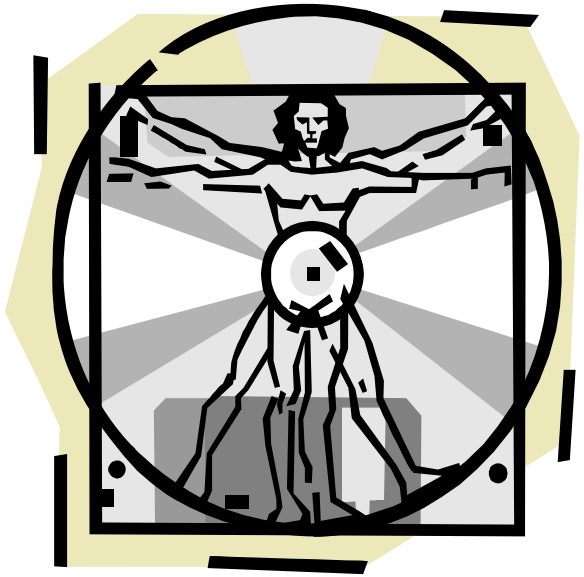
Nanoparticle Delivery

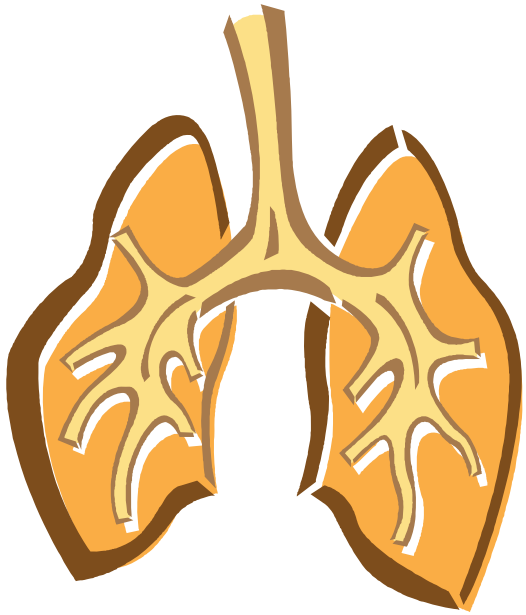
ROUTES OF ADMINISTRATION

- Oral
- Intravenous
- Nasal
- Ophthalmic
- Rectal/Vaginal
- Trans Dermal
- Pulmonary



Local delivery vs. systemic

- Aerosol route of administration
  - Local effect (reduced systemic site effects)
  - Systemic (prevent Gi-tract or invasive administration)
- Aerosol target
  - Treatment Organ
  - Absorption Organ



Lungs as Treatment organ

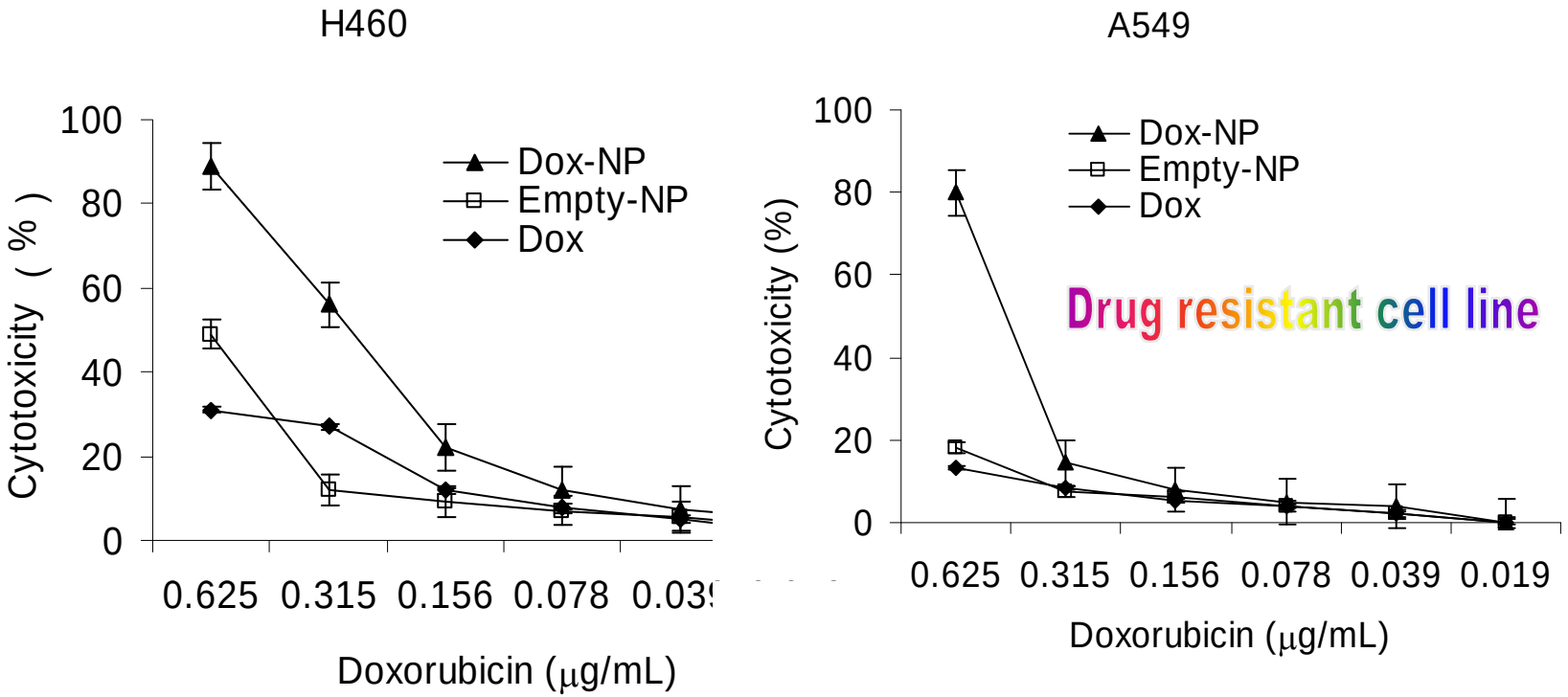
- Asthma (Hardy and Chadwick, 2000)
- Cystic fibrosis (Garcia-Contreras and Hickey, 2002)
- Lung cancer (Rao et al., 2003)
- Tuberculosis (Pandey and Khuller, 2005; Zahoor et al., 2005)

NANOPARTICLES in Cancer Treatment

- Nanoparticles are drug vehicles able to accumulate in tumor tissues or cells, while protecting the drug from premature inactivation during the transport…
- Promising drug carriers…

Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Advanced Drug Delivery Reviews 2002;54(5):631-651.

Biological activity of the Nanoparticles



Shirzad Azarmi, Xia Tao, Hua Chen, Zhaolin Wang, Warren. H. Finlay, Raimar Löbenberg, Wilson. H. Roa; Formulation and Cytotoxicity of Doxorubicin Nanoparticles Carried by Dry Powder Aerosol Particles
Int J Pharm 2006

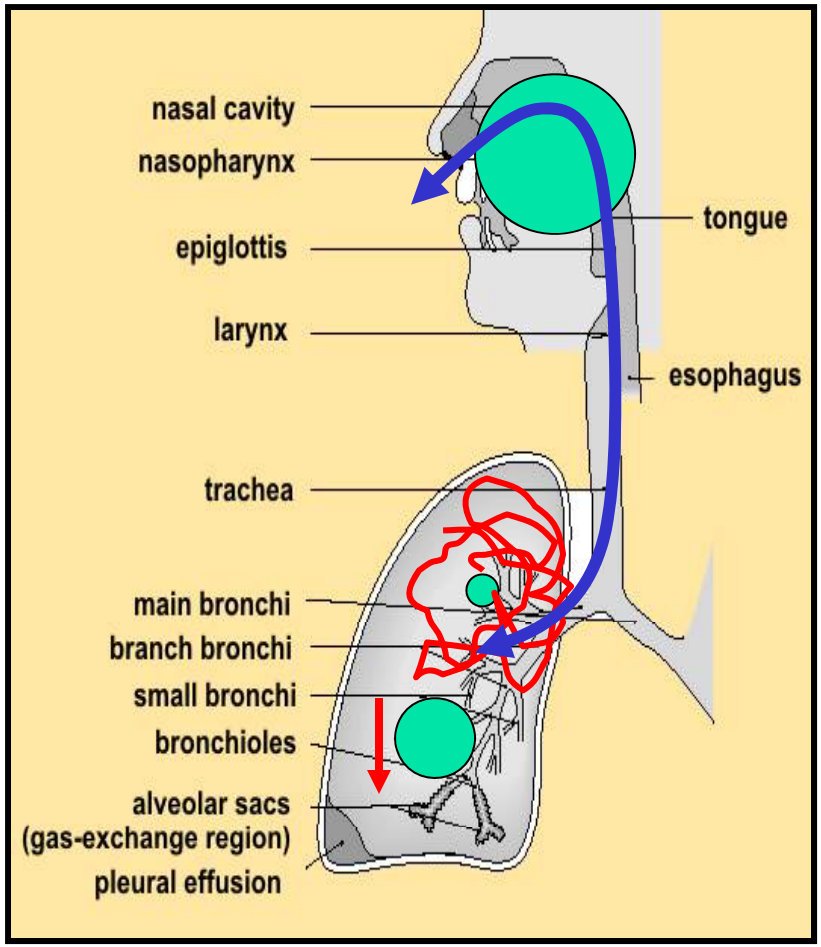
DEPOSITION MECHANISM

General air flow through the respiratory tract

Large particles will Impact in the upper respiratory tract (>5 um)

