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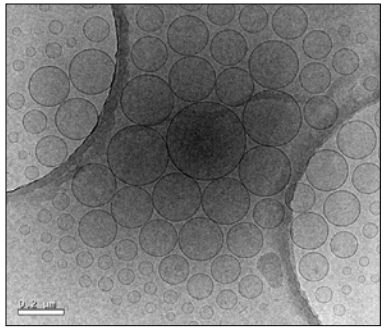
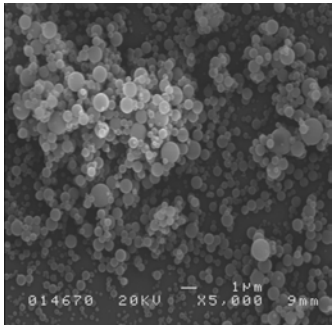
Particulate Molecular Materials for Drug delivery: Challenges in its Large-Scale Preparation

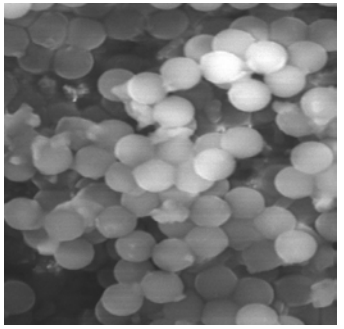
Jaume Veciana

Institut de Ciència de Materials de Barcelona (CSIC)-CIBER-BBN

vecianaj@icmab.es







"IMAGINENANO 2011"

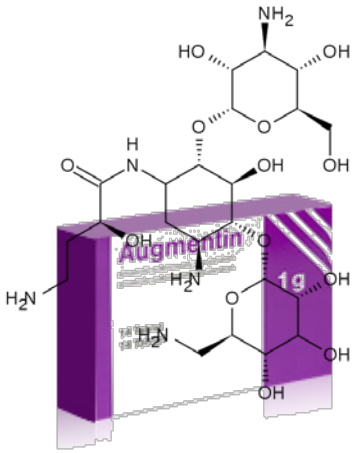
NanoBioMed , 14-16 April 2011 Bilbao Exhibition Center (Spain)

Pharmaceutical companies

20th Century

Research based on the discovery of new molecular entities (APIs)

Analgesics



Antibiotics

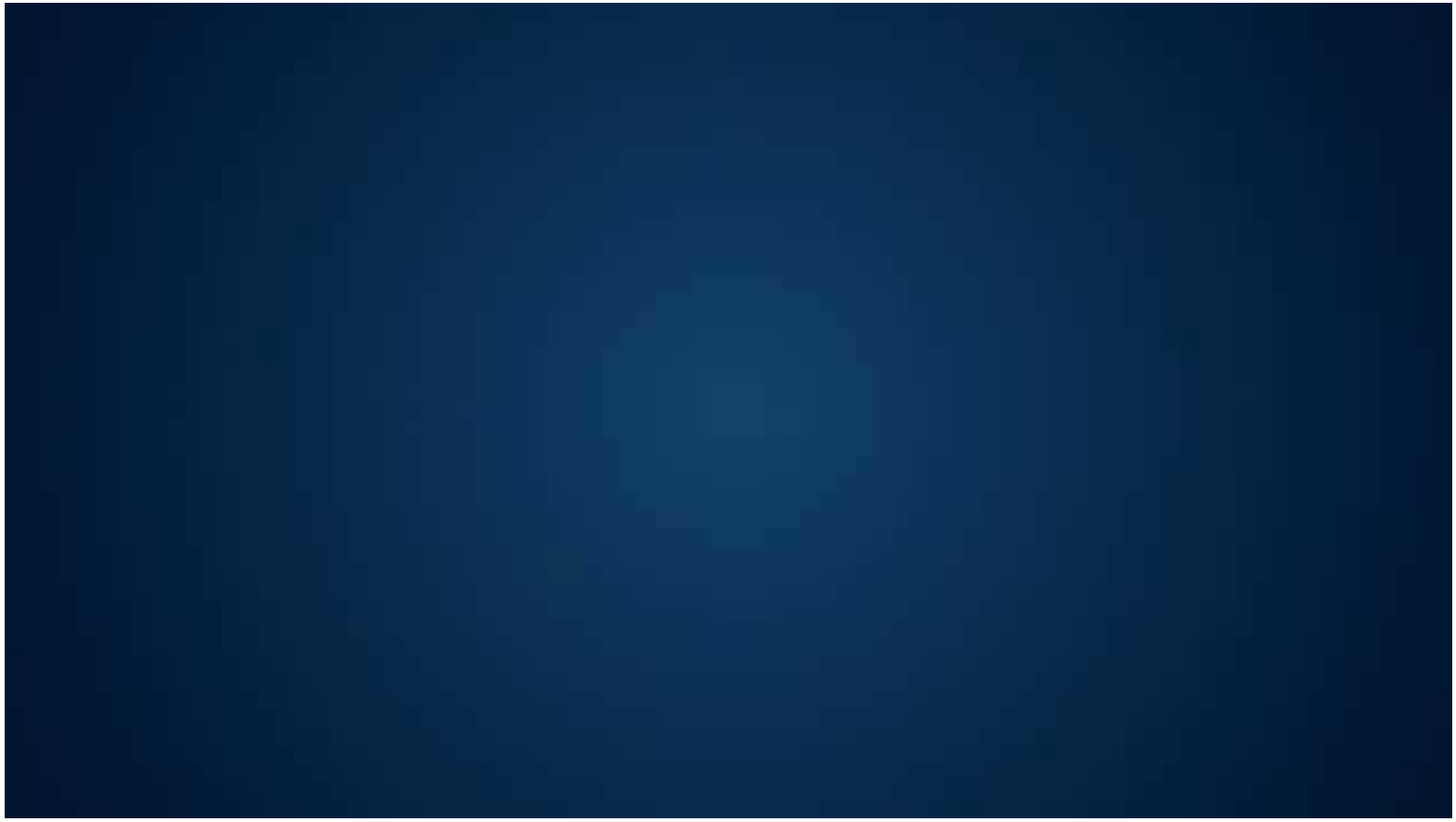
Cancer treatment

Keys: chemical synthesis, molecular and bioactivity characterization

Drug therapies

20th Century

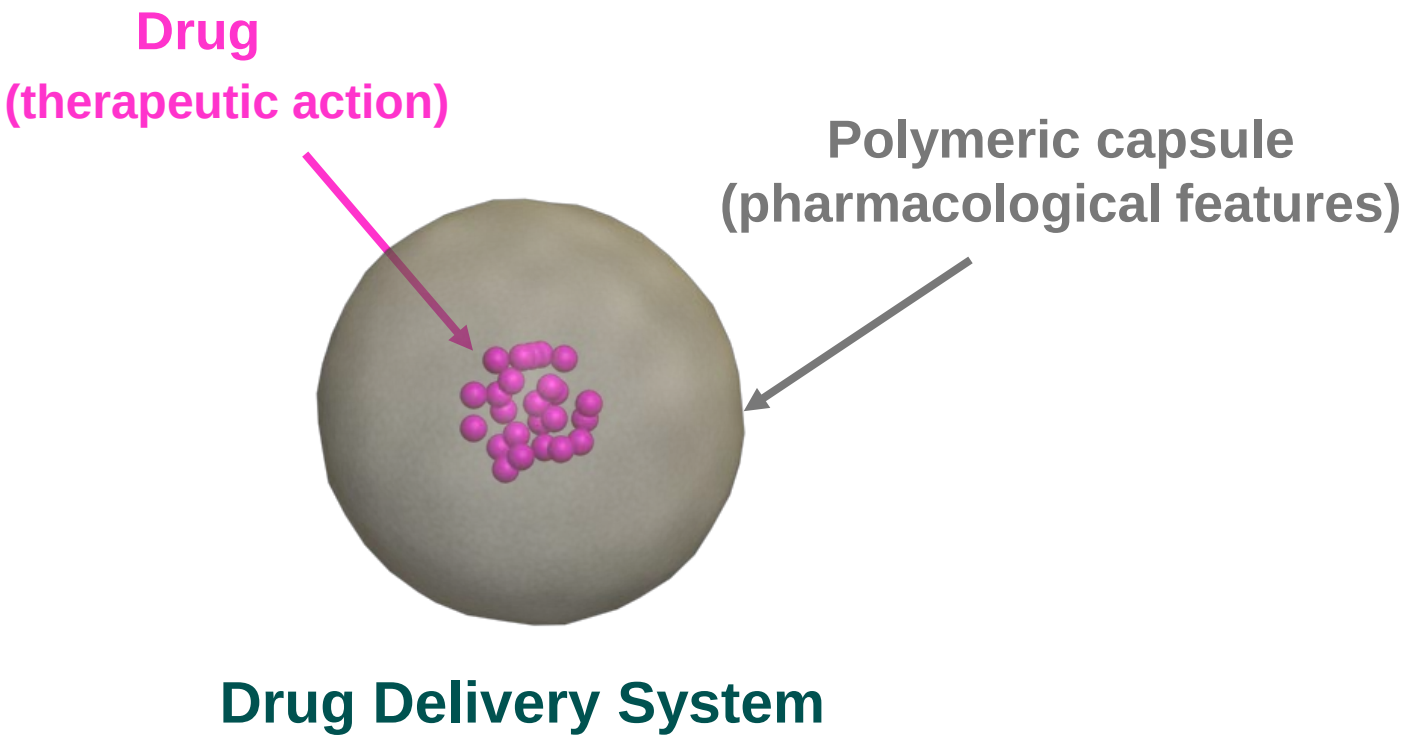
Current therapies with classical drugs



Pharma companies need new ways to develop new drugs

Drug Delivery Systems (DDS)

