Nanoparticles as Drug Delivery Carriers

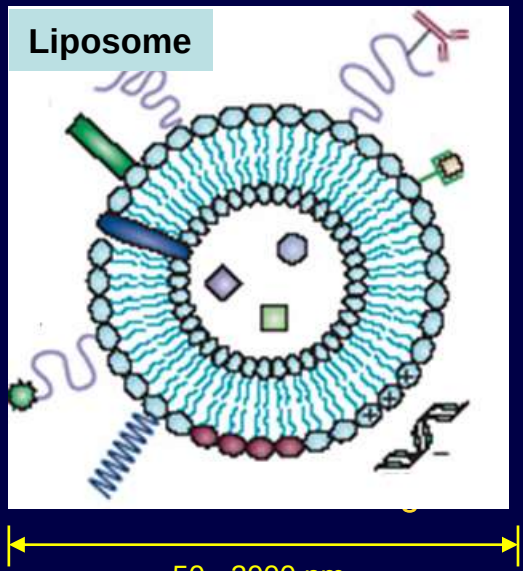
Outline of Presentation：

1. Advantages and Stages of Nanoparticle Delivery Systems
2. Fabrications and **Characterizations** of Nanoparticles
3. Cytotoxicity and Biodistribution of Nanoparticles
4. Interactions between Nanoparticles and Cell membrane (model)
5. Nanotechnology and Cosmetics

Advantages of Nanoparticles - By Convention

- Deliver hydrophilic and hydrophobic drugs
- Targeting ability via surface modification
- Reduce carcinogenic /irritant reactions
- **Advantages**
- Control release properties
- Facilitate transport across membrane
- Offer protection (Stability)

Schematic Structure of Liposome Loading with Drug



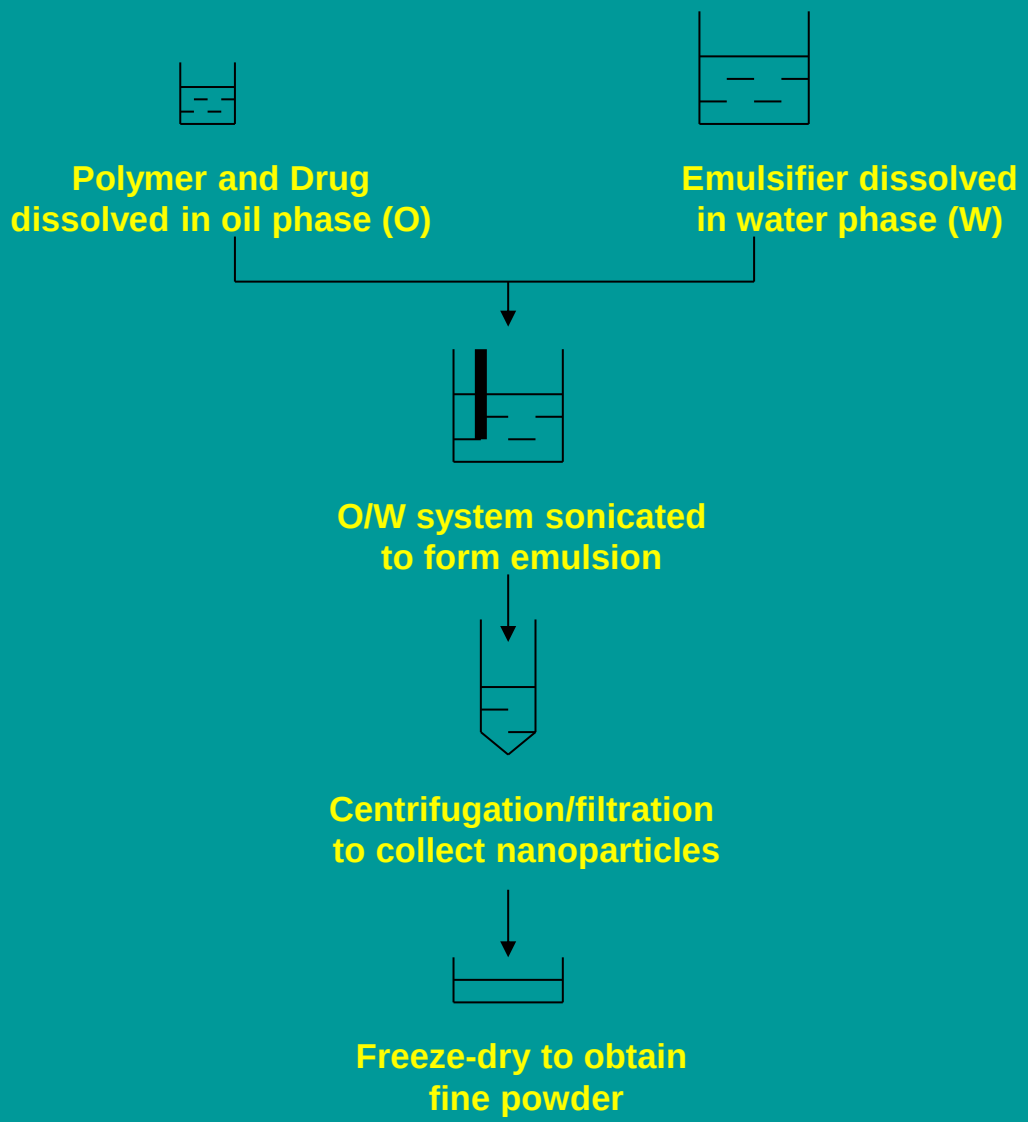
Stages for Developing Nanoparticle Delivery Systems：

1. Materials studies
2. Fabrications
3. **Characterizations** (various analytical methods)
4. Interactions between drug or nanoparticles and cell membrane
5. *In vitro* cytotoxicity (cell viability)
6. Animal tests
7. Clinical trials
8. Commercialisation

Fabrication of Nanoparticles:

- Modified Solvent Extraction/Evaporation Technique
- Spray Drying & Spray Freeze Drying
- Supercritical Fluid Spraying
- Coacervation
- Polymerisation of Monomers
- High-Pressure Hot or Cold Homogenization Process
- Hydration and Extrusion of Lipids or Lipid-polymer Conjugates

Preparation of Polymeric Nanoparticles by Single emulsion solvent extraction/evaporation



Important parameters:

- Polymer type, MW. and co-polymer blend ratio
- Polymer concentration in oil phase
- Emulsifier/Stabilizer/Additive
- Volume ratio between oil phase (O) and water phase (W)
- Property of organic solvent
- Drug loading proportion to polymeric material
- Mechanical type and strength of mixing
- Drying technique
- Temperature, pH, container, etc.

Methodology

Fabrication

Characterization

- Particle Morphology
  - Scanning Electron Microscopy (SEM)
  - Atomic Force Microscopy (AFM)
- Particle Size
  - Particle Size Analyser/Laser Light Scattering
- Particle Surface Charge
  - Zeta Potential Measurement
- Particle Surface Chemistry
  - X-Ray Photoelectron Spectroscopy (XPS)
  - Fourier Transform Infra-Red (FTIR)
- Drug Encapsulation Efficiency
  - High Performance Liquid Chromatography (HPLC)
- *In Vitro* Release Kinetics
- Drug Physical Status
  - Differential Scanning Calorimetry (DSC)
- Interaction between Nanoparticles and model bio-membrane
  - Langmuir-Blodgett Trough

In Vitro Cytotoxicity (Cell Viability)

