"ωφελέειν, εἰ μη βλάπτειν"

'benefit and do not harm'

NANOSIMILARS:
THE SCIENTIFIC DEBATE HAS JUST BEGUN

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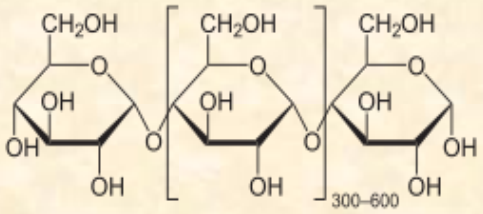
We can propose a definition on What a medicine is

- *Medicine is the commodity that is composed of the **bioactive substance**, known as drug (that is pharmacologically active) and of the biomaterials, known as **excipients** (without pharmacological action and toxicity) that affect the therapeutic efficacy, that are rationally chosen and interact with the bioactive substance in an extent that is defined by their physical, chemical and biologicall properties, aiming to maximize the bioactive substance effectiveness that will be used to improve or to restore the physiological functions of the human organism.*
- We have to take into account that the medicine in its parts (bioactive substance and excipients) and as a final marketed product should be considered as a ***biomaterial*** and apart of its chemistry it should be studied and evaluated under the principles of physics, biophysics, thermodynamics and mathematics, in order to maximize its efficacy and to reduce its adverse drug reactions.

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

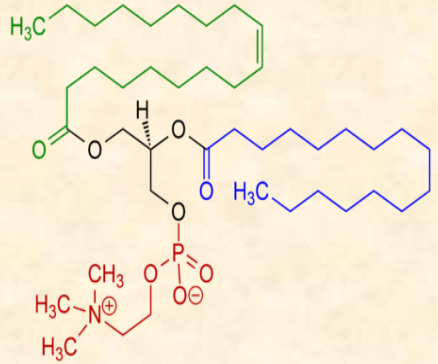
WHICH IS THE CONTRIBUTION OF THE EXCIPIENTS AS BIOMATERIALS TO THE EFFICACY OF A MEDICINE ?

CLASSIC EXCIPIENTS- BIOMATERIALS

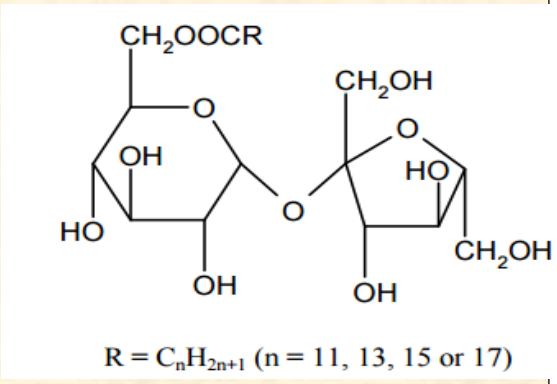


STARCH

FUNCTIONAL EXCIPIENTS - BIOMATERIALS



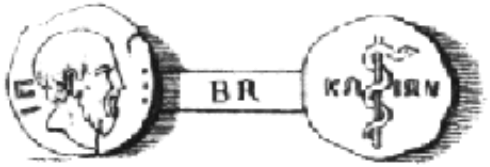
PHOSPHOLIPID



SUCROSE ESTERS

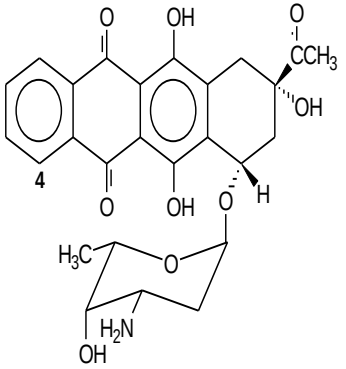
An excipient is a biomaterial that contribute to the formulation process of the bioactive substance in order to produce the final medicinal products. It should also be able due to its properties to easily manage during the scale up process in Industry, to efficiently use by the doctors and to uptake by the patient promoting their compliance

"ωφελέειν, εἰ μη βλάπτειν"



'benefit and do not harm'

An innovative medicine consists of the bioactive substance and of the excipient that could be classified as *innovative excipient* in the case



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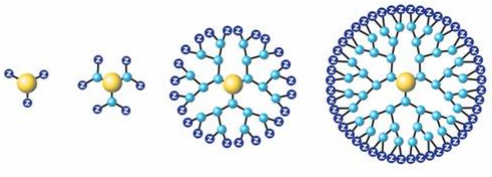
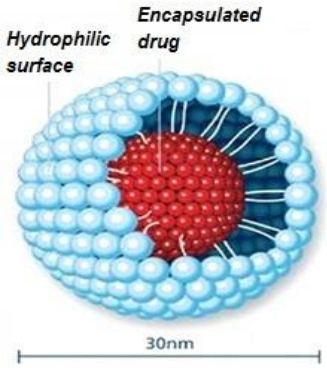
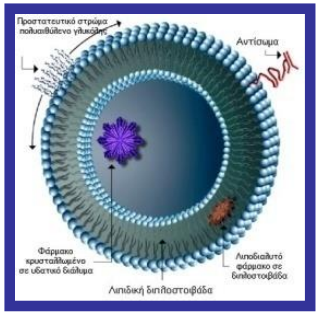




