Bioceramics
Lecture 9
Drug Delivery
Using Ceramic Nanoparticles

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➢ Course Outline „Bioceramics”

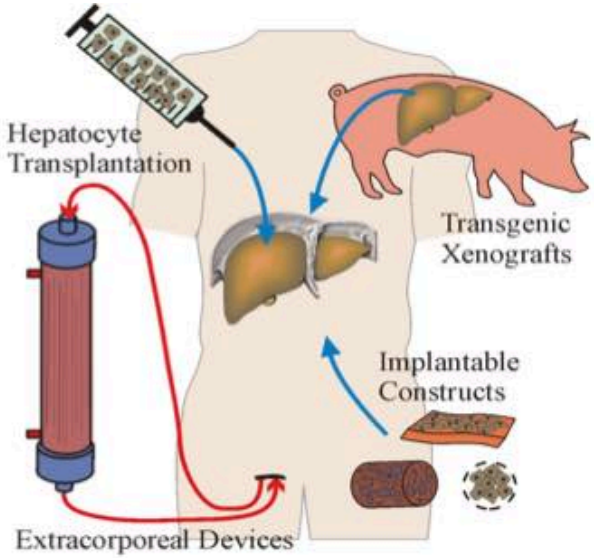
1. Introduction: Applications, Goals and Challenges
2. A short Introduction to Proteins and Cells
3. Ceramics at the Biology Interface: Fundamental Interactions
4. Characterization of Biomolecule Adsorption
5. Bones and Teeth: Composites of Ceramics and Proteins
6. Ceramics for Orthopedic and Dental Implants: Alumina and Zirconia
7. Scaffolds for Bone Tissue Engineering: Calciumphosphates
8. Scaffolds for Bone Tissue Engineering: Bioglass® and Glass-Ceramics
9. Drug Delivery Using “Ceramic” Nanoparticles
10. Biomineralization
11. Biomimetic Materials
12. Student Talks on Selected Topics
13. Summary

The summary lecture will be right before the exams.

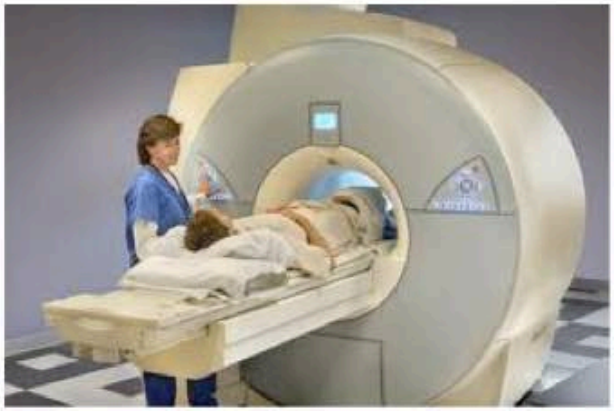
➢ Lecture Outline

- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using “Ceramic” Nanoparticles

