"ωφελέειν, εἰ μη βλάπτειν"

'benefit and do not harm'

National & Kapodistrian University of Athens

Pharmaceutical Nanotechnology

Liposomes as drug delivery systems

Biopysical and Thermodynamical considerations

Costas Demetzos

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Faculty of Pharmacy,
National and Kapodistrian University of Athens

President of Hellenic Pharmaceutical Society

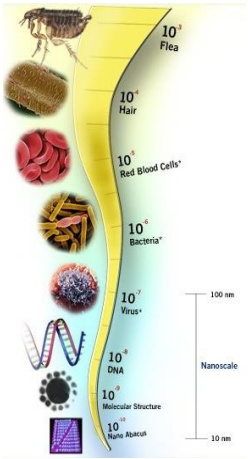
Member of the Executive Committee of European Federation of Pharmaceutical Sciences (EUFEPS)

What is nanotechnology ? Milestones

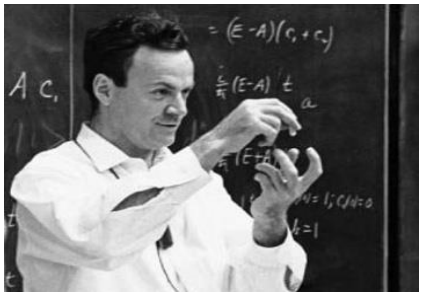
- Nanotechnology is defined as the application of the technology in the gray area between the classical mechanism and quantum mechanics.
- The first report of nanotechnology was from Richard Feyman
- Prof. Nario Tanaguchi was the first to introduce the term nanotechnology from the University of Sciences in Tokyo, in 1974.
- In 1995, FDA approved Doxil (liposomal doxorubicin) to cure cancer.
- In 2012 the first report on bio-mimetic drug delivery nano systems was published
- In 2015 ThermoDox (thermosensitive liposomal doxorubicin) successfully evaluated in clinical trials (Phse III).
- In 2015 FDA approves Onivyde (liposomal irinotecan) for adavanced pancreatic cancer

Ref. Saladin Nanotechnology for the development word. *Chaos Solition Fractals* 30 (4): 769-773, 2006

Ref. C. Demetzos. Pharmaceutical Nanotechnology. 2016, Springer



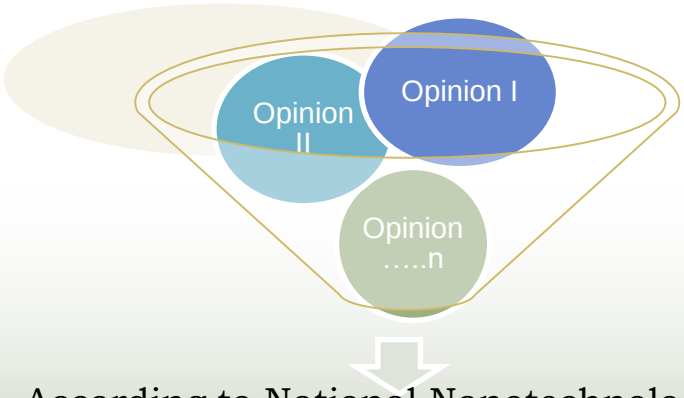
Nanotechnology is the art for producing little devices and machines at the mesoscopic and molecular scale.



Pharmaceutical Nanotechnology

is considered to be an attractive area of colloidal drug delivery nanocarriers.

Could be defined as the novel and practical applications of the scientific knowledge



According to National Nanotechnology Initiative (U.S.A)

Nanotechnology is the understanding and control of matter at dimensions between 1 to 100 nanometers

Nanotechnological platforms can

- alter the pharmacokinetic properties and tissue distribution
- ↑ therapeutic efficiency
- ↓ adverse effects

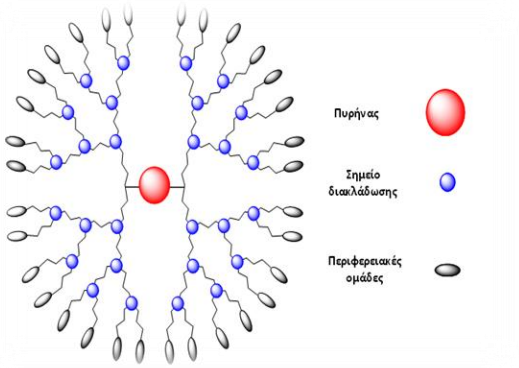
According to E.M.A :

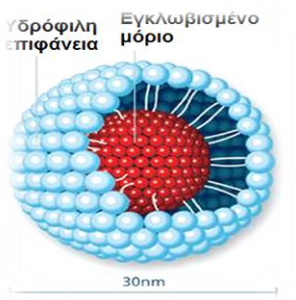
*Nanotechnology is defined as the production and application of structures, devices and systems by controlling the **shape** and size…..*

Ref. National Nanotechnology Initiative. U.S.A government initiative launched in 2001 2007; http://www.nano.gov; Bloomberg Law Reports, Bloomber Finance L.P.2010

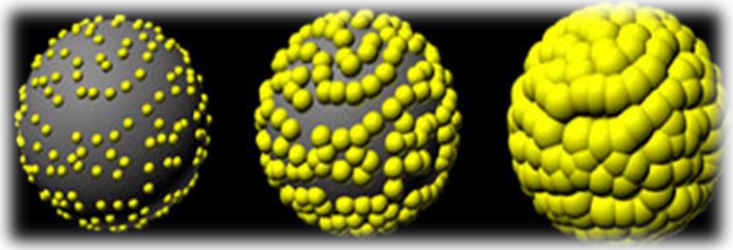
Biomimetic materials with self-assembly abilities are used for producing nano-systems.

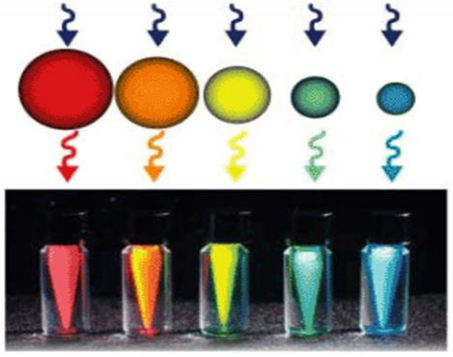
These nano-systems can be used as drug delivery platform, in imaging and in diagnosis

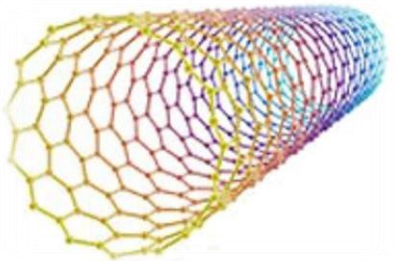


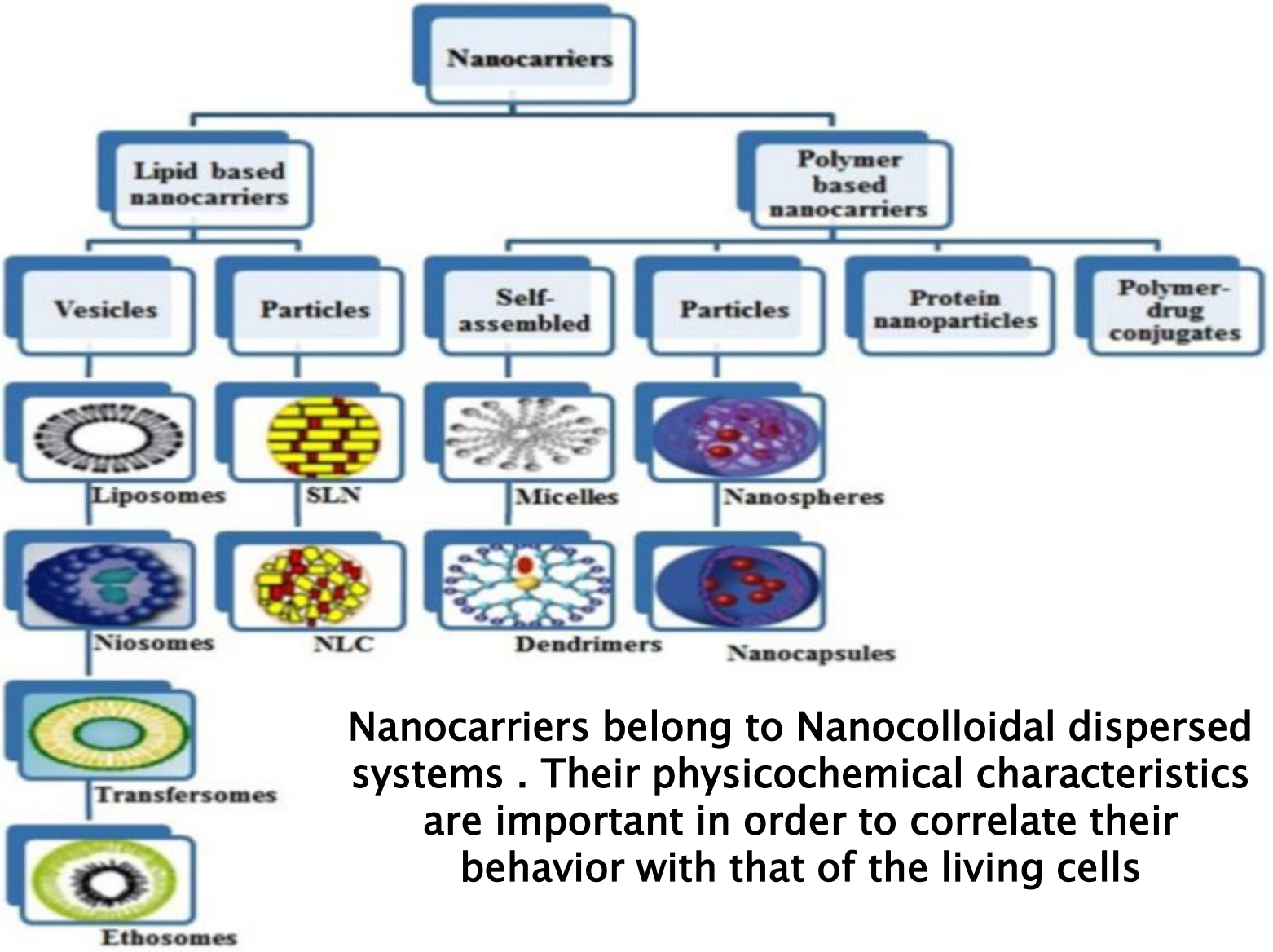


- **Liposomes**
- **Lipidic nanostructures**
- **Nanotubes**
- Nanoemulsions
- **Polymeric micelles**
- **Polyelectrolytes**
- **Dendrimers**
- **Chimeric nanostructures**
- Nanocapsules and nanospheres (10-1000nm)
- Nanoshells
- Nanocrystals Qd
- Magnetic nanoparticles
- etc.