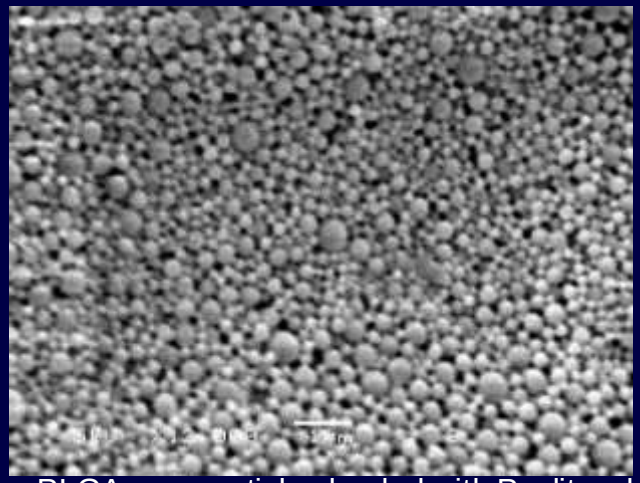
- MTS & SRB Assay
- ELISA Plate Reader

Animal Experiment

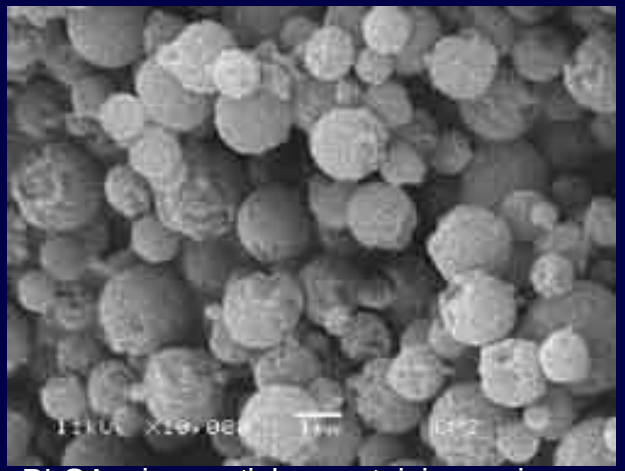
- Biodistribution
- Maximum Tolerable Doses (MTD)
- Antitumor Efficacy

Morphology of Drug-loaded Polymeric Nanoparticles

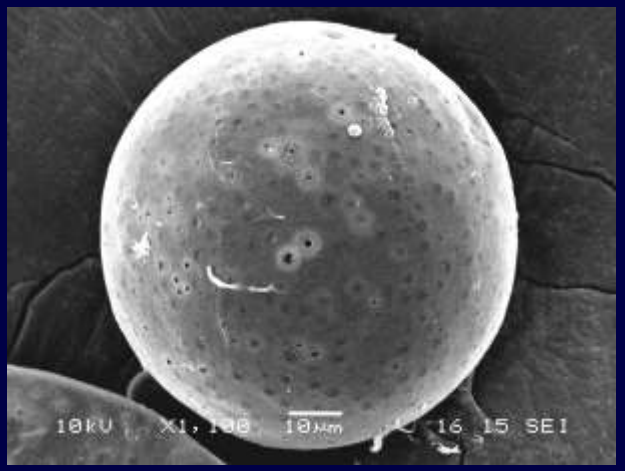
Scanning Electron Microscopy & Atomic Force Microscopy



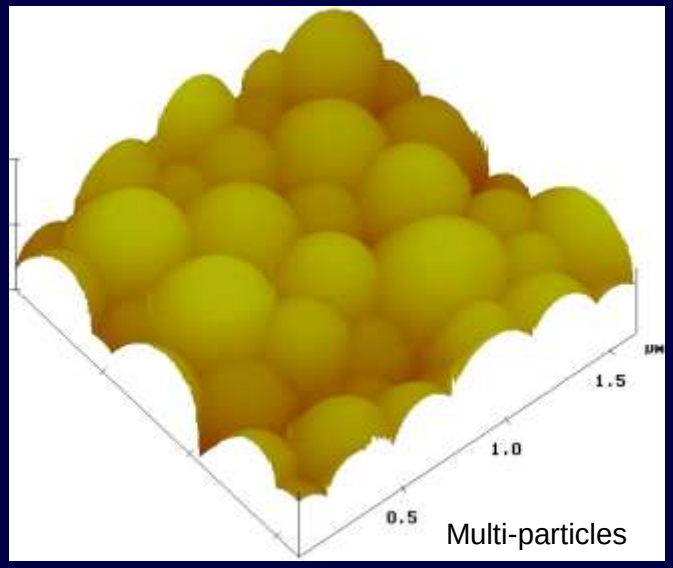
PLGA nanoparticles loaded with Paclitaxel prepared by single emulsification method



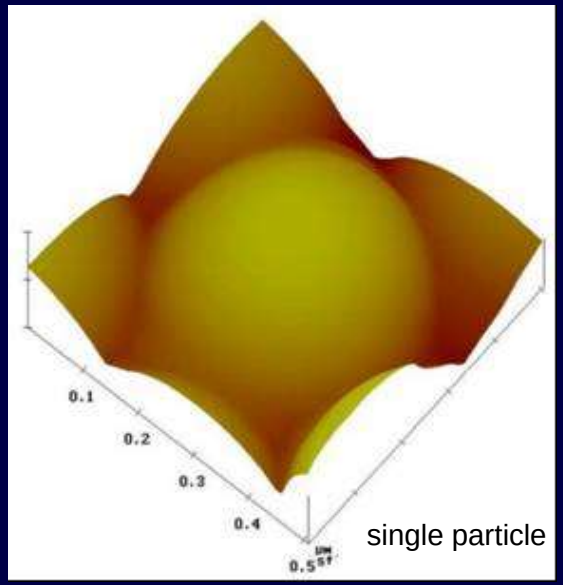
PLGA microparticles containing various additives and prepared by spray-drying