Nanocarrier

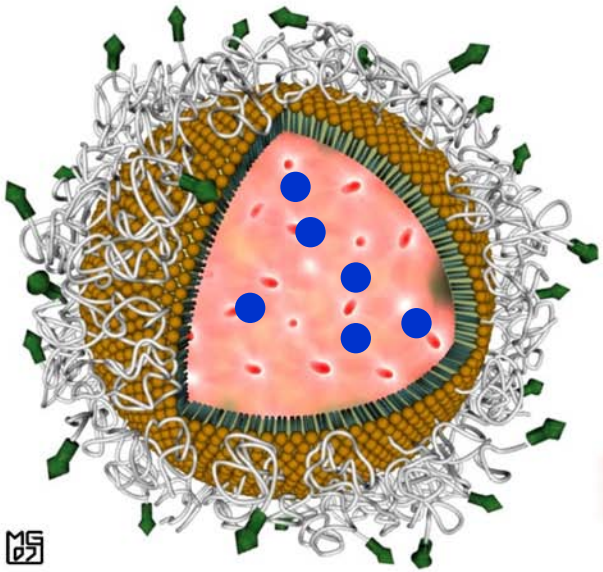


Increasing the therapeutic efficiency of drugs….

Drug Delivery Systems (DDS)

Ideal Nanocarriers for Drug Delivery

Multifunctional nanobjects



Components	Functions
Oil	
Phospholipids	Container
Pegylated surfactant	Protector
Biological ligand	Targeting
Magnetic particle	Diagnosis
Drug	Therapy

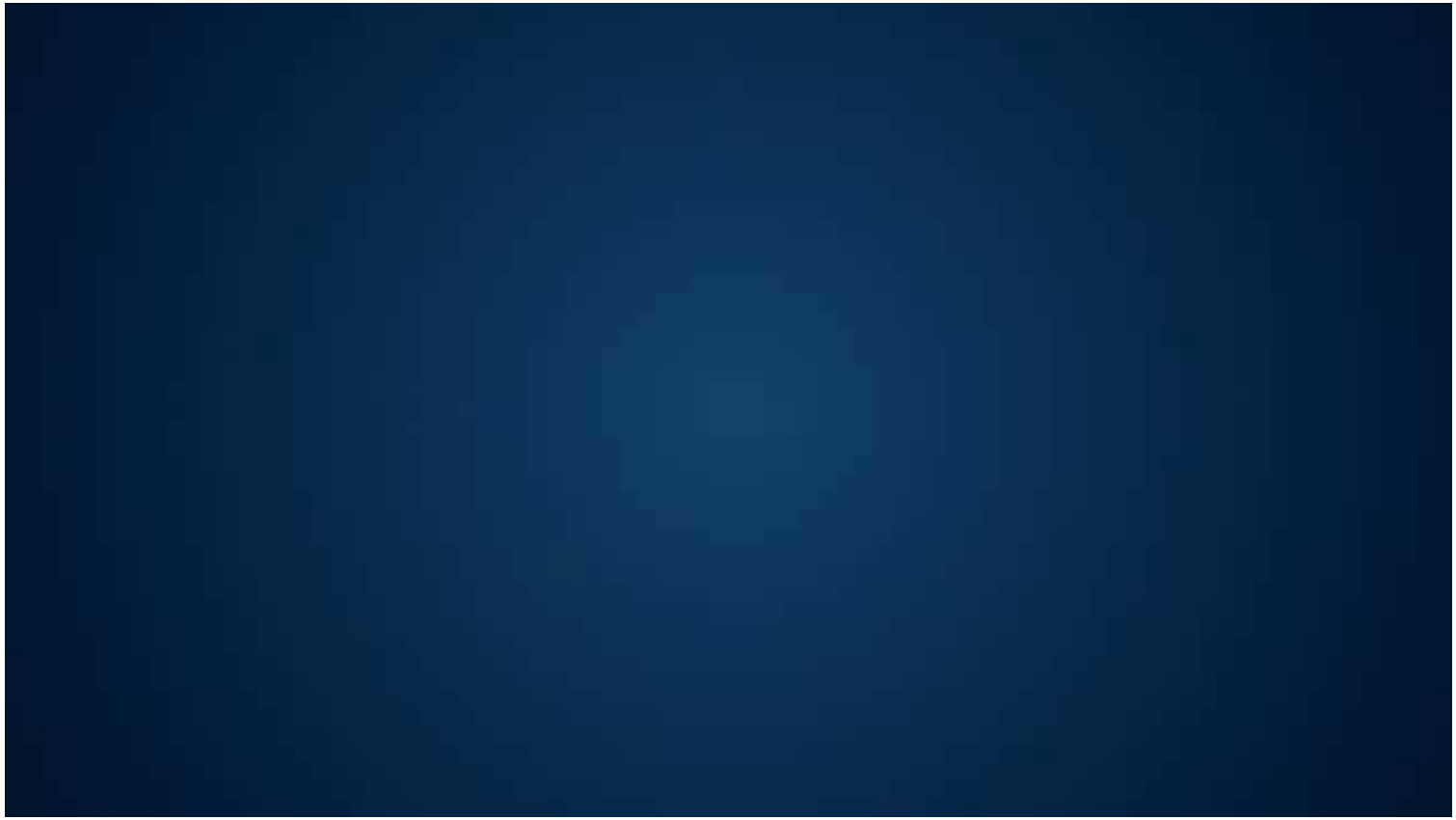
Adding new properties to the drug molecules increasing its therapeutic efficiency

P. Couvreur *et al*., *Pharm. Res.*, 2006, *23*, 1417-1450.

Drug therapies

21th Century

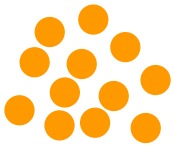
Therapies based in targeted drug delivery systems

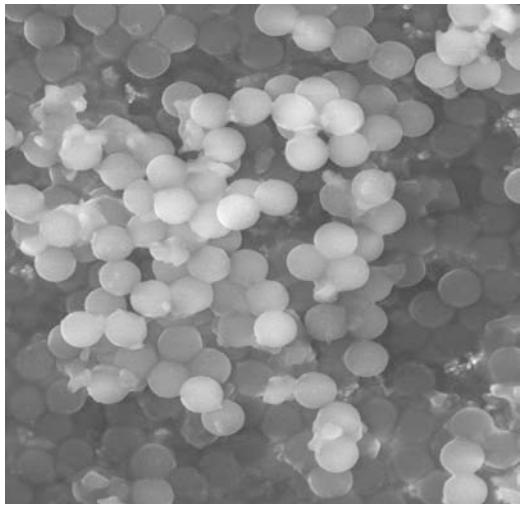


Keys: Preparation of drug delivery systems at the nanoscale with scale-up methods

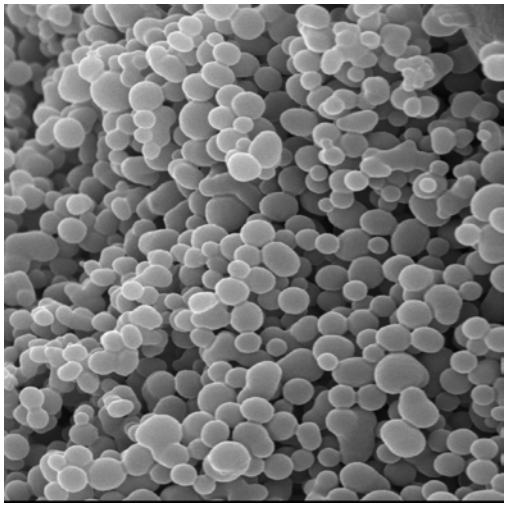
New Methods to Prepare Particulate Drug Delivery Systems

Nanoparticles Nanosuspensions

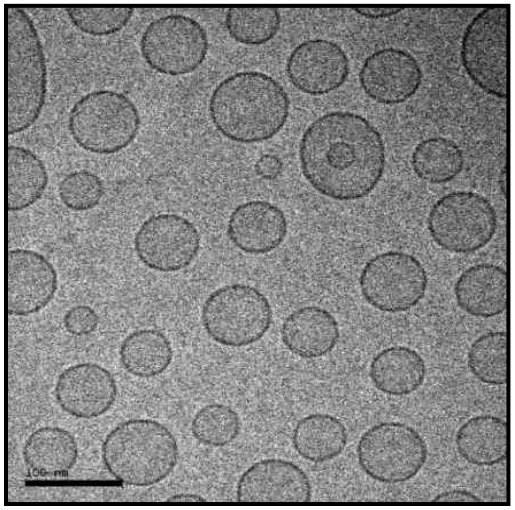




Polymeric-drug conjugates



Vescicles Liposomes



New Methods to Prepare Particulate Drug Delivery Systems

Using compressed CO_2 as a green solvent

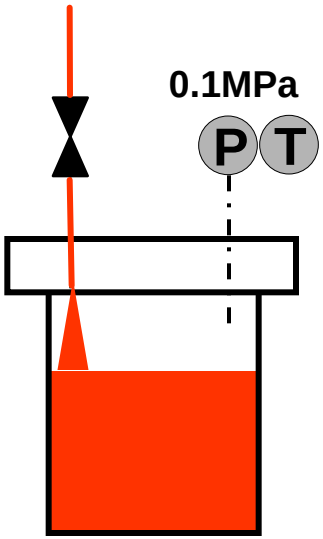
- **Non-toxic**
- **Non-flammable**
- **Cheap**
- **Easy separated from products**
- **Enabling to control particles**
- **Scale-up methods**