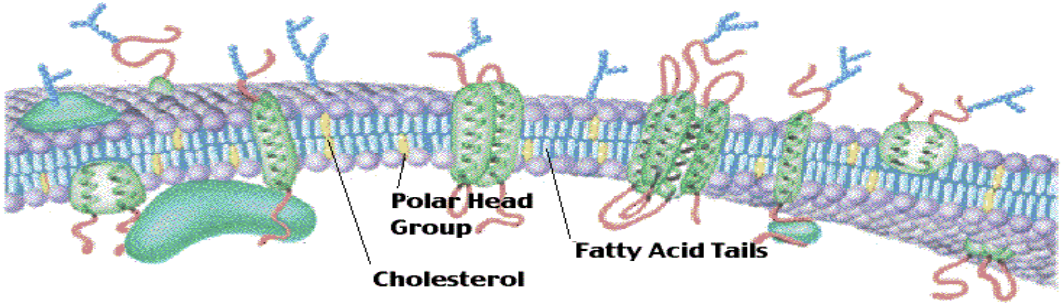


Nanocarriers belong to Nanocolloidal dispersed systems . Their physicochemical characteristics are important in order to correlate their behavior with that of the living cells

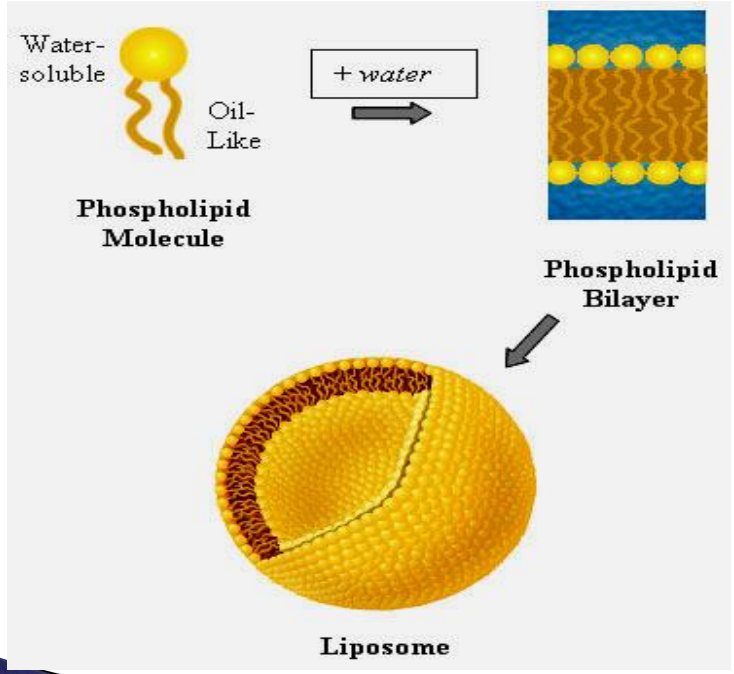
M. Estanqueiro et al. / Colloids and Surfaces B: Biointerfaces 126 (2015)631–648

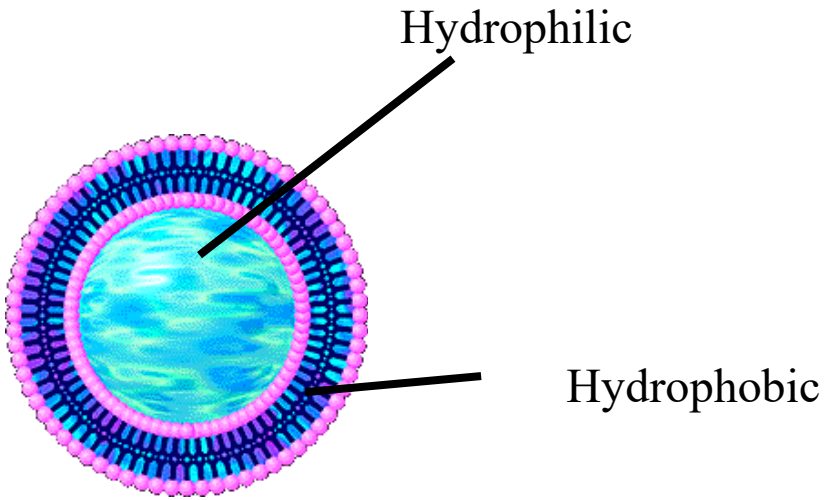
LIPIDIC NANO-PARTICULATE DRIG DELIVERY NANO-SYSTEMS

What is a liposome?



- Pseudo-Spherical vesicles with a phospholipid bilayer





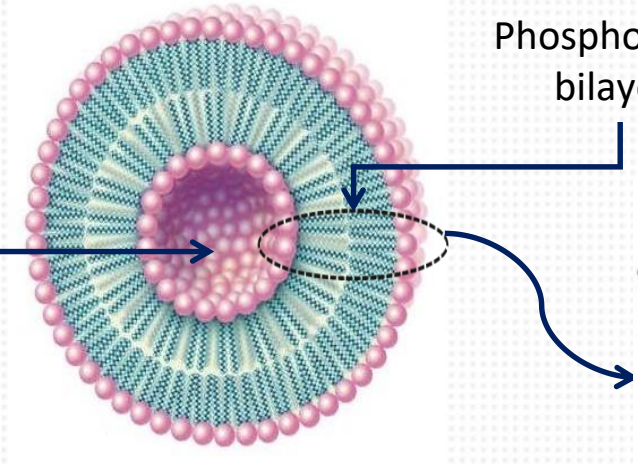
Lipidic self-assembled nano-systems

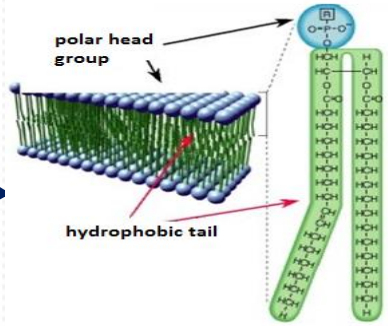
LIPOSOMES

- **Liposomes are colloidal dispersed systems that are able to incorporate bioactive molecules (drugs) and deliver them to the tissues increasing their effectiveness.**