PLGA microparticles prepared by double emulsification method

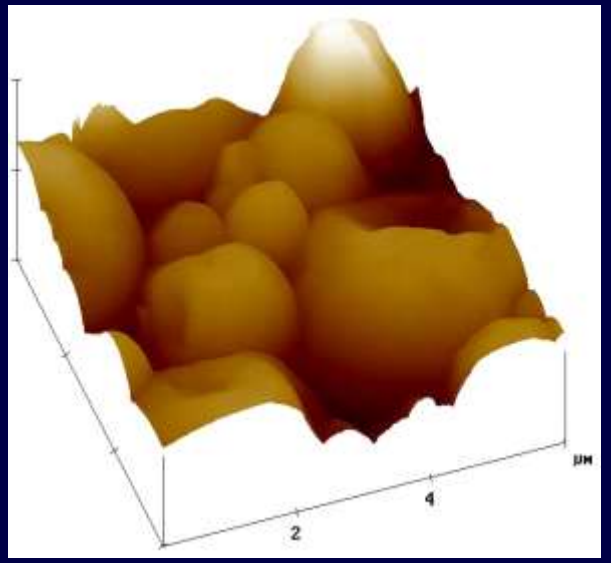


Multi-particles



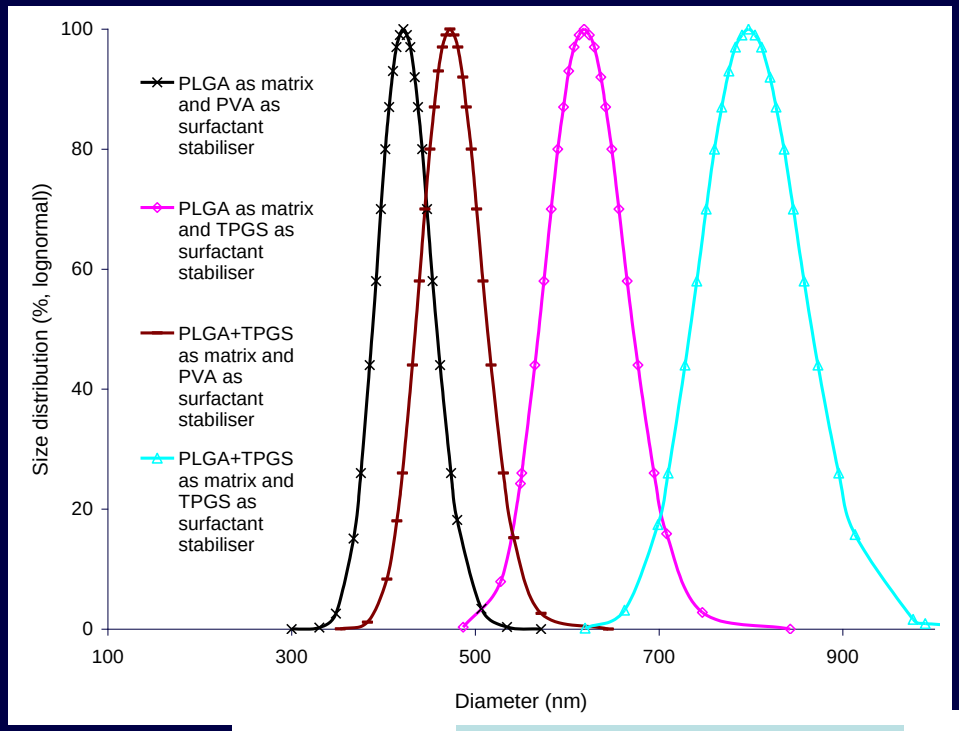
single particle

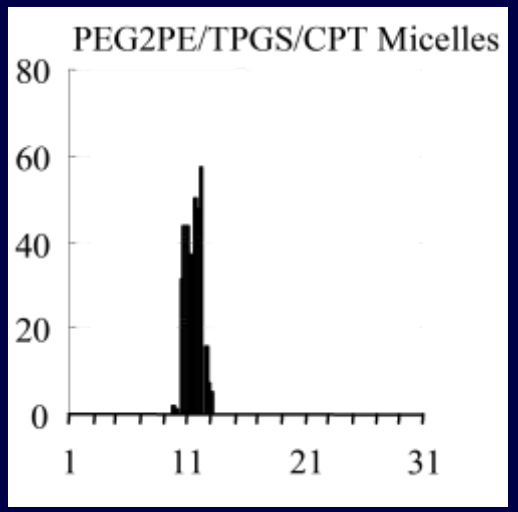
PLGA-TPGS nanoparticles prepared by single emulsification