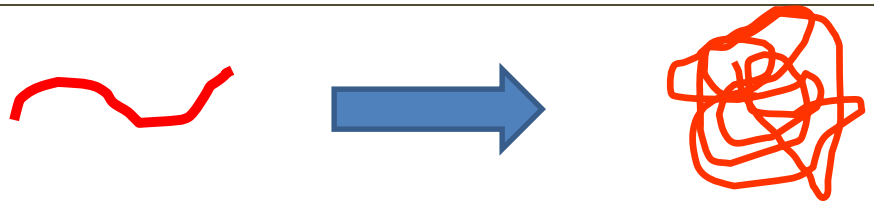


An Innovative excipient is an excipient **that has self-assembled behavior and can create functionality and new surface properties**

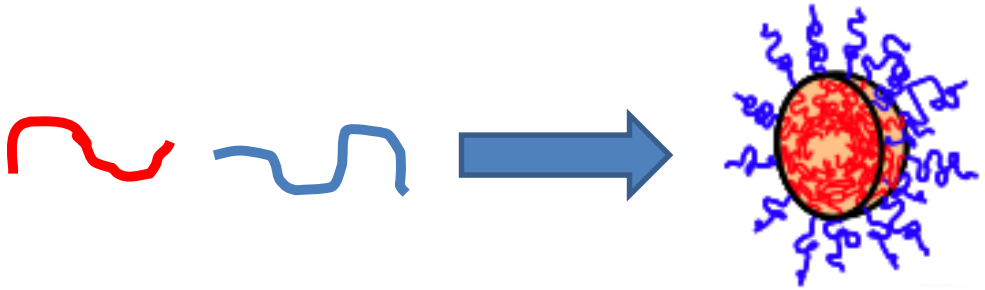
Ref. Demetzos C., Pippa N. , 2015. Fractal geometry as a new approach for proving the nanosimilarity. Int. J. Pharm. 483:1-5.