➢ Nanotechnology and Life Sciences

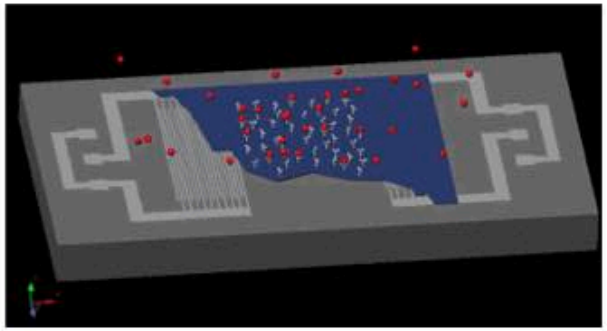


Tissue Engineering

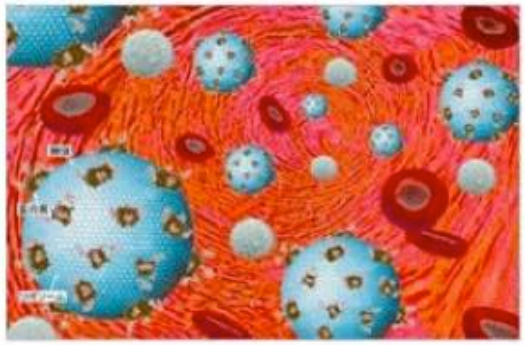


Bioimaging

Nanotechnology

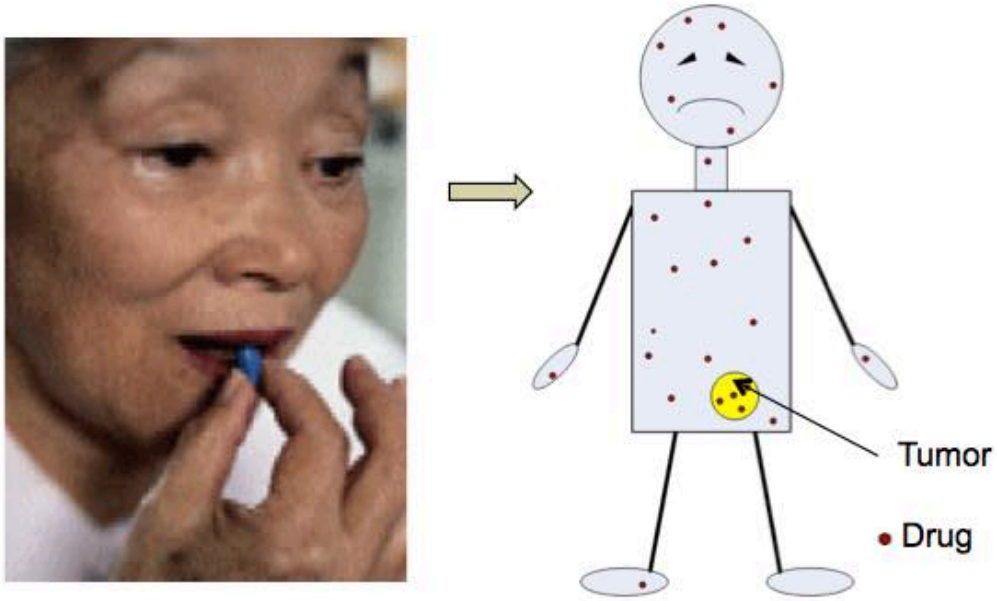


Biosensors



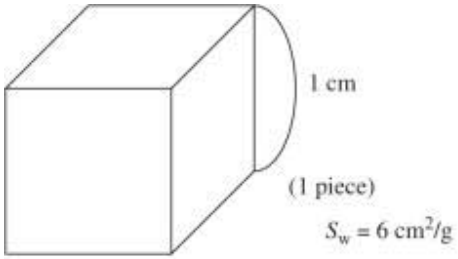
Drug delivery

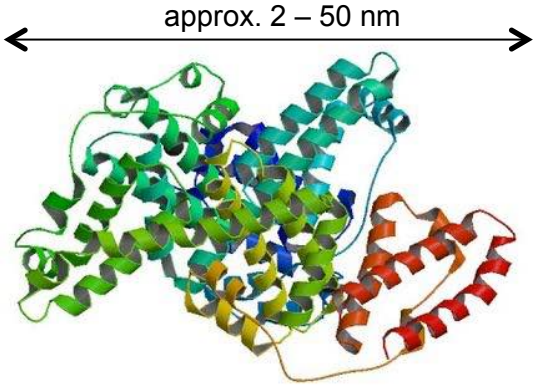
➢ Targeted Drug Delivery (it's all about the patient!)



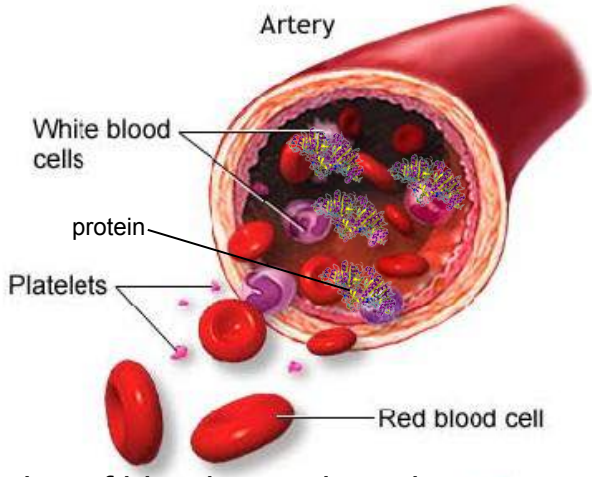
Conventional systemic drug delivery

➢ Nanoparticles in contrast to tissue material (length scales)