Small particles will have no deposition because of Brownian diffusion (<1 um)

Sedimentation in the alveolar region (1-5 um)



www.becomehealthynow.com

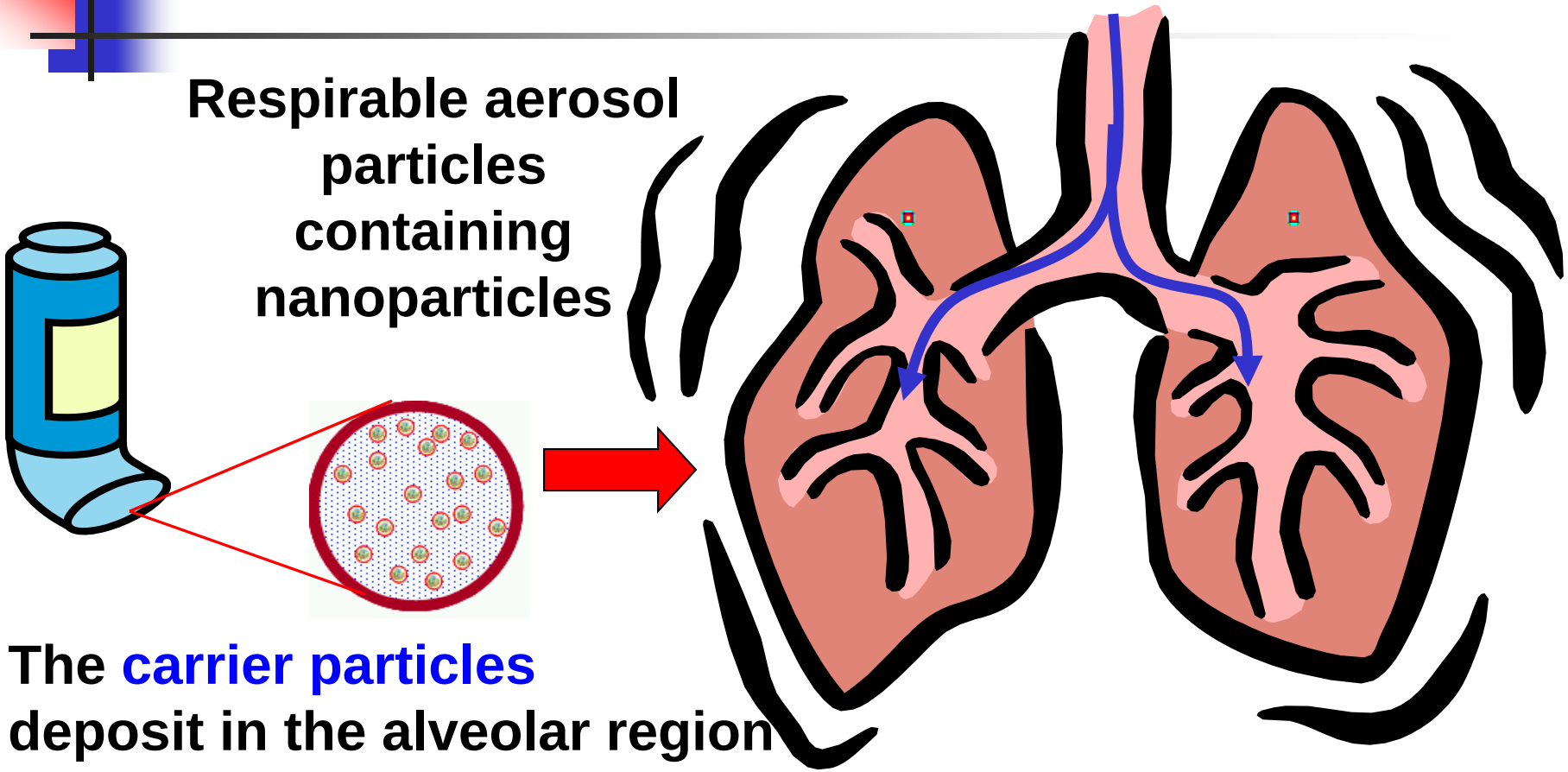
Pulmonary Nanoparticle delivery

- Solid colloidal particles < 1000 nm
- But how can you deliver them to the lungs?
- Suitable size is between 1000 and 5000 nm?

We had to go back to the lab
and do some experiments

THE CONCEPT

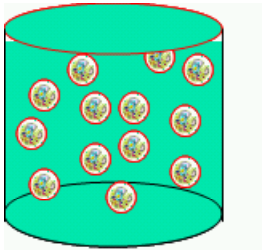
Respirable aerosol particles containing nanoparticles



The carrier particles deposit in the alveolar region
The carrier dissolves
The nanoparticles are released

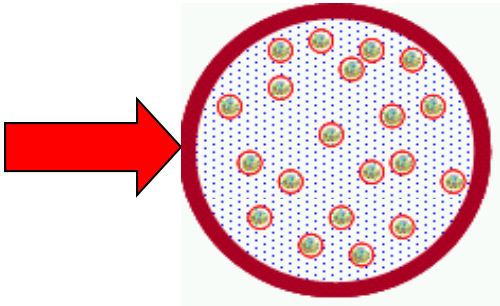
THE CONCEPT

Suspension of lactose and nanoparticles

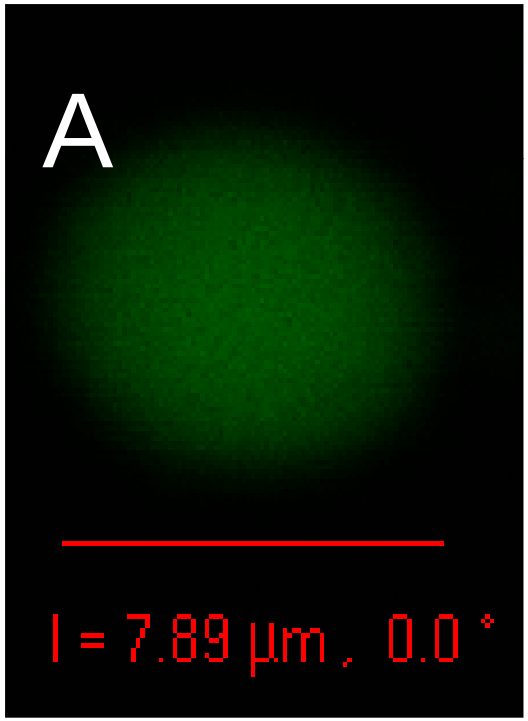


Spray drying

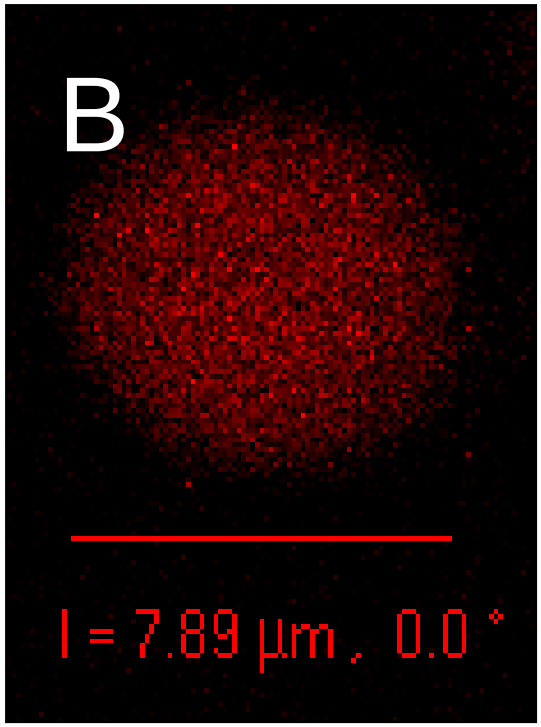
Respirable lactose aerosol particles containing nanoparticles