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

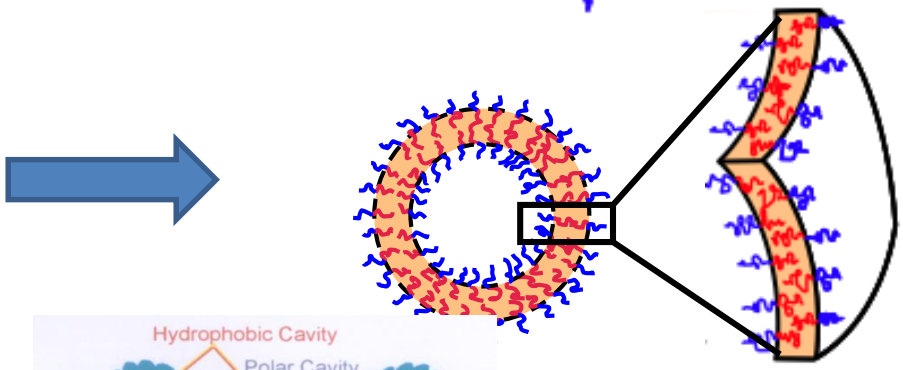
- Globules



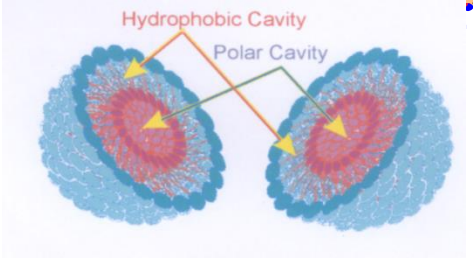
- Micelles



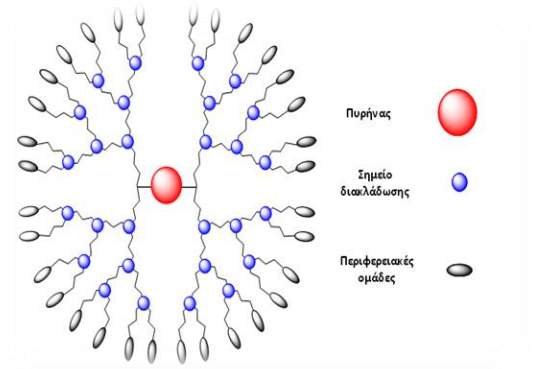
- Polymersomes



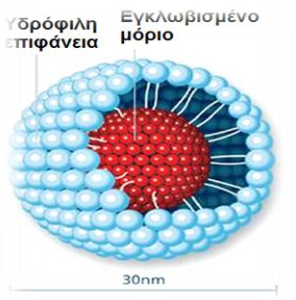
- Liposomes

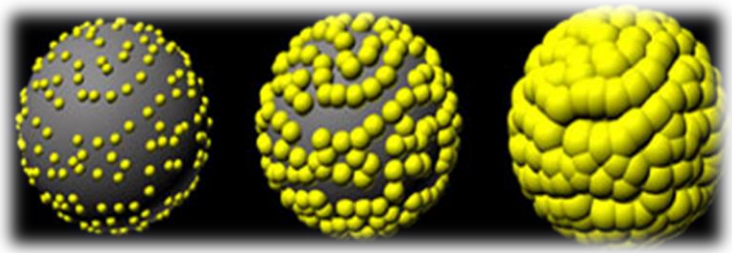


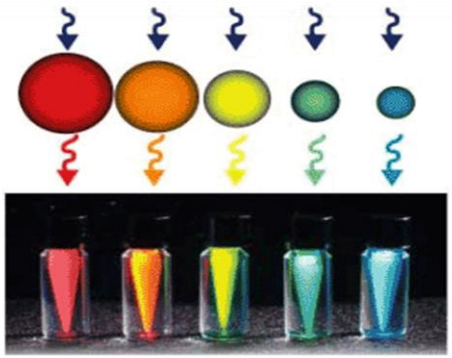
SELF ASSEMBLED SUPRAMOLECULAR STRUCTURES THAT ARE USED IN THERAPEUTICS, IMAGING AND DIAGNOSIS.

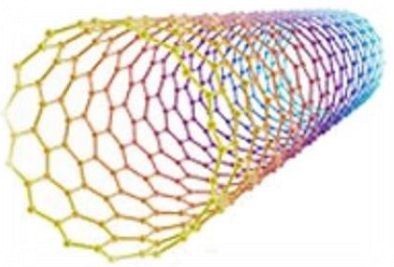


- **Liposomes**
- **Lipidic nanostructures**
- Nanoemulsions
- **Polymeric micelles**
- **Polyelectrolytes**
- **Dendrimers**
- **Chimeric nanostructures**
- Nanocapsules and nanospheres (10-1000nm)
- Nanoshells
- Nanocrystals Qd
- Magnetic nanoparticles
- etc.



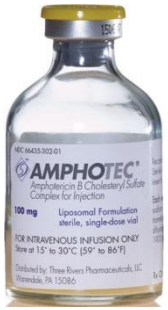




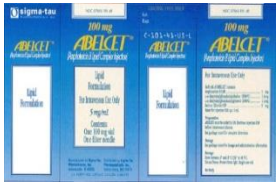


- **Abraxane (nab-paclitaxel)** it consists of 130 nm particles of albumin-bound paclitaxel. It was approved by US FDA in 2005 for the treatment of metastatic breast cancer. Abraxane is the first Cremophor –free paclitaxel product. By avoiding the use of cremophor, this formulation potentially offers to overcome the toxicity problems associated with the use of cremophor.

Abelcet. This formulation is composed of amphotericin B, DMPC, DMPG in a 1:1 drug to lipid ratio. It forms ribbon-like complexes with a size around 1.6- 11 µm.



Amphotec. This formulation consists of amphotericin B in a complex with cholesteryl sulfate at a 1:1 molar ratio to form stable colloidal disc – like structures with a diameter of 100-140 nm in size



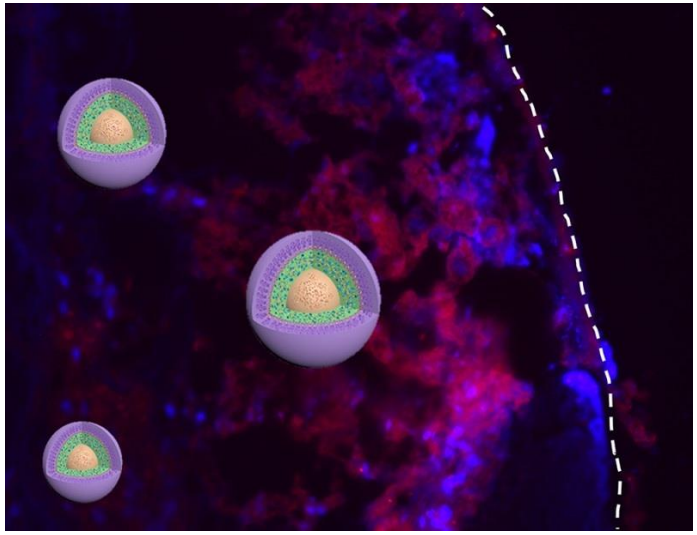
AmBisome. This is a small unilamellar liposomal formulation with a size of liposomes around to 80 nm. The drug amphotericin B is intercalated within the liposomal membranes