Liposomal technology

- **Drug Delivery**
- **Cosmetics**
- **Food Technology**



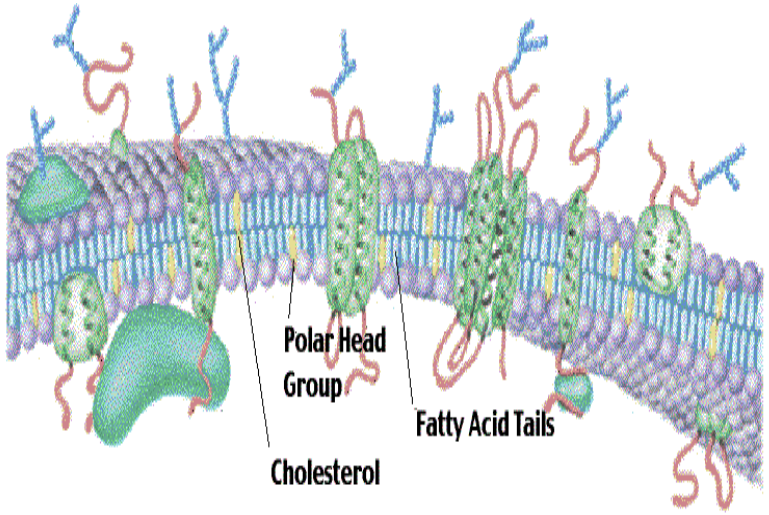


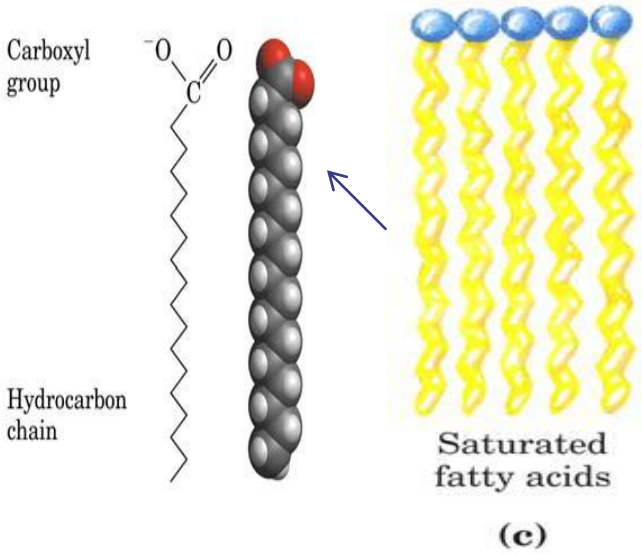
They are composed of

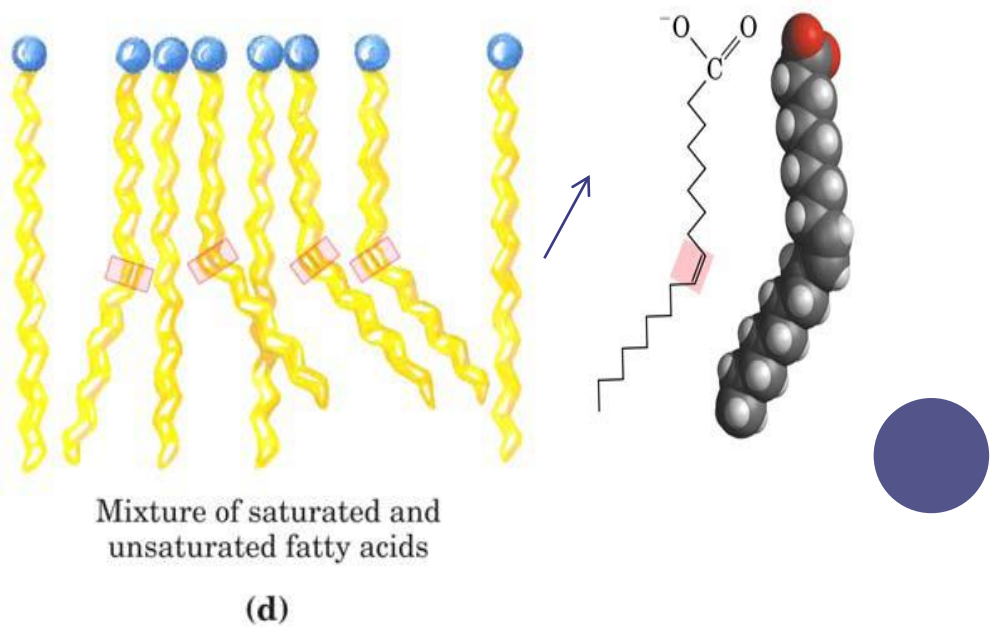
Ref. Demetzos C., '*Pharmaceutical Nanotechnology. Fundamentals and Practical Applications*', Springer, 2016.

ARTIFICIAL PHOSPHOLIPIDIC MEMBRANES FORMING BILAYER CAN MIMIC THE FUNCTIONALITY OF BIOMEMBRANES AND MIMIC THEIR BEHAVIOUR.

The Differences in fatty acid acyl chain of phospholipids explain differences in fluidity of lipid bilayers while the *tans–gauche* conformational transitions are affect biophysical properties and their thermodynamics