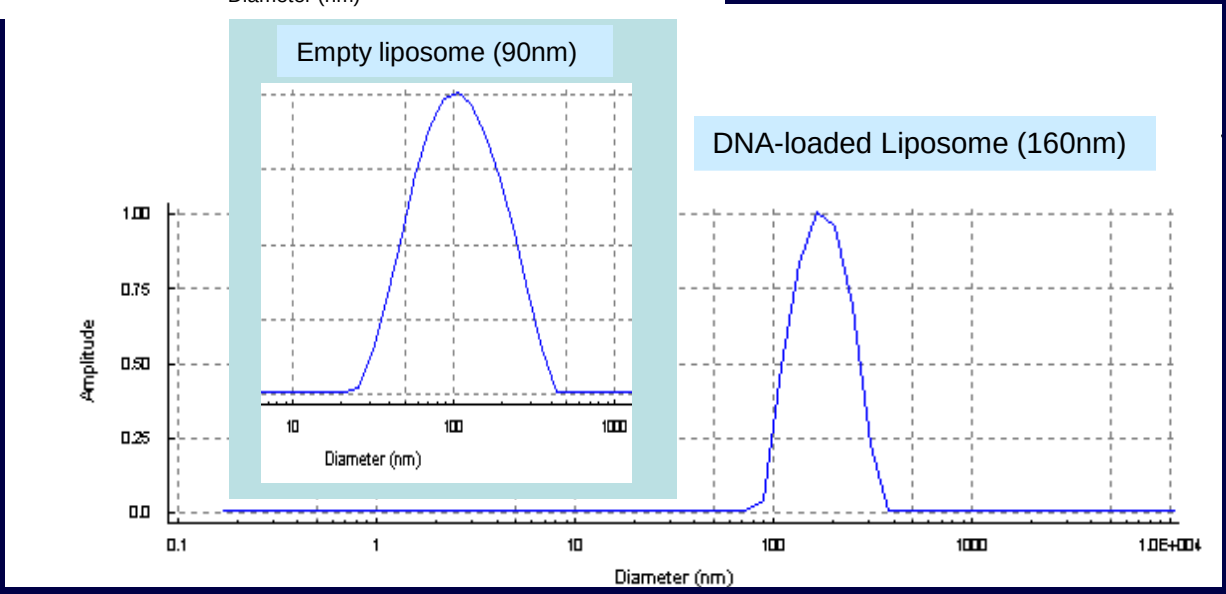


PLGA-TPGS microparticles prepared by spray-drying technique

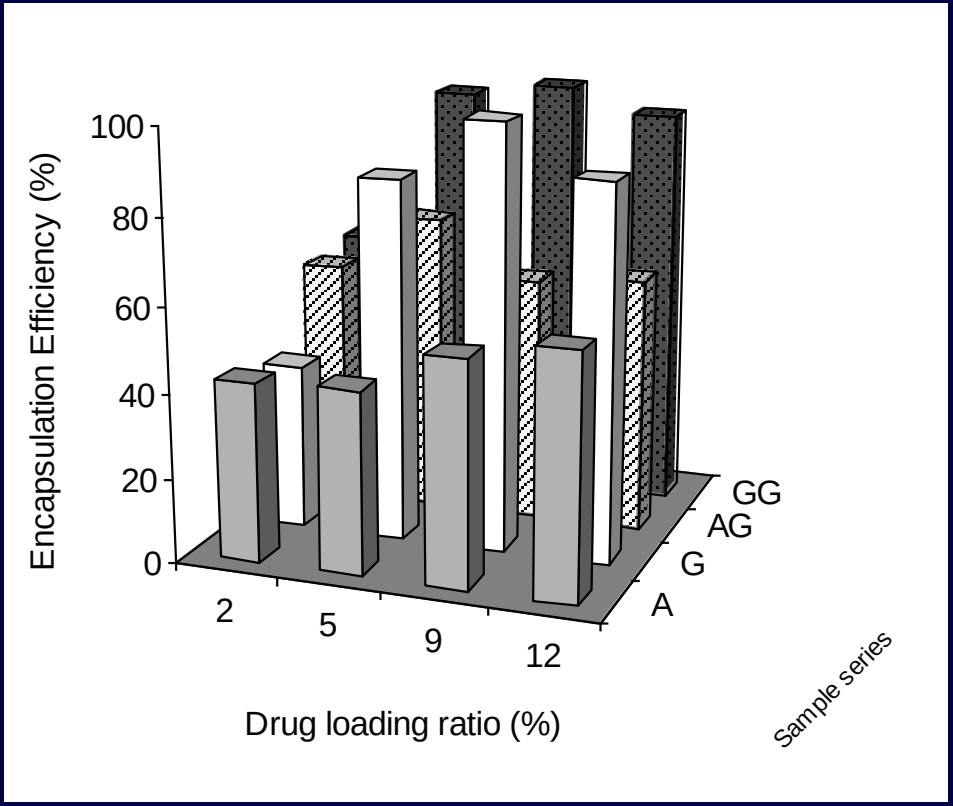
Particle Size and Size Distribution







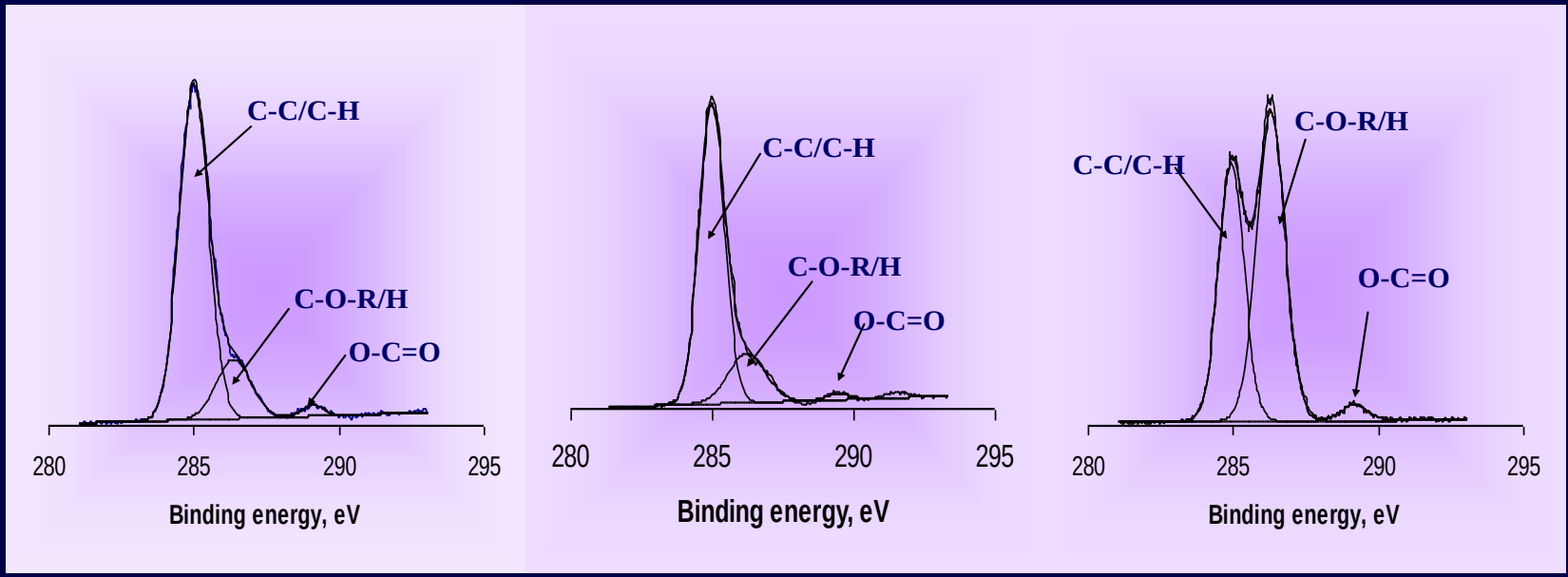
Drug Encapsulation Efficiency



Paclitaxel encapsulation efficiency of various nanoparticulate formulations (Nanoparticles prepared with TPGS as surfactant stabilizer (G and GG series) exhibited higher drug EE compared with those prepared with PVA as emulsifier (A and AG series))

X-ray Photoelectron Spectroscopy Analysis of Particle Surface

Samples	XPS C1s envelope ratio (%)		
	C-C/C-H	C-O-H/C-O-R	O-C=O
Uncoated Polystyrene particles	81.24	16.85	1.91
Pure TPGS	84.77	13.73	1.50
TPGS-coated particles	84.33	12.32	3.35
Pure PVA	48.91	42.55	8.54
PVA-coated particles	41.84	55.52	2.64

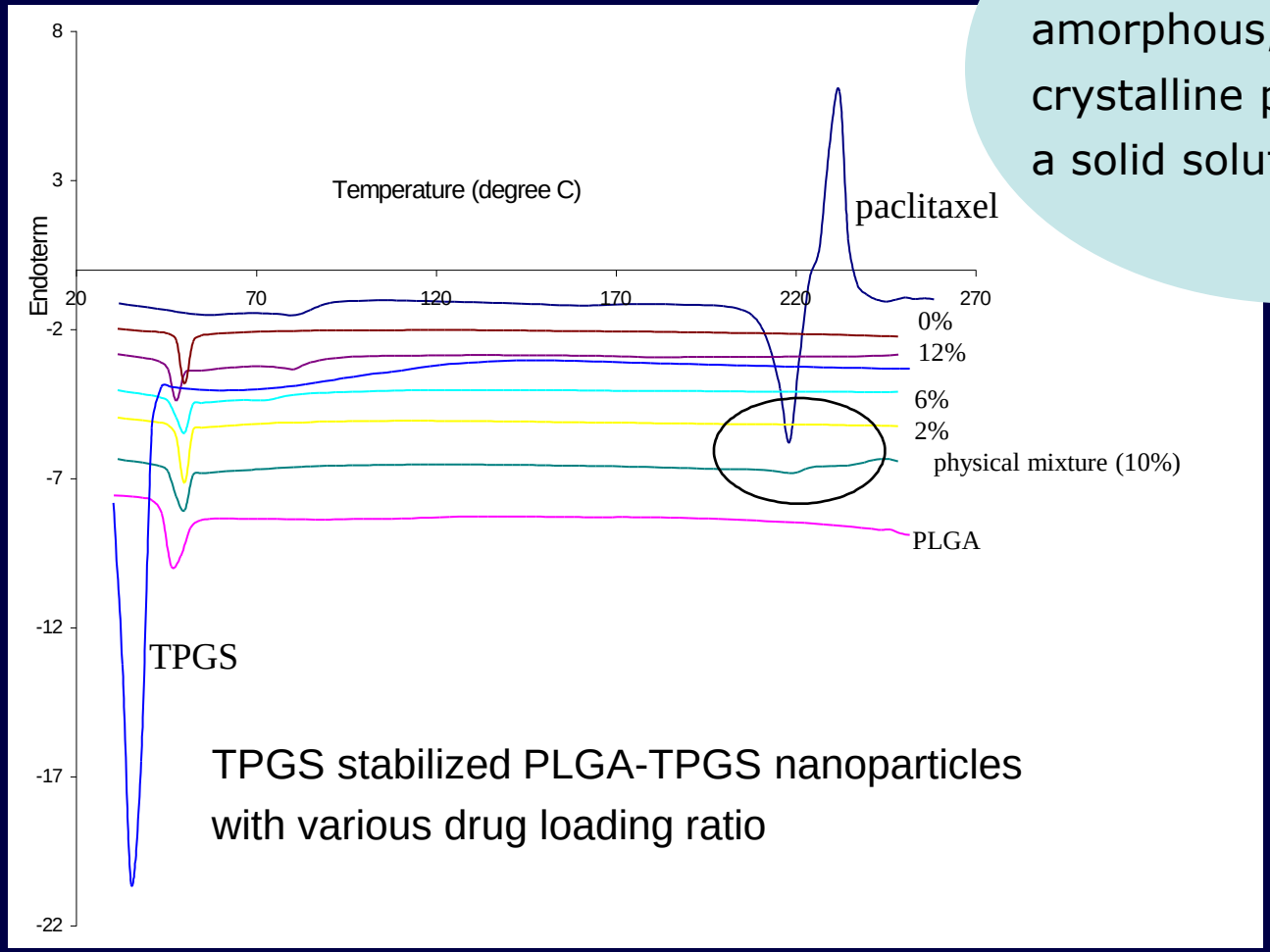


Uncoated PS Particles | TPGS-Coated Particles | PVA-Coated Particles

Thermal Analysis & Drug Physical Status

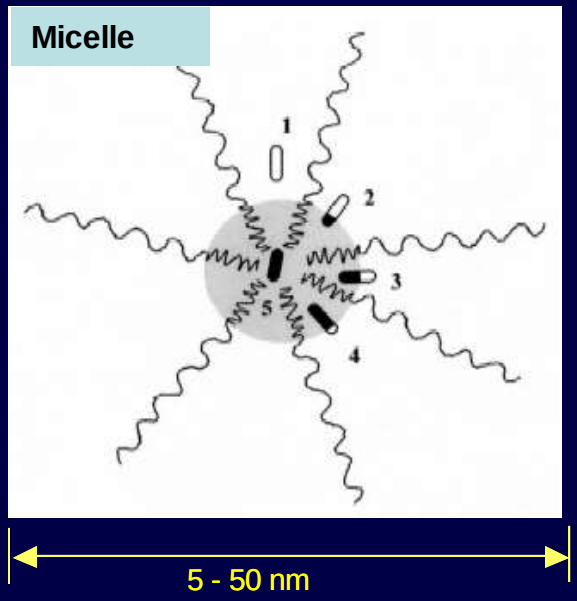
Differential Scanning Calorimetry (Paclitaxel Encapsulated in Polymeric Nanoparticles)