- **Caelyx** contains doxorubicin entrapped within liposomes 80- 100 nm in size. It composed of HSPC Cholesterol and PEG 2000-DSPC and α-tocopherol 956:38:5:0.2 mol%). The PEG 2000-coating gives the liposomes stealth properties. The formulation is used for the treatment of metastatic breast cancer, related Kaposi's syndrome,.
- **Myocet** Doxorubicin in self assembling lamellar liposomes. The size of liposomes is 180 nm and it composed of EPC and Cholesterol (55:45 mol%). Due to their size are rapidly taken up by the MPS (Mononuclear Phagocyte System). This avoids peak plasma levels and reduces toxicity. The liposomes by this procedure create a 'MPS depot' from which the drug re-enters the blood stream, mimicking a slow infusion.

DaunoXome. This liposomal formulation is composed of DSPC, Cholesterol (2:1 mol %) and have dimaeter of 45 nm with entrapped doxorubicin. Whilst this is not a 'stealth' formulation, the small vesicle size helps prolong blood residence time.

Follow- on Nanomedicines …..

- Approximately **48 nanomedicines and nanoimaging agents** are currently under clinical development (Phase I–III) in Europe, with others progressing through earlier stages of drug discovery and nonclinical development.
- In addition, approximately **70 cancer clinical trials** are ongoing in the USA involving nanomedicines and, therefore, the number of marketed pharmaceuticals using nanotechnology is expected to continuously grow and, thus, benefit patients and public health.



The European Medicines Agency has evaluated 11 marketing authorization applications for nanomedicines, out of which eight have been authorized and three have been withdrawn.

Ref. The assessment reports are publicly available (***www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid= WC0b01ac058001d124***

Definitions:

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- a **generic medicine** is defined as a medicine that is developed, as the reference medicine and it contains the same active substance, and it is used at the same doses to treat the same diseases. Generic medicines are manufactured according to the same quality standards as all other medicines (EMA/393905/2006 Rev. 2).
- The scientific approach for realeasing them to the market is based on bioequivalence studies.

Definitions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- a **similar biological** or **"biosimilars"** medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use (**EMA/837805/2011**). Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast (**EMA/837805/2011**). They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies."

"ωφελέειν, εἰ μη βλάπτειν"

'benefit and do not harm'

The technological complexity of nanomedicines is considered as a barrier to develop identical '*copies*' of the prototype.

However, the similarity between prototype and nanosimilar is a demand and efforts should be focused on this approach in order to develop new and effective analytical tools for proving nanosimilarity.

The approaches for proving similarity, cannot be applied to nanosimilars as in the case of generic drugs (bioequivalence studies), while the structural complexity and the immunogenicity of biosimilars seem to be the major concern in the manufacturing process.

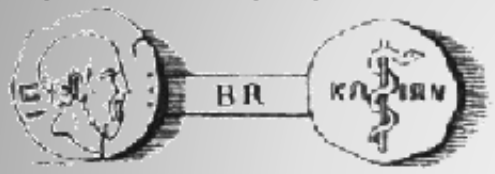
Demetzos C (2015) Biophysics and Thermodynamics: the scientific blocks of bio-inspired drug delivery nano systems. AAPS PharmSciTEch 16(3):491-495. ;

Ahmed I, Kaspar B, Sharma U (2012) Biosimilars: impact of biological products life cycle and European experience on the regulatory trajectory in the United States Clin Ther 34: 400-419

Holloway C, Mueller-Berghaus J, Lima BS et al (2012) Scientific consideration for complex drugs in light of established and emerging regulatory guidance Ann N.Y Acad Sci 1276: 26-36

Demetzos C, Pippa N, Tountas Y (2013) Advanced therapies : New guidelines and the approval process Pharmakeftiki 25 (II): 49-54

"ωφελέειν, εἰ μη βλάπτειν"



'benefit and do not harm'

Nanosimilars are considered as new medicinal outcomes combining the generic drug and the nanocarrier which could be classified as an innovative excipient giving floor to the regulatory agencies for discussions and to promote a new regulatory environment for their approval.

The similarity could be studied based on the pharmacological activity of the bioactive substances (generic drug) and of the physicochemical, biophysical and thermodynamic properties of the innovative excipient with self-assembled properties

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

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

EMA has Reflection Papers (RP) on this subject

Specific Reflection Papers

- ❑ Nanosimilar iron medicinal products (EMA/CHMP/SWP/100094/2011)
- ❑Coated nanomedicine products (EMA/325027/2013)
- ❑Nanosimilar liposomal product (EMA/CHMP/806058/2009/Rev.02)

Draft Specific Reflection Papers

These papers are under public consultation with a view to developing guidelines for specific nanosimilar products

- ❑Block copolymer micelle medicinal products (EMA/CHMP/13099/2013)
- ❑Nanosimilar intravenous iron-based nano-colloidal products (EMA/CHMP/SWP/620008/2012)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 March 2011
EMA/CHMP/SWP/100094/2011
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2013
EMA/325027/2013
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

According to the "**Reflection Paper (RP)** on nanotechnology –based medicinal products for human use" (**EMEA/CHMP/79769/2006**) the nanosizing does not imply novelty, but it is expected that nanotechnology will yield innovative products.