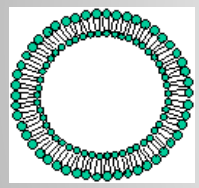




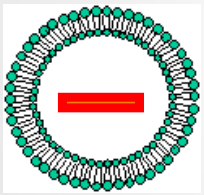


CONVENTIONAL LIPOSOMAL DRUG DELIVERY nanoSYSTEMS

Simple liposomes

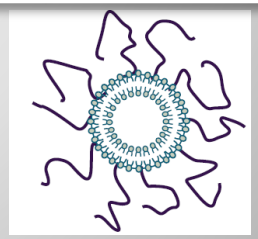


Anionic liposomes



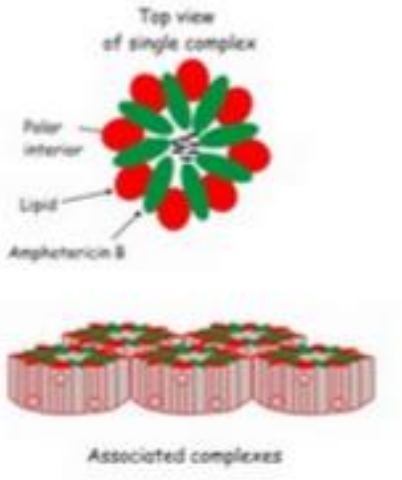
Cationic liposomes

PEGylated (stealth) liposomes



VIDEO

Abelcet ® ABLC

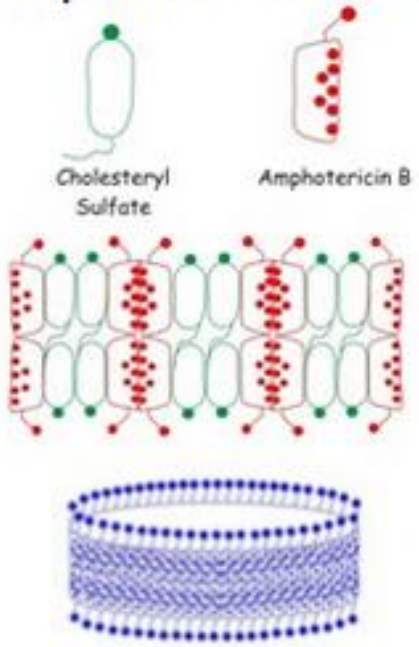


Ribbon-like particles

Carrier lipids: DMPC, DMPG

Particle size (μm): 1.6-11

Amphotec ® ABCD

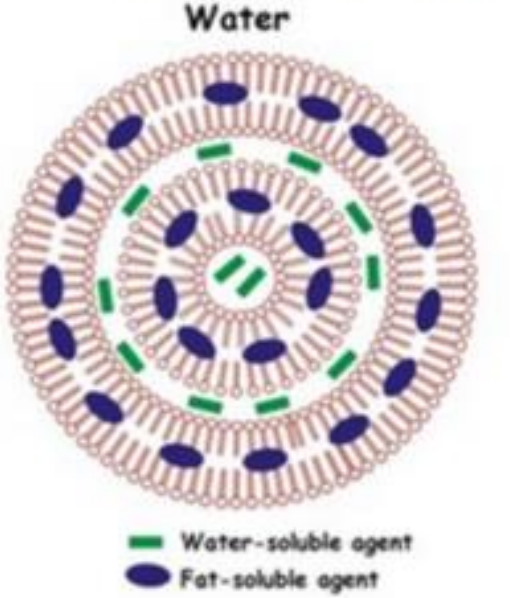


Disk-like particles

Carrier lipids: Cholesteryl sulfate

Particle size (μm): 0.12-0.14

Ambisome ® L-AMB



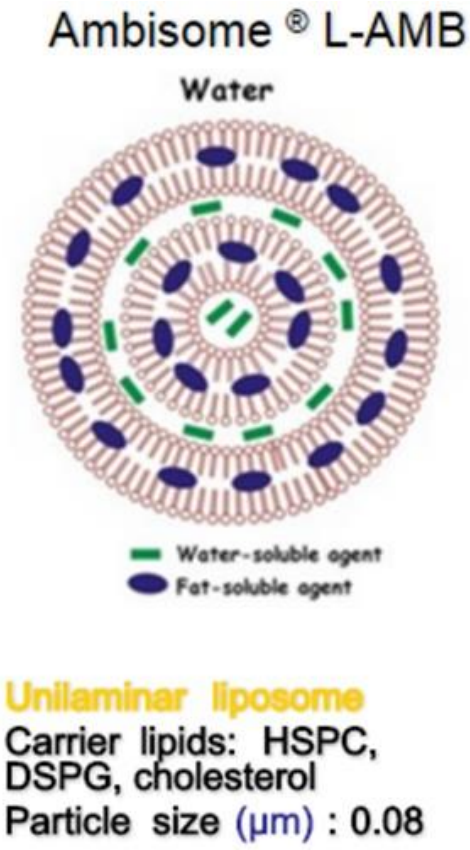
Unilaminar liposome

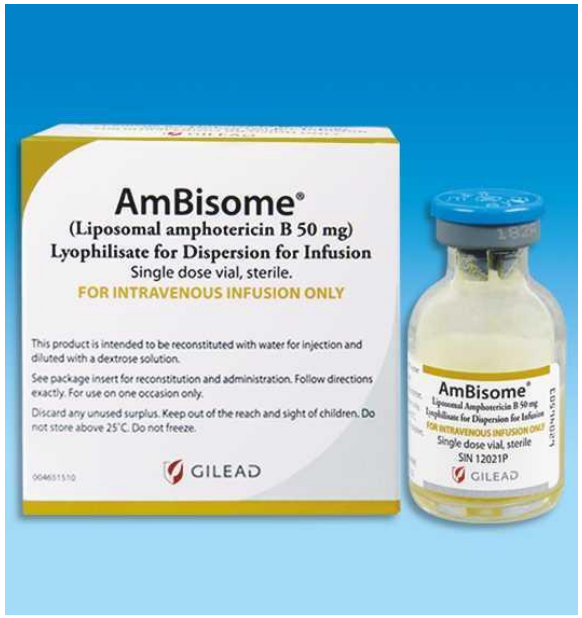
Carrier lipids: HSPC, DSPG, cholesterol

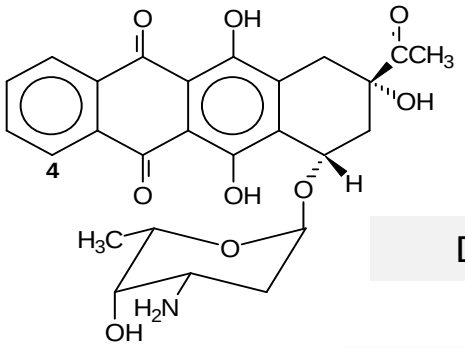
Particle size (μm) : 0.08

VIDEO

LIPOSOMAL AMPHOTERICIN B



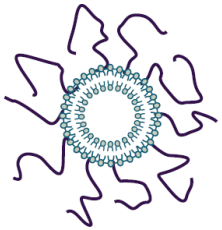




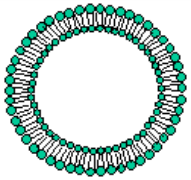
HCl

DOXORUBICIN HCL

PEGylated (stealth) Liposomal formulation



Simple liposomes

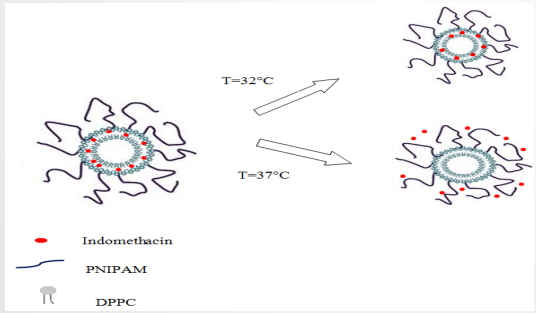


Liposomal medicines in market

Encapsulated drug	Trade Name	Company	Indication	Approval	Innovator Company
Amphotericin B	Abelcet	Sigma-Tau PharmaSource, Inc, Indianapolis, IN	Sever fungal infections	1995	The Liposome Company
Amphotericin B	Ambisome	Gilead Sciences, Inc, San Dimas, CA	Sever fungal infections	1997	Vestar
Amphotericin B	Amphotec	Ben Venue Laboratories, Inc, Bedford, OH	Sever fungal infections	1996	Sequus, Pharmaceutical Inc.
Cytarabine	DepoCyte	Enzon/Skye Pharma	Lymphomatous meningitis (intrathecal administration)	1999	Chiron Corporation and SkyePharma
Daunorubicine	DaunoXome	Gilead Sciences, Inc	Kaposi sarcoma	1996	Gilead
Doxorubicin	LipoDox (generic of Doxil)	TTY Biopharm Company Ltd, Taipei Taiwan	Kaposi's sarcoma, ovarian/breast cancer	2013 (FDA approved; USA)	Sun Pharma
Doxorubicin	Doxil (USA), Caelyx (Europe)	Essex (Europe) Ortho Biotech (USA)	Breast and ovarian cancer, Kaposi sarcoma	1995 (conditional)	Sequus, Inc.
Doxorubicin	Myocet	Novartis Pharma AG, Basel, Switzerland	Breast cancer	2000 (EU)	The Liposome Company
Irinotecan	Onivyde	Merrimack Pharmaceutical Inc. of Cambridge, Massachussetts	Advanced pancreatic cancer	2015 (FDA approved; USA)	Merrimark Pharmaceuticals
Verteporfin	Visudyne	Novartis Pharma AG, Basel, Switzerland	Age-related molecular degerneration, pathologic myopia, ocular histoplasmosis	2000	QLT
Vincristine	Marquibo	Spectrum Pharmaceuticals Inc.	Philadelphia chromosome–negative (Ph–) acute lymphoblastic leukemia (ALL)	2012 (FDA approved; USA)	Inex and Enzon

Advanced Liposomal Drug Delivery nanoSystems

- **STIMULI - RESPONSIVE LIPOSOMAL nanoSYSTEMS**



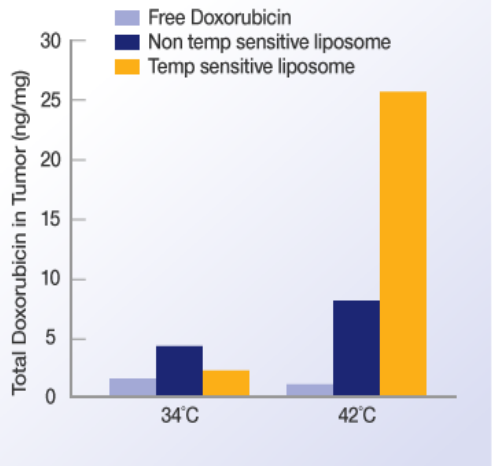
- **CHIMERIC LIPOSOMAL nanoSYSTEMS**

Stimuli-responsive liposomes
Thermosensitive liposomes
as drug delivery systems

ThermoDox Chemotherap

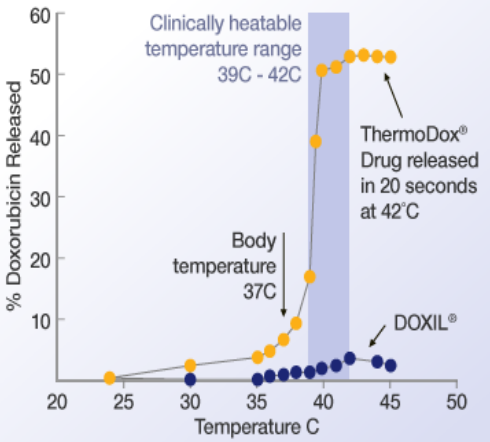
In Vivo

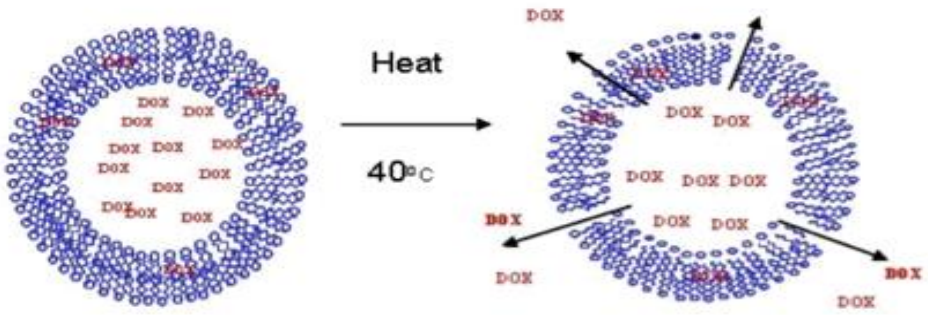
After 1 hour at 42°C, heat-sensitive formulation delivered most drugs to tumor.



In Vitro

Drug release occurs at clinically achievable temperatures





▸Thermodox® is a nanoengineered drug delivery system in **Phase III** and is a temperature sensitive liposomal formulation incorporating **doxorubicin** (anthracycline) for the treatment of **metastatic malignant melanoma** and liver cancer.

▸ThermoDox is the first **heat-activated liposomal formulation**, which is consisted of three synthetic low phase transition temperature phospholipids and release the anticancer agent at **39.5ºC**

International Journal of Pharmaceutics 485 (2015) 374–382

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

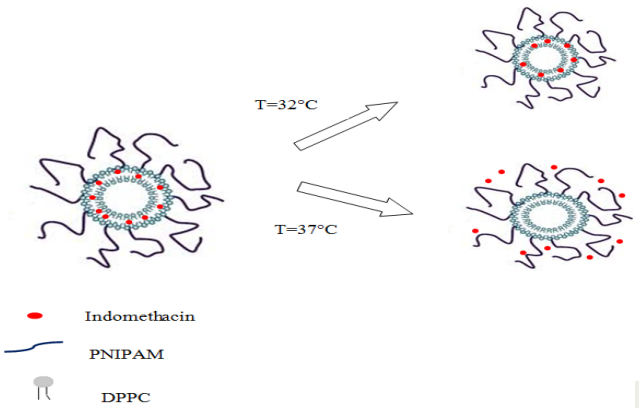
Pharmaceutical nanotechnology

Temperature-dependent drug release from DPPC:$C_{12}H_{25}$-PNIPAM-COOH liposomes: Control of the drug loading/release by modulation of the nanocarriers' components

Natassa Pippa [a,b], Anastasia Meristoudi [b], Stergios Pispas [b], Costas Demetzos [a,*]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, National and Kapodistrian University of Athens, Panepistimioupolis Zografou 15771, Athens, Greece

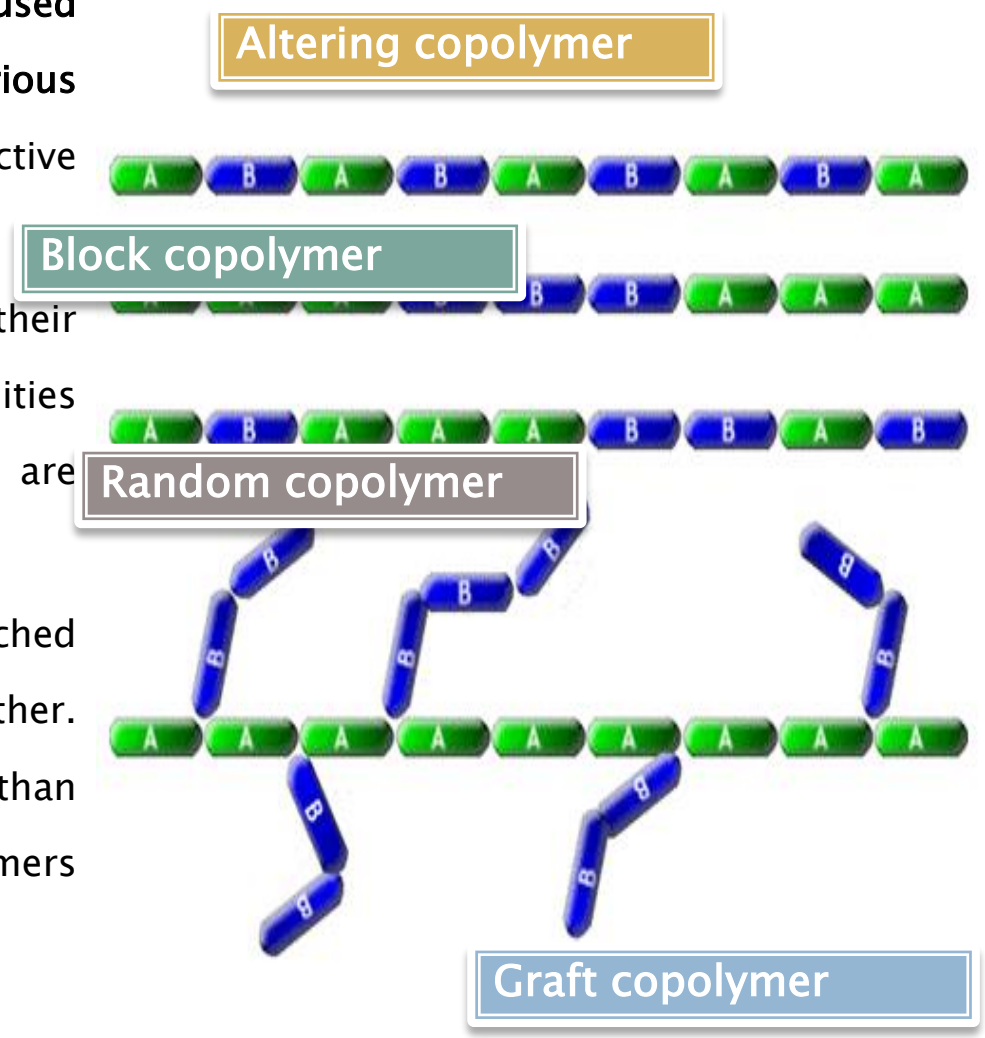
[b] Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 48 Vassileos Constantinou Avenue, Athens 11635, Greece