Drug entrapped was in an amorphous, or disordered-crystalline phase state, or a solid solution state

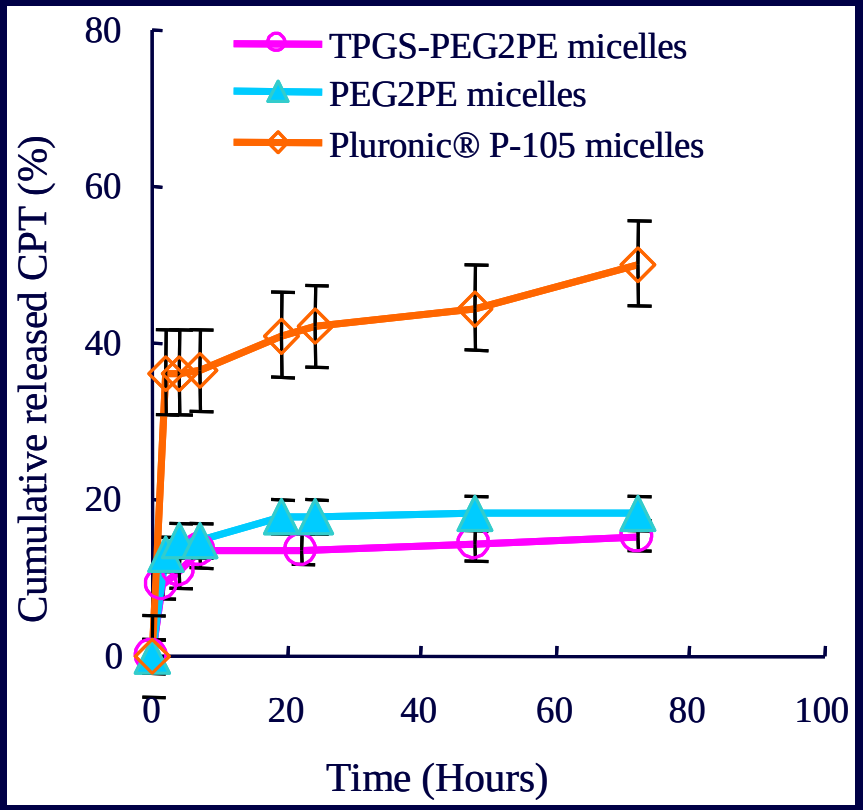


TPGS stabilized PLGA-TPGS nanoparticles with various drug loading ratio

In Vitro Release Property



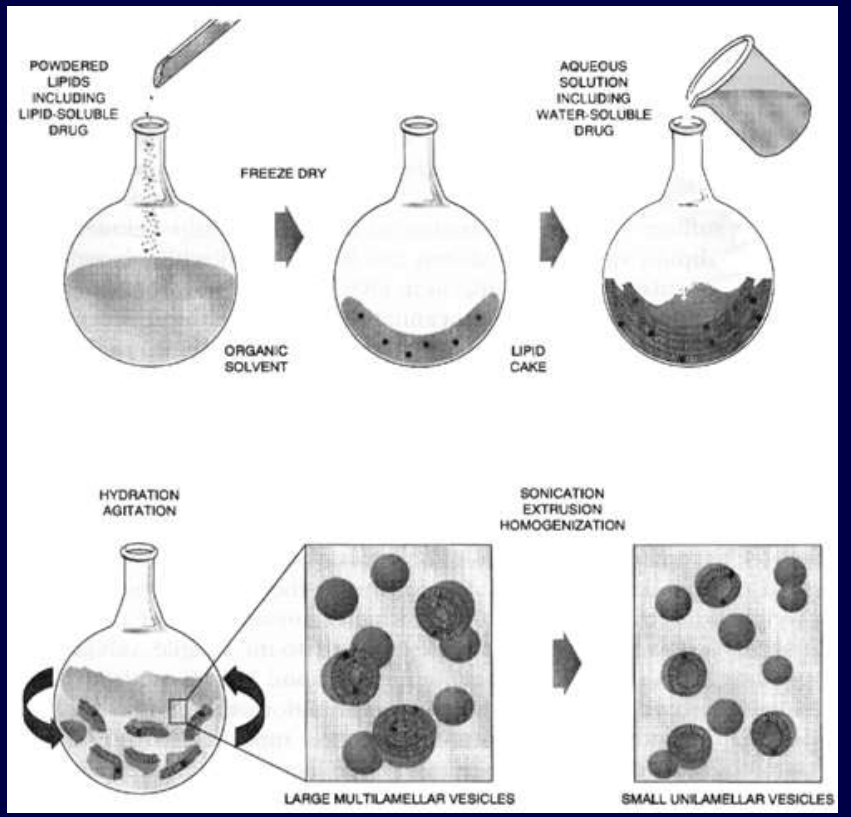
Micellar nanoparticle from lipid-polymeric conjugate is good carrier for water insoluble drug.



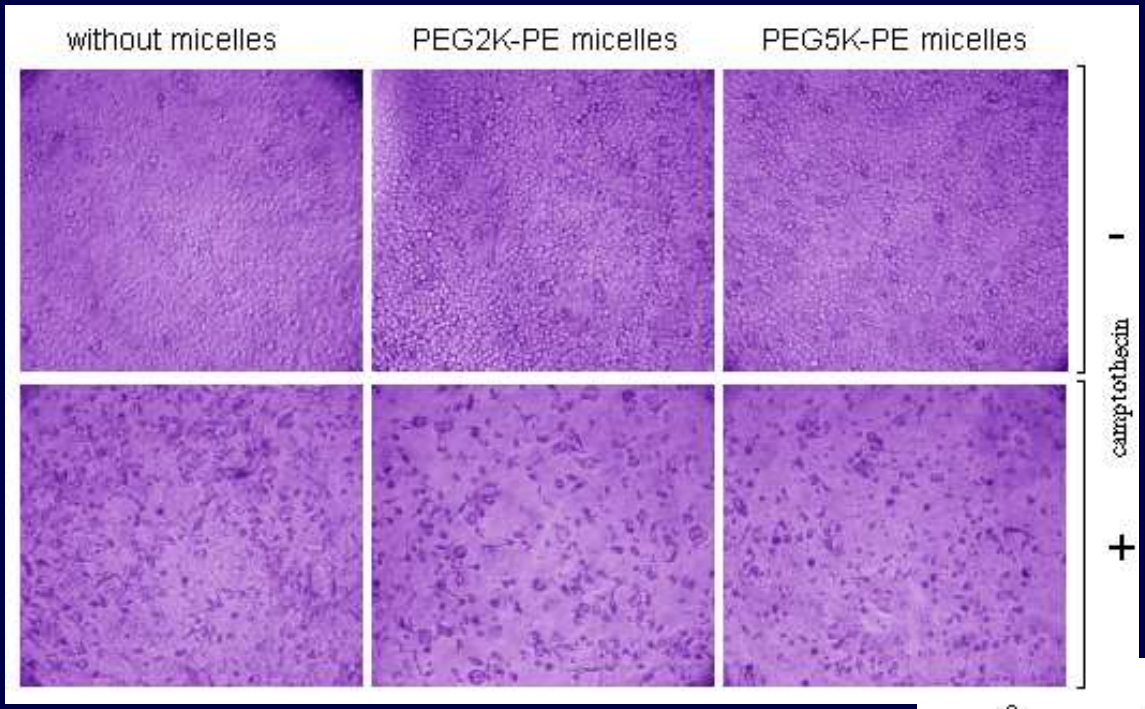
In vitro release of camptothecin from various micelle formulations