In EU there is a highly evolved system for the evaluation of benefit risk of medicinal products that has accommodated effectively in the past new technologies and even some nanosize products.

"Such products (i.e **nanomedicines**) could span the regulatory boundaries between medicinal products and medical devices, challenging current criteria for classification and evaluation. Appropriate expertise will need to be mobilized for the evaluation of the quality, safety, efficacy and risk management of nanomedicinal products and the need for new or updated guidelines will be reviewed in the light of accumulated experience."

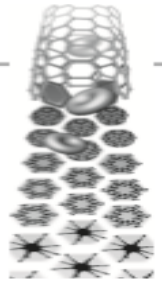
The **generic paradigm cannot be applied** to complex drugs as biologics and a number of other therapeutic modalities, i.e. nanotechnology-based products.

In proportion to biosimilars, European Union posted guidelines for nanosimilars on the 11th October 2011.

- The nanosimilarity, which is proposed as a new term, reflects the process of the evaluation of the final medicines

According to Prof. Duncan et al., the 'follow-on ' nanomedicine products are defined as: **first generation products come off-patent products**.

Such products are described as 'similar nanomedicines' (i.e., 'nanosimilars')

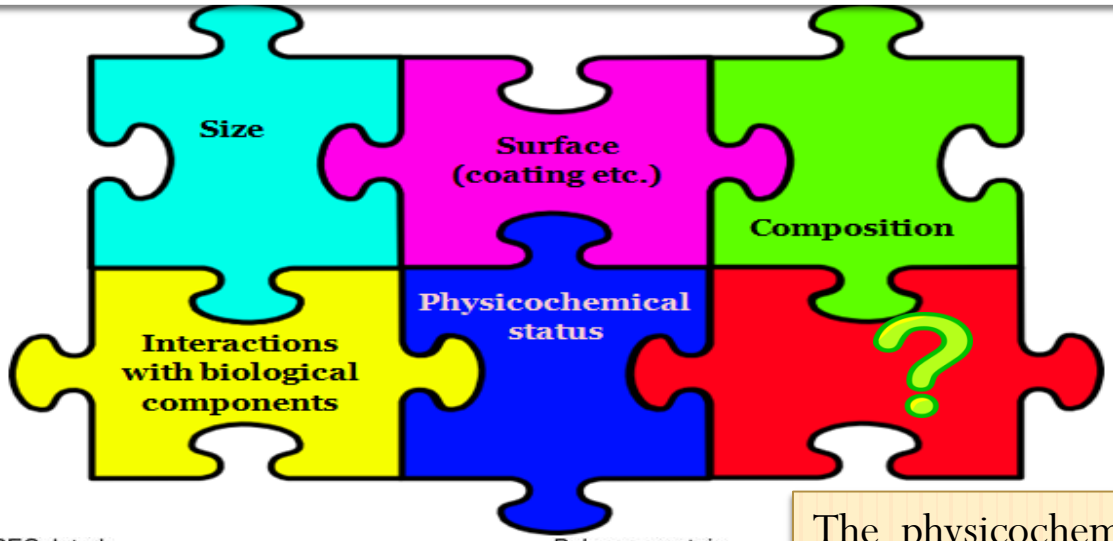


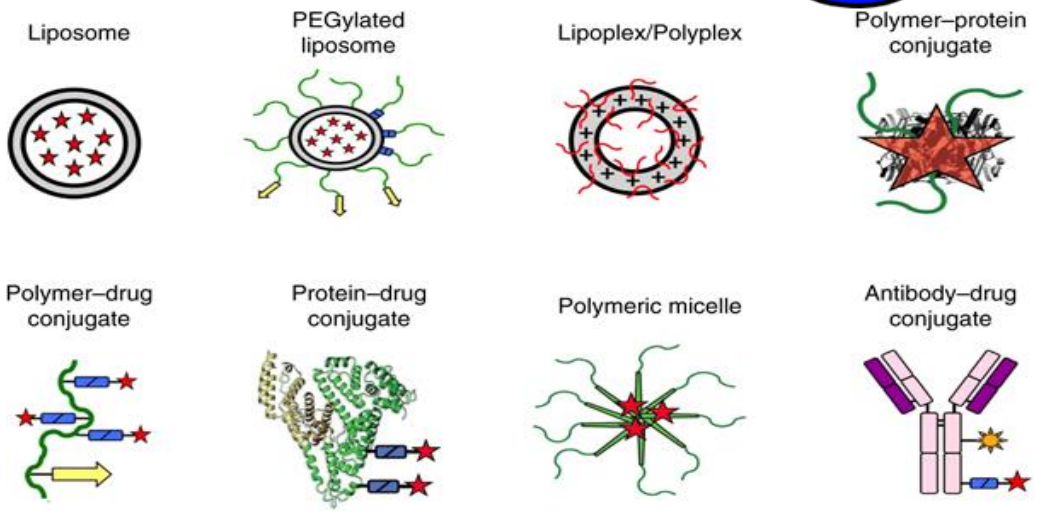
SPECIAL REPORT

Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines

Over the last three decades many first-generation nanomedicines have successfully entered routine clinical use and it is now important for medicines regulatory agencies to consider the mechanisms needed to ensure safe introduction of 'follow-on' nanomedicine products, 'nanosimilars'. Moreover, drug regulators need