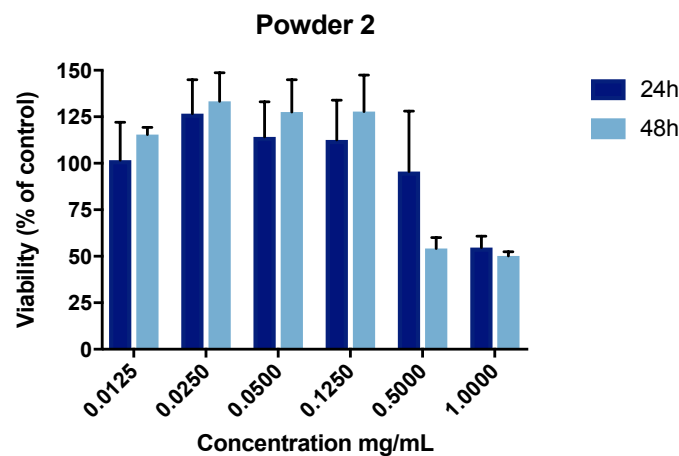
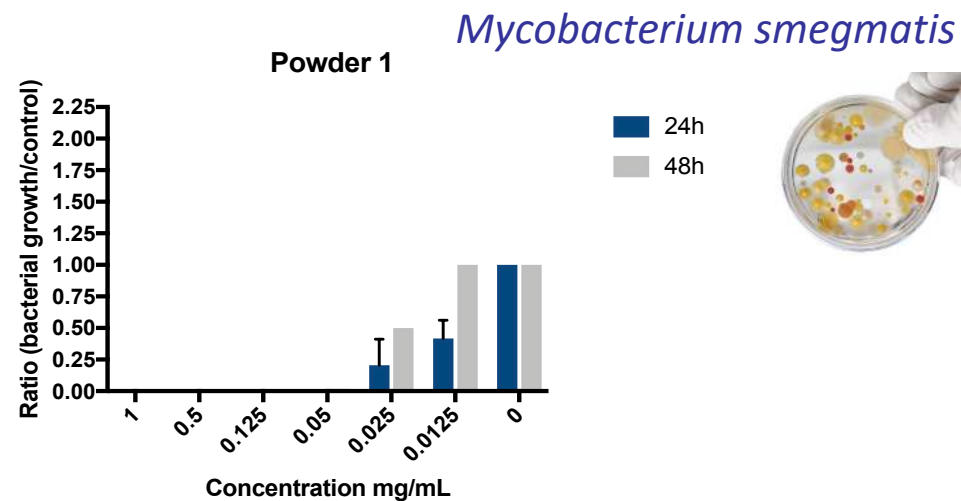
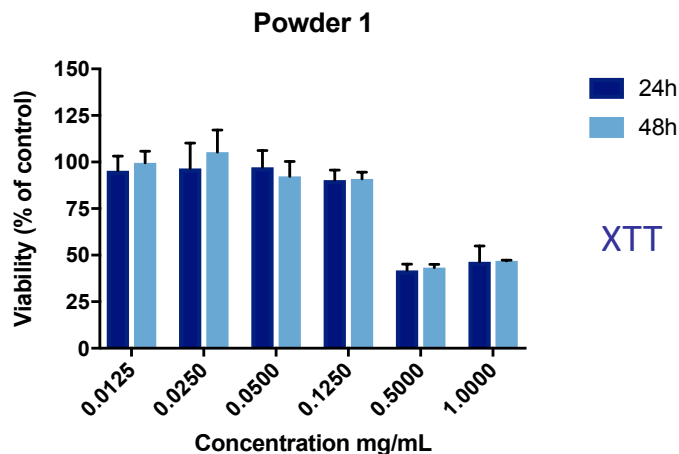


	EF %	FPF %
Isoniazide	50.73± 5.92	90.62± 8.15
Rifampicina	48.96± 6.07	93.55± 5.69
Verapamil	51.90± 5.35	93.89± 5.72