J.J. Watkins *et al., Science* ***2004,*** **J.D. Holmes** *et al. Chem. Eur. J.* ***2003***

DELOS method

DELOS: Depressurization from an Expanded Liquid Organic Solution

1: Addition



Solution or dispersion:
Drug + Organic solvent

N. Ventosa et al, *Cryst. Growth Des*. 2001, *1*, 299-303
N. Ventosa *et al, J. Supercrit. Fluids* 2003, *26*, 33-45
M. Gimeno *et al*, *Cryst. Growth Des.* 2006, *6*, 23-25
S. Sala et al, *Cryst. Growth Des.,* 2010*, 10*, 2126-2132

DELOS method

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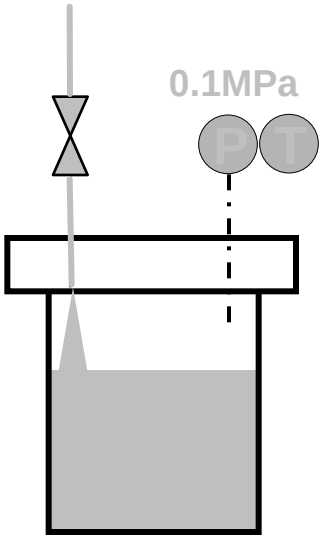
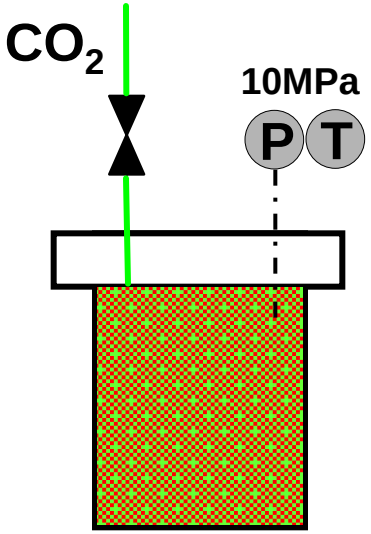


Solution or dispersion:
Drug + Organic solvent

2: Expanded solution



Solution:
Drug in CO_2-expanded solvent (X_{CO2}>0.5)

CO_2=co-solvent

N. Ventosa et al, *Cryst. Growth Des*. 2001, *1*, 299-303
N. Ventosa *et al, J. Supercrit. Fluids* 2003, *26*, 33-45
M. Gimeno *et al*, *Cryst. Growth Des.* 2006, *6*, 23-25
S. Sala et al, *Cryst. Growth Des.,* 2010*, 10*, 2126-2132

DELOS method

DELOS: Depressurization from an expanded liquid organic solution

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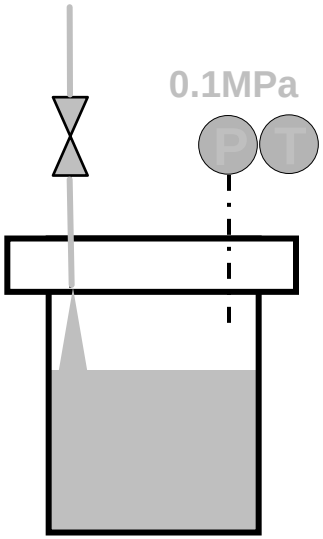
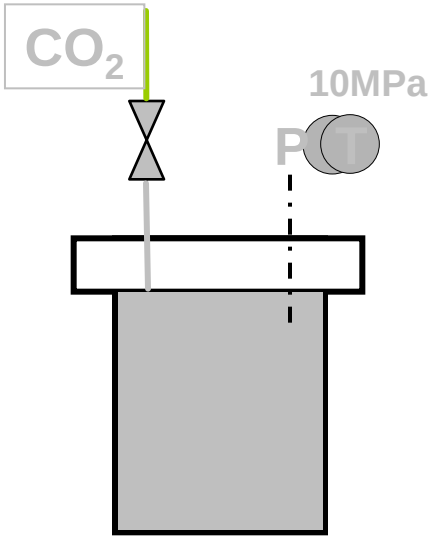


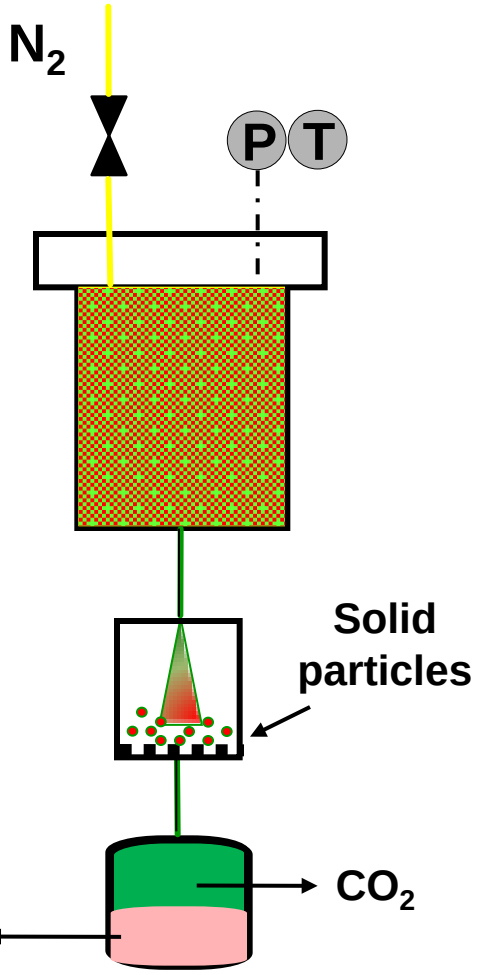
Solution or dispersion:
Drug + Organic solvent

2: Expanded solution



Solution:
Drug in CO_2-expanded solvent (X_{CO2}>0.5)

3: Depressurization



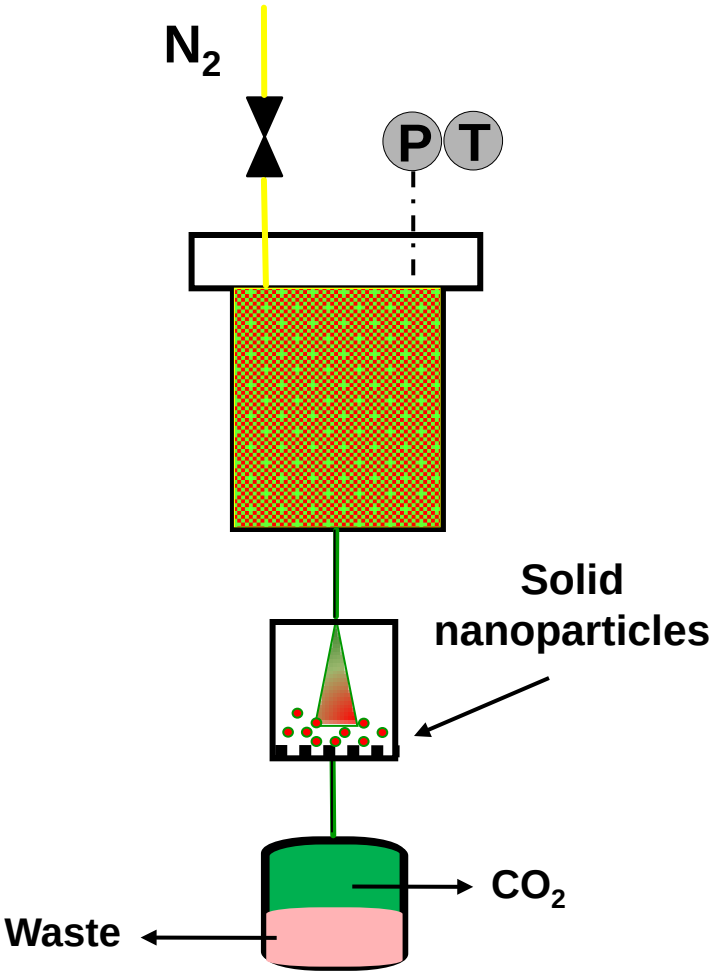
Fast and extremely homogeneous temperature decrease

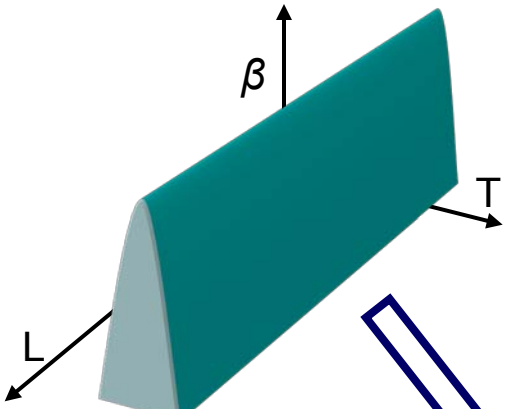
S. Sala *et al*, *Cryst. Growth Des*., 2010, *10*, 2126-2132

DELOS method

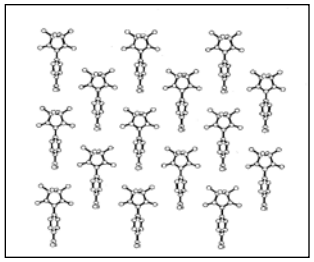
Large, fast and ideally homogeneous solution cooling