to ensure that 'next'-generation nanomedicines enter clinical development and consequently the market in a safe and timely way for the benefit of public health. Here we review recent European Medicines Agency activities that relate to the effective development and evaluation of nanomedicine products while keeping patient and consumer safety at the forefront.

The quality of the self assembled nanoparticles in terms of their physicochemical and surface properties is a very crucial issue and depends on:





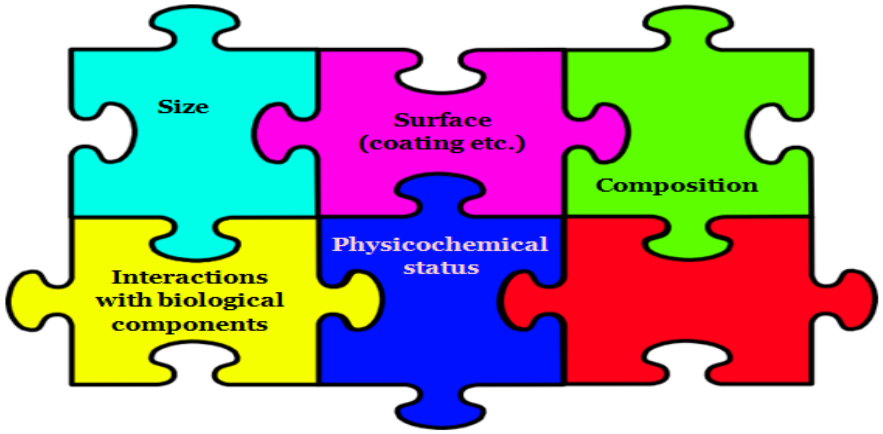
The physicochemical characteristics of nanosystems (the formulation system) play key role of Administration, Distribution, Metabolism and Excretion (ADME profile) of the encapsulated drug. It should be noted that the minimum requirements of nanosimilar products are the highly similar physicochemical characteristics (i.e. size, size distribution, ζ-potential etc.).

What we need …

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

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

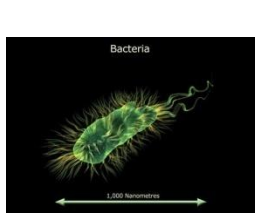
size, size distribution, ζ-potential, shape, surface properties, etc

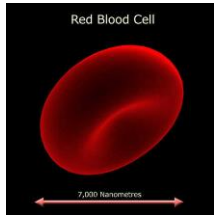


but something is missing for the physicochemical puzzle to be completed

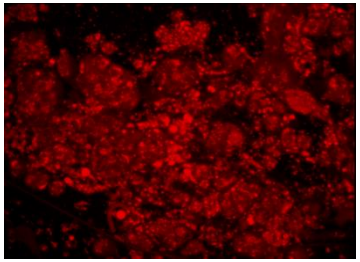
According to J.A.Champion and co-workers (*JCR*, 121, 2007) *.....the particle shape which has not been thoroughly investigated , may have a strong impact on carrier performance.... .....the most basic functions of particles ....will depend on particle shape.*

CAN WE IDENTIFY THE SHAPE OF NATURAL OBJECTS ?

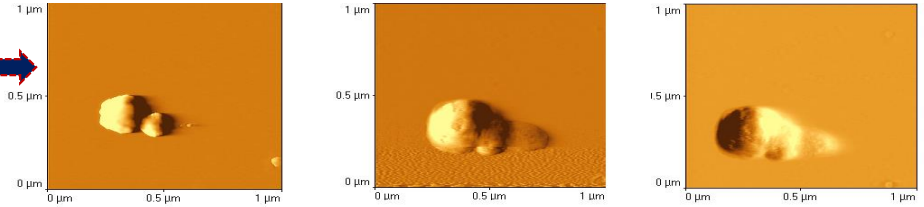




CAN WE IDENTIFY THE SHAPE OF NANOPARTICLES OF A NANOPARTICULATE MEDICINE?



