ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
National Hellenic Research Foundation

Design and development of multi wall-carbon nanotube –liposome drug delivery platforms

Natassa Pippa, Demetrios D Chronopoulos
Costas Demetzos, Nikos Tagmatarchis

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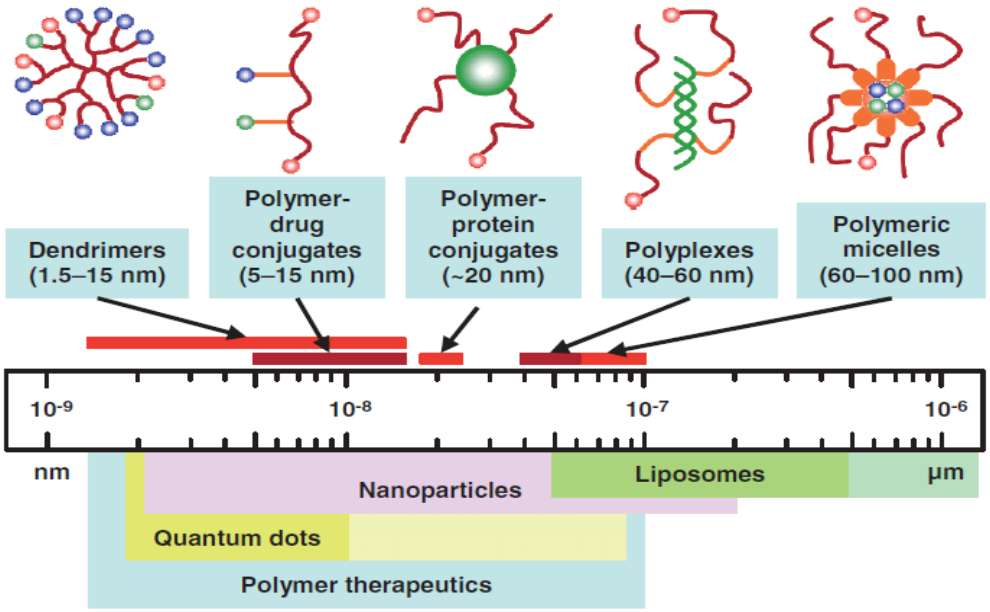
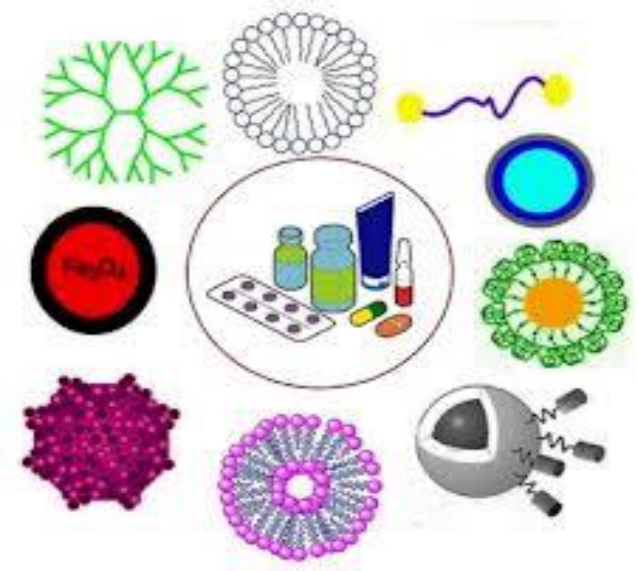
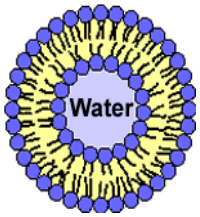
Drug Delivery Systems

According to Rowland et al., (2012):
"A Drug Delivery System (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body."

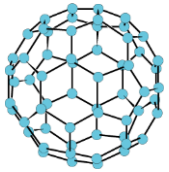




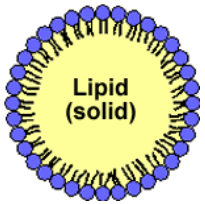
Drug Delivery nano Systems:

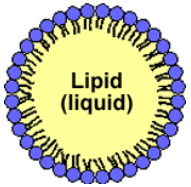


Liposomes



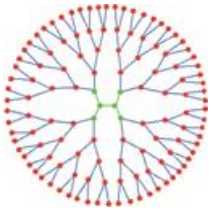
Fullerenes



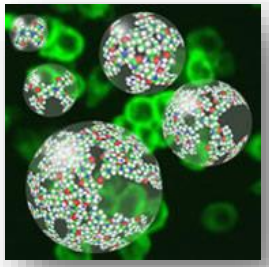


Solid Lipid Nanoparticles

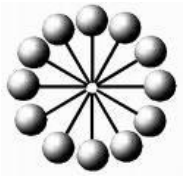
Nanoshells



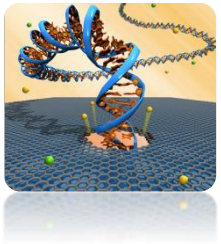
Dendrimers

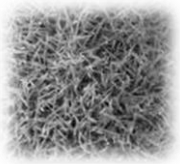


Nanoemulsions

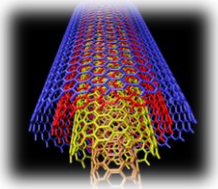


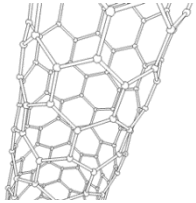
Micelles





nanopores and nanoneedles



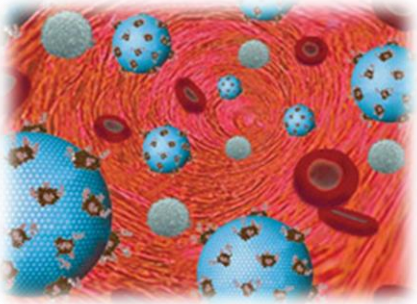


Nanotubes

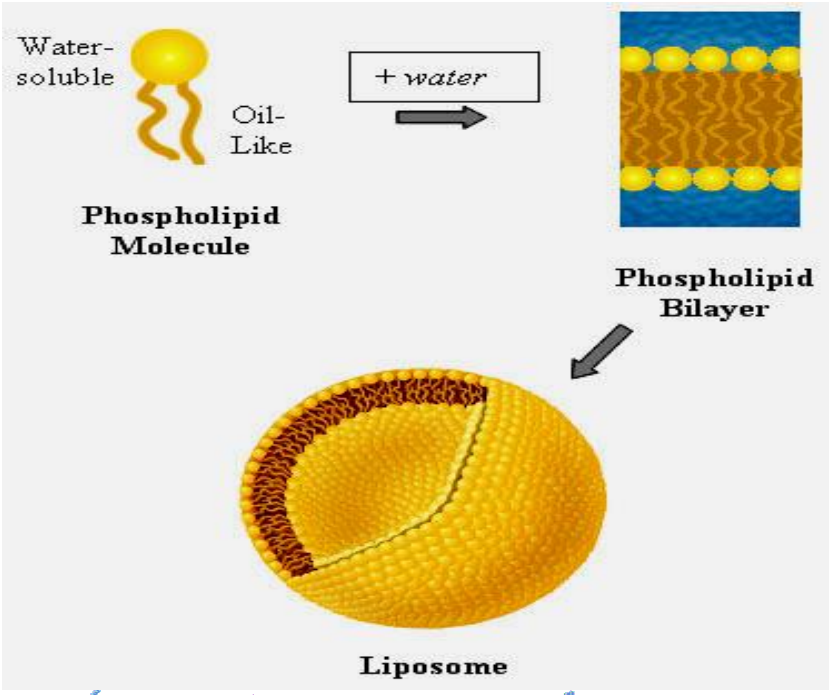
These materials are characterized by softness (synonymous with deformability).

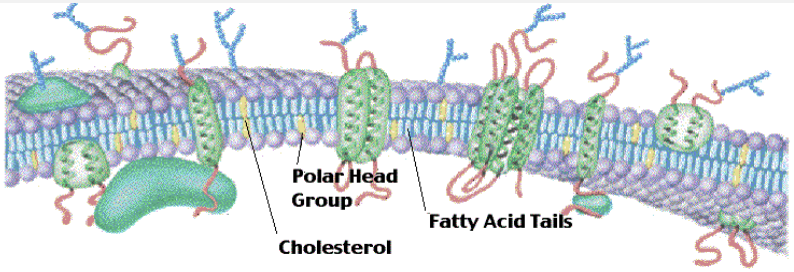
Nanostructured drug carriers allow for the delivery not only small-molecule drugs but also the delivery of nucleic acids and proteins.

Liposome in drug delivery:



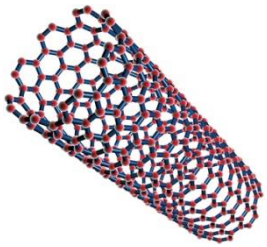
Spherical vesicles with a phospholipid bilayer





- Pharmacokinetics- efficacy and toxicity
- Change the distribution and absorption
- Deliver drug in desired form
- Multidrug resistance
- Decrease harmful side effects

Carbon nanotubes in drug delivery:

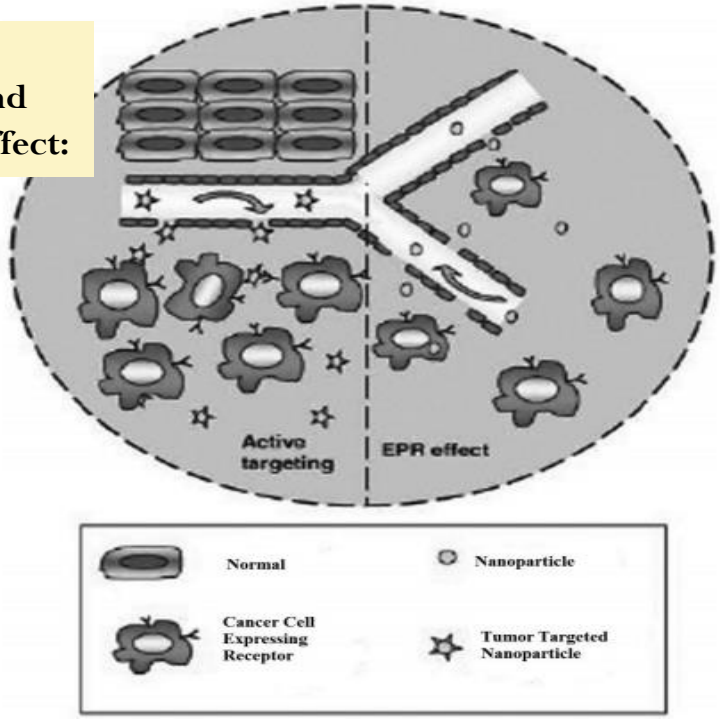


- Functionalized CNTs
  - Diagnosis and Imaging
    - Cancer therapy
    - Gene therapy
    - Tissue engineering
    - As antioxidants
  - Therapeutics
    - Biosensors
    - Enantioseparation of chilar drugs
    - Extraction of chemicals

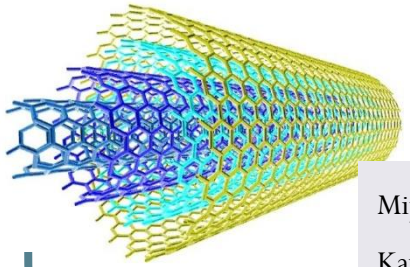
Delivery of anticancer drugs:

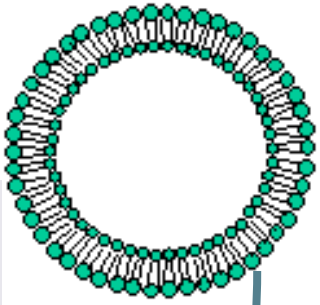
- Reduced toxicity
- Increased circulation period
- Active targeting
- Reduced side effects
- Controlled toxicity

Enhanced permeability and retention (EPR) effect:



Advanced drug delivery nano systems:





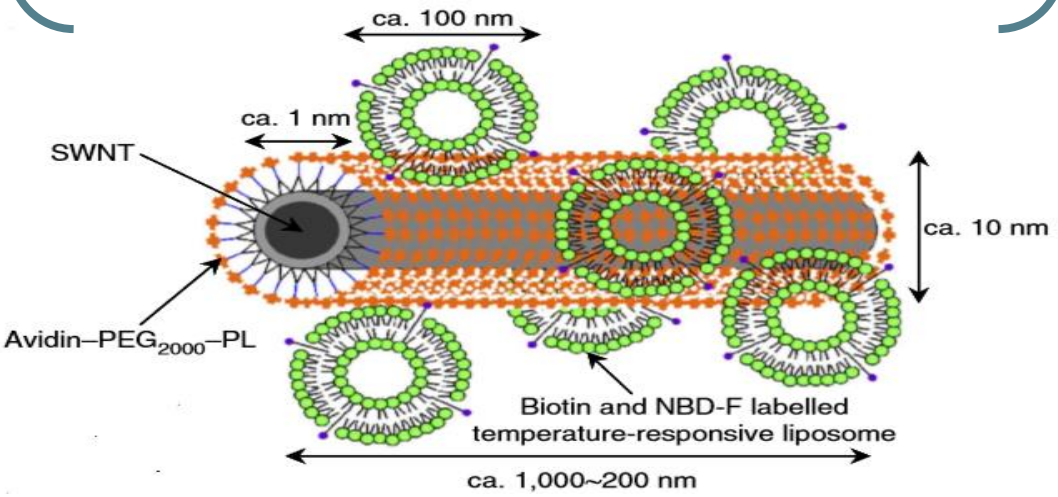
Miyako et al., 2012

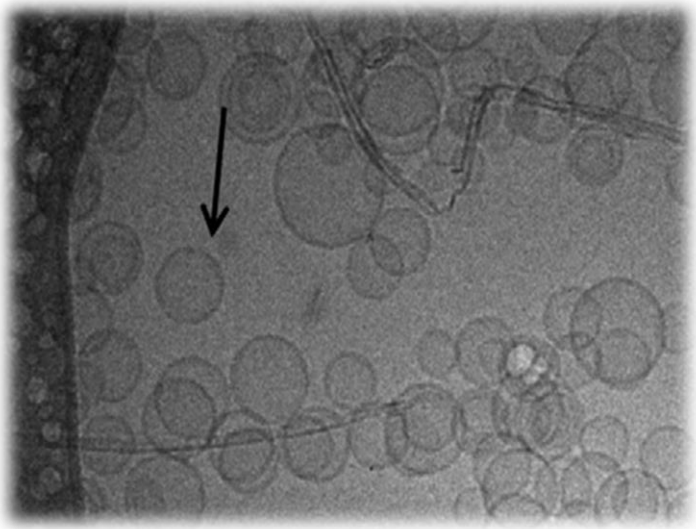
Karchemchi et al., 2012

Pereira et al., 2015

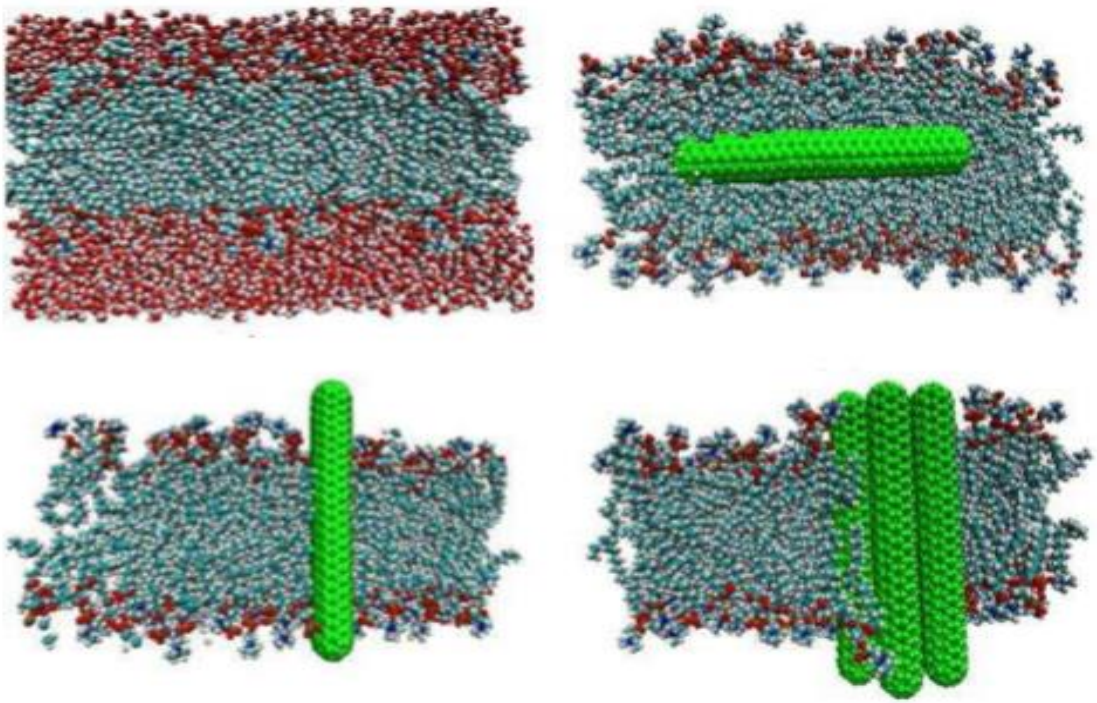
- Carbon nanotubes –liposome **conjugate**
- Carbon nanotube –liposome **supramolecular nanotrains**
- Cationic liposome-multiwalled carbon nanotube **hybrids**

- Co-delivery of si-RNA and cytotoxic drugs
- Efficient cell uptake
- High drug loading
- Biomimetic molecular transport systems
- Lab-on-chip applications





Differential Scanning Calorimetry: interactions between lipid bilayers and MWCNTs

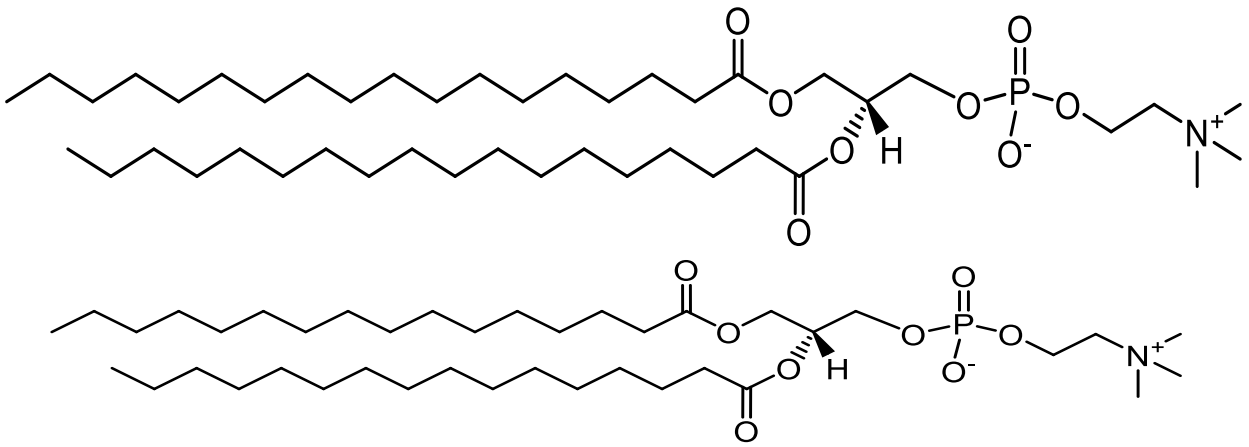


Local perturbations in the lipid structure caused by the nanotubes could lead to enhance penetration of molecular compounds across the membrane.

The membrane swells due to the presence of the nanotubes, in particular, when a bundle of nanotubes is found within the membrane. When one nanotube is parallel to the membrane and located at its center, only small structural differences are observed compared to the pristine membrane.