3: Depressurization

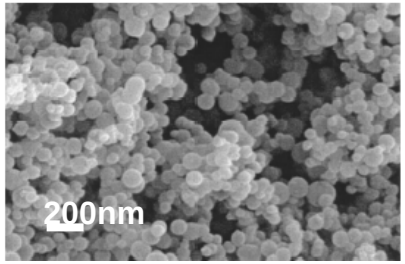




Homogenous β profile



Homogeneous supramolecular organization



Micro and nano-particulate solids

... high potential for micro- and nano-particulate drugs preparation

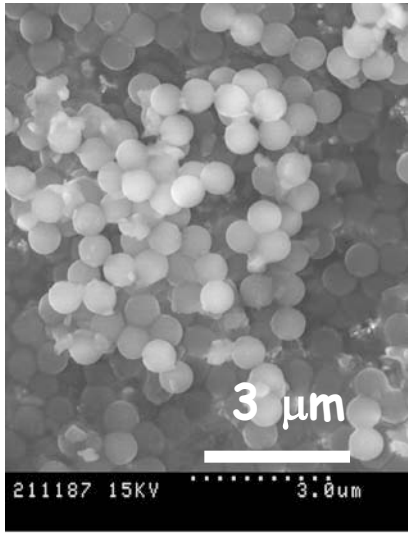
DELOS method

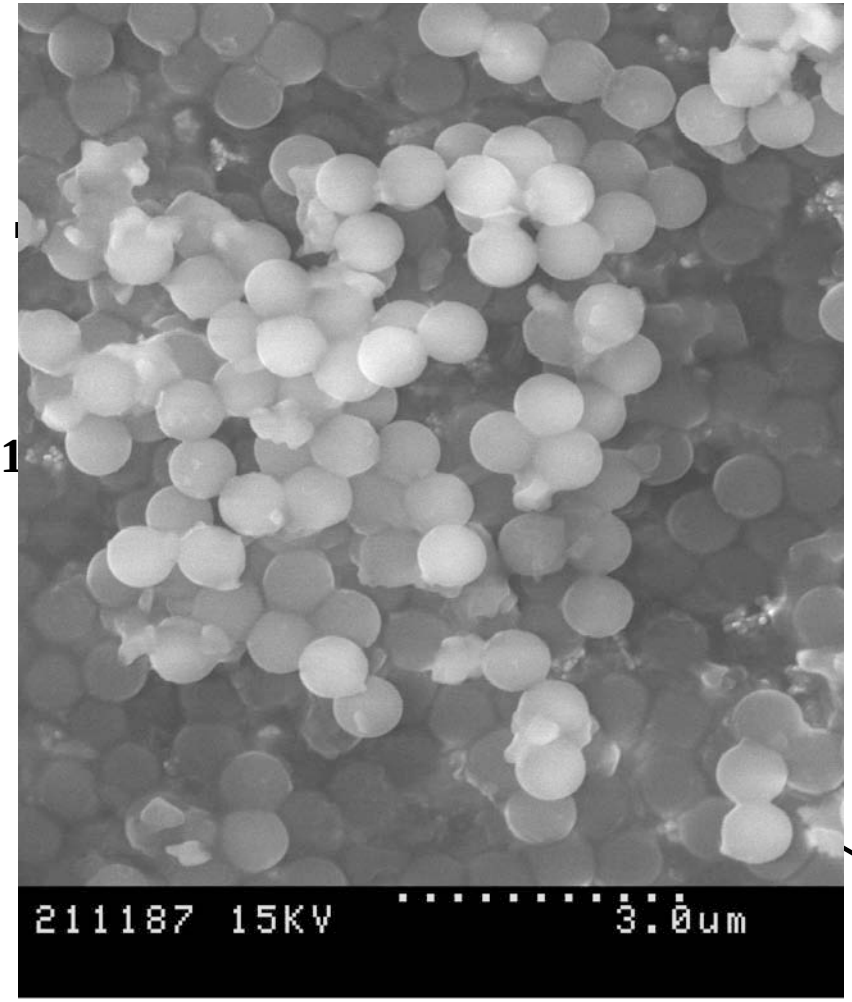
Preparation of pure drug micro- and nano-particles

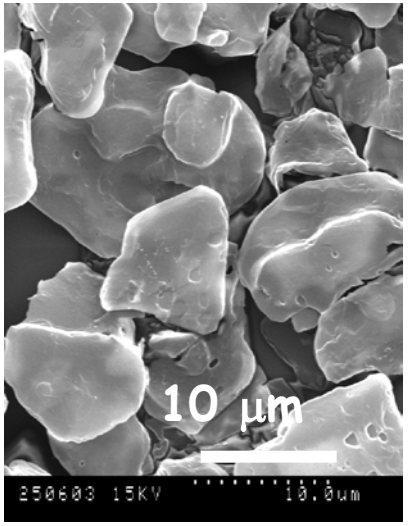
DELOS method

Homogeneous size & size distributions:

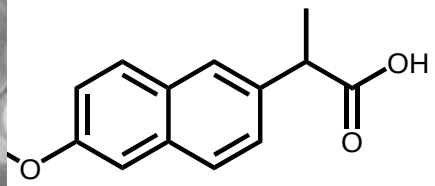
Tuning of particle size







Naproxen

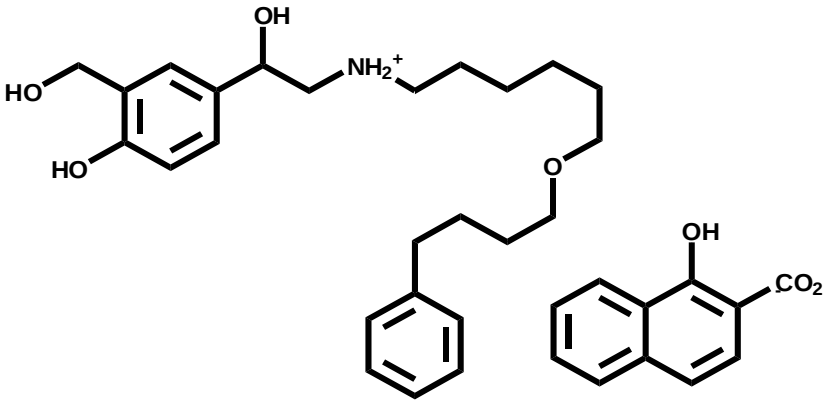


M. Muntó *et al*, *J. Supercritical Fluids*, 2008, 47, 147-153

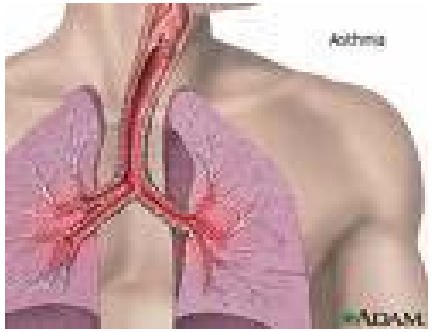
DELOS method

Processing of a drug for bronquial asthma by PCA method

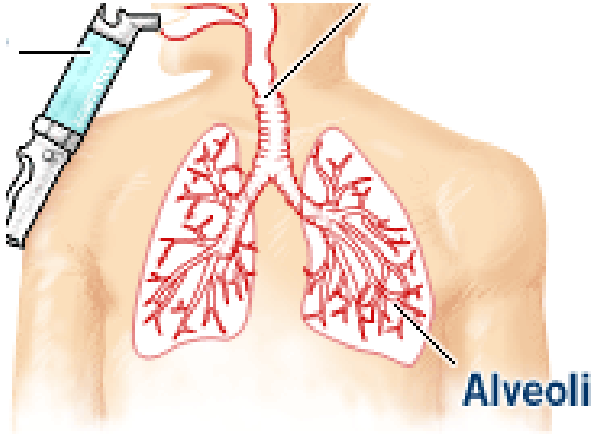
Salmenterol xinafoate (SX)

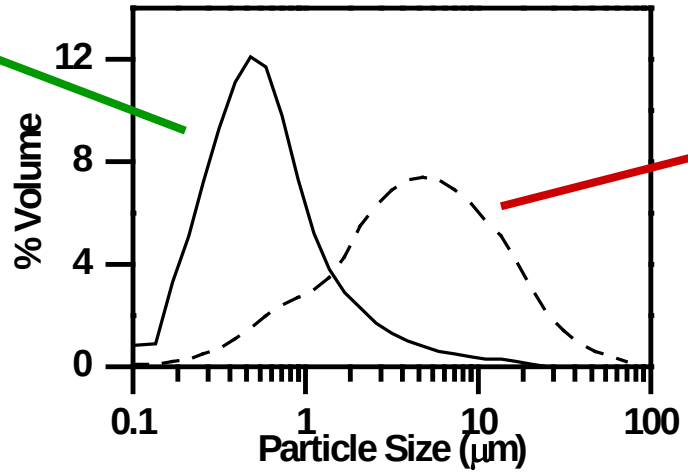


Drug for inhalatory asthma treatment



Bioavailable





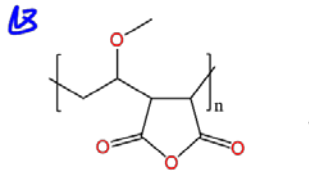
Non-bioavailable

DELOS method

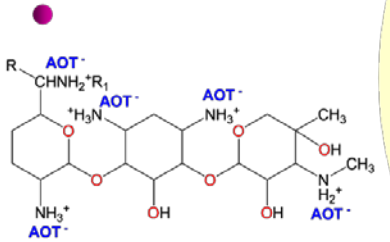
Preparation of dispersions of drugs into a polymeric matrix