Nanoparticulate systems. Photos have been taken in collaboration with the NTUA (Prof. Makropoulou)



In our point of view *shape* is not the appropriate term in order to describe the **effective dimensionality** of nanoparticles .
Instead we should use the term MORPHOLOGY

Ref. Champion J.A., et al. *JCR,* 121, 2007

Do we need new analytical tools ?

- 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

YES

WE NEED ANALYTICAL TOOLS TO OVERCOME THE EXCISTING CONVENTIONAL METHODOLOGIES AND THE EUCLIDIAN GEOMETRY LIMITATIONS FOR EVALUATING NANOPARTICULATE MEDICINES IN TERMS OF THEIR *MORPHOLOGICAL* PROPERTIES WHICH ARE RELATED TO THEIR *IN VIVO* AND IN CLINICAL TRIALS BEHAVIOUR

Reflection Paper (RP)

A Reflection Paper is developed to communicate the current status of discussions or to invite comments on a selected area of medicinal product development or a specific topic.
It can provide a framework for discussion or clarification, in areas where scientific knowledge is quickly evolving or experience is limited.
A Reflection Paper does not provide direct scientific, technical or regulatory guidance, but may contribute to the future development of such guidelines or related documents, as it provides clear statements or current expectations from the regulator.
Therefore, it becomes possible for researchers to define the potential weak or controversial points and further clarify these with the regulators.

International Journal of Pharmaceutics 483 (2015) 1–5

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Note

Fractal geometry as a new approach for proving nanosimilarity: A reflection note

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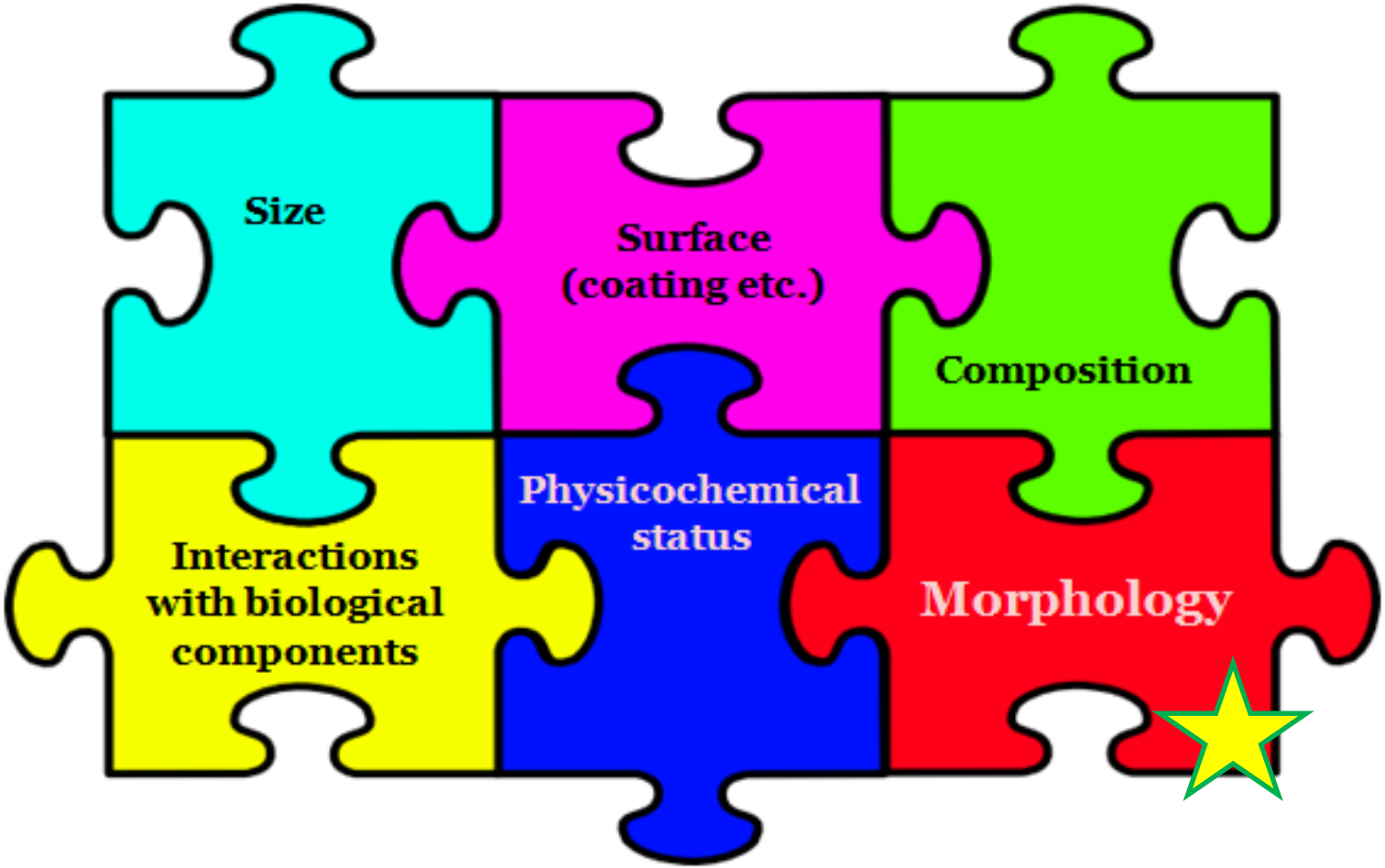
The contribution of our Lab. in this subject , was the publication of the first Reflection Note on Nanosimilars proposing new analytical tools **for proving nanosimilarity** . This Reflection Note wishes to strengthen the consultation process from proving the safety and efficacy of nanosimilar drugs