Special attention to liposome delivery formulations for protein/DNA (Issues/Challenges):

- Dosage variability (Possible over- or under-dosing of the recipient):
  - Special training of personnel
  - Preparation of the complex by admixture prior to each use
- Inconvenient for large scale production
- Purification
- Different effects in different cells types
- Storage/formulation stability (Forming large and less active aggregates)
- Lyophilization



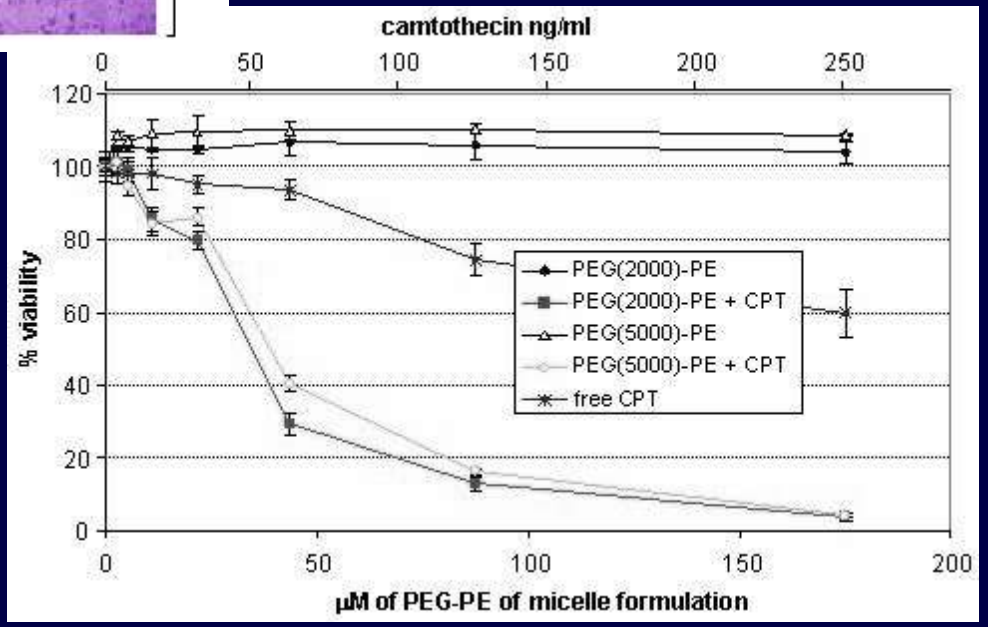
Cell Cultures & Cytotoxicity Assays



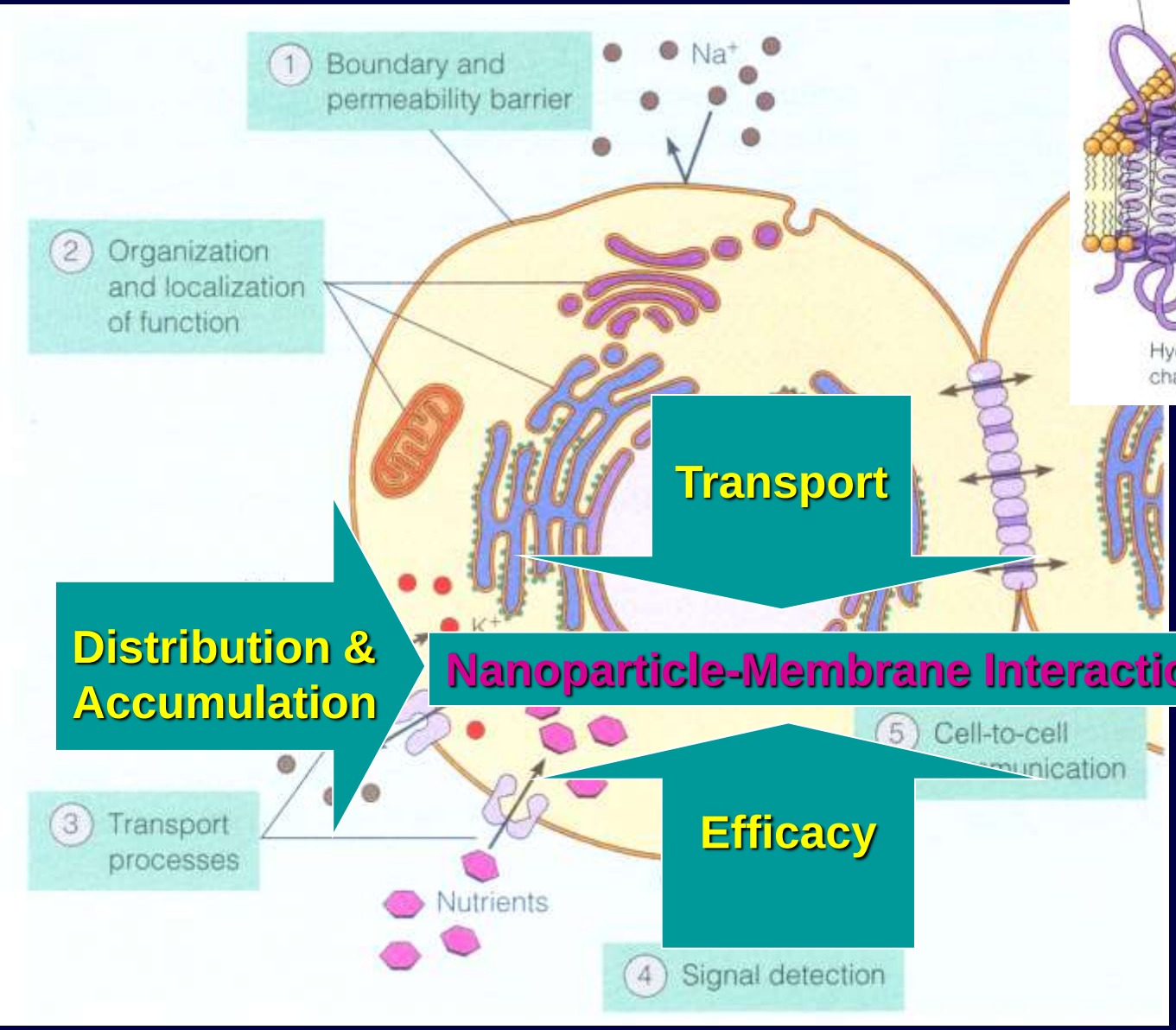
Cell morphology and cytotoxicity of free CPT and CPT-loaded PEG-PE micelles in HT-29 cell Culture. (Picture was taken at CPT conc. about 130 ng/ml)

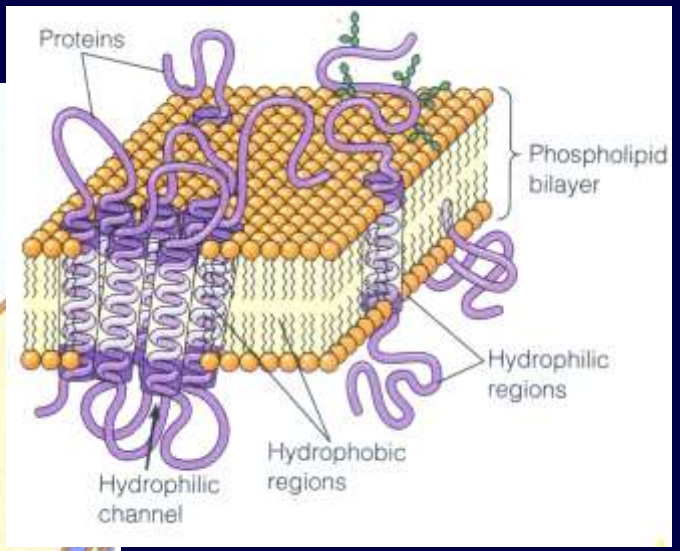
Reason of enhanced cytotoxicity of the micellar drug:

- Increased solubility of the poorly soluble drug in micelle solution;
- Increased stability of the drug molecule inside the micelle core;
- Better uptake of drug-containing micelle nanoparticles by the cells.