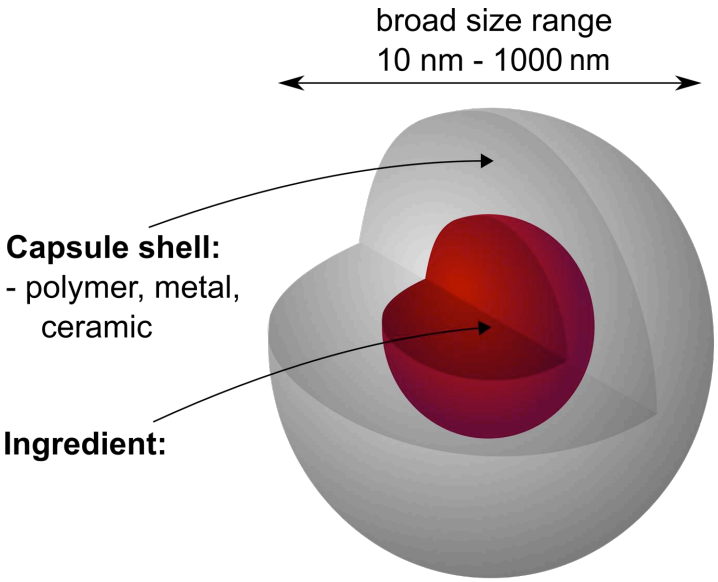


Proteins usually posses radii between **2** and **50nm**



The size of blood vessels varies enormously, from a diameter of about **25 mm** in the aorta to only **8 µm** in the capillaries.

➢ Nanoparticle Drug Delivery – an interdisciplinary science



Chemistry

- Particle synthesis
- Surface modification
- Composition characterization

Physics

- Quantify „physical“ properties:

→ fluorescence
→ superparamagnetism
→ plasmonic coupling
→ etc.

NANOPARTICLE DRUG DELIVERY

Biology

- Pharmaceutical/Drug development
- Cell testing
- Animal models

Medicine

- Clinical trials/ implementation
- Determine dosing

➢ (Targeted) Drug Delivery with Nanocarriers

Conventional drug delivery systems (DDS) such as oral ingestion or intravascular injection, the drug is distributed throughout the body through the systemic blood circulation. For most therapeutic agents, only a small portion of the drug reaches the affected organ. E.g. distribution of Aspirin.

- **Targeted drug delivery** is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to other.