DELOS method

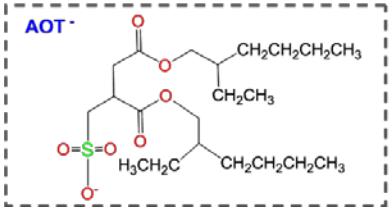
Gentamicine loaded in bioadhesive PVM/MA nanostructured microparticles

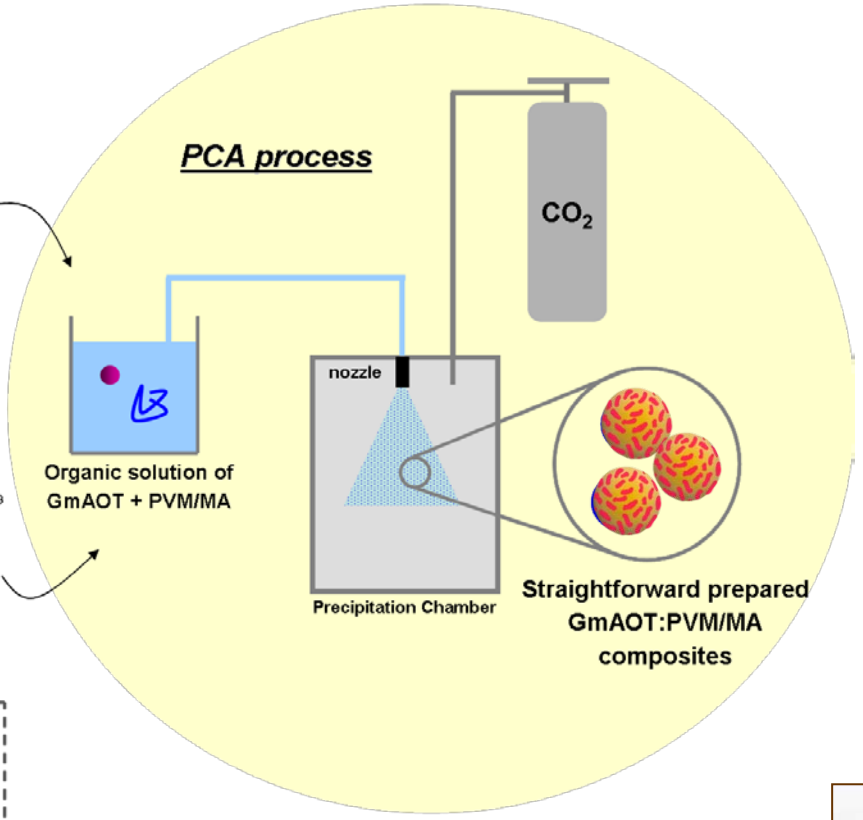


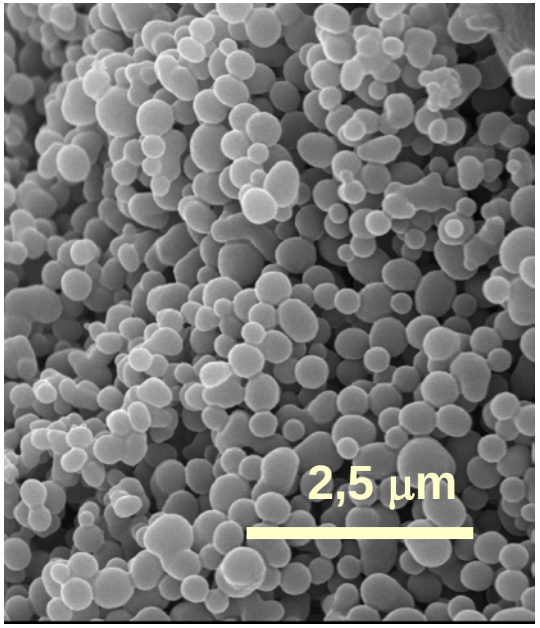
Molecular structure of PVM/MA



Molecular structure of GmAOT





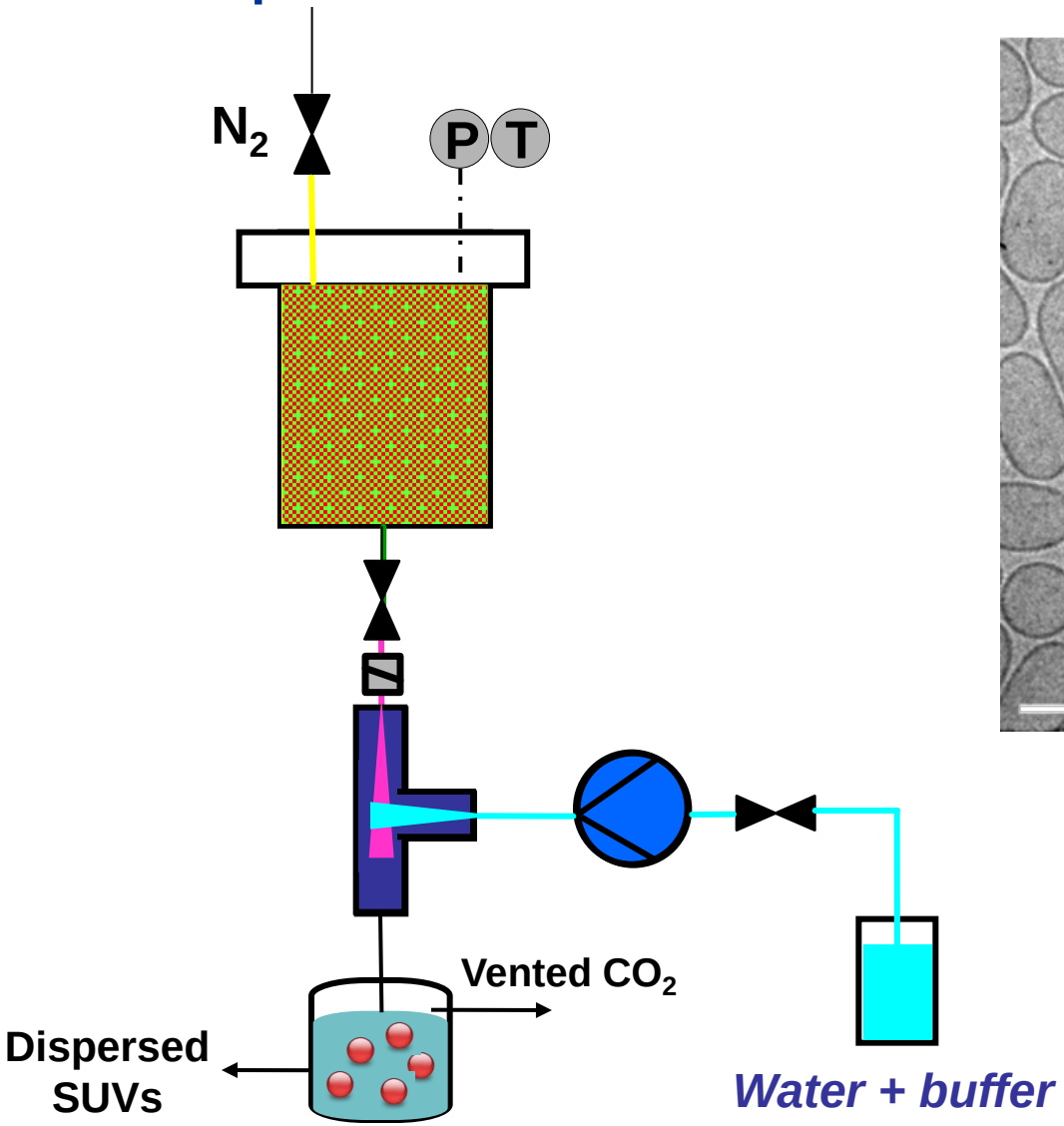


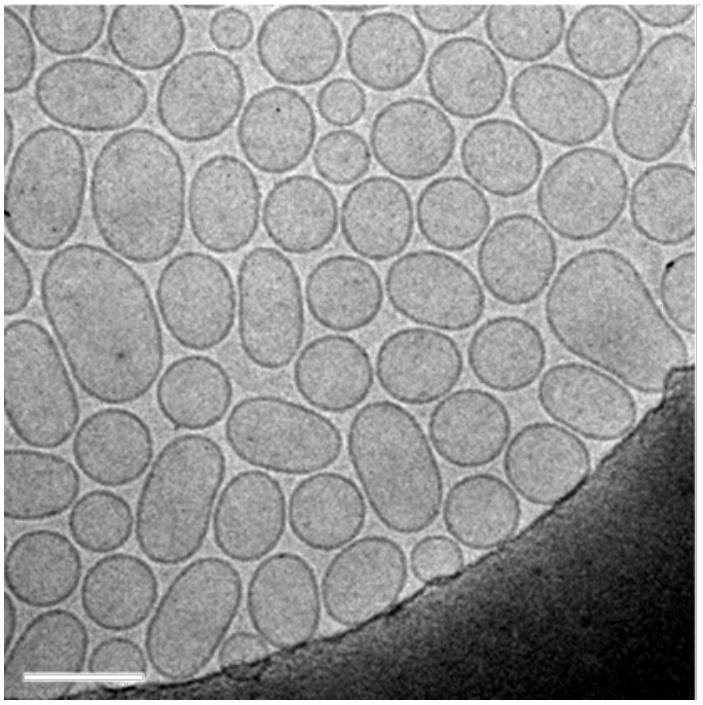
Oral Delivery

E. Elizondo *et al, Pharm. Res*., 2011, 28**, 309-321**

DELOS-SUSP method

3: Depressurization

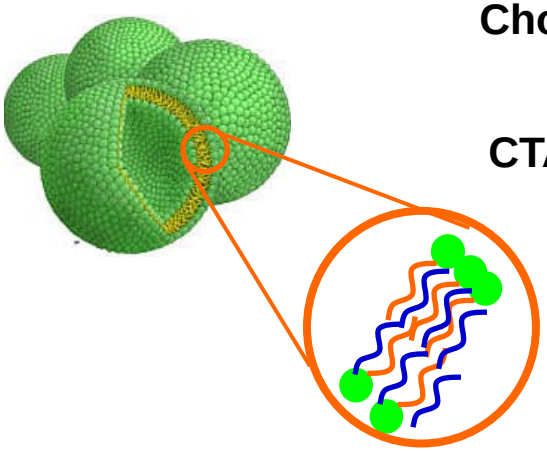




Dispersed SUVs in water

***Patents*: ES2265262, EP1843836.**

DELOS-SUSP: Preparation of Small Unillamelar Vesicles (SUVs)