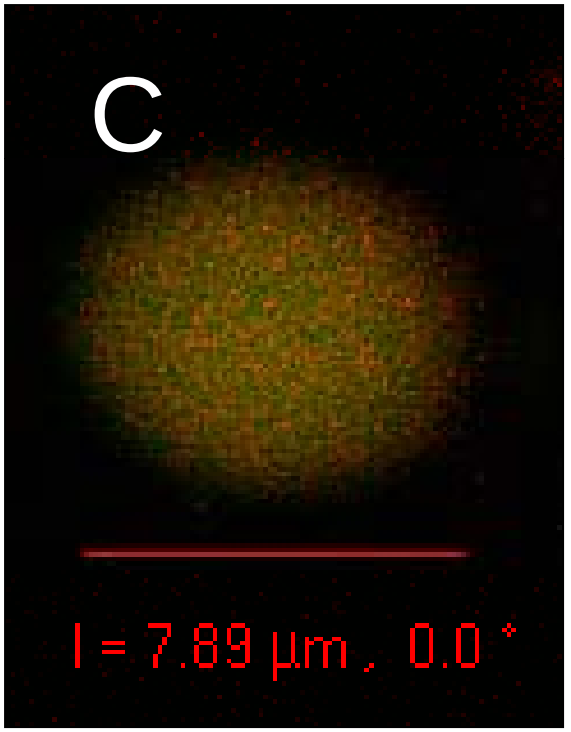
RESULTS



CARRIER PARTICLES



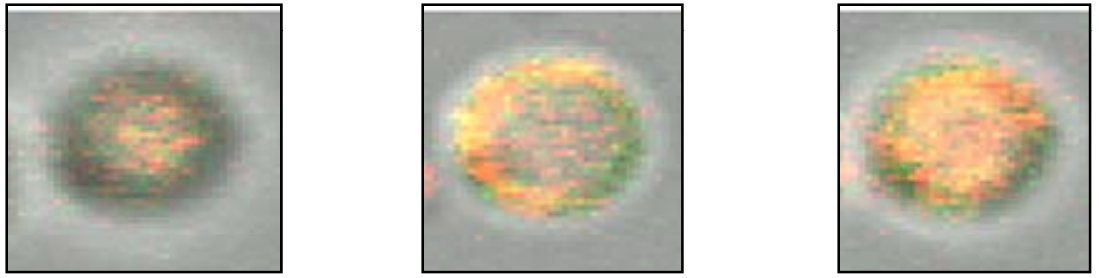
NANOPARTICLES



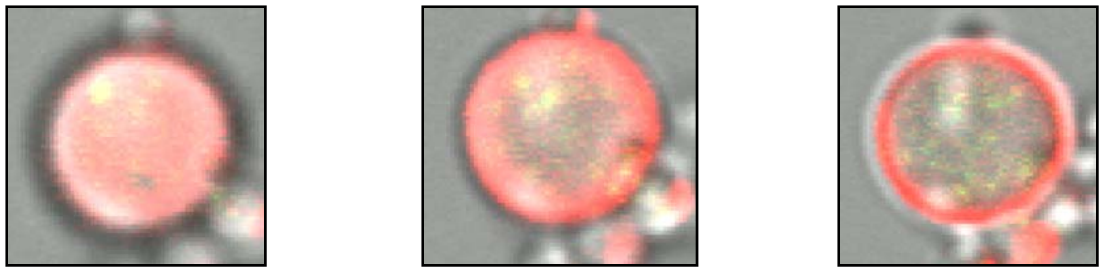
CARRIER PARTICLES
and NANOPARTICLES

CUTTING THROUGH THE PARTICLES

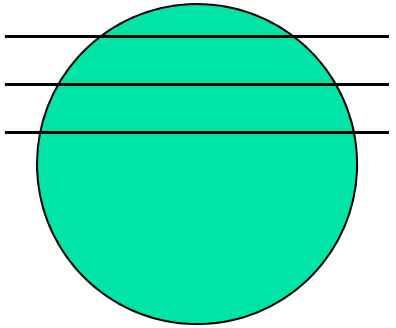
Continuous matrix of carrier particles



Hollow carrier particles

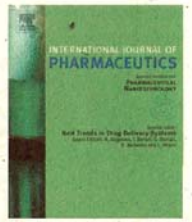


Confocal laser scanning microscopy



Most Cited Paper

ELSEVIER



International Journal of Pharmaceutics

Most Cited Paper 2004 Award

Awarded to:

J.O.-H. Sham, Y. Zhang, W.H. Finlay, W.H. Roa, R. Löbenberg

For the paper entitled:

"Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung"

By:

J.O.-H. Sham, Y. Zhang, W.H. Finlay, W.H. Roa, R. Löbenberg

This paper was published in:

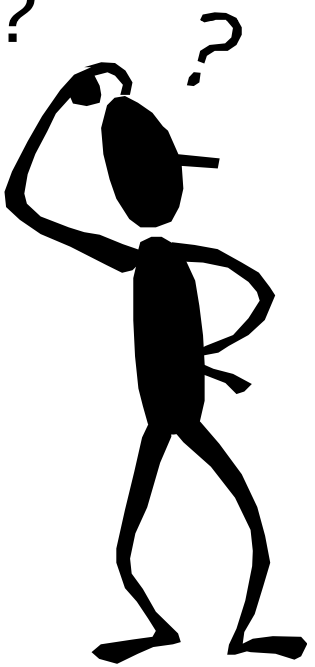
International Journal of Pharmaceutics, Volume 269, Issue 2 (2004), Pages 457-467

Jaap van Harten, PhD, Publisher Pharmaceutical Sciences
Federica Rosetta, Publishing Editor Pharmaceutical Sciences
Elsevier, Amsterdam, The Netherlands

Active Release of Nanoparticles from the Carrier Particle

- How to create forces which increase the disperse-ability of the nanoparticles?

We had to go back to the lab and do some experiments



NEW SYSTEM OF CARRIER PARTICLES with Active Release

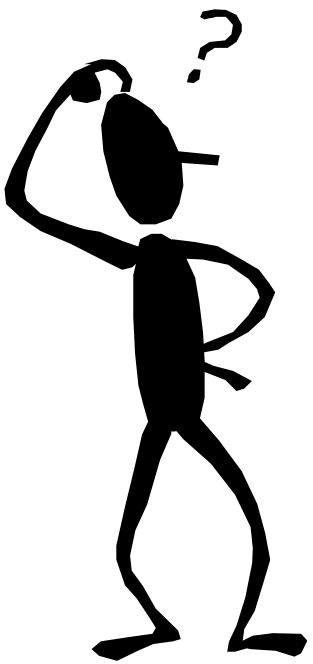
Our approach:

- The *in situ* generated gas pressure may help to disperse the content of the carrier particle

Active Release of Nanoparticles from the Carrier Particle

- How to how to avoid that the reaction is happening while spray drying?

We had to go back to the lab and do some experiments



NEW SYSTEM OF CARRIER PARTICLES

- Effervescent carrier particles:

FORMULATION

Lactose

Sodium Carbonate

Acid Citric

Ammonia

Water

Evaporation

MAJOR PARAMETERS

Machine parameters

Atomization

- Pressure

Temperatures

- inlet
- outlet

Pump

Aspirator

MAJOR PARAMETERS

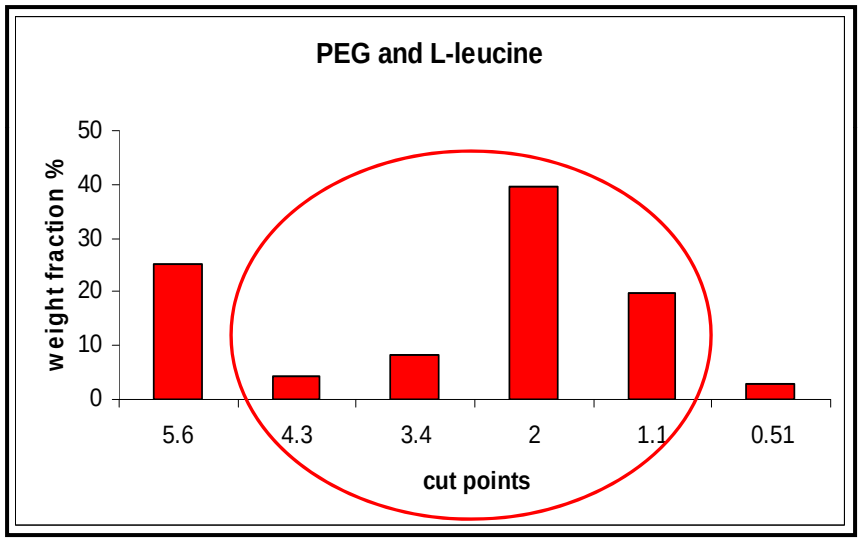
Formulation parameters

Solid concentration

Excipients:

- leucine
- polyethylene glycol
- ethanol
- surfactants

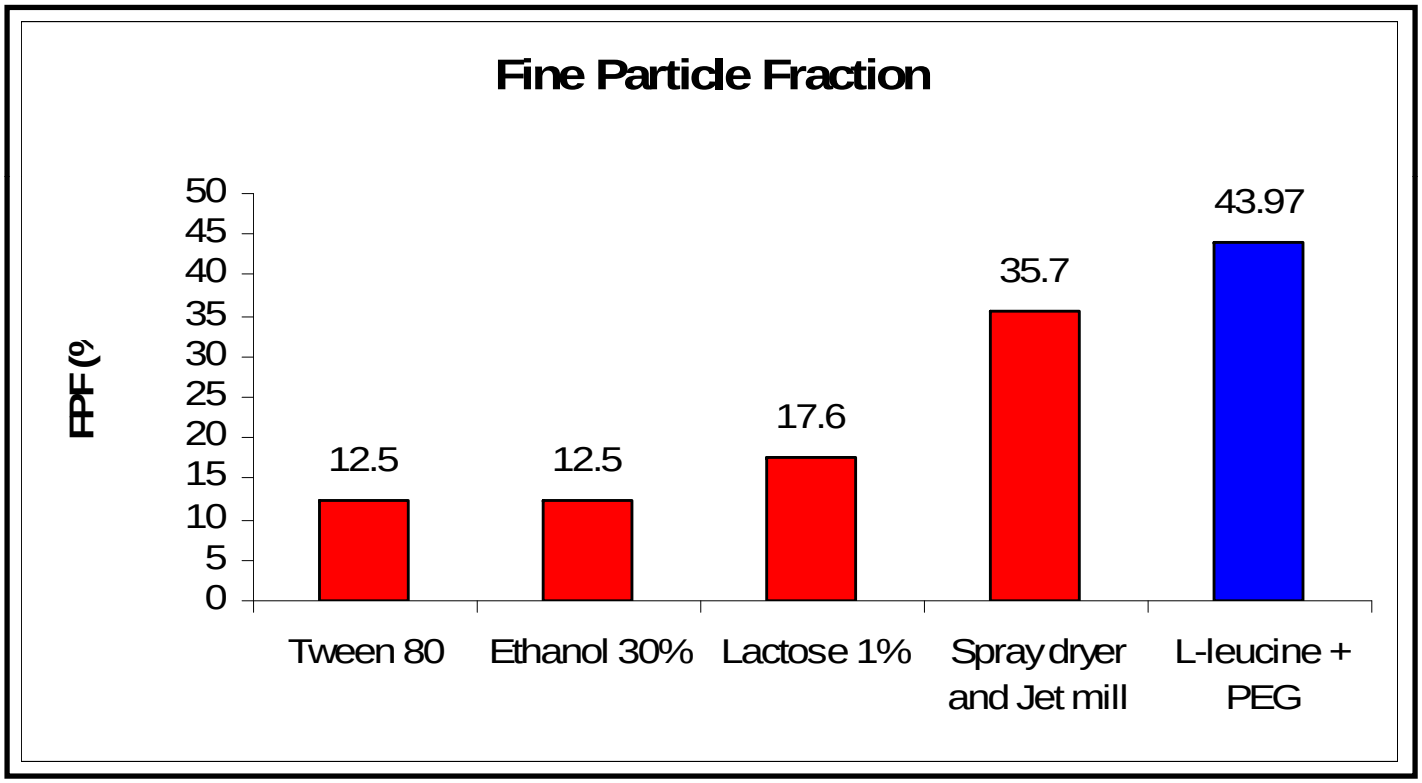
RESULTS: Polyethylene glycol (PEG) and L-leucine



PEG and l-leucine both work as a lubricant

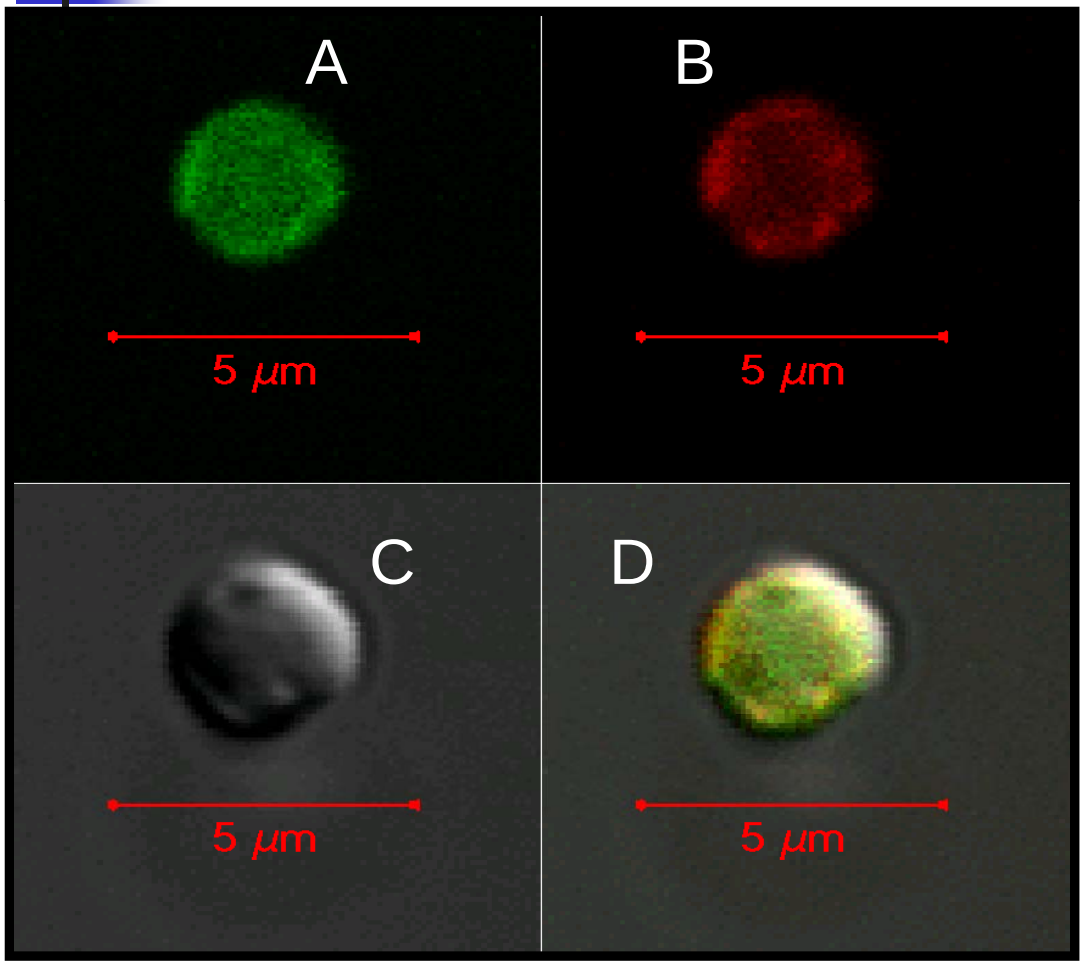
L- leucine can decrease the aggregation of spray dried particles

Fine Particle Fraction (FPF)



FPF means particle fraction that can be delivered to the lungs

Carrier particles with active release mechanism



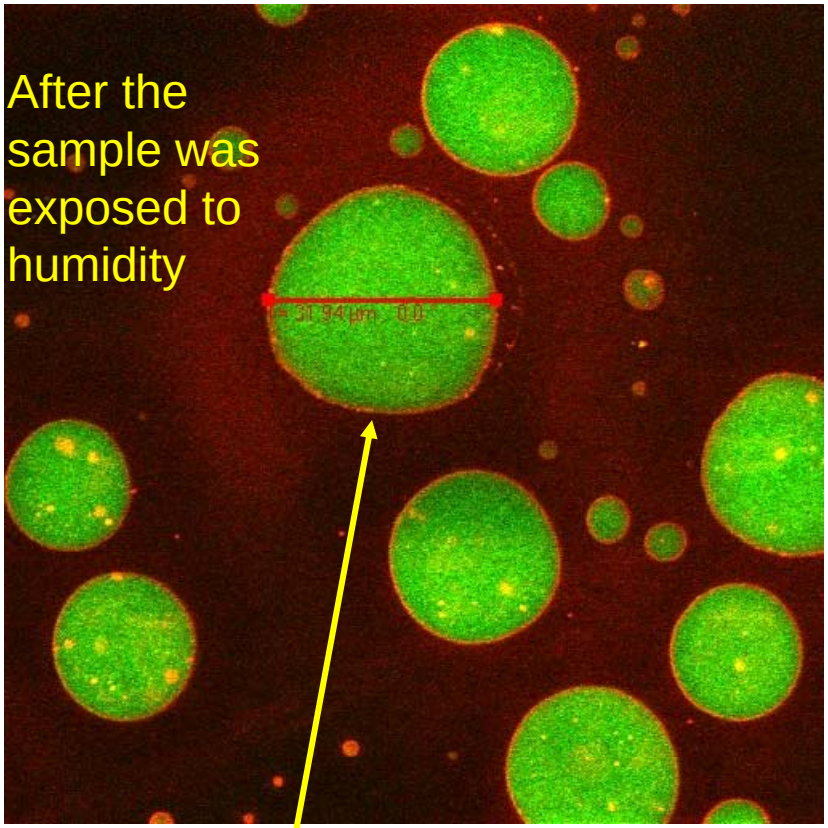
(A) green nanoparticles.

(B) red carrier matrix

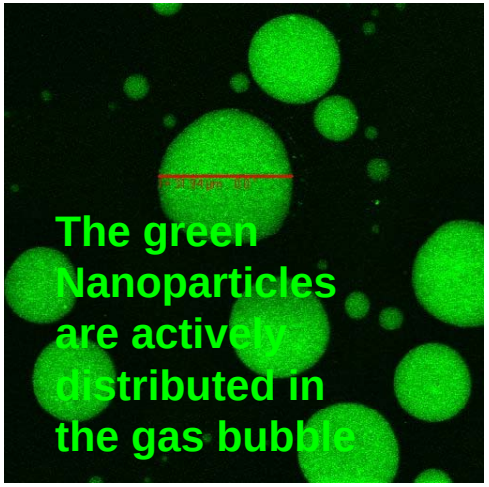
(C) normal light

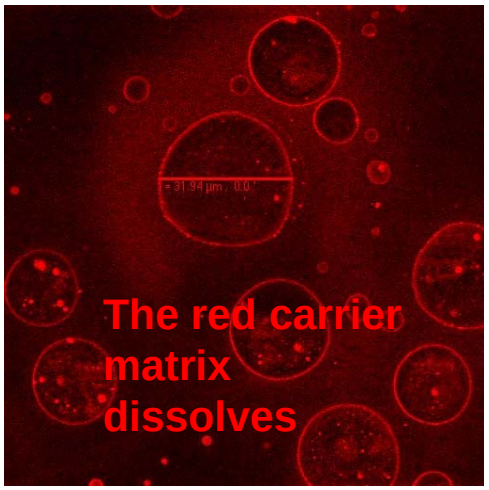
(D) superimposed

Carrier particles with active release mechanism



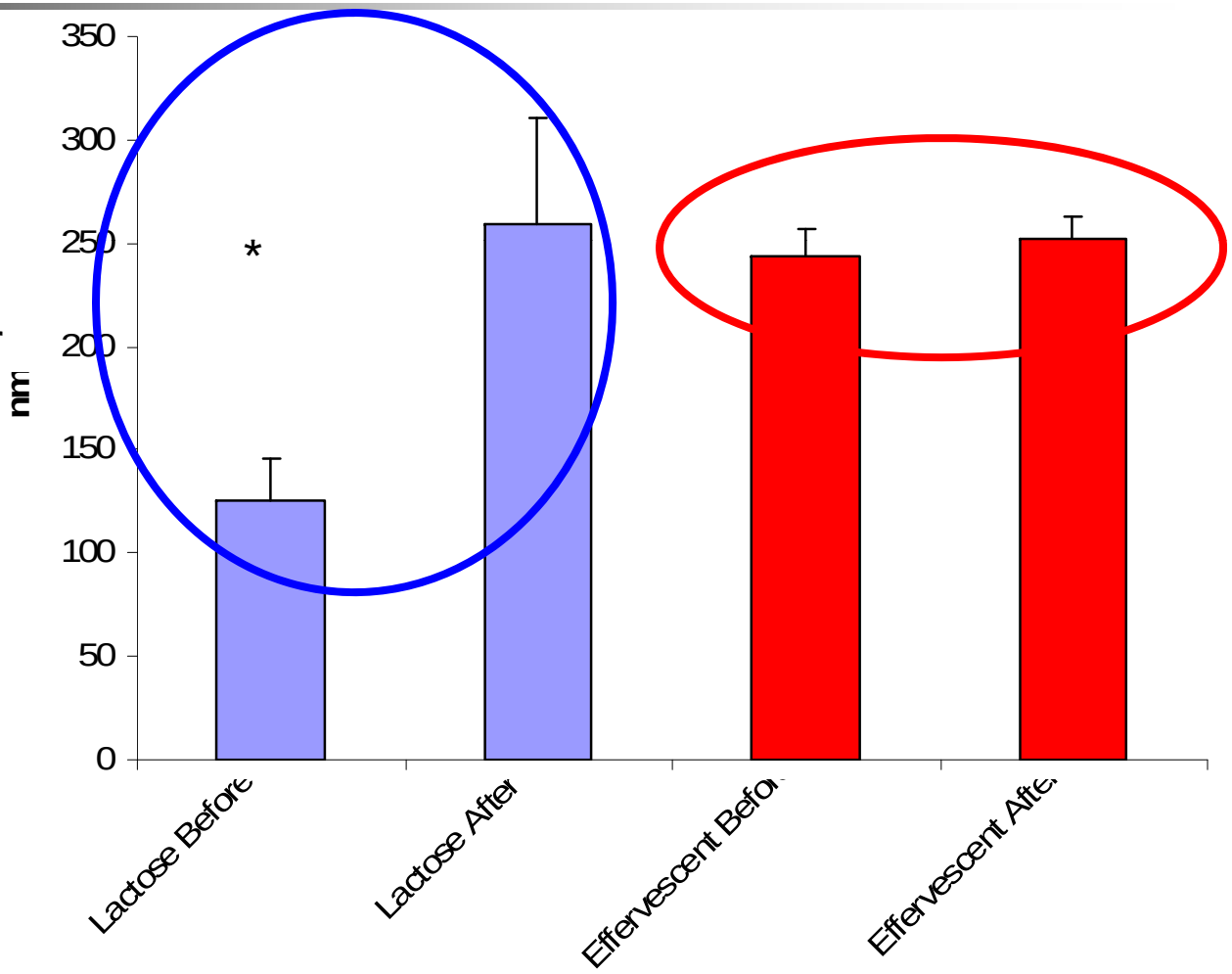
The gas bubble is about 30 μm





RESULTS: Influence of the formulation on the size of nanoparticles

Effervescent Dry Powder for Respiratory Drug Delivery;
Leticia Ely, Wilson Roa, Warren H. Finlay, Raimar Löbenberg;
Eur J Pharm Biopharm 2007



Publication

ELSEVIER

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European Journal of Pharmaceutics and Biopharmaceutics 65 (2007) 346–353

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejpb

Research paper

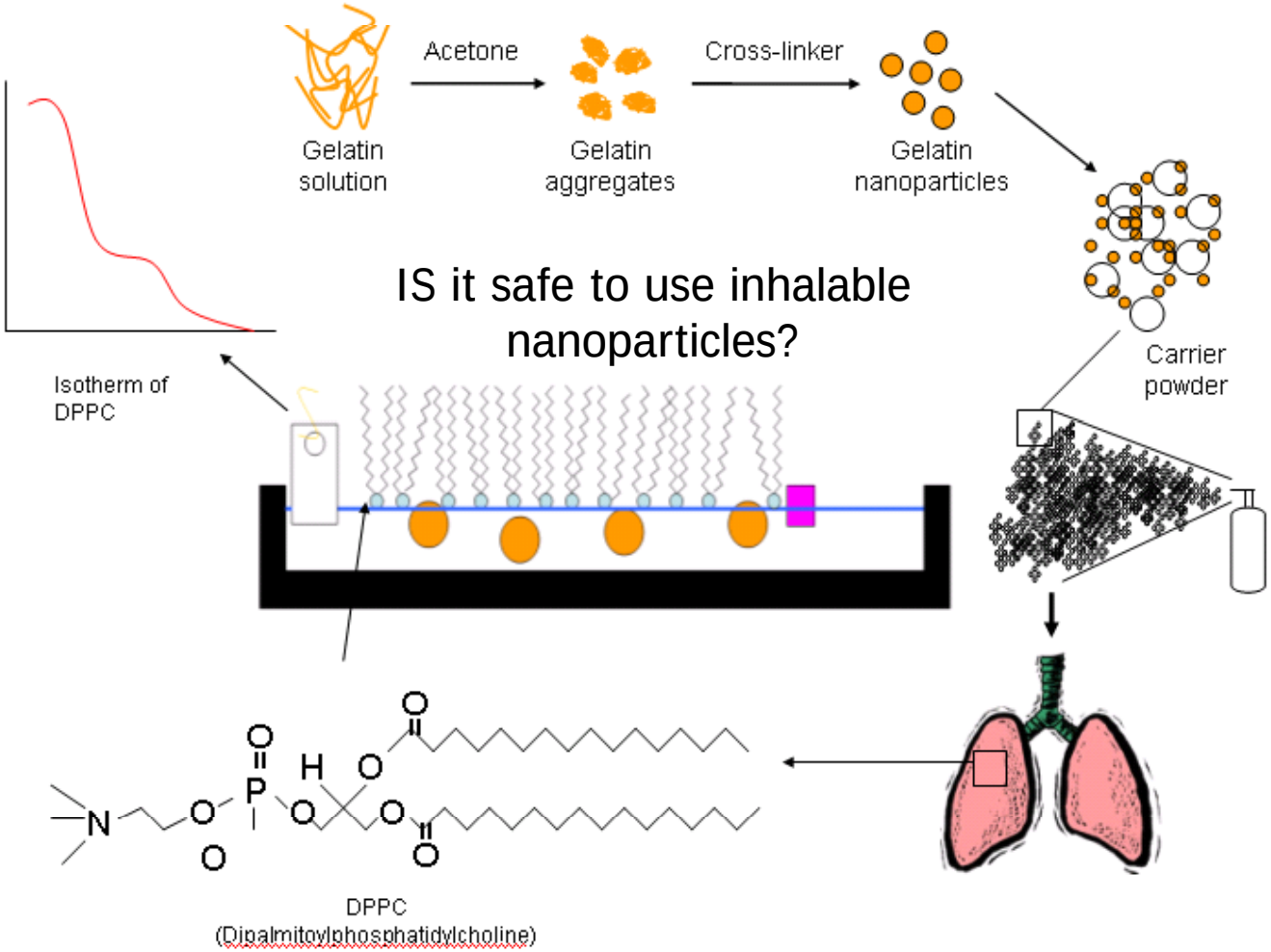
Effervescent dry powder for respiratory drug delivery

Leticia Ely [a], Wilson Roa [b], Warren H. Finlay [c], Raimar Löbenberg [a,*]

[a] *Faculty of Pharmacy, University of Alberta, Edmonton, AB, Canada*
[b] *Department of Oncology, University of Alberta, Edmonton, AB, Canada*
[c] *Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada*

Received 4 July 2006; accepted in revised form 24 October 2006
Available online 7 November 2006

Nanotoxicology of Inhalable Nanoparticles



Lung surfactant

- Lung surfactant are a mixture of about 80% phospholipids,
- 5-10 proteins and
- 5-10% cholesterol containing compounds

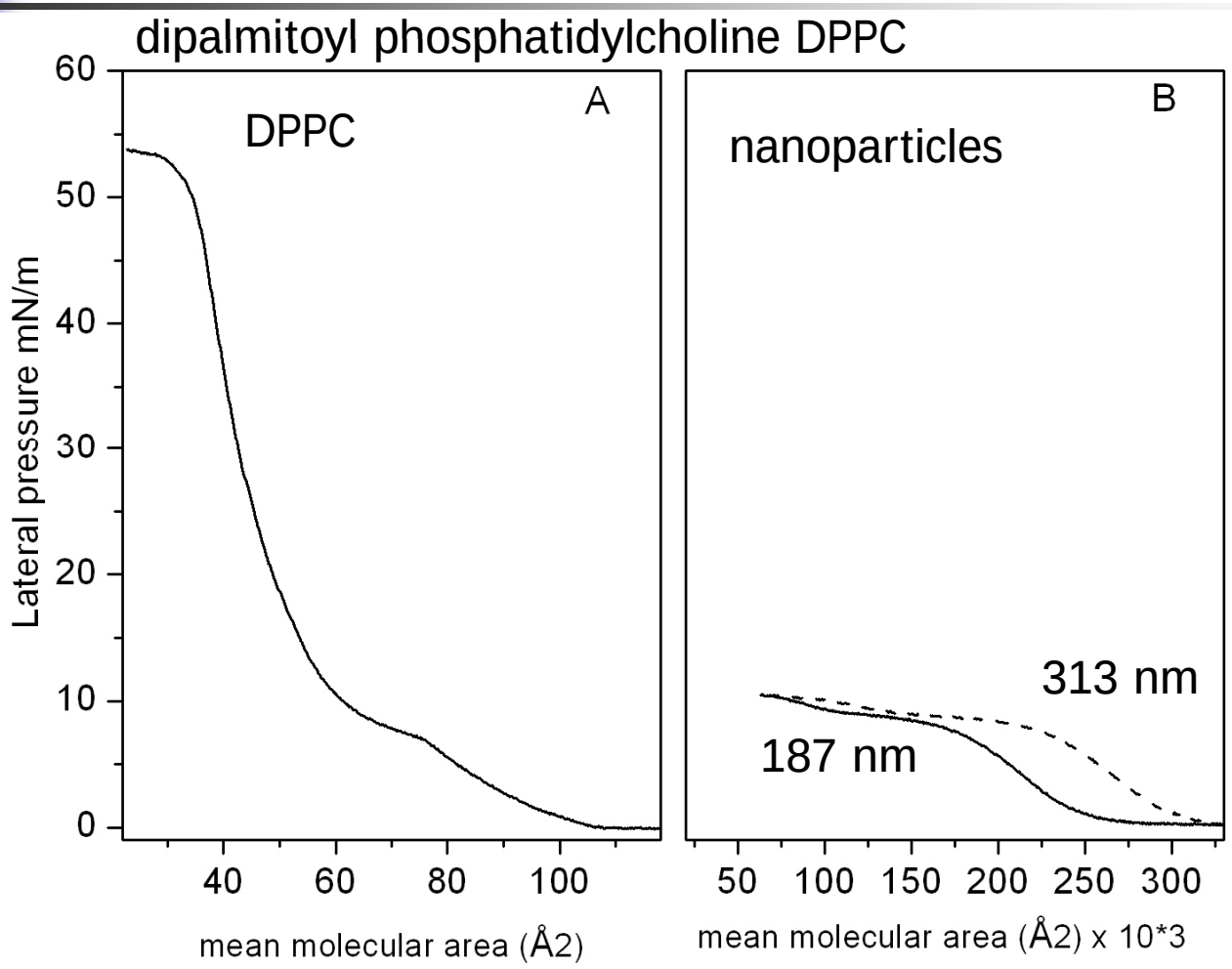
- Major components of the phospholipids are phosphatidylcholine PC and dipalmitoyl phosphatidylcholine DPPC.

Lung surfactant

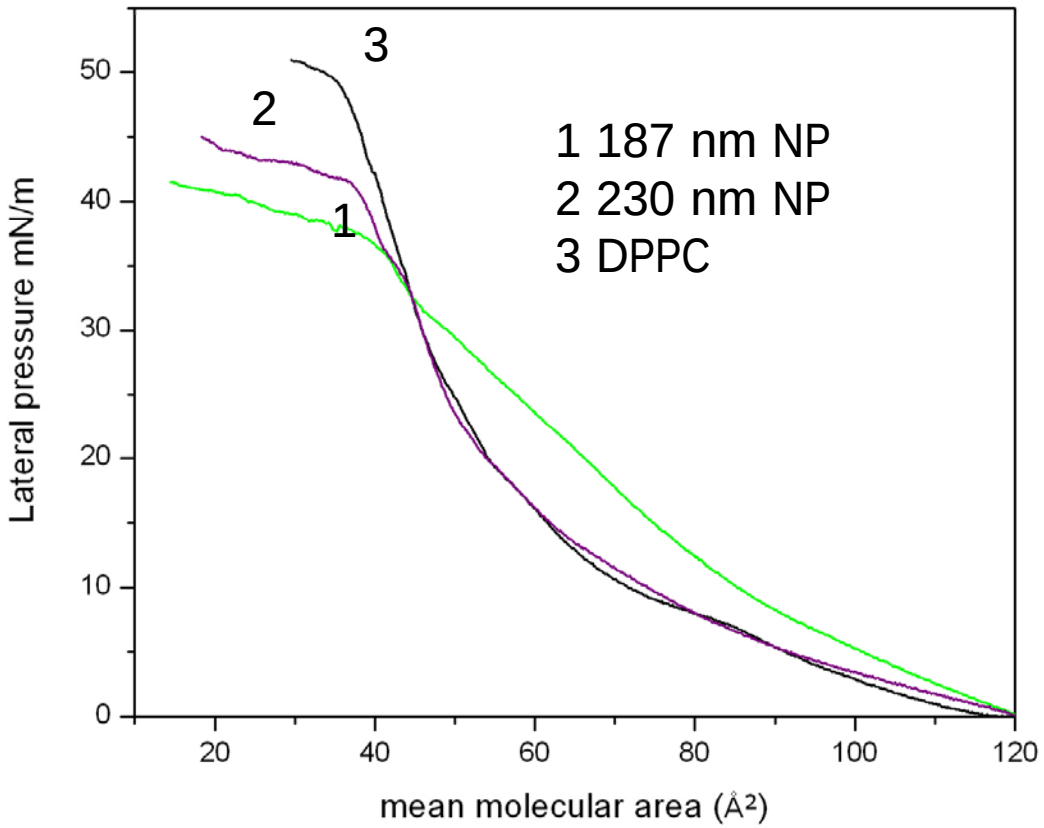
Function:

- Reduction of Surface Tension
- Gas Exchange

Surface pressure versus molecular area isotherms



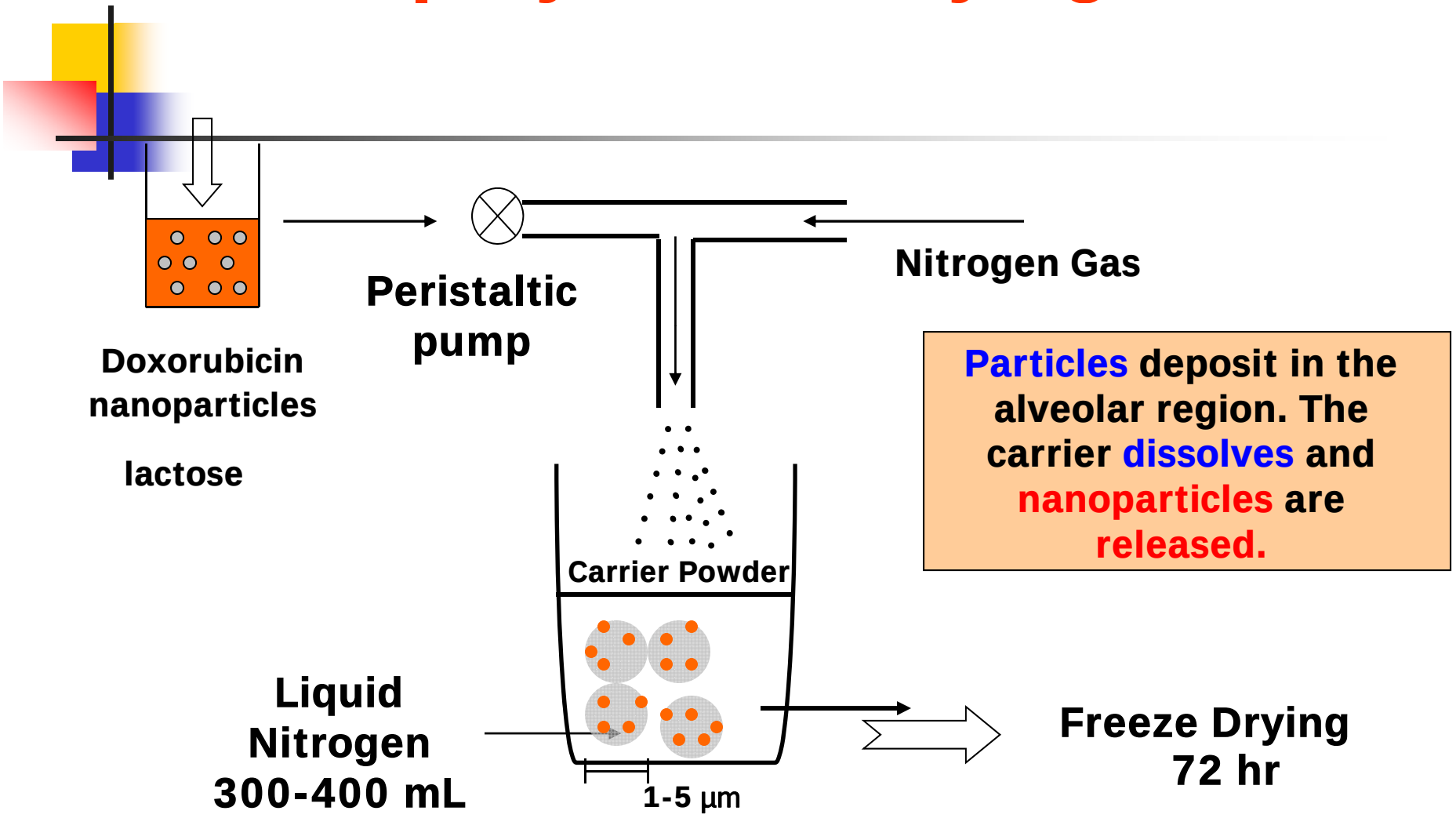
Surface pressure versus molecular area isotherms



The study concluded that: The high surface pressure values obtained from the isotherms of the binary mixtures indicates the notion that their size dependent incorporation does not destabilize the monolayer film. The study results demonstrated that pulmonary nanoparticle delivery is a possible route of administration.

Biophysical investigation of nanoparticle interactions with lung surfactant model systems; Diana Stuart, Raimar Löbenberg, Tabitha Ku, Shirzad Azarmi, Leticia Ely, Wilson Roa and Elmar J. Prenner J Biomed Nanotech Vol 2 p1-8 2006

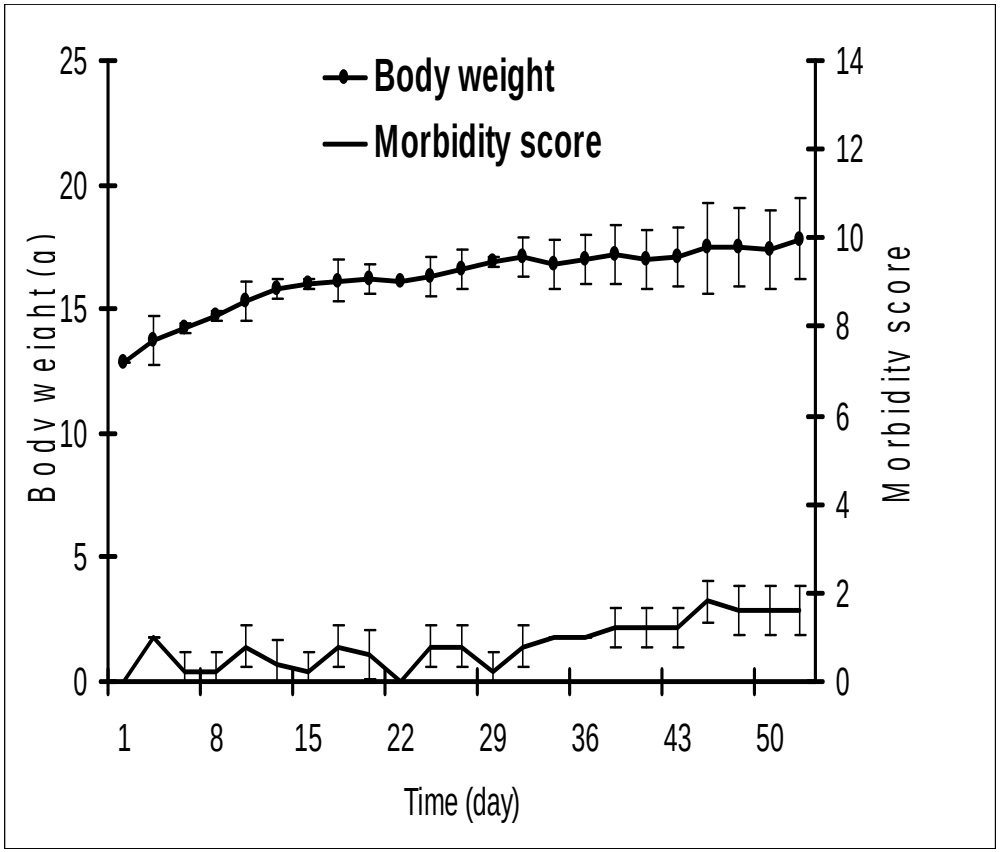
Spray freeze-drying



Particles deposit in the alveolar region. The carrier **dissolves** and **nanoparticles** are **released.**

Density: ~ 0.1 g/cm^3

Morbidity Scores



Project/Animal Identification:	Score
Appearance	
Normal	0
General lack of grooming	1
Coat staring, ocular or nasal discharge	2
Piloerection, hunched up	3
Body Weight	
Normal < 5%	0
body wt. drop 6-15%	1
body wt. drop 16-25%	2
body wt. drop 26-35%	3
body wt. drop > 35%	4
Food Intake	
Normal	0
food intake drop 10-33%	1
food intake drop 34-75%	2
food intake drop > 75%	3
Clinical Signs	
Normal resp. rate and hydration	0
Slight changes	1
Resp. rates up or down 30%, measurable dehydration	2
Resp. rates changes 50% or very low, severe dehydration	3
Behavior	
Normal	0
Minor inactivity or exaggerated responses	1
Moderate change in expected behavior, isolated or listless	2
Reacts violently, or very weak and precomatose	3
Total	

Study design

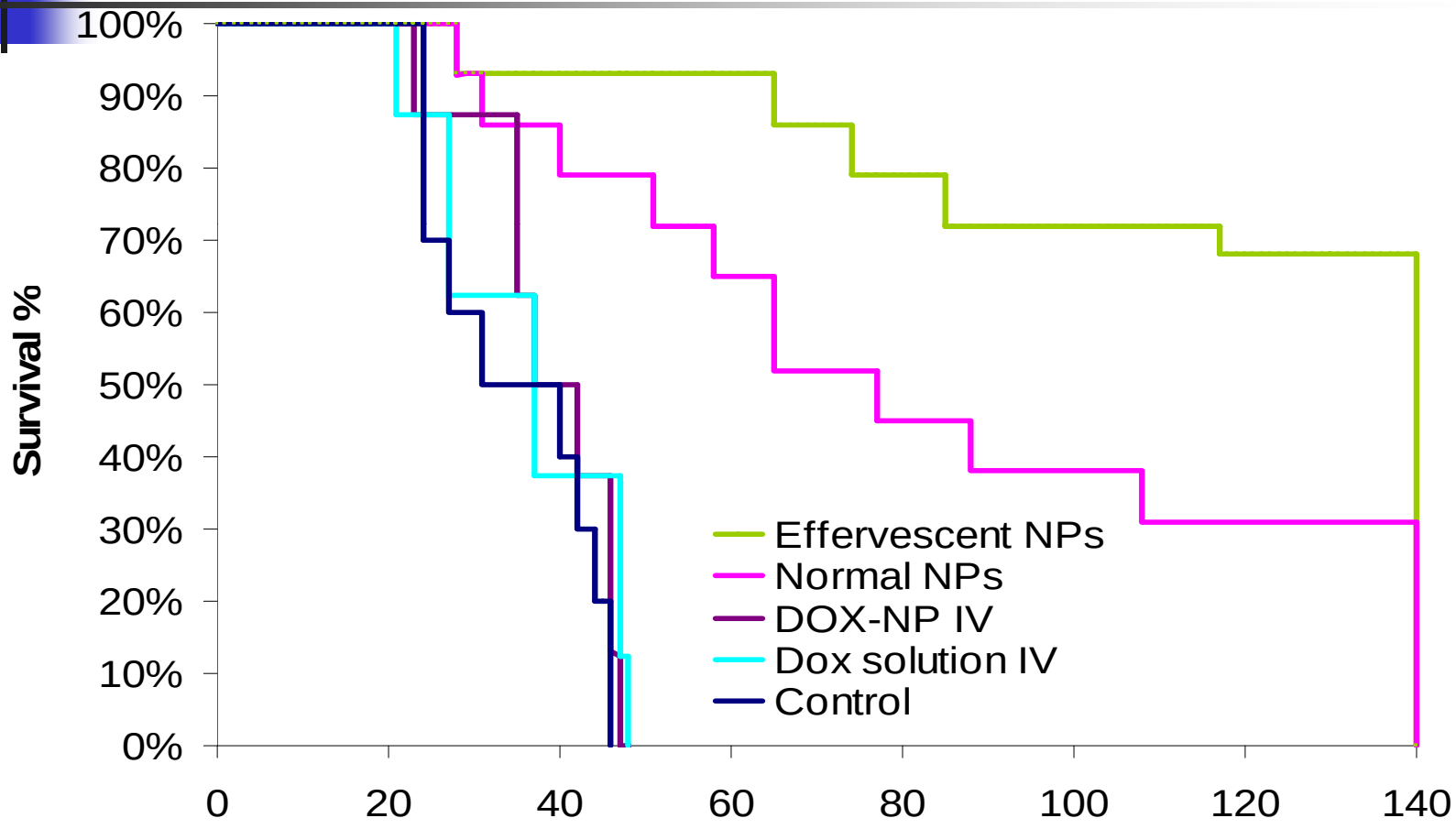
- Female 4-5 weeks old BALB/c nude mice
- NCI-H460 injection
- Small lung metastatic nodules develop in 15 days
- Treatment over 4 weeks with
  - Free Drug
  - Inhalable NPs
  - Blank NPs
  - No treatment

Expectation

- The cancer will spread throughout the body
- The animals will die because of cancer in other organs
- The Lungs might show less cancer compared to other tissues due to the treatment

Summary of what accomplished and performed

Assessing the efficacy of DOX-loaded effervescent inhalable NPs in vivo



Summary

- Inhalable nanoparticles with active release mechanism were successfully synthesized
- In vitro results demonstrate that nanoparticles do not compromise the biological function of the lung surfactant film
- In vitro cell culture test show that doxorubicin bound to nanoparticles is more effective against lung cancer cells than free doxorubicin
- In vivo studies demonstrate that the survival of mice can be improved if doxorubicin loaded nanoparticles are administered via the pulmonary route of administration

Conclusions

- New dry powder technology is available to deliver NP or drugs to the lungs
- Improved pulmonary drug delivery for cytotoxic molecules is possible using nanoparticles
- Drug delivery is the key to improve (lung cancer) treatments.

Articles

- **Formulation and in vivo evaluation of effervescent inhalable carrier particles for pulmonary delivery of nanoparticles.**
  Azarmi S. Lobenberg R. Roa WH. Tai S. Finlay WH.
  Drug Development & Industrial Pharmacy. 34(9):943-7, 2008 Sep.
- **Targeted delivery of nanoparticles for the treatment of lung diseases**
  Shirzad Azarmi, Wilson H. Roa and Raimar Löbenberg,
  Advanced Drug Delivery Reviews, 0(8):863-75, 2008 May 22.
- **Nanoparticles: characteristics, Mechanisms of Action and Toxicity in Pulmonary Drug Delivery – A Review**
  S Gill, R Löbenberg, T Ku S Azarmi, W Roa and EJ Penner
  J Biomed Nanotechnology 2007
- **Effervescent Dry Powder Aerosols for Respiratory Drug Delivery**
  Leticia Ely, Warren H Finlay, Wilson H Roa, Raimar Löbenberg
  Eur J Pharm Biopharm 2007 (65) 346-353
- **Biophysical investigation of nanoparticle interactions with lung surfactant model systems**
  Diana Stuart, Raimar Löbenberg, Tabitha Ku, Shirzad Azarmi, Leticia Ely, Wilson Roa and Elmar J. Prenner
  J Biomed Nanotechnology Volume 2, Numbers 3-4, October/December 2006, pp. 245-252(8)
- **Formulation and Cytotoxicity of Doxorubicin Nanoparticles Carried by Dry Powder Aerosol Particles**
  Shirzad Azarmi, Xia Tao, Hua Chen, Zhaolin Wang, Warren. H. Finlay, Raimar Löbenberg, Wilson. H. Roa
  Int J Pharm 2006 319 (1-2), pp. 155-161 (ranked # 23 for the journal in Jul – Sep 2006)
- **Optimization of a two-step desolvation method for preparing gelatin nanoparticles and cell uptake studies in 143B osteosarcoma cancer cells**
  Azarmi S, Huang Y, Chen H, McQuarrie S, Abrams D, Roa W, Finlay WH, Miller GG, Löbenberg R
  JPPS 9 (1): 124-132 2006
- **Dry Powder Inhalation Aerosols Containing Nanoparticulate Doxorubicin**
  L.G. Sweeney, H. Chen, Z. Wang, R. Löbenberg, W. Roa, W.H. Finlay
  Eur J Pharm Sci 305 (1-2): 180-185 NOV 23 2005
- **Formulation and Characterization of Spray-Dried Powders Containing Nanoparticles for Aerosol Delivery to the Lung**,
  Jeffrey O.-H. Sham, Yu Zhang, Warren H. Finlay, Wilson H. Roa, and Raimar Löbenberg
  Int. J. Pharm. Vol 269, (2), Pages 457-467 ranked Top 25 in 2004

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- Leticia Ely
- Kamal Al-Hallak
- NSERC, AHFMR, CIHR, ACB