Interactions Between Nanoparticles and Model Membrane





Transport

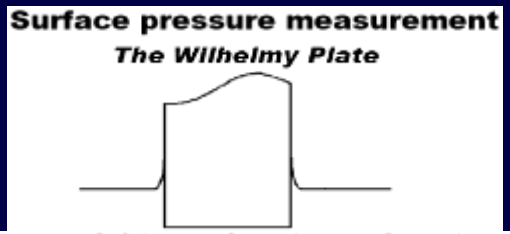
Distribution & Accumulation

Nanoparticle-Membrane Interaction

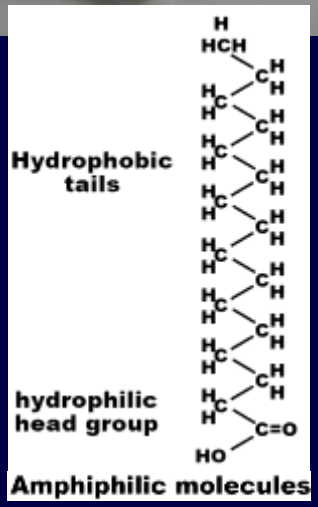
Drug Resistance

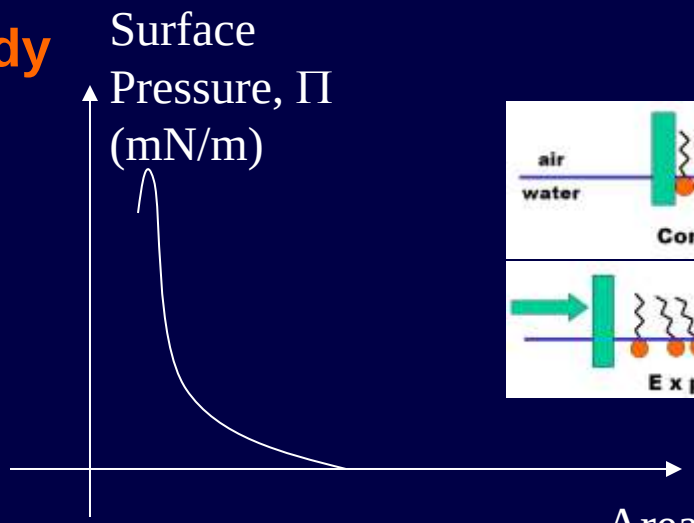
Efficacy

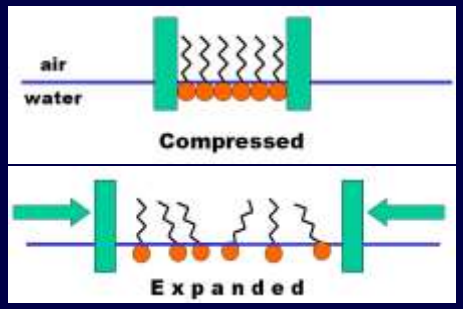
Langmuir Trough for Monolayer Study

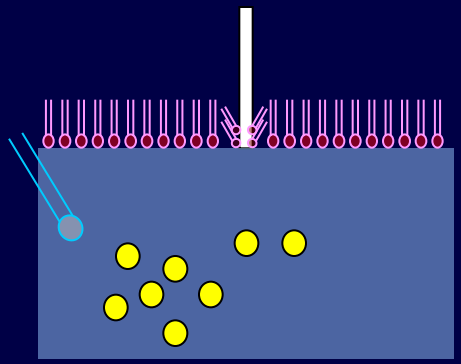


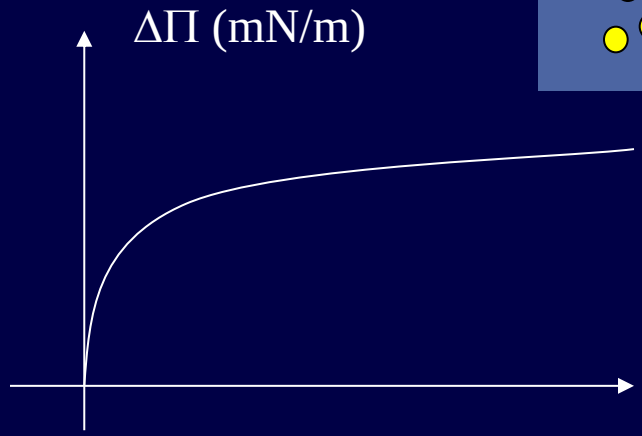
Force = weight – upthrust + surface tension