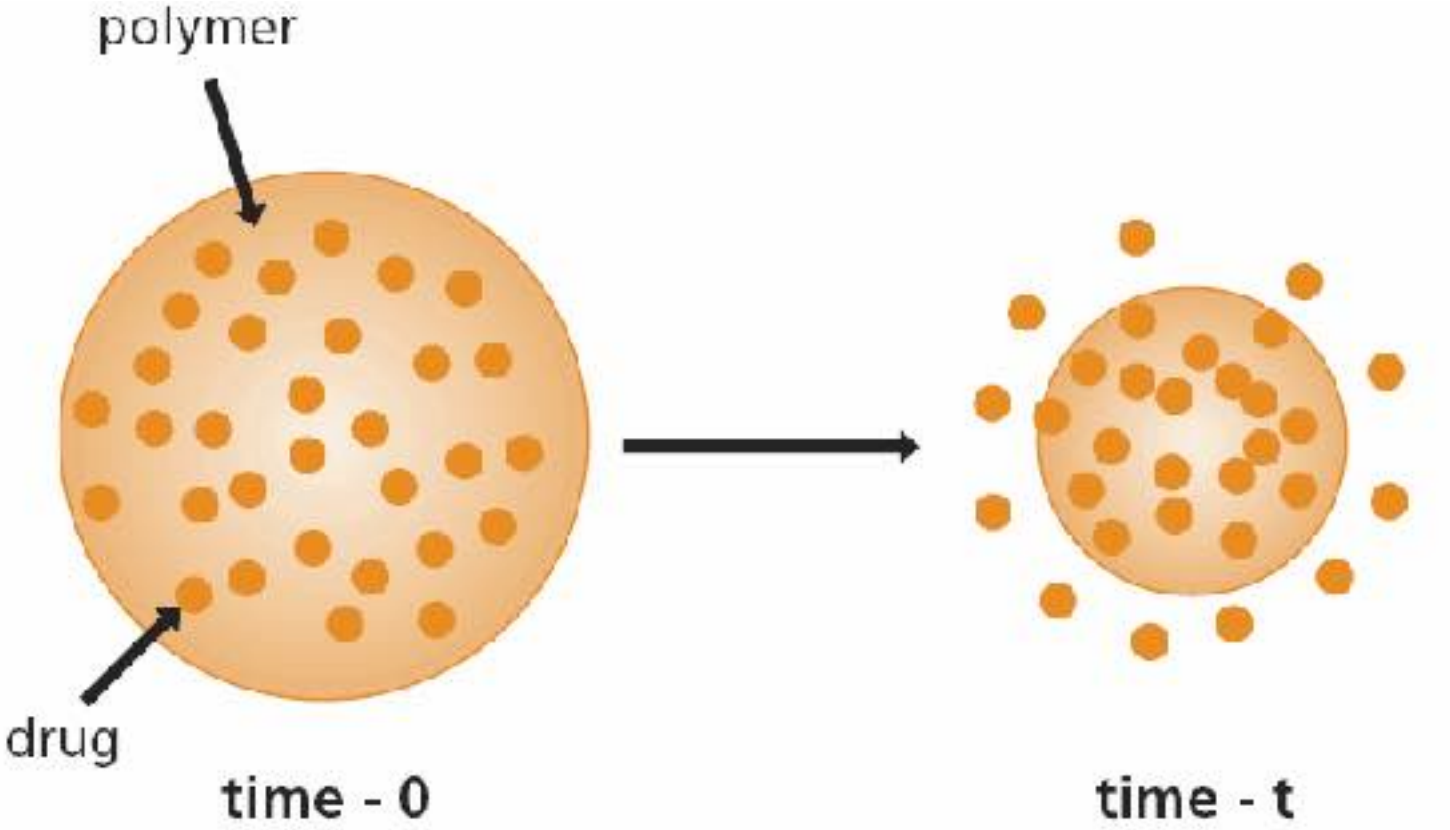
- Targeted drug delivery seeks to concentrate the drug in the tissues of interest while reducing the relative concentration of the drug in the remaining tissues. This improves efficacy of the drug while reducing side effects.

- Two kinds of targeted drug delivery:
  - *Passive targeting:* Enhanced permeability and retention effect (EPR-Effect)
  - *Active targeting:* Attachment of specific ligands to the surface of pharmaceutical carriers to recognize and bind pathological cells

➢ Targeted Drug Delivery in Nanomedicine

https://www.youtube.com/watch?v=2VcNpl8-PRI

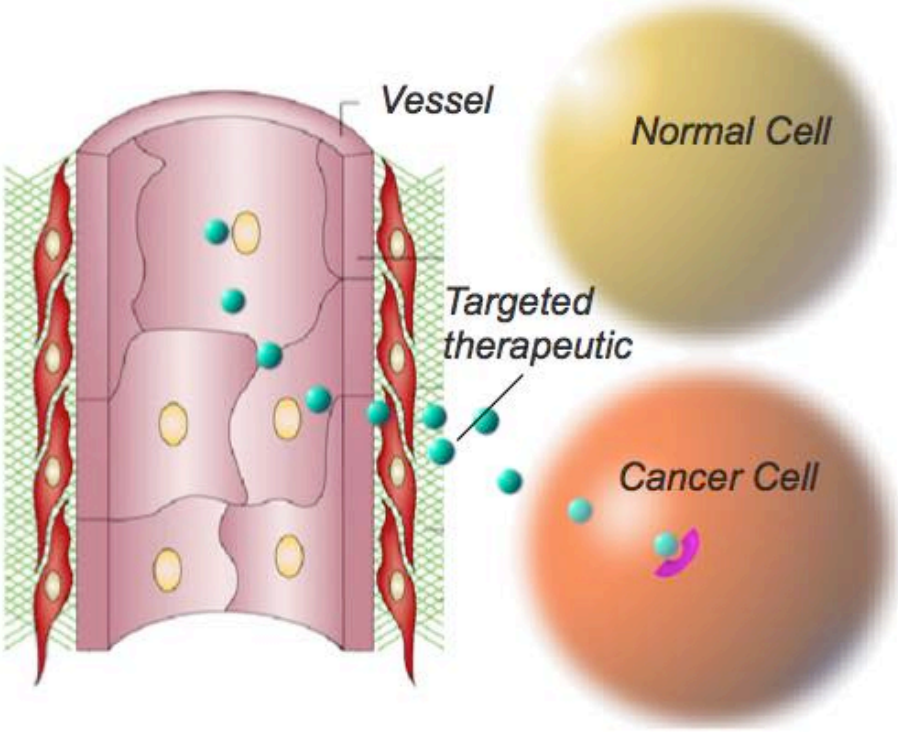
➢ Targeted Drug Delivery using Nanoparticles