HYA LMW
Rifampicin
Isoniazid
Verapamil

HYA LMW
Rifampicin
Isoniazid

Citotossicità e attività battericida in vitro

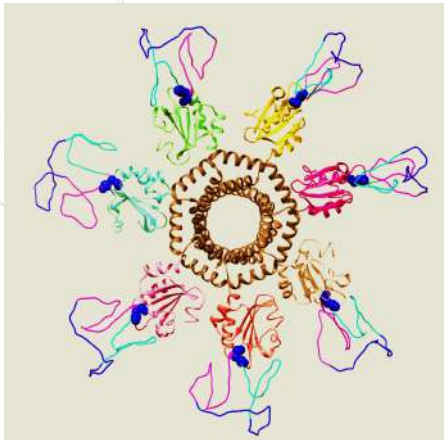
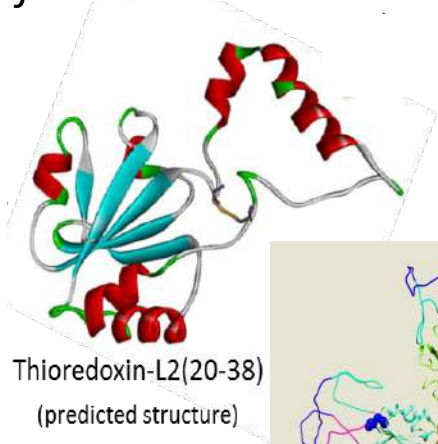


Approccio ai vaccini

Engineered protein/peptide antigens

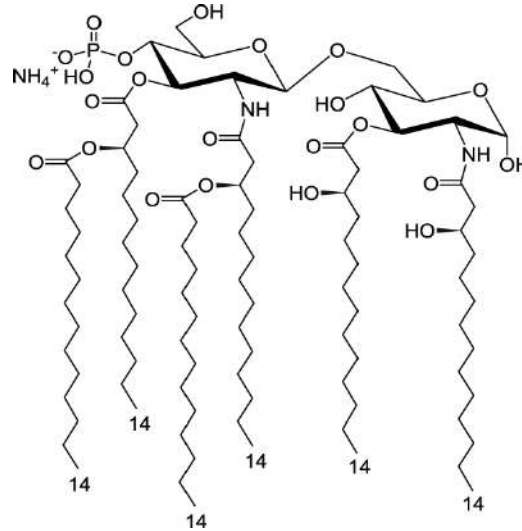
PfTrx-HPV-L2

PfTrx-HPV-L2-IMX



Immune-adjuvant

Mono-Phosphoryl Lipid A a Toll-Like Receptor (TLR) 4 agonist



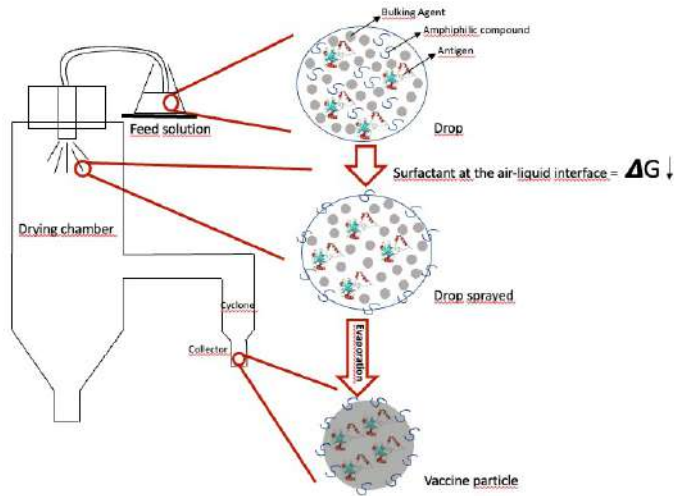
A respirable HPV-L2 dry-powder vaccine with GLA as amphiphilic lubricant and immune-adjuvant

Irene Rossi^{a,*,1}, Gloria Spagnoli^{b,c,1}, Francesca Buttini^{a,c}, Fabio Sonvico^{a,c}, Fabio Stellari^d, Davide Cavazzini^e, Quixin Chen^f, Martin Müller^g, Angelo Bolchi^{b,c}, Simone Otronello^{a,c,*,2}, Ruggero Bettini^{a,c,3}