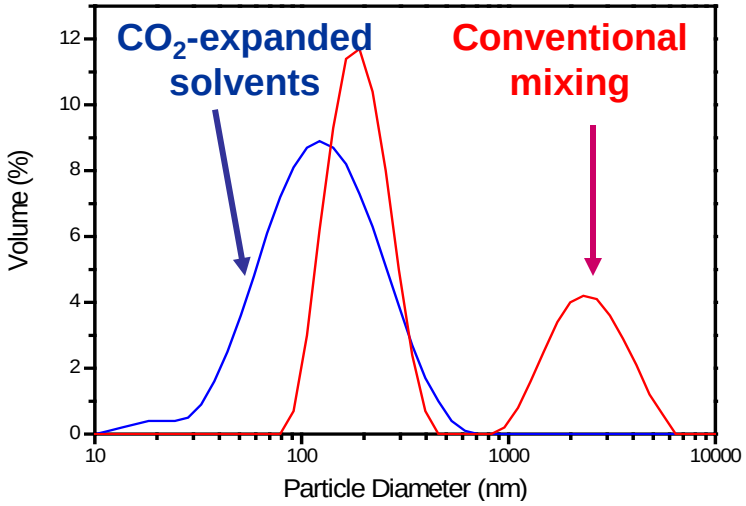


Cholesterol

+

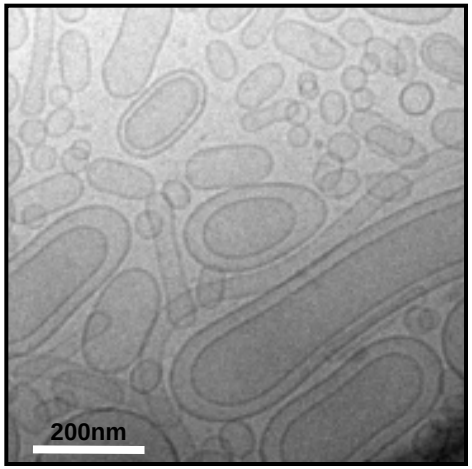
CTAB (1:1)

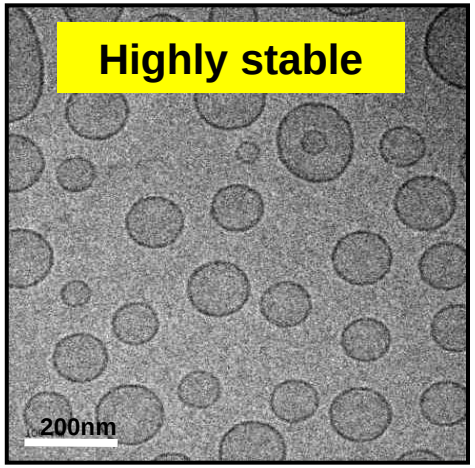
Conventional mixing **DELOS-SUSP**



Nanoscopic SUVs (~100 nm)

Cryo-TEM images

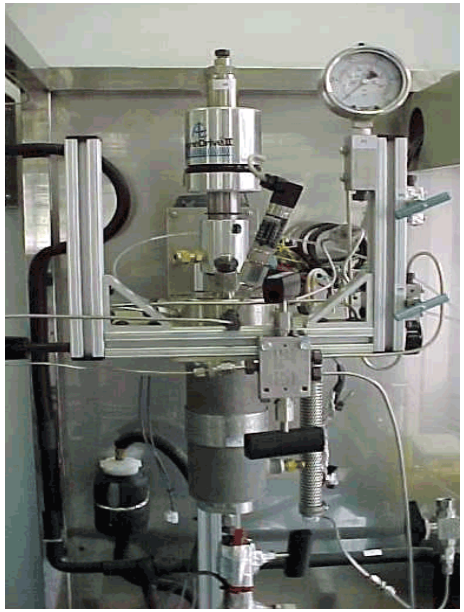




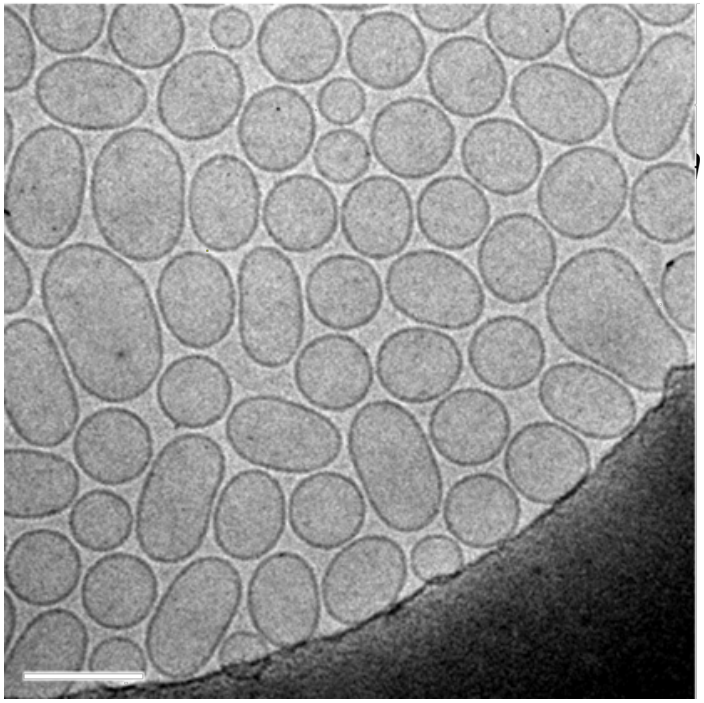
M. Cano- *et al, Langmuir*, 2008, 24, 2433-2436

***Patents*: WO2006079889; EP 1843836; US2007259971; CA 2566960**

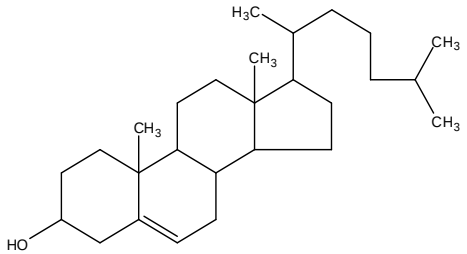
DELOS-SUSP: Preparation of Small Unillamelar Vesicles (SUVs)



Compressed CO_2



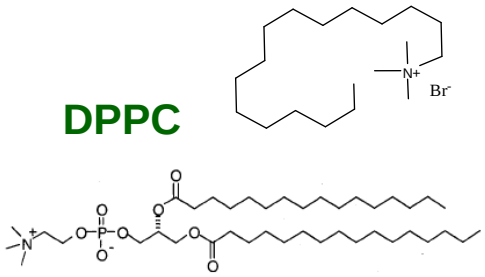
Cholesterol (Col)



CTAB

EPC

DPPC



Nanovesicles with ϕ ~ 100 nm

Prepared in different buffers and organic solvents

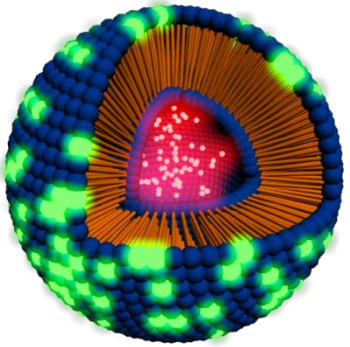
DELOS-SUSP method

Aqueous dispersions of drugs encapsulated or integrated in nanovesicles

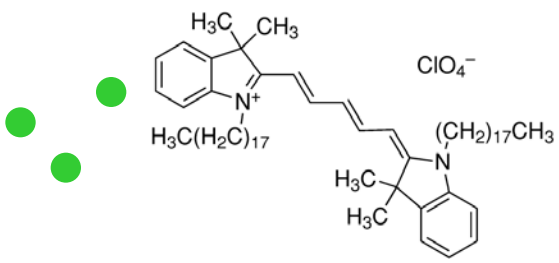
Integration of Bioactive Principles into SUVs