➢ Challenges in Targeted Drug Delivery

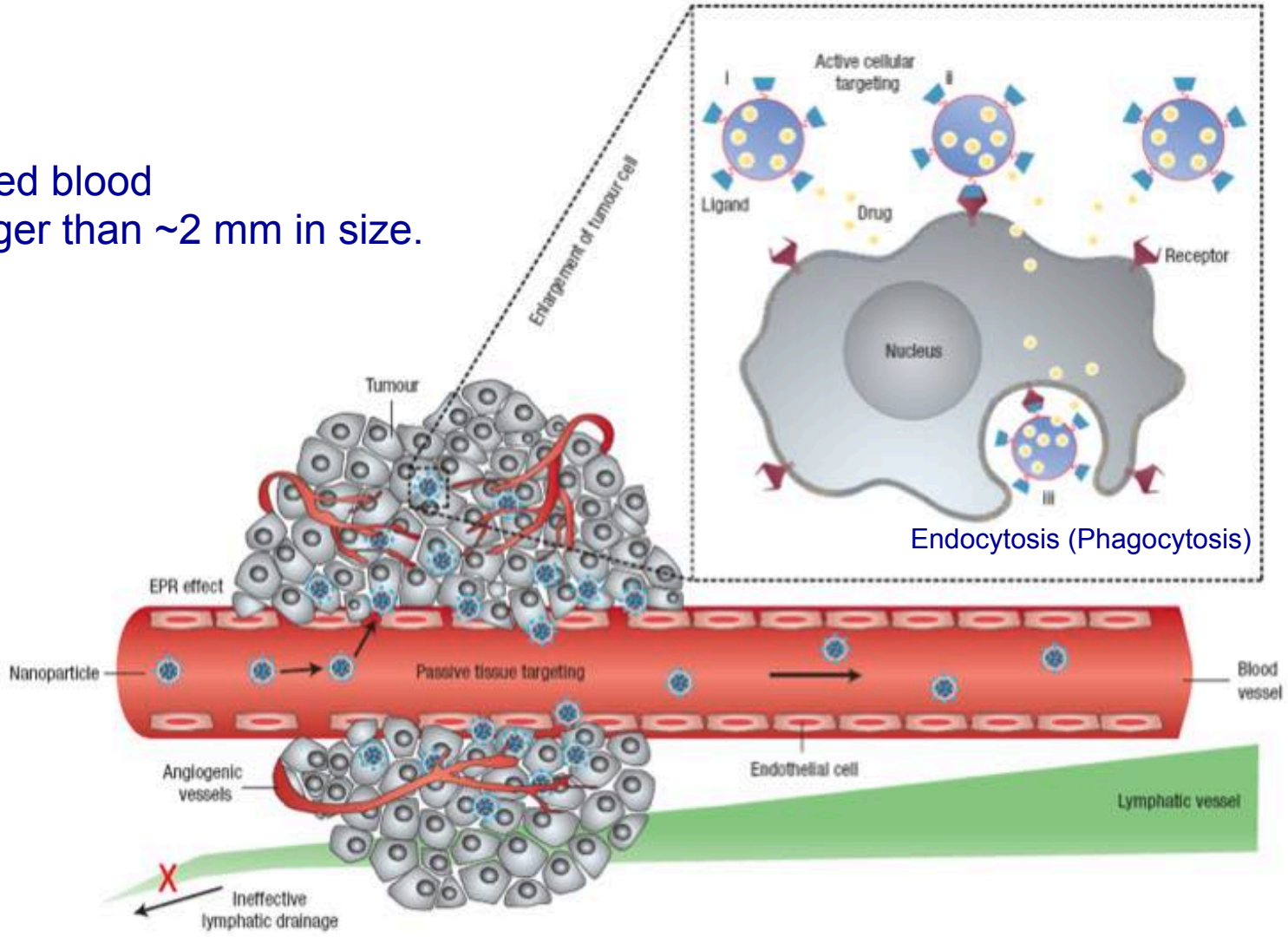
Targeted therapeutics must:

1. Diffuse out of vasculature openings that measure around 500 nm
2. Recognize target cells and bind with high avidity and specificity to extracellular binding domain
3. Internalize and intracellularly traffic to site of intended action
4. Avoid “normal” tissue
5. Remain intact until reaching its intended site of action
6. Carrier should be stable and biologically inert (ceramic or polymer)



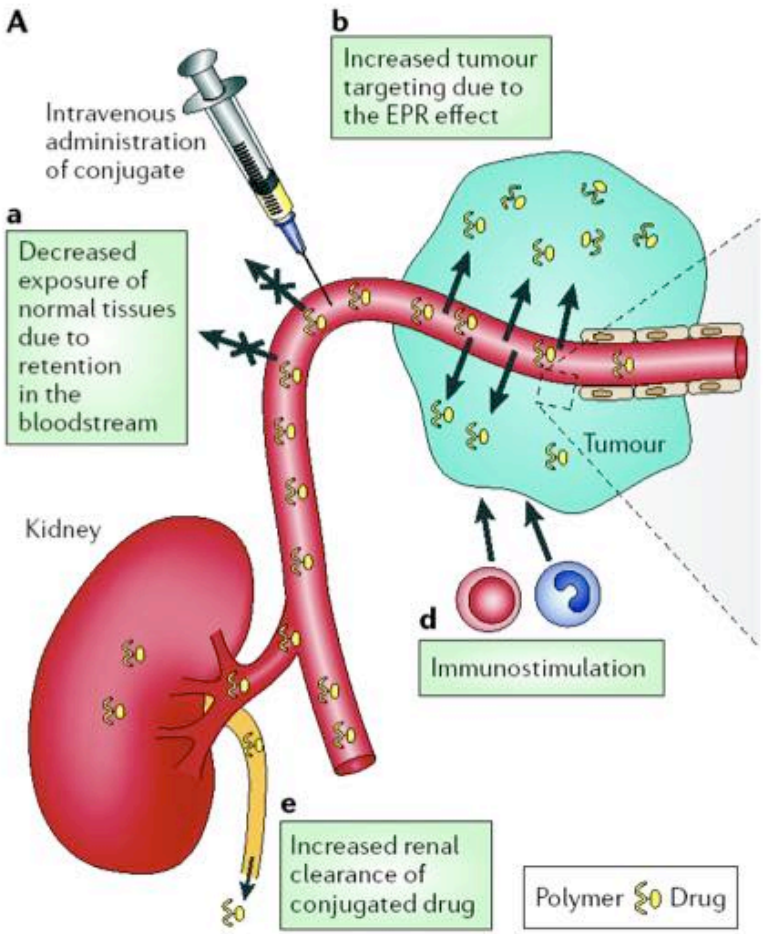
➢ Drug Delivery: EPR Effect (passive drug targeting)

Tumors need blood
to grow larger than ~2 mm in size.