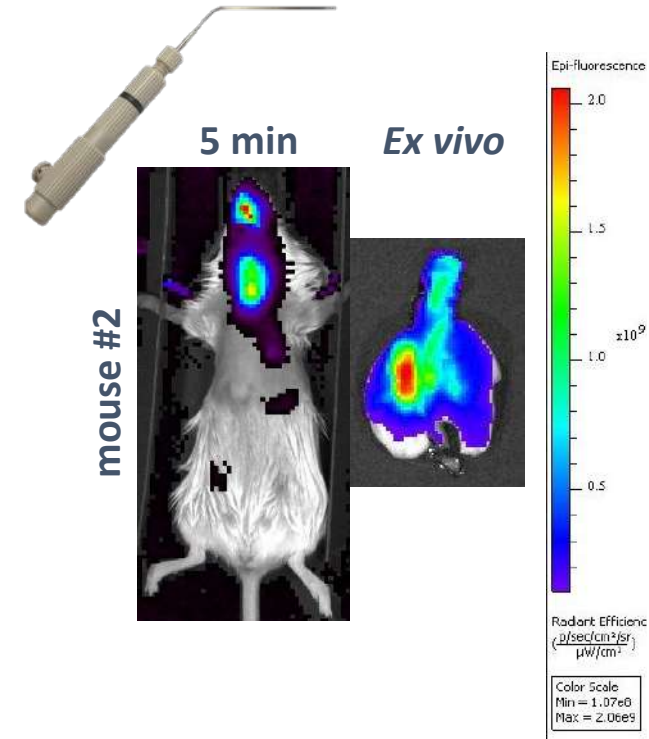
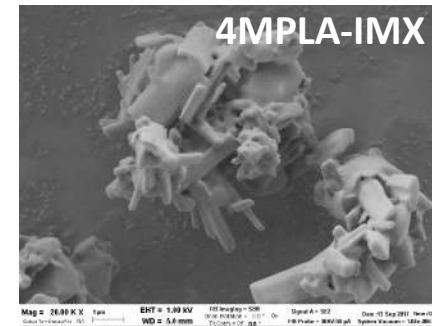
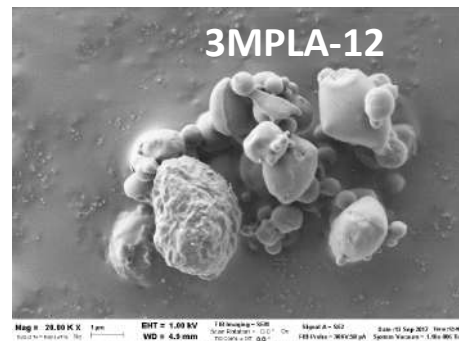
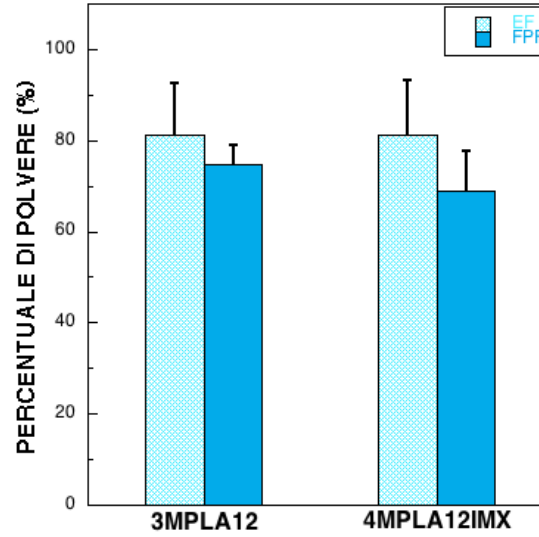
^a Department of Food and Drug Sciences, University of Parma, Parco Area delle Scienze Parma, Italy
^b Department of Chemistry, Life Sciences and Environmental Sustainability, Faculty of Parma, Parco Area delle Scienze Parma, Italy
^c Interdepartmental Center Biopharmaceutics, Faculty of Parma, Parco Area delle Scienze Parma, Italy
^d Chiesi Farmaceutici SpA, Largo Belli 11a, Parma, Italy
^e German Cancer Research Center, Im Neuenheimer Feld 280, Heidelberg, Germany

- TLR4: highly represented in the lung tissue
- human-use approved djuvants
- commercially available in both a preclinical-and clinical-grade

Formazione particelle per S.D.