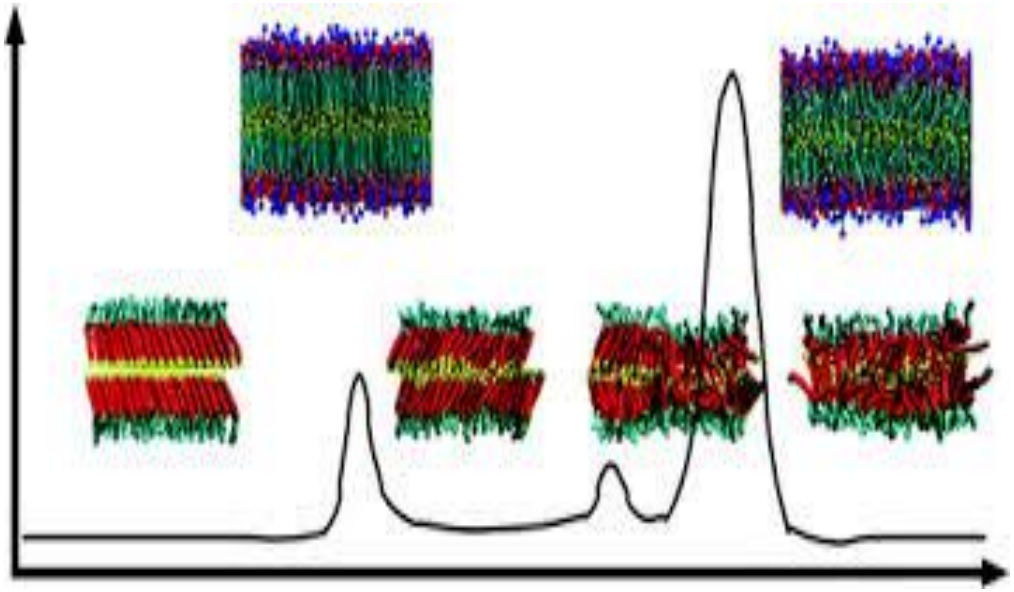
J. Phys. Chem. B 2012, 116, 12769−1278

Materials:



HSPC Tm=52°C

DPPC Tm=41°C



The pure DPPC and HSPC membranes hydrated in HPLC grade water undergo two endothermic phases: a broad low enthalpy pretransition from gel ($L_{\beta'}$) to rippled ($P_{\beta'}$) phase centered at 36.5°Cand 47.9°C and a sharp-major transition from $P_{\beta'}$to liquid crystal phase (L_a) at 41.9°C and 53.6°C, respectively.

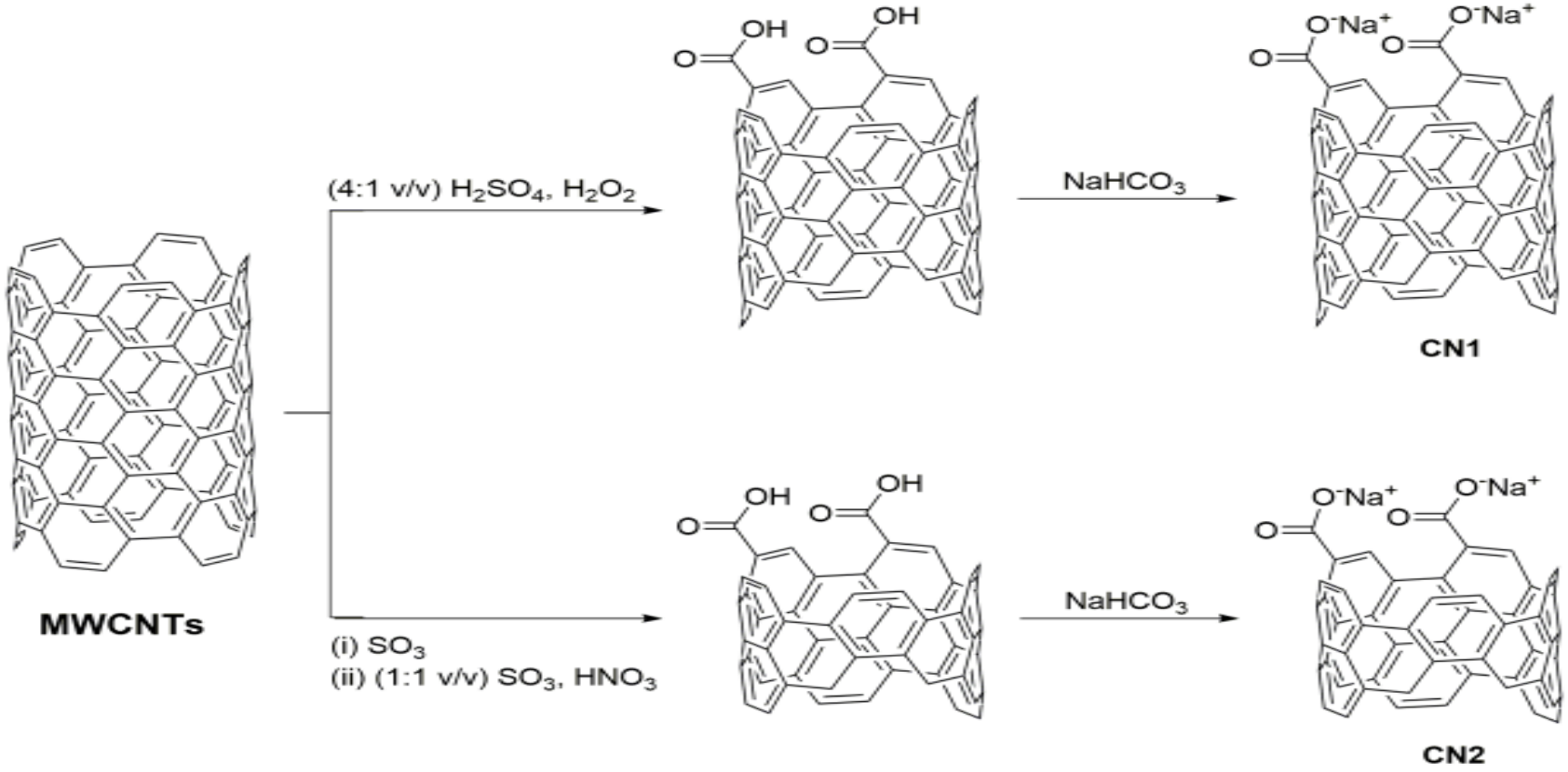
Ref. Koynova R., Caffrey M., Phases and phase transition of the phosphatidylocholines, Biochim. Biophys. Acta 1376, 91-145, 1998


phillipmartin.info

Synthesis:

Dr. Nikos Tagmatarchis

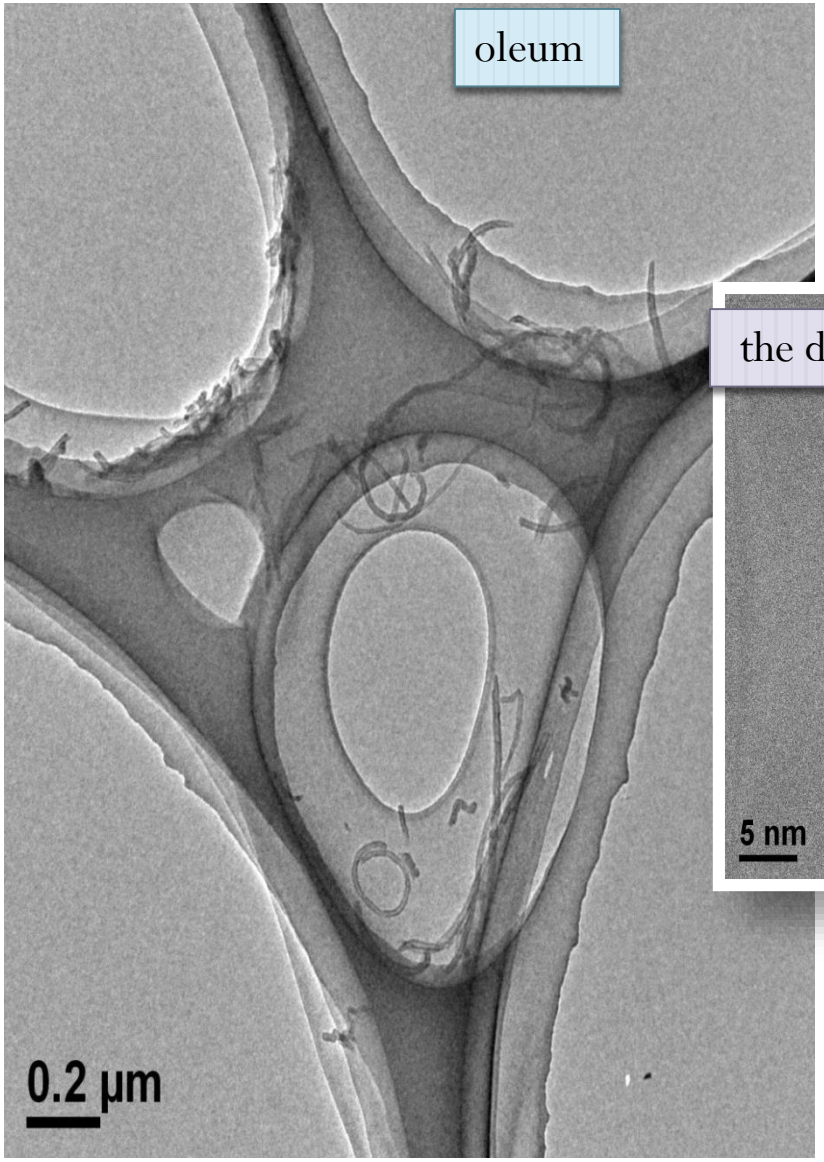
Dr. D. Chronopoulos



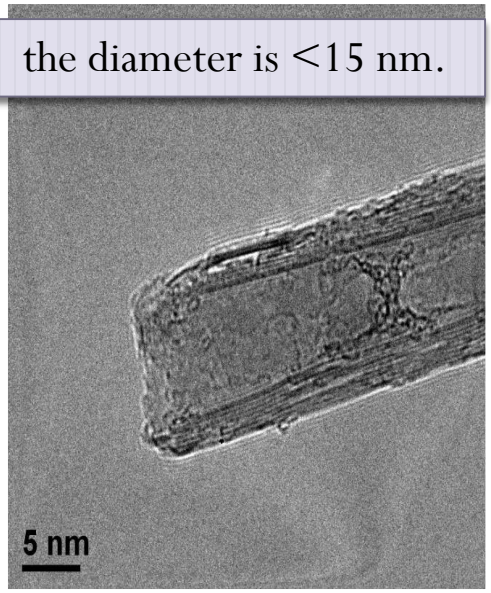
Images

mixture sulfuric acid and hydrogen peroxide

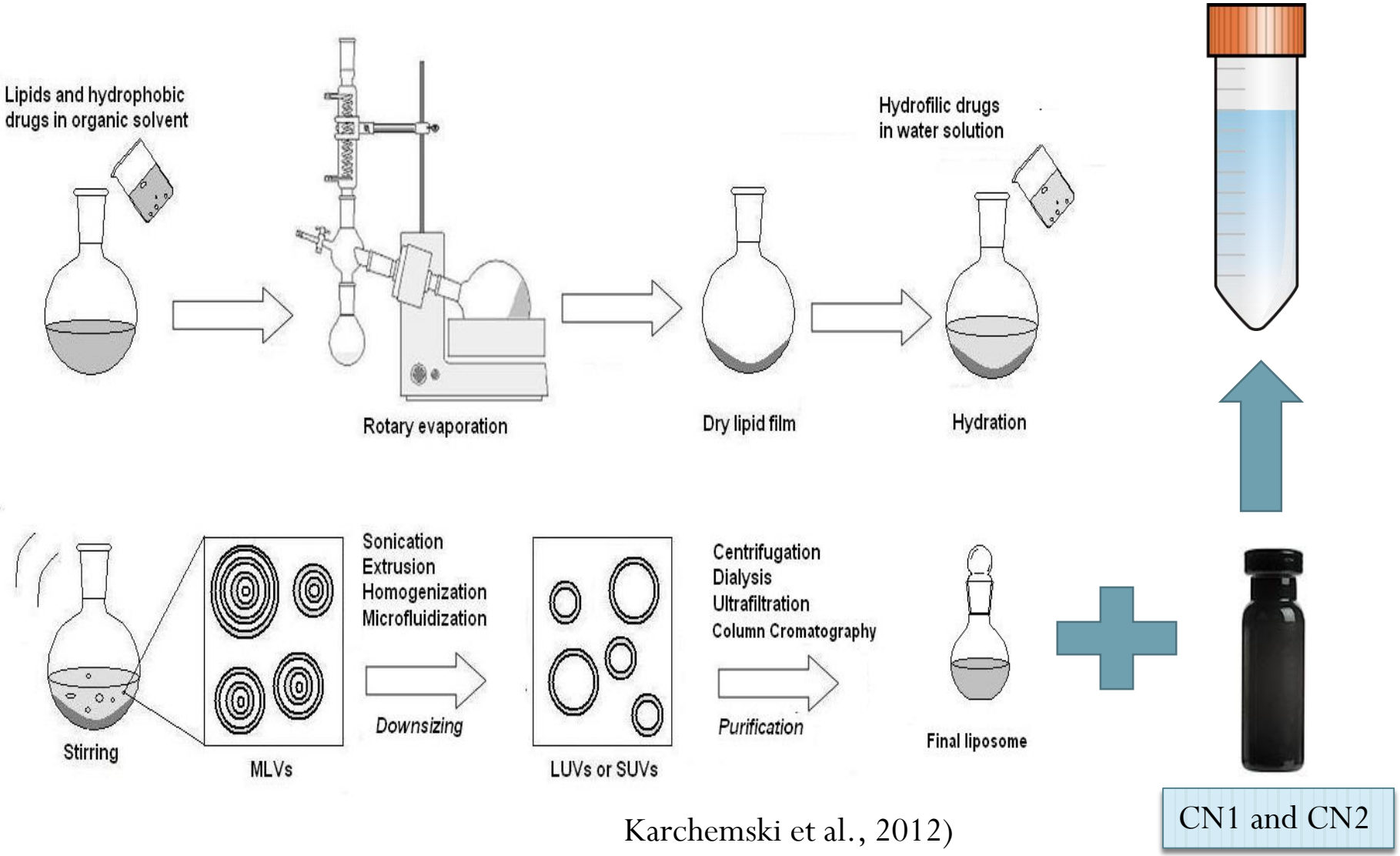
oleum



the diameter is <15 nm.



Preparation of multi wall-carbon nanotube –liposome drug delivery platforms



Karchemski et al., 2012)

Methods:

Thermodynamic and Biophysical Characterization

- Differential Scanning Calorimetry

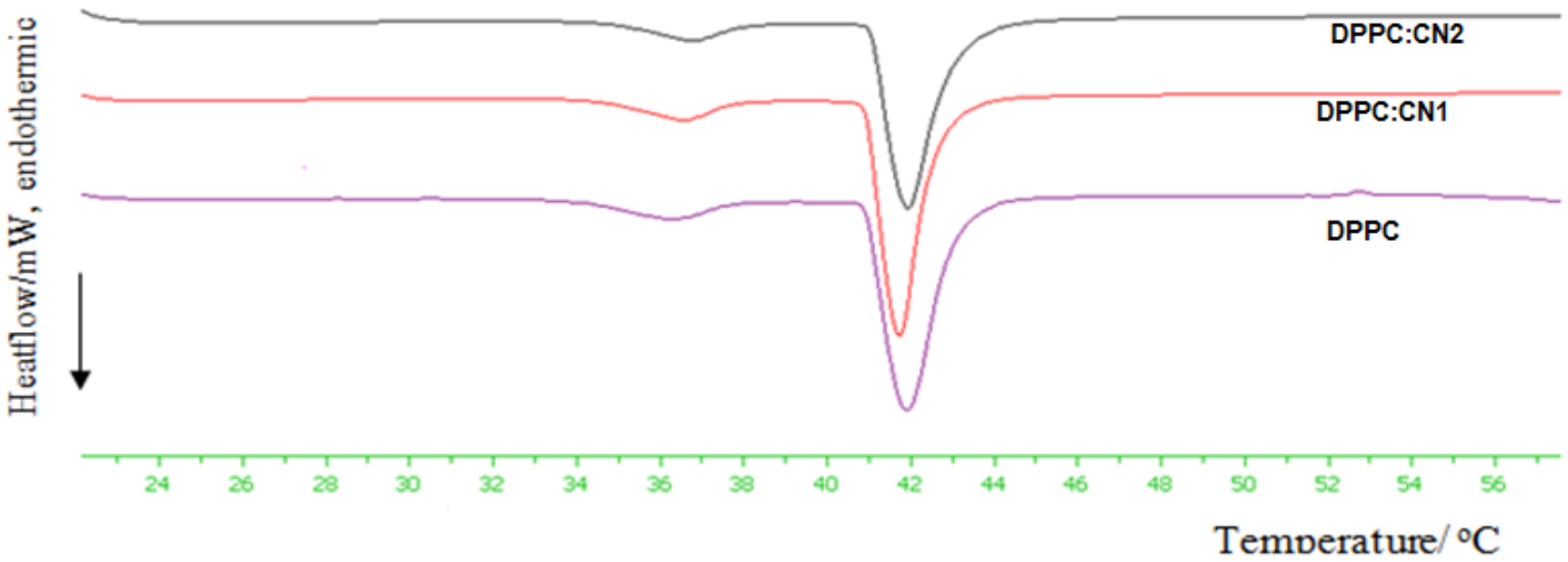
Physicochemical Characterization

- Dynamic and Electrophoretic Light Scattering

Biological evaluation

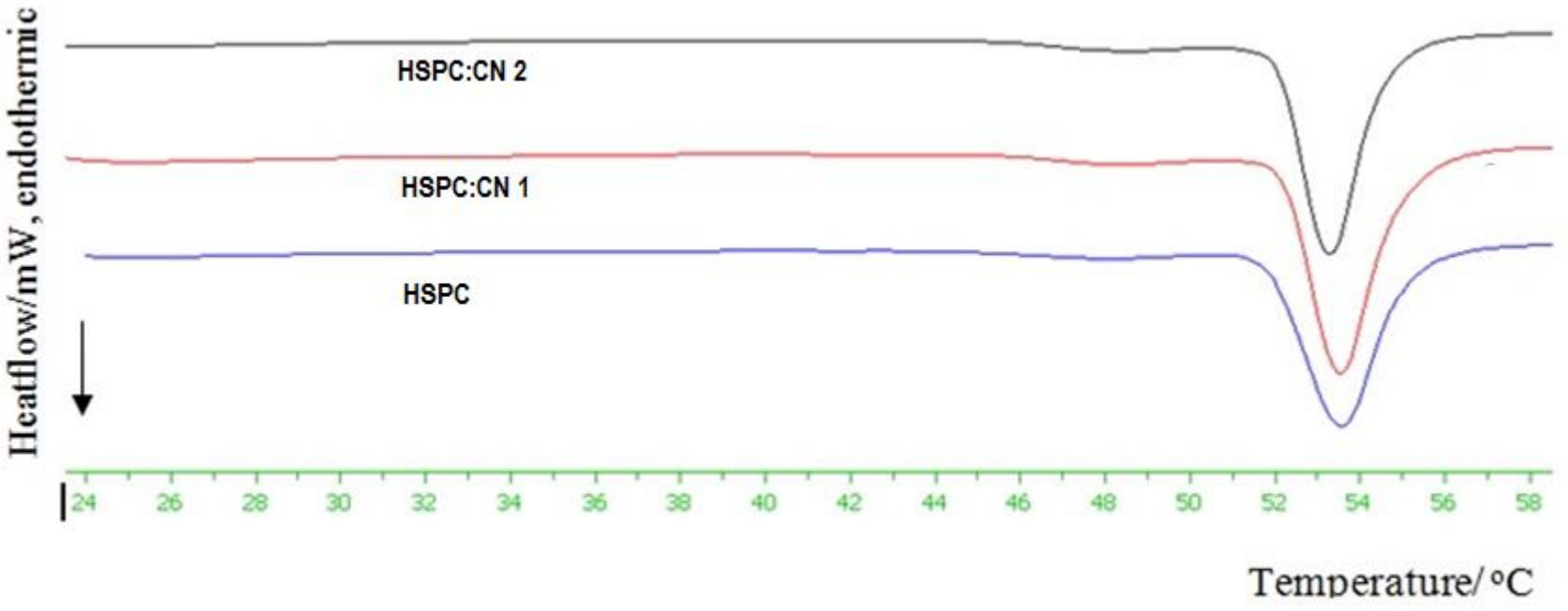
- In vitro screening

Differential Scanning Calorimetry: DPPC bilayers



- The main transition temperature, which corresponds to the mobility of the acyl chains of phospholipids, remains unaffected for all the samples.
- The transition enthalpy ΔH_m decreased with the presence of MWCNTs. According to the phase transition behavior of liposomes, on heating, there is increased head group mobility and water penetration into the interfacial region of the bilayer.
- The temperature or the pretransition effect decreased and this phenomenology indicates strong interactions between the polar groups of DPPC lipid and MWCNTs.

Differential Scanning Calorimetry: HSPC bilayers



- the pretransition effect decreased and this phenomenology indicates strong interactions between the polar groups of HSPC lipid