Peer, D, et al. *Nature Nanotechnology* **2007**, 2, 751-760

➢ Drug Delivery: EPR Effect



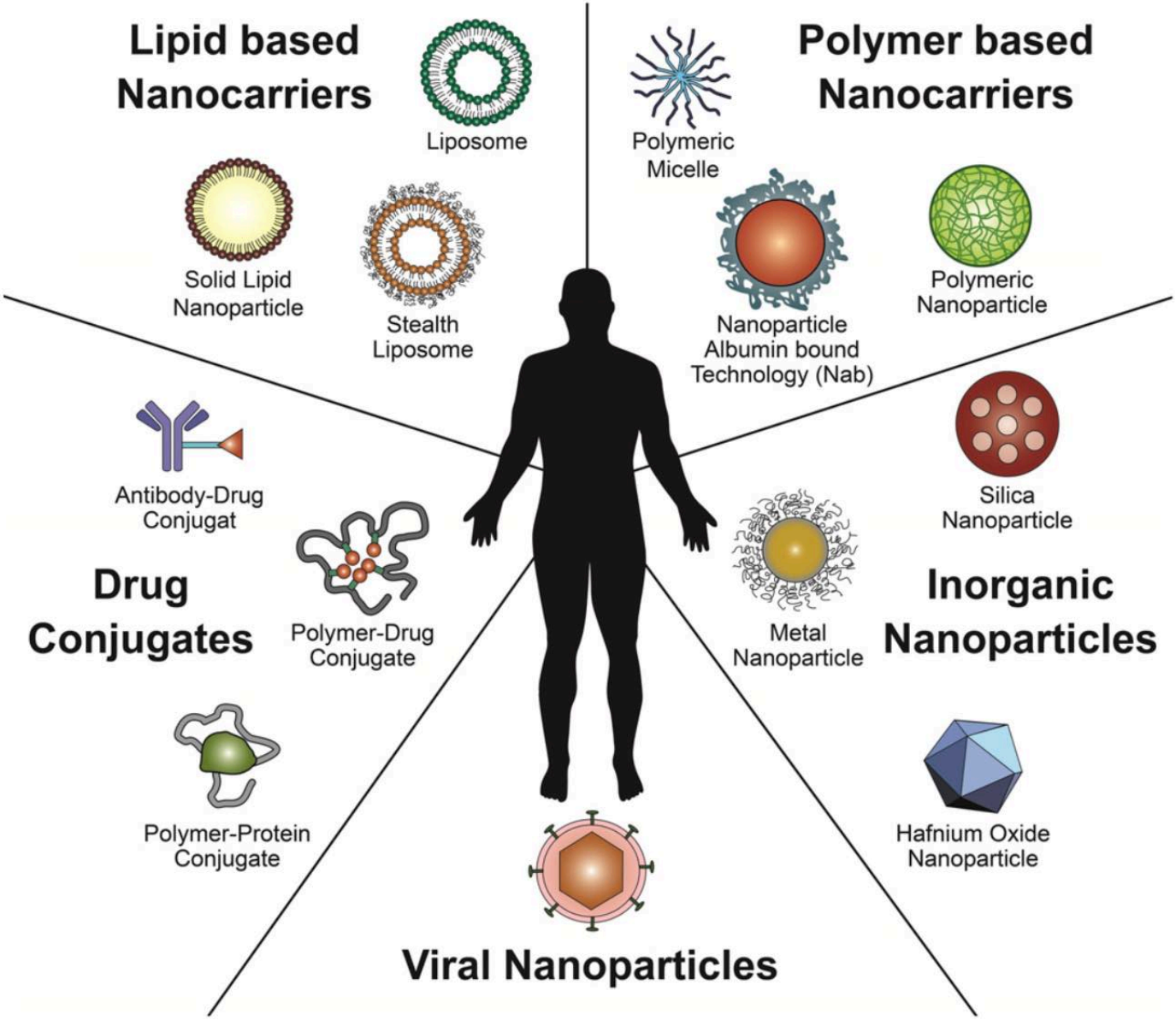
Tumors have “leaky” blood vessels, which allow relatively large nano-sized drug carriers to enter.

This is called Enhanced Permeability and Retention (EPR) Effect.

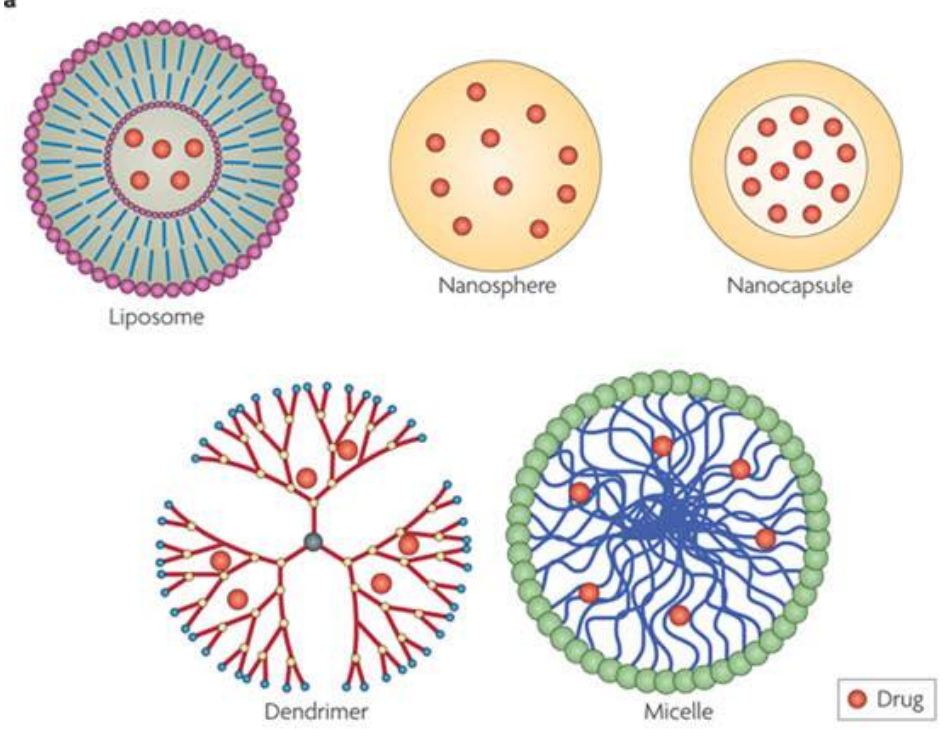
Normal blood vessels are not “leaky” and nanoparticles are prevented from entering. This allows one to selectively target tumors.