- The presence of the polymeric component plays a key role in the thermal behavior of mixed lipid based nanovectors due to the structural rearrangement of liposomal membrane.
- Temperature-dependent release of IND was observed from chimeric liposomes, due to the well known thermotropic conformational transition of the grafted PNIPAM chains.

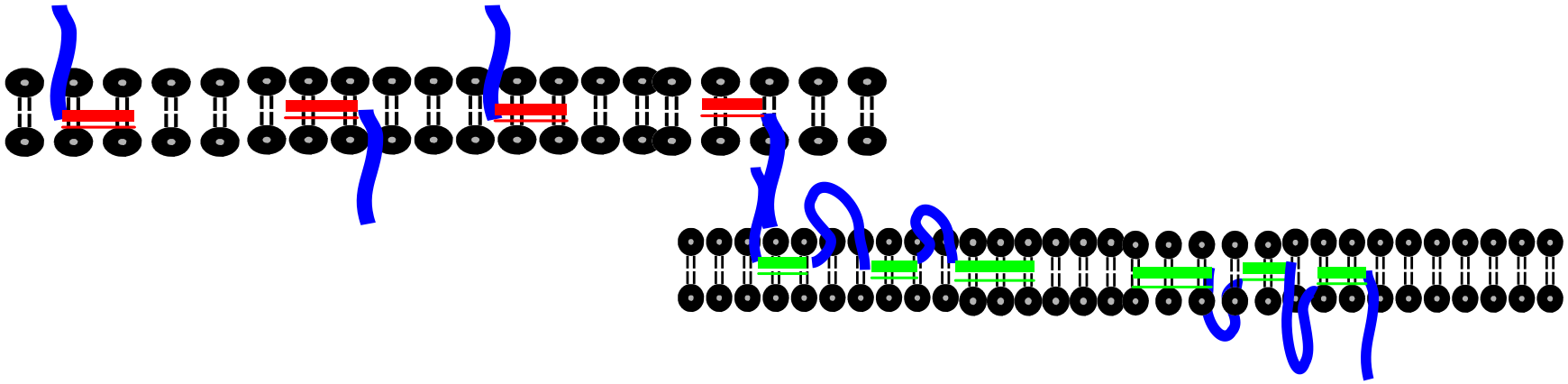
Polymers in Pharmaceutics:

1) **Polymers are materials that are widely used in the pharmaceutical industry in various technological formulations** and in bioactive molecule delivery system coating.
2) Polymer behavior is directly related to their chemical structure. Also, their abilities depend on the way that monomers are connected to each other.
3) Polymers can have linear or branched chains that may cross each other. Copolymers are composed of more than one monomer and develop new polymers with completely new properties.



Chimeric liposomal systems are composed of phospholipids and polymers

Polymer grafted liposomes



Soft Matter

RSCPublishing

PAPER

PEO-*b*-PCL–DPPC chimeric nanocarriers: self-assembly aspects in aqueous and biological media and drug incorporation†

Cite this: Soft Matter, 2013, 9, 4073

Natassa Pippa,[ab] Eleni Kaditi,[a] Stergios Pispas*[a] and Costas Demetzos[b]

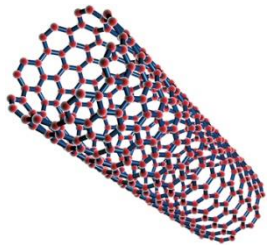
J Nanopart Res (2013) 15:1685
DOI 10.1007/s11051-013-1685-3

RESEARCH PAPER

DPPC/poly(2-methyl-2-oxazoline)-grad-poly(2-phenyl-2-oxazoline) chimeric nanostructures as potential drug nanocarriers

Natassa Pippa · Eleni Kaditi · Stergios Pispas · Costas Demetzos

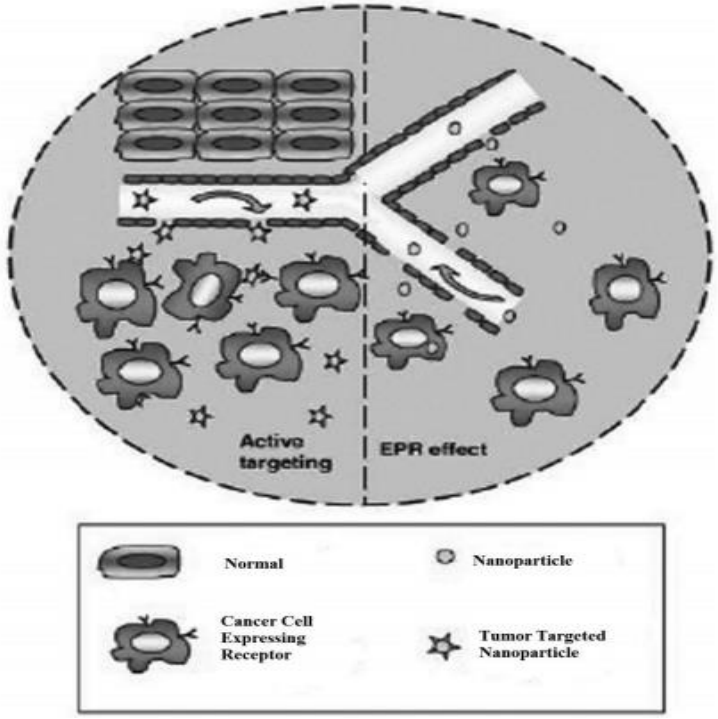
Carbon nanotubes in drug delivery:



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

Delivery of drugs:

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

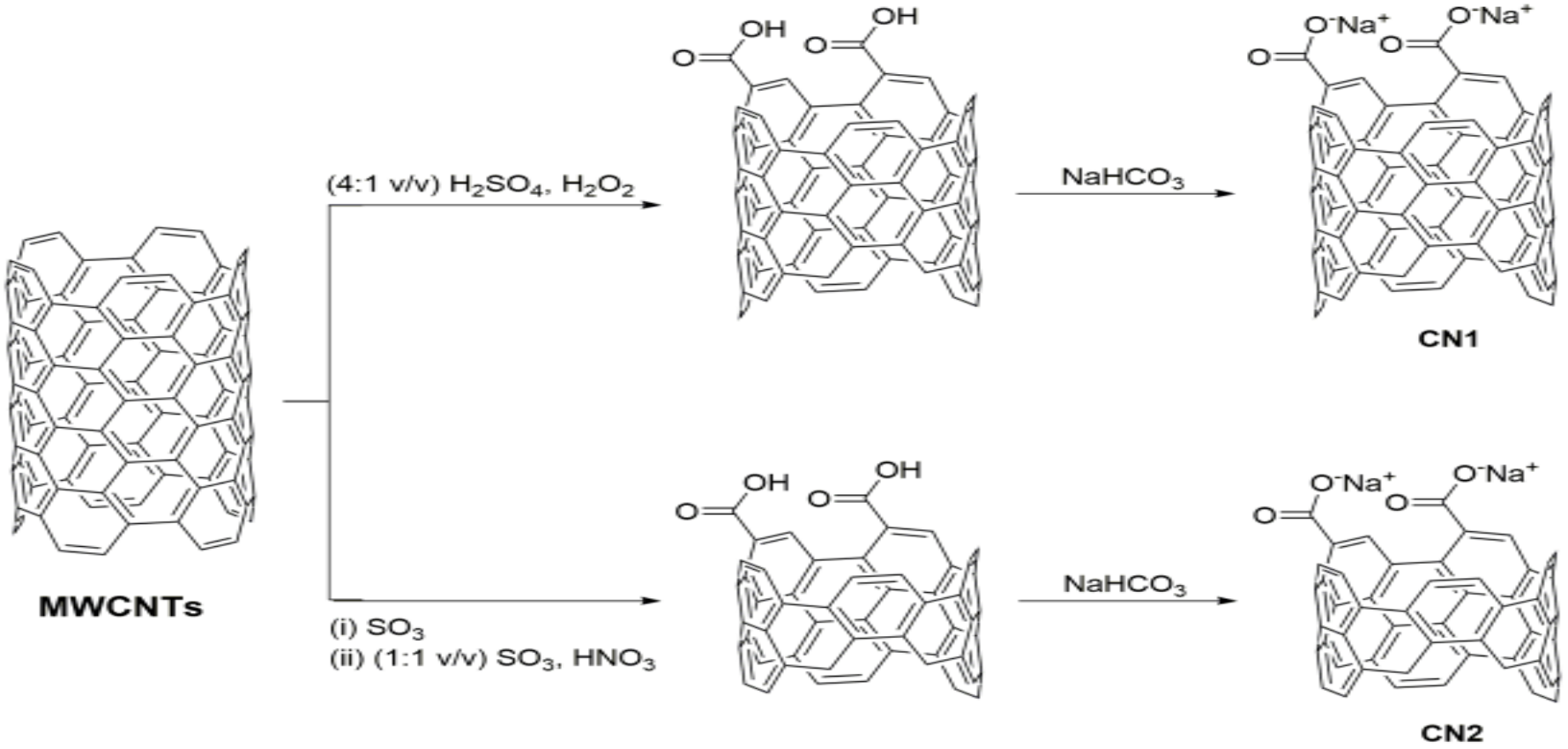


Synthesis

Dr. Nikos Tagmatarchis

Dr. D. Chronopoulos

Functionalized CNTs



Advanced drug delivery nano systems:

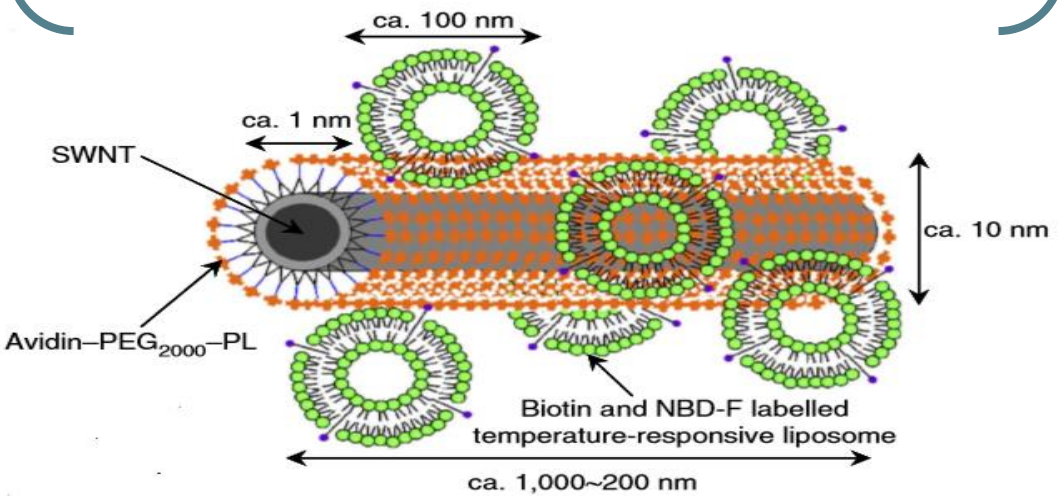
Miyako et al., 2012

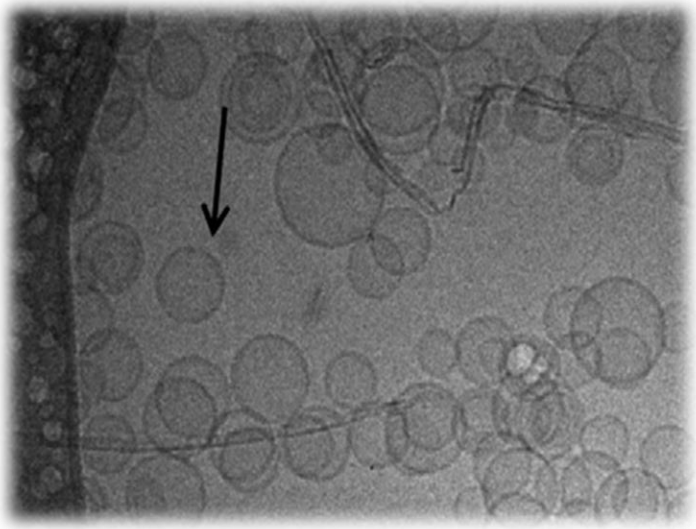
Karchemchi et al., 2012

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





What we need …

We need specific tools that can meet the requirements for characterizing nanoparticulate medicines and to control the manufacturing process for their developement.

Determination *of the* physicochemical functionality *of nanomedicines is related to their surface characteristics.*

size, size distribution, ζ-potential, shape, surface properties, etc

- The nature and stability of surface properties/coatings in the final nanomedicine product can be very important in determining safety and efficacy.
- Thus, the need for sensitive and accurate **analytical methods** to identify and quantify the nanomedicine is considered as essential for its quality in part and as final product

Methods:

Thermodynamic and Biophysical Characterization

- Differential Scanning Calorimetry

Physicochemical Characterization

- Dynamic and Electrophoretic Light Scattering

Morphological Characterization

- Static Light Scattering, cryo-TEM, Atomic Force Microscopy

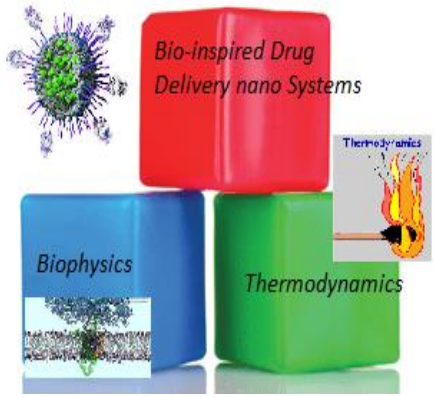
Biological evaluation

- In vitro screening, in vivo toxicity

BASIC SCIENTIFIC TOOLS FOR STUDYING LIPOSOMAL PHOSPHOLIPIDIC MEMBRANES

The **Biophysics** and **Thermodynamics** are considered as the basic scientific elements for studying artificial cell membranes and provide projection of the behavior of nano systems as artificial cell models.

The synergy regarding the biophysical behavior of artificial biomembranes and of cell biology has promoted nanoparticulate systems as drug delivery nano-platforms, while their thermotropic behavior can be correlated with cell functionality



Ref. Demetzos C (2015) *Biophysics and Thermodynamics: the scientific blocks of bio-inspired drug delivery nano systems.* AAPS PharmSciTEch 16(3):491-495.

AAPS PharmSciTech, Vol. 16, No. 3, June 2015 (© 2015)
DOI: 10.1208/s12249-015-0321-1

Mini-Review

Biophysics and Thermodynamics: The Scientific Building Blocks of Bio-inspired Drug Delivery Nano Systems

Costas Demetzos[1,2]

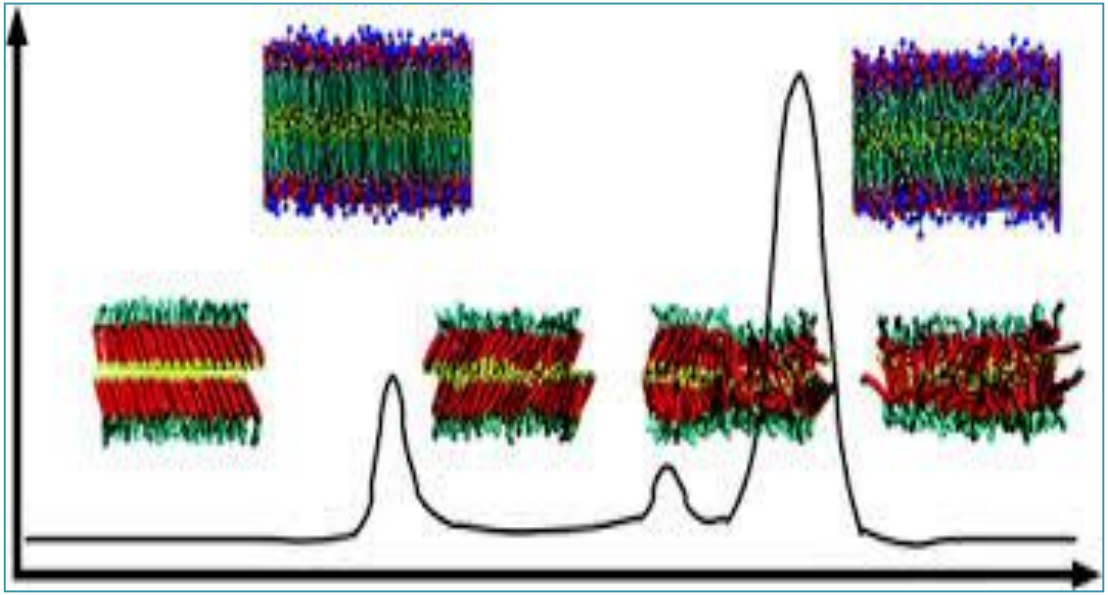
Received 9 March 2015; accepted 7 April 2015; published online 22 April 2015

Abstract. Biophysics and thermodynamics are considered as the scientific milestones for investigating the properties of materials. The relationship between the changes of temperature with the biophysical variables of biomaterials is important in the process of the development of drug delivery systems. Biophysics is a challenge sector of physics and should be used complementary with the biochemistry in order to discover new and promising technological platforms (*i.e.*, drug delivery systems) and to disclose the 'silence functionality' of bio-inspired biological and artificial membranes. Thermal analysis and biophysical approaches in pharmaceuticals present reliable and versatile tools for their characterization and for the successful development of pharmaceutical products. The metastable phases of self-assembled nanostructures such as liposomes should be taken into consideration because they represent the thermal events can affect the functionality of advanced drug delivery nano systems. In conclusion, biophysics and thermodynamics are characterized as the building blocks for design and development of bio-inspired drug delivery systems.

KEY WORDS: biophysics; drug delivery nano systems; pharmaceutics; thermal analysis; thermodynamics.

Thermodynamics is the fundamental scientific element that could efficiently be used for studying and analyzing the behavior of artificial biological membranes that could be correlated with biological networks and create scientific platforms for the system therapeutics concept.