- when nanotubes are parallel to the membrane and located at its center, only small structural differences are observed compared to pure lipid membrane

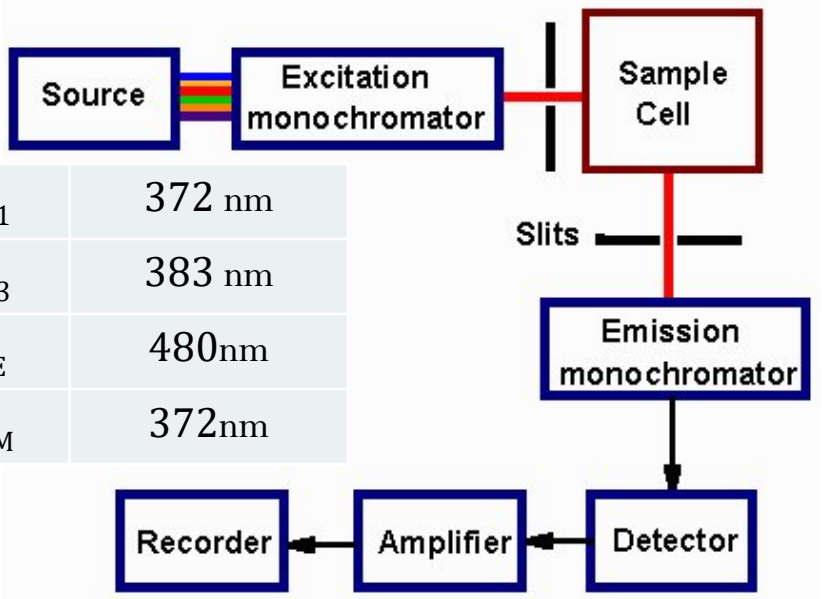
Physicochemical characteristics:

System	D_h (nm)	SD	ζ-pot (mV)	SD
CN1	349.0	10.0	-23.3	2.1
CN2	149.2	0.7	-21.4	0.1
HSPC	126.6	1.6	+3.5	0.1
DPPC	178.4	0.7	+3.6	0.1
HSPC:CN1	148.8	2.4	-1.9	0.8
HSPC:CN2	196.0	4.2	-3.2	2.7
DPPC:CN1	193.6	2.6	+4.5	0.8
DPPC:CN2	282.1	10.6	+3.1	0.6

- The presence of CNTs reduce the size of HSPC/DPPC mixed nanocarriers
- The ζ-potential values of mixed nanocarriers are near zero
  - This observation indicates the effective incorporation of MWCNTs into the lipid bilayer of liposomes and absence of surface charge into mixed liposomal surface

Fluorescence spectroscopy:

System	I_1/I_3	I_E/I_M
HSPC	1.42	0.29
DPPC	1.55	0.26
HSPC:CN1	1.58	0.59
HSPC:CN2	1.65	0.18
DPPC:CN1	1.37	0.66
DPPC:CN2	1.58	0.61



I_1	372 nm
I_3	383 nm
I_E	480nm
I_M	372nm

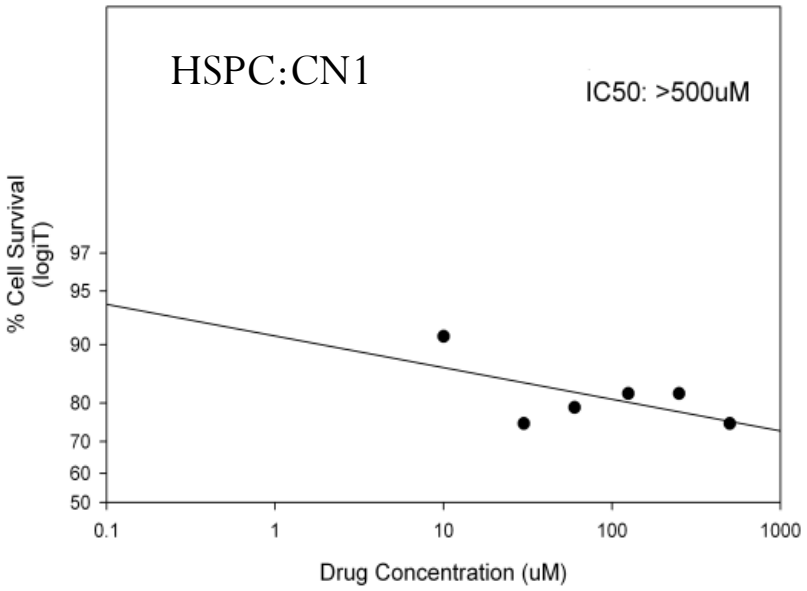
- $\uparrow I_1/I_3 \rightarrow \uparrow$ micropolarity
- $\uparrow I_E/I_M \rightarrow \uparrow$ microfluidity $\rightarrow \downarrow$ micro-viscosity