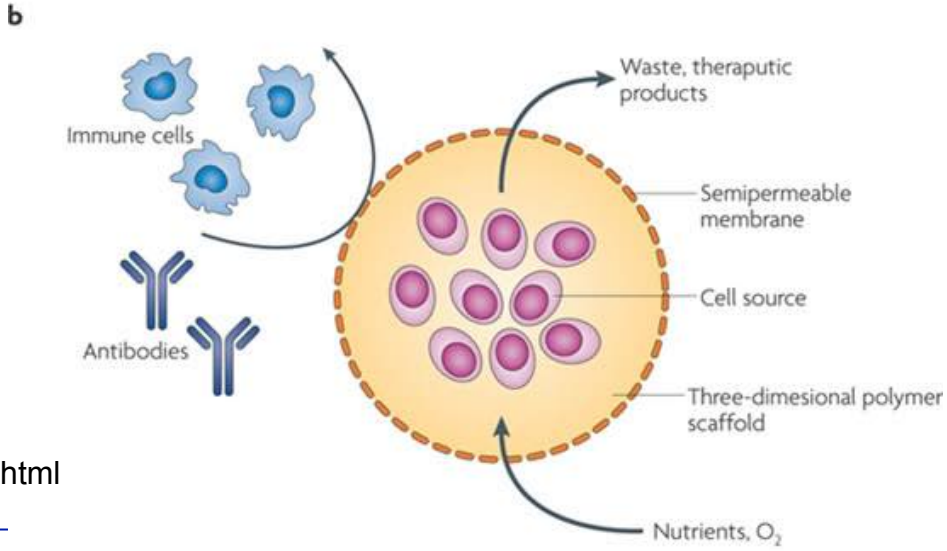
Particles with sizes around 50nm – 200nm ideal

Drug Delivery Carriers



➢ Drug Delivery Carriers





http://www.nature.com/nrn/journal/v10/n9/full/nrn2685.html

➢ Drug Delivery Carriers

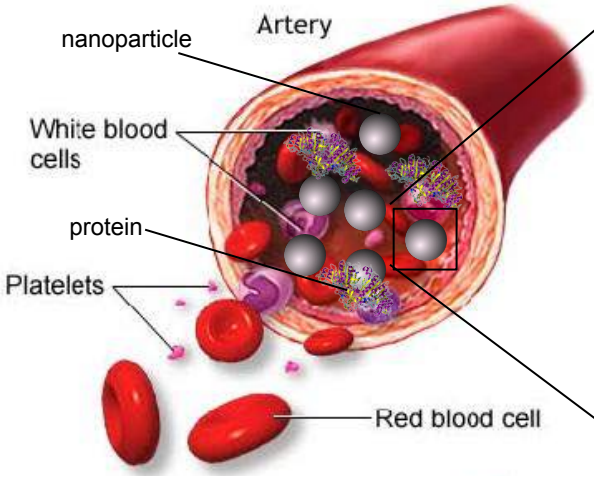
S. No.	Terminologies used	Particle size distribution (nm)
Polymeric systems		
1	Dendrimers	1–10
2	Polymer micelles	10–100
3	Niosomes	10–150
4	Nanoparticles	50–500
5	Nanocapsules	100–300
6	Nanogels	200–800
7	Polymer–drug nanoconjugates	1–15
8	Chitosan polymers	100–800
9	Methacrylate polymers	100–800
Lipid systems		
1	Solid lipid nanoparticles	50–400
2	Lipid nanostructured systems	200–800
3