Liquid crystalline phases of phospholipids



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

- The regulatory issues concerning the drug development process have incorporated DSC as a valuable technique for the analysis of the physical and energetic properties of drugs and of excipients, and its use is essential under standard procedures, as is described in the *United States Pharmacopeia.*

Journal of Liposome Research, 18:159–173, 2008

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DOI: 10.1080/08982100802310261

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Differential Scanning Calorimetry (DSC): A Tool to Study the Thermal Behavior of Lipid Bilayers and Liposomal Stability

COSTAS DEMETZOS

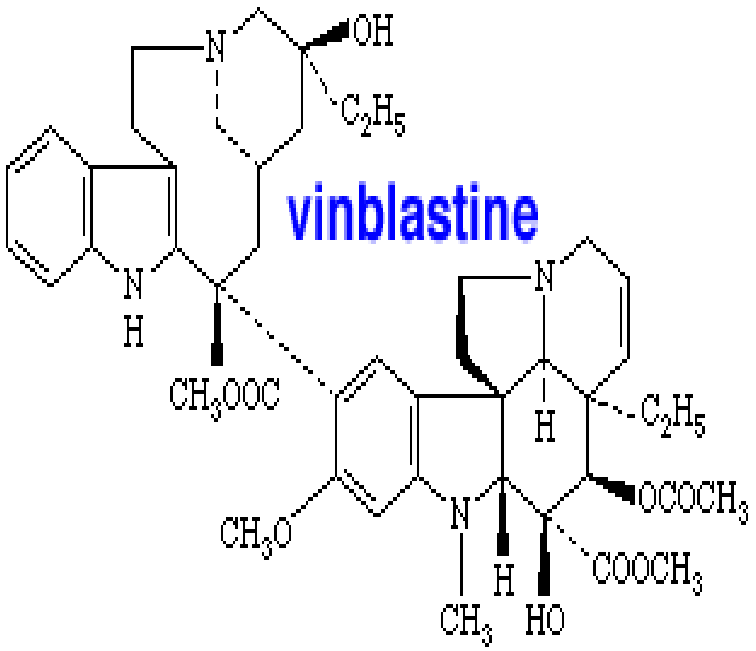
Department of Pharmaceutical Technology, School of Pharmacy, University of Athens, Greece

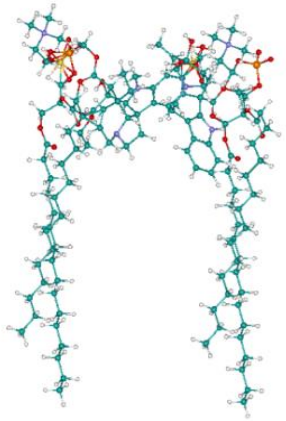
DSC is a useful tool for designing lipidic drug delivery systems by determining the cooperativeness of the mixed substances.

☑**VINBLASTINE** is an anticancer drug.

☑It is toxic to the normal tissues and appropriate ***DDSs are needed in order to reduce its toxicity and improve its pharmacokinetic parameters.***

☑Studies concerning the thermotropic properties of Lipid Bilayers composed of DPPC phospholipids incorporating Vinblastine and changes of the thermodynamic parameters can be used to predict the Physical Stability of Liposomal Formulation composed by DPPC Phospholipids.

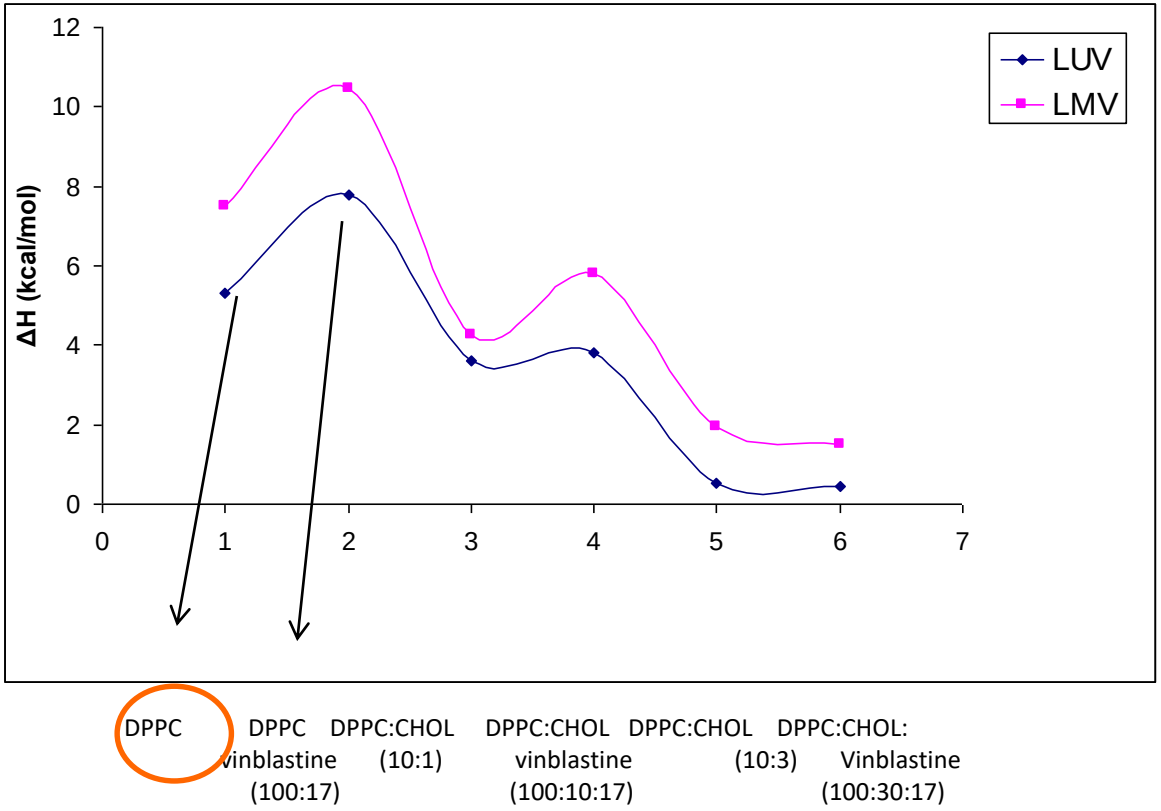




Ref: Maswadeh, Demetzos, Mavromoustakos et al., *BBA*, 2002

Large **U**nilamellar liposomal **V**esicles and
Multi **L**amellar liposomal **V**esicles have been prepared

THE CHANGES OF THE PARAMETERS **Tm** AND **ΔH** WERE MEASURED AND
IT WAS FOUND THAT THEY WERE AFFECTED BY THE LIPOSOMAL COMPOSITION (pure DPPC or DPPC incorporated Vinblastine or DPPC incorporated cholesterol or cholesterol and Vinblastine)



Quantitative Thermal data for DPPC LUVs and MLVs liposomal vesicles

Lipid Composition	LUV T_m (° C)	LUV ΔH (Kcal/ mol)	MLV T_m (° C)	MLV ΔH (Kcal/ mol)
DPPC	41.2	5.3	42.3	7.5
DPPC/ VIN (100:17)	41.7	7.7	40.5	10.4
DPPC/CHL (10:1)	41.5	3.6	40.6	4.2
DPPC/CHL/ VIN (100:10:17)	41.0	3.8	40.0	5.8
DPPC/CHL (10:3)	40.4	0.5	42.8	1.9
DPPC/CHL/ VIN (100:30:17)	40.2	0.4	43.0	1.5

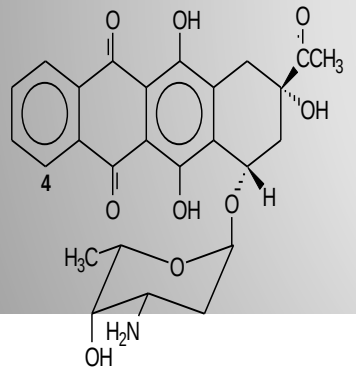
Ref**:** Kyrikou, Daliani, Mavromoustakos, Demetzos et al., *BBA-Biomembranes*, 2004.

The results from the DSC experiments based on calculated thermodynamic parameters could be used to select appropriate biomaterials for designing an effective and stable liposomal DDnS incorporating the anticancer drug vinblastine.

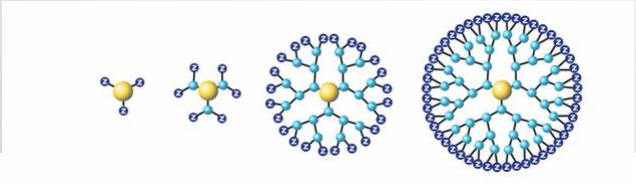
"ωφελέειν, εἰ μη βλάπτειν"

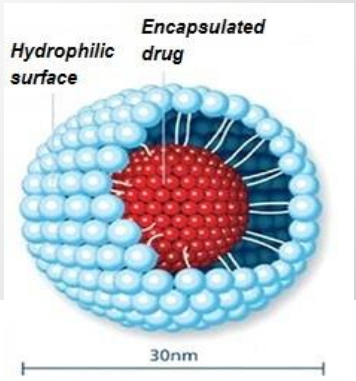
'benefit and do not harm'

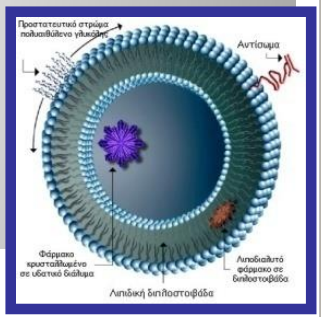
An innovative medicine consists of the bioactive substance (drug) and of the excipient that are mentioned as *innovative excipient*