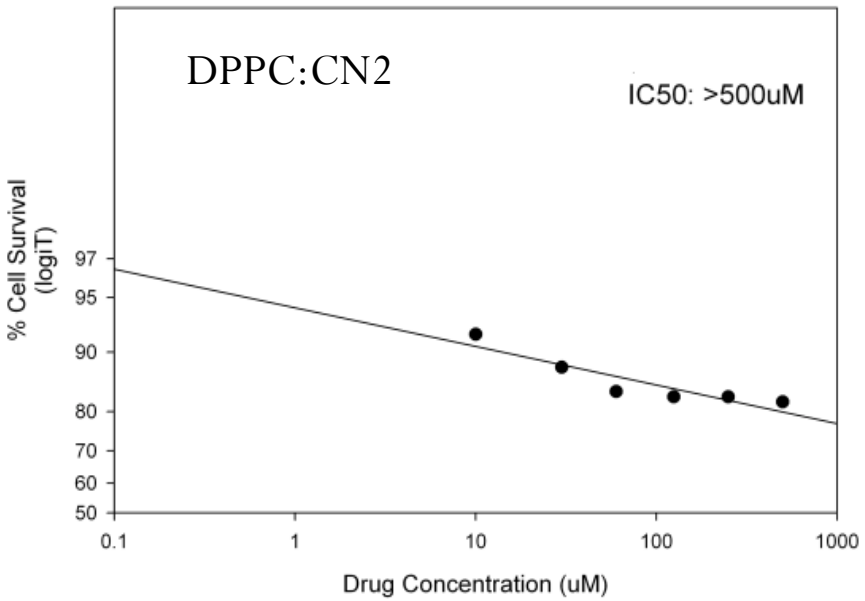
•For mixed nanostructures the micropolarity increased.

•This may be correlated to the way that the carbon nanotubes are incorporated into the lipid tails region, which apparently results in minimum changes in the micropolarity.

•The microfluidity also increased.

Toxicity studies: *In vitro* screening:



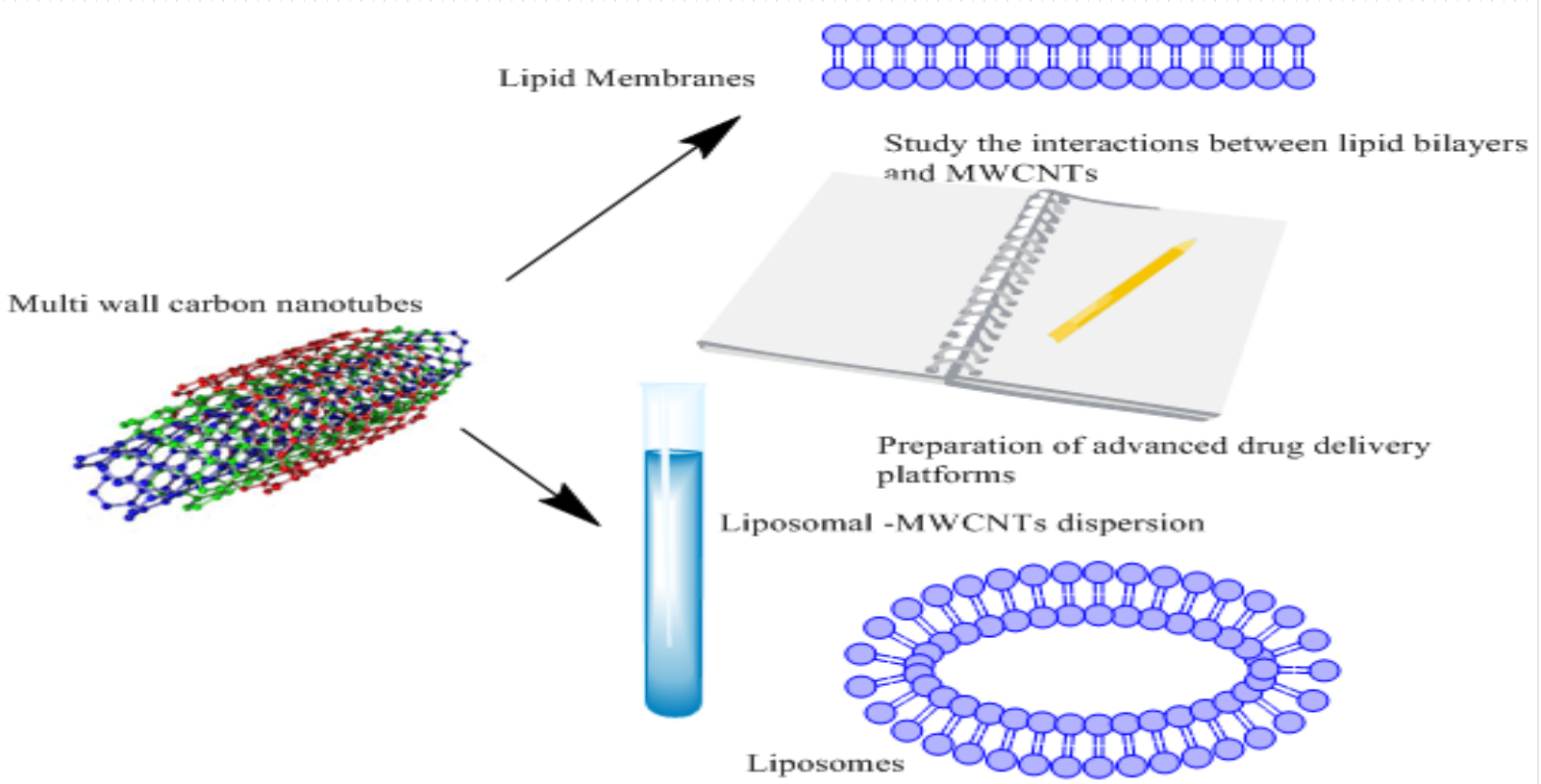


- Low toxicity of the vast majority of the lipid/MWCNTs nanocarriers, even at high concentrations i.e. 500μM
- The IC50 values for HSPC/MWCNTs vesicles and DPPC/MWCNTs nanocarriers are grater than 500 μMin all cases

Conclusions:

Design and Development of advanced drug delivery systems

Interactions between the components



Acknowledgements:

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Dr. D. Chronopoulos

Organizing Committee
Hellenic Society for Biomaterials

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ESB 2017

4-8 September 2017 *Athens*

Megaron Athens International Conference Centre

Save the Date

Important dates

On-line registration opens:	1 December 2016
On-line abstract submission opens:	1 December 2016
Abstract Submission deadline:	31 January 2017
Notification to authors:	20 May 2017
Early-bird registration deadline:	31 May 2017

CONVENTION

Organizing Secretariat
PCO CONVIN S.A. 27 Kostis Varnalis St.
15233, Chalandri Athens, Greece
T.: +30 210 6833600 F.: +30 210 6827700
E.: congress@pco-convin.gr W.: www.pco-convin.gr

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