Compressed CO_2

Integration on surface & inside of SUVs

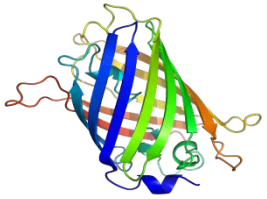


Functionalization



DiD

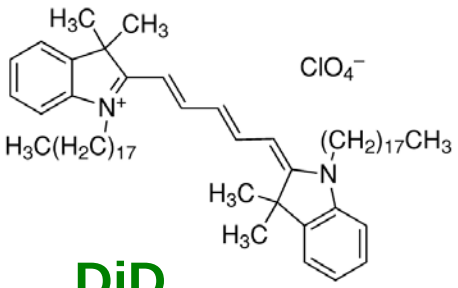
Encapsulation



GFP

Integration of Bioactive Principles into SUVs

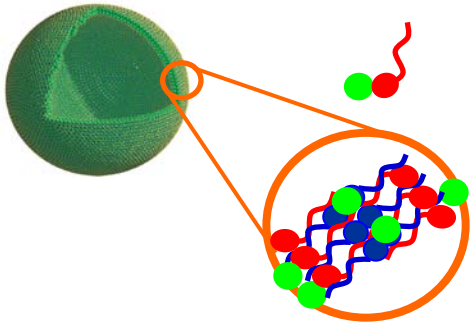
Functionalization on the surface of SUVs



DiD

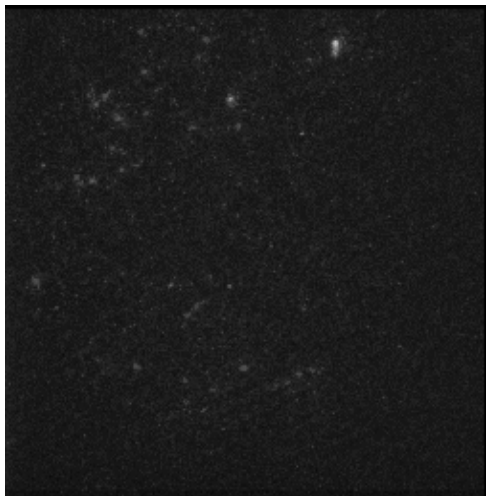
Compress CO_2 methodology

Cholesterol:CTAB and Cholesterol:DPPC vesicles

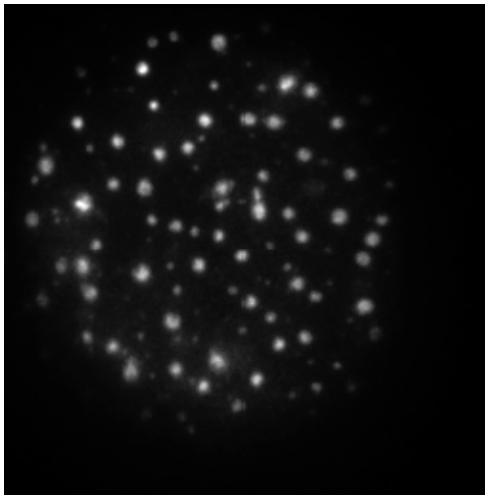


Total Internal Reflextion Fluorescence (TIRF) microscopy images

Beads 100 nm



Free Did

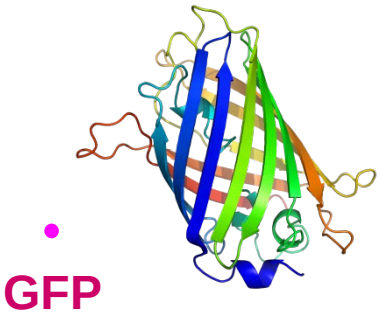


Chol:CTAB vesicles funtionalized with DiD

Collaboration with Dr. María García-Parajo (IBEC)

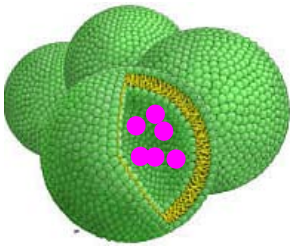
Integration of Bioactive Principles into SUVs

Encapsulation of SUVs with Green Fluorescent Protein (GFP)

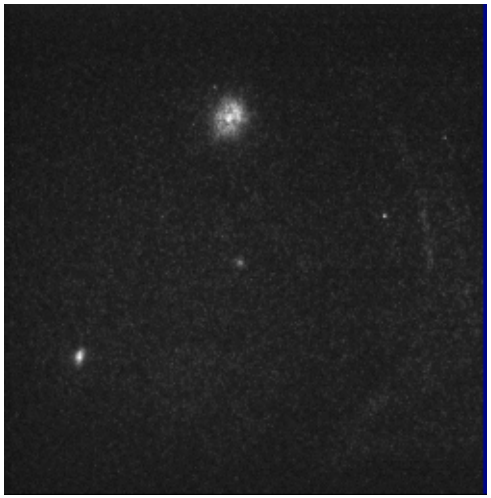


Compressed CO_2 methodology

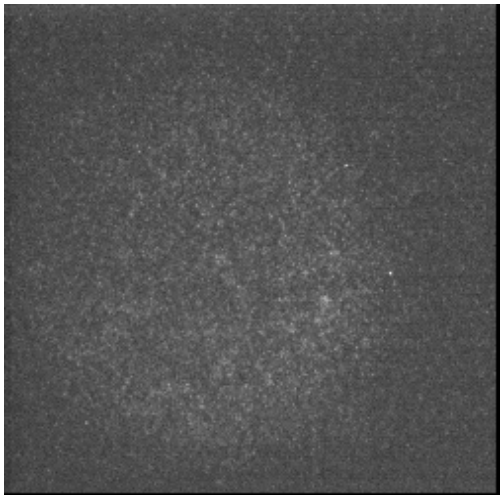
Cholesterol:CTAB vesicles



TIRF microscopy images



GFP



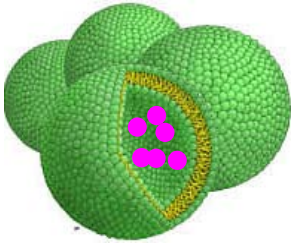
SUVs

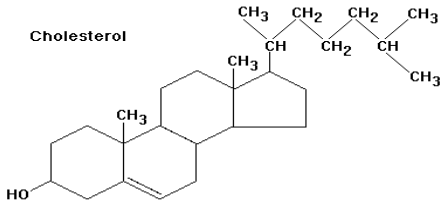
GFP encapsulation in SUVs

Collaboration with María García-Parajo (IBEC-UB)/Antonio Villaverde (IBB-UAB)

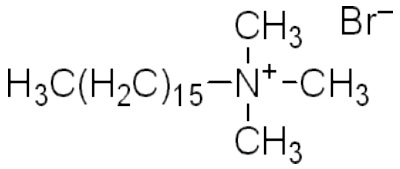
Integration of Bioactive Principles into SUVs

CO_2

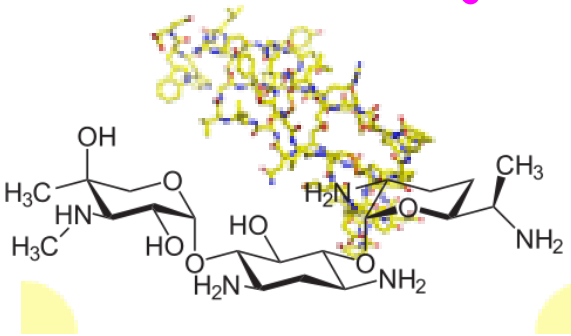




Cholesterol



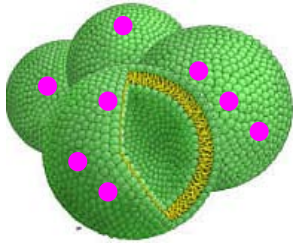
CTAB

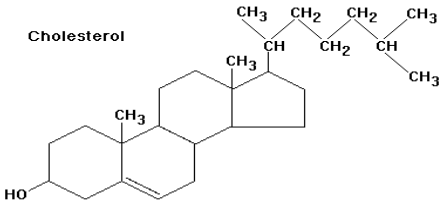


Bioactive small molecules

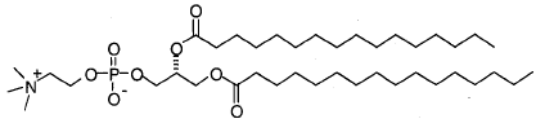
Decoration of Surfaces of SUVs with Bioactive molecules