HCl





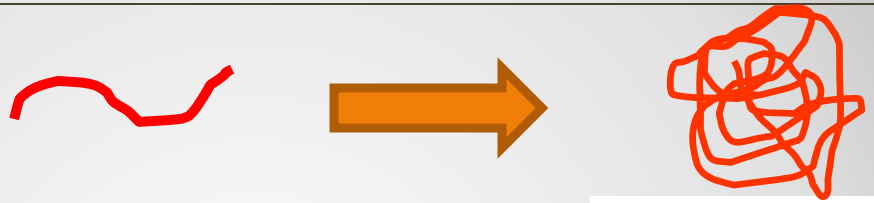


An Innovative excipient is an excipient **that has self-assembled behavior and can create functionality and new surface properties**

Ref. C. Demetzos, Pharmaceutical Nanotechnology, Springer, 2016

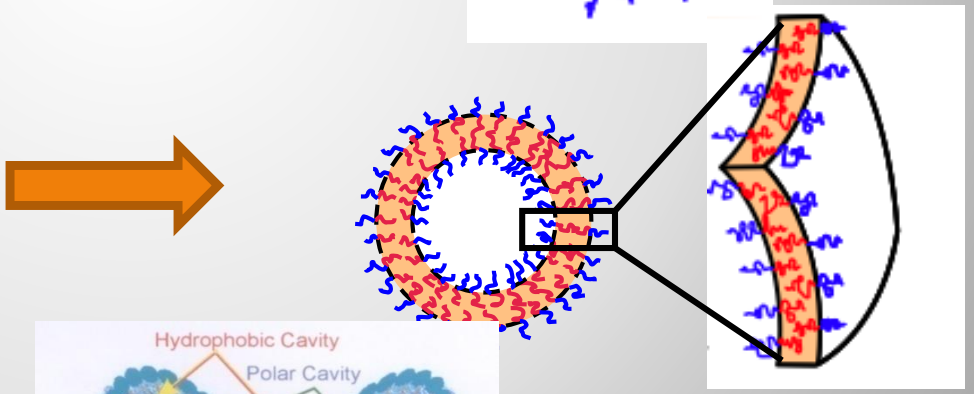
INNOVATIVE PHARMACOLOGICALLY INACTIVE EXCIPIENTS-BIOMATERILAS THAT ARE ABLE TO CREATE SELF-ASSEMBLED NANOSTRUCTURES

- Globules

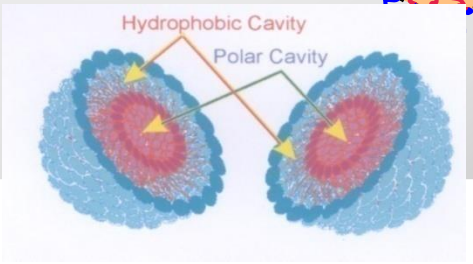


- Micelles

- Polymersomes



- Liposomes

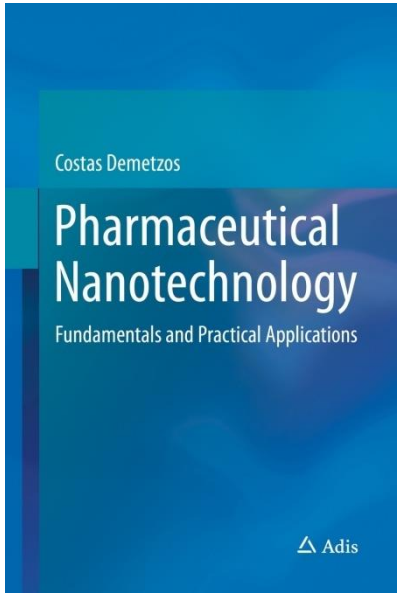


Προλογίζει

Gregory Gregoriadis, PhD, DSc

Professor Emeritus,
UCL School of Pharmacy London

…….It has been therefore a great personal pleasure to write the Preface of the present book by Professor Costas Demetzos.
His monograph, 'Pharmaceutical Nanotechnology', is a unique publication . ……



Laboratory of Pharmaceutical Nanotechnology University of Athens, Greece

http://nanopharmlab.gr/index.php/en/

Conclusions:

- Basic sciences such as Physics (biophysics and thermodynamics) and Mathematics are needed to assist the research and development process of nanomedicines
- A regulatory approach that promotes self-assembled nanoparticulate systems as innovative excipients complementary to the already existing regulatory framework for the classical and functional excipients, could produce new guidelines for the regulatory authorities to create a framework process for the approval of nanomedicines and consequently of nanosimilars.

- An analytical concept on **fractal analysis** based on non Euclidian approach of the geometry of nanoparticles (complementary to the QbD approach) has been proposed from our lab. to EMA offering an added value to the '*mapping process*' for developing nanomedicinal products.
- The regulatory authorities should take into consideration that efficient analytical evaluation of nanomedicines should be developed and new analytical tools should be considered as part of the dossier to be submitted to the regulatory body of experts.

Demetzos C., Pippa N. , 2015. Fractal geometry as a new approach for proving the nanosimilarity. Int. J. Pharm. 483:1-5.

Our contribution……

International Journal of Pharmaceutics 465 (2014) 63–69

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

The interplay between the rate of release from polymer grafted liposomes and their fractal morphology

Natassa Pippa[a,b], Aristides Dokoumetzidis[a], Stergios Pispas[b], Costas Demetzos[a,*]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece
[b] Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, Athens, Greece

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informa healthcare

Incorporation of dimethoxycurcumin into charged liposomes and the formation kinetics of fractal aggregates of uncharged vectors

Marilena Hadjidemetriou[1], Natassa Pippa[1,2], Stergios Pispas[2], and Costas Demetzos[1]

CrossMark

J Nanopart Res (2013) 15:1685
DOI 10.1007/s11051-013-1685-3

RESEARCH PAPER

DPPC/poly(2-methyl-2-oxazoline)-grad-poly(2-phenyl-2-oxazoline) chimeric nanostructures as potential drug nanocarriers

Natassa Pippa · Eleni Kaditi · Stergios Pispas · Costas Demetzos

International Journal of Pharmaceutics 450 (2013) 1–10

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

DPPC:MPOx chimeric advanced Drug Delivery nano Systems (chi-aDDnSs): Physicochemical and structural characterization, stability and drug release studies

Natassa Pippa[a,b], Maria Merkouraki[a], Stergios Pispas[b], Costas Demetzos[a,*]

ΑΡΘΡΟ ΕΠΙΣΚΟΠΗΣΗΣ REVIEW ARTICLE

ΦΑΡΜΑΚΕΥΤΙΚΗ 24, ΙΙΙ, 57-62, 2012 PHARMAKEFTIKI 24, III, 57-62, 2012

Fractal Analysis of Liposomal Aggregation.

Natassa Pippa, Costas Demetzos*
Faculty of Pharmacy, Department of Pharmaceutical Technology, University of Athens, University Campus Zografou, 15784 Athens, Greece

Our contribution……

International Journal of Pharmaceutics 430 (2012) 65–73

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

The fractal hologram and elucidation of the structure of liposomal carriers in aqueous and biological media

Natassa Pippa[a,b], Stergios Pispas[b], Costas Demetzos[a,*]

Pharm Res
DOI 10.1007/s11095-013-1082-8

RESEARCH PAPER

The Shape/Morphology Balance: A Study of Stealth Liposomes via Fractal Analysis and Drug Encapsulation

Natassa Pippa • Faidra Psarommati • Stergios Pispas • Costas Demetzos

International Journal of Pharmaceutics 437 (2012) 264–274

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Pharmaceutical Nanotechnology

The delineation of the morphology of charged liposomal vectors via a fractal analysis in aqueous and biological media: Physicochemical and self-assembly studies

Natassa Pippa[a,b], Stergios Pispas[b], Costas Demetzos[a,*]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Panepistimioupolis Zografou, 15771 Athens, Greece
[b] Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 48 Vass. Constantinou Avenue, 11635 Athens, Greece

Journal of Liposome Research, 2012; 22(1): 55–61
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ISSN 0898-2104 print/ISSN 1532-2394 online
DOI: 10.3109/08982104.2011.590142

RESEARCH ARTICLE

The formalism of fractal aggregation phenomena of colloidal drug delivery systems

Natassa Pippa[1], Costas Demetzos[1,*], and Emmanuel Danezis[2]

Our research group has published several research articles on **the fractal morphology** of nanoparticles.

A comment was submitted to the EMA regarding the 'concept paper on the revision of the guideline on immunogenicity assessment of biotech therapeutic proteins –EMA/CHMP/BMWP/42832/2005). This comment included the adaption of fractal analysis in the evaluation process of biotech biosimilar and nanomedicinal products

Soft Matter

RSC Publishing

PAPER

Cite this: Soft Matter, 2013, 9, 4073

PEO-*b*-PCL–DPPC chimeric nanocarriers: self-assembly aspects in aqueous and biological media and drug incorporation†

Natassa Pippa,[ab] Eleni Kaditi,[a] Stergios Pispas*[a] and Costas Demetzos[b]

ACKNOWDELEGMENTS

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Faculty of Pharmacy, Lab. of Pharm. Techn. and Nanotechnology

Natassa Pippa senior researcher

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- Dr. **Barry Steele**

Dr.N. Tagmatarchis, NHRF,

Institute of Theoretical and Physical Chemistry

- Dr. **Stergios Pispas**

Prof. **Nissim Garti**

Casali Institute of Applied Chemistry, The Institute of Chemistry, The Hebrew University of Jerusalem, Israel

Dr. ***Zoe Cournia***, BRFAA

Prof. **Dimitrios Fessas,**

Department of Food Science, Technology and Microbiology, University of Milan, Milan, Italy

Prof. D.Tomalia Prof. **M. Makropoulou**, NTUA,

Thank you for your kind attention

Vincent van Gogh
Branch of almond – tree in flowers, 1890