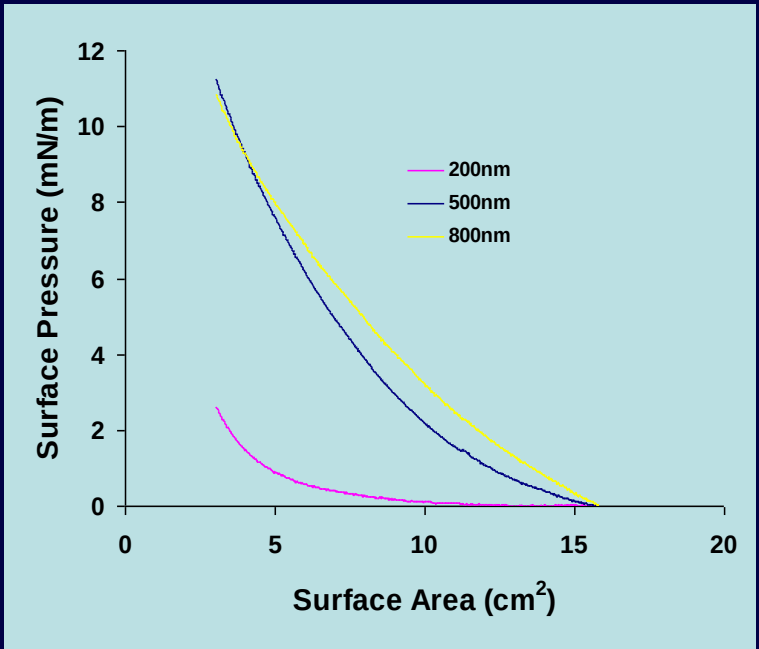


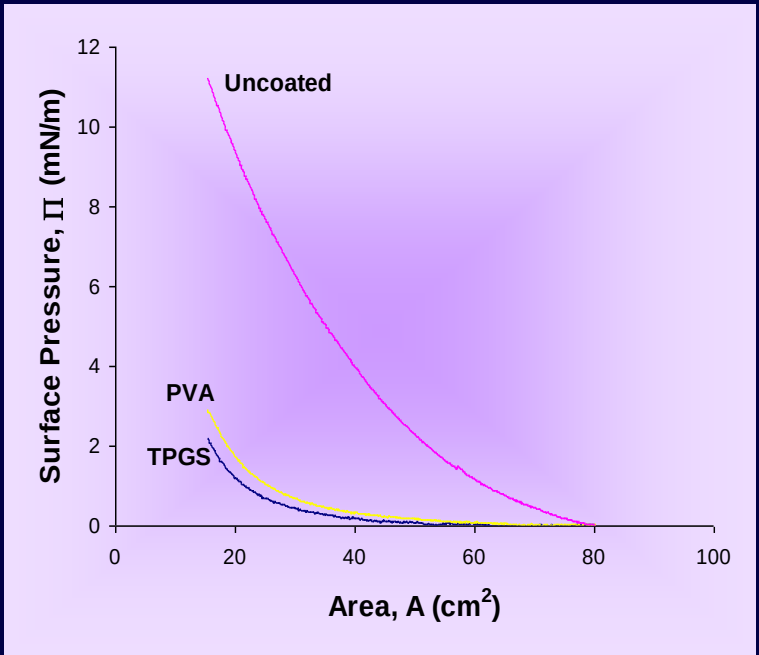






Inter-particle Forces and Pi-A Isotherms

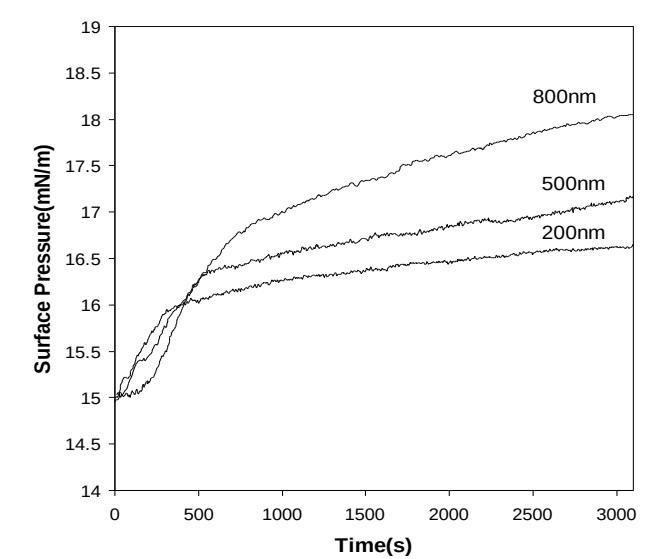




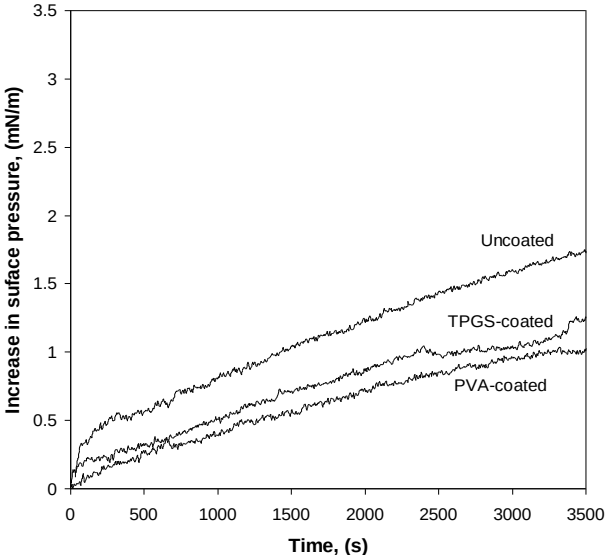
Surface pressure Pi is a function of following interfacial forces

Kinetic & **Van der Waals** & **Capillary** & **Electrostatic charge repulsion**

Particle-Membrane Interaction and Penetration



Penetration profiles of 200, 500 and 800nm particles when 500uL of suspension is injected



Penetration profile of the various particles at initial Pi = 25mN/m

The particle penetration process may involve:

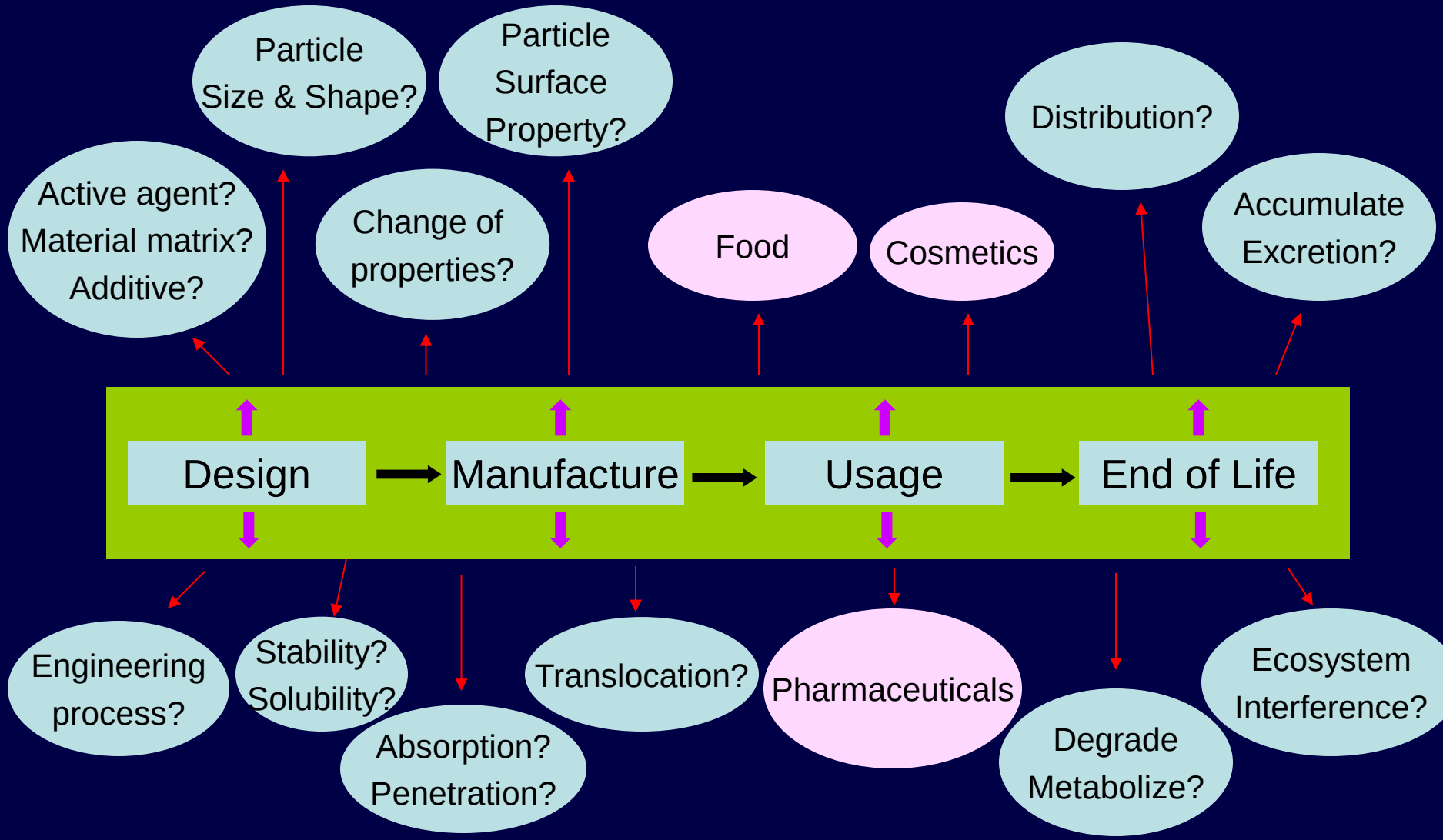
- **Diffusion** of particles to the monolayer interface
- **Insertion** of the particles into the monolayer
- **Rearrangement** of the adsorbed particles at the interface

http://en.wikipedia.org/wiki/List_of_nanotechnology_applications

Bioavailability

Toxicity!

Environmental Impacts and Health Effects


Particle Size & Shape?
Particle Surface Property?
Distribution?
Active agent? Material matrix? Additive?
Change of properties?
Food
Cosmetics
Accumulate Excretion?
Design
Manufacture
Usage
End of Life
Engineering process?
Stability? Solubility?
Absorption? Penetration?
Translocation?
Pharmaceuticals
Degrade Metabolize?
Ecosystem Interference?

Thank you for your attention!