Aerosolizzazione in vitro



Immunogenicità

Test groups (intra-tracheal administration):

1T (13 animals): PfTrx HPV16 L2(20-38)₃ (DPI-MPLA => IP)

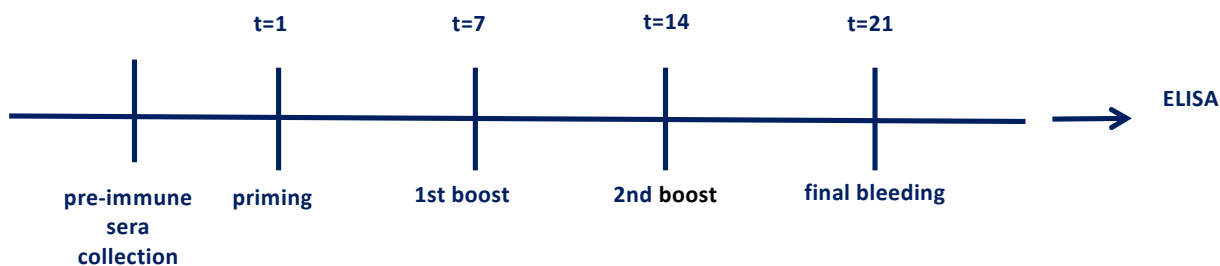
2T (13 animals): PfTrx HPV16 L2(20-38)₃-OVX313 (DPI-MPLA => IP)

Control groups (sub-cutaneous administration):

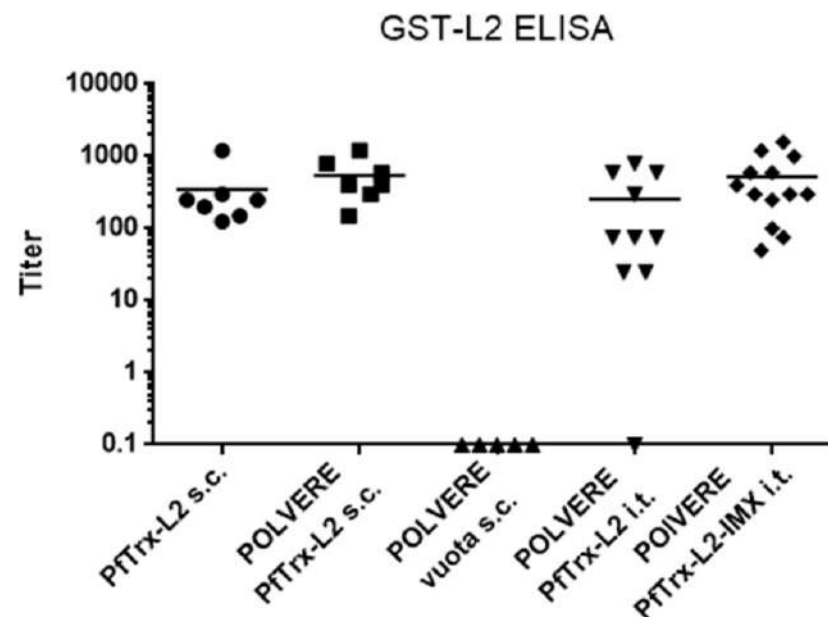
3S (7 animals): PfTrx HPV16 L2(20-38)₃ + Alum (50µg)+ MPLA (10µg)

4S (7 animals): PfTrx HPV16 L2(20-38)₃ DPI-MPLA dissolved in PBS

5S (5 animals): Antigen-free DPI-MPLA powder dissolved in PBS



Balb/c mice (6-8 weeks)
5 Groups



Conclusioni

- Un complesso mix di aspetti ingegneristici, anatomo- e fisiopatologici, biofarmaceutici.
- Una sfida non banale
 - il paziente è una variabile difficile da controllare
- Grande spazi di intervento e innovazione