Fractal analysis could be proposed as a new analytical toolkit in the production process of nanomedicines and of nanosimilars

Fractal analysis could be an attractive and alternative tool for characterizing the morphology instead of shape of nanosimilar products.



The **European Medicinal Agency (EMA)** recommends to develop new rules and regulations for innovative and new drugs.

FRACTAL ANALYSIS CAN OFFER AN OPPORUNITY TO

QUANTIFY THE MORPHOLOGY OF NANOPARTICULATE SYSTEMS OVERCOMING THE LIMITATIONS OF THE EUCLEDIAN GEOMETRY

_This could be the 'gold standard' technique for characterizing nanoparticles and possibly to prove similarity

EMA HAS TO DISCUSS SUCH APPROACH IN ORDER TO PROMOTE NEW GUIDELINES TO THE MANUFACTURERS DURING THE DEVELOPING PROCESS OF NANOMEDICINES AND NANOSIMILARS.

N. Pippa, **C. Demetzos**, E. Danezis *Journal o Liposome Res.*, 1-7, 2011 ;, N. Pippa, S.Pispas, C. **Demetzos** *Int. Journal of Pharmaceutics,* ,430(1-2):65-73, *2012 ;* The delineation of the morphology of charged liposomal vectors via a fractal analysis in aqueous and biological media: physicochemical and self-assembly studies. N. Pippa, S. Pispas, **C. Demetzos**, in press *Int. Journal of Pharm.*, 2012; Incorporation of dimethoxycurcumin into charged liposomes and the formation kinetics of fractal aggregates of corresponding uncharged vectors. M. Hadjidemetriou, N. Pippa, S. Pispas[2] **C.Demetzos** *submitted to J. of Liposme Res.*

Fractals and fractal concept in Pharmaceutical Sciences

International Journal of Pharmaceutics 456 (2013) 340–352

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Review

On the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences: A review

Natassa Pippa, Aristides Dokoumetzidis, Costas Demetzos, Panos Macheras*

Department of Pharmaceutical Technology, Faculty of Pharmacy, Panepistimiopolis Zografou 15771, National and Kapodistrian University of Athens, Athens, Greece

The fractal approach can be characterized as the driving force to explore new paths for developing bio-inspired drug delivery systems, which are fractal objects that can be able to deliver pharmacomolecules to the specific sites of the organism.

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
© 2012 Informa Healthcare USA, Inc.
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.

In the same context, 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 and biosimilar 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]

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,*]

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Journal of Liposome Research

http://informahealthcare.com/lpr
ISSN: 0898-2104 (print), 1532-2394 (electronic)

J Liposome Res, Early Online: 1–7
© 2012 Informa Healthcare USA, Inc. DOI: 10.3109/08982104.2012.747534

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

Conclusions:

- 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 prove the similarity and to create a framework process for the approval of nanosimilars.
- Basic sciences such as Physics (biophysics and thermodynamics) and Mathematics are needed to assist such an approach
- An analytical concept based on fractal analysis (complementary to the QbD approach) has been proposed offering an added value to the *'mapping process'* for developing nano-similar medicinal products.
- The regulatory authorities should take into consideration that efficient analytical evaluation of nanomedicines and consequently of nanosimilars 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.

ACKNOWDELEGMENTS

UNIVERSITY OF ATHENS

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

Natassa Pippa senior researcher

for her outstanding contribution and for her valuable collaboration

Dr. **A. Dokoumetzidis**,

NATIONAL HELLENIC RESEARCH FOUNDATION

Institute of Organic and Pharmaceutical Chemistry

- Dr. **Maria Micha-Screttas**
- Dr. **Barry Steele**

Dr.N. Tagmatarchis, NHRF,

Institute of Theoretical and Physical Chemistry

- Dr. **Stergios Pispas**

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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