CO_2

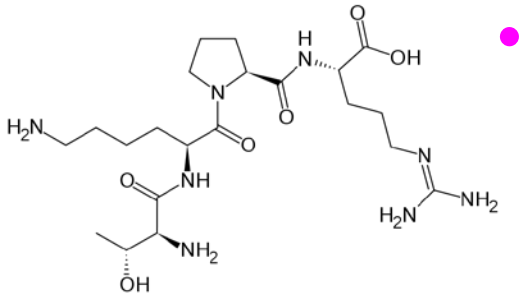




Cholesterol



DPPC



Bioactive small peptides

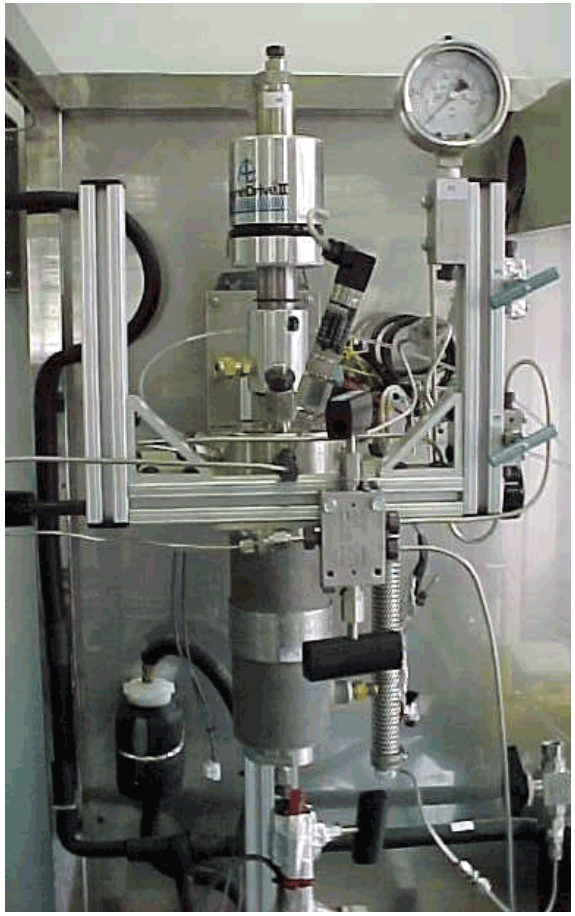
Scaling-up the DELOS methodology

6 mL system

25mL

X 50

300 mL system



1250mL

X 50

2000 mL system

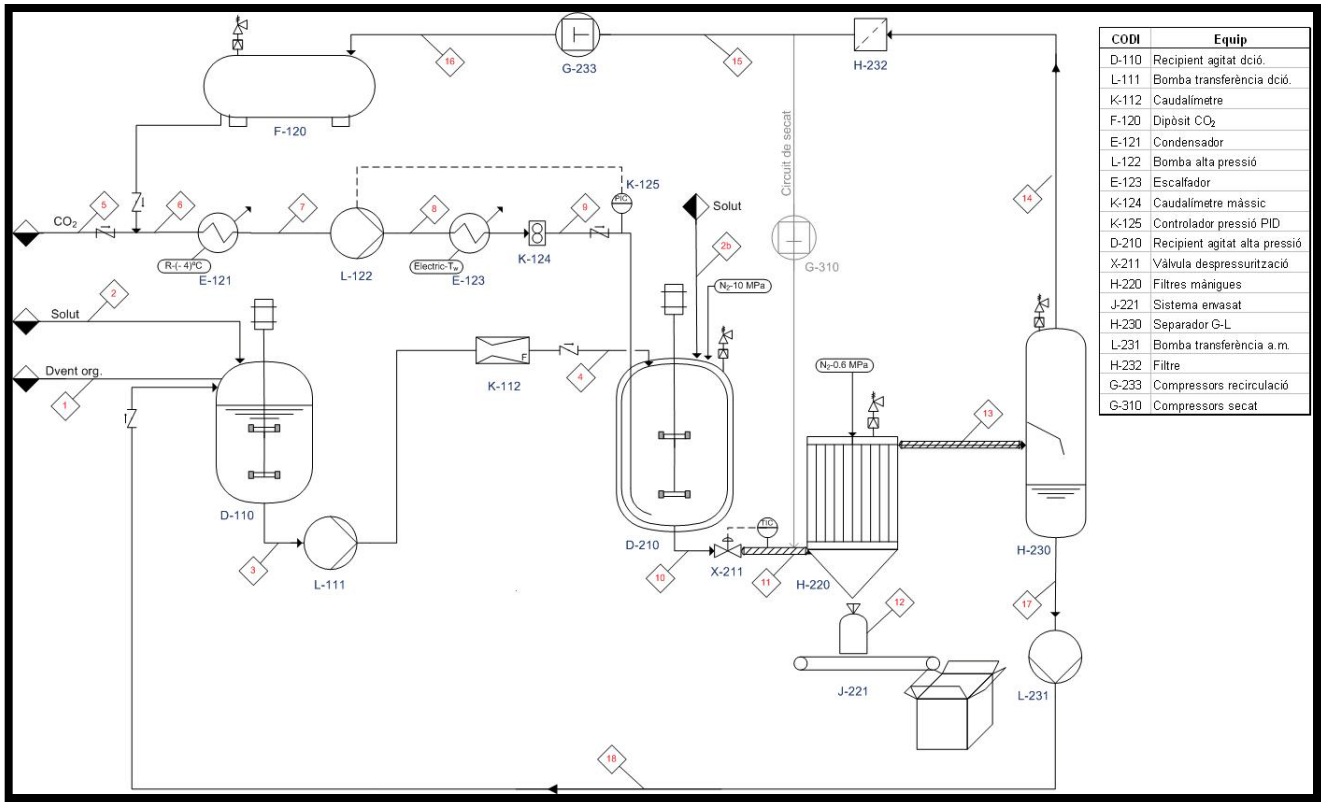
8300mL

E. Elizondo, Doctoral Thesis, 2010

Scaling-up the DELOS methodology

Scale-up viability

Large scale plant (50tons/year)



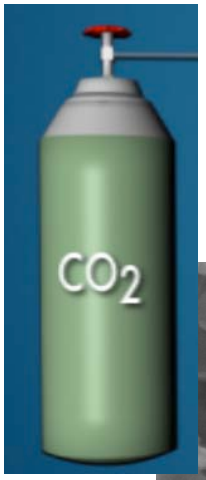
CODI	Equip
D-110	Recipient agitat dció.
L-111	Bomba transferència dció.
K-112	Caudalímetre
F-120	Dipòsit CO_2
E-121	Condensador
L-122	Bomba alta pressió
E-123	Escalfador
K-124	Caudalímetre màssic
K-125	Controlador pressió PID
D-210	Recipient agitat alta pressió
X-211	Vàlvula despressurització
H-220	Filtres mànigues
J-221	Sistema envasat
H-230	Separador G-L
L-231	Bomba transferència a.m.
H-232	Filtre
G-233	Compressors recirculació
G-310	Compressors secat

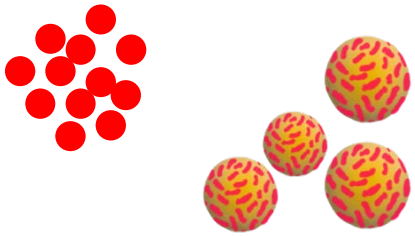
Economically and environmentally viable in comparison to conventional precipitation processing

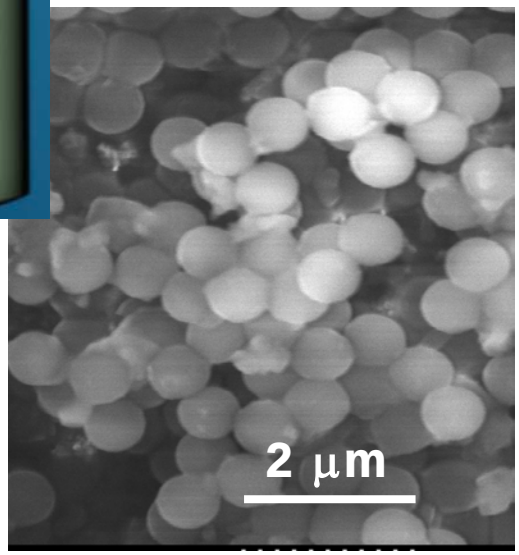
A. Cordoba *et al.* submitted

Conclusions

DELOS as a technological platform for particle engineering with compressed fluids





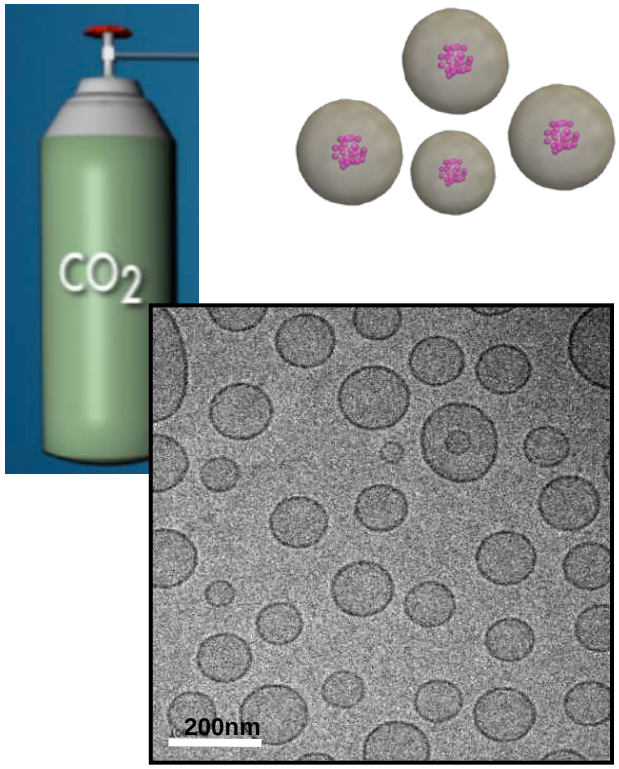


- Single-step process
- High batch-to-batch conformity
- Low solvent consumption
- Pure polymorphic phases produced
- Processing fragile drug molecules

Easy scale-up and low environmental impact

Conclusions

DELOS-SUSP as a technological platform for vesicle engineering with compressed fluids



- Single-step process
- High batch-to-batch conformity
- Low solvent consumption
- Fragile bioactive molecules can be processed
- SUVs with high uniformity
- Functionalization of SUV membranes
- Encapsulation of drugs

Easy scale-up for drug loading into nanovesicles

Acknowledgments

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Bioingenieria, Biomateriales y Nanomedicina

CSIC

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Thanks for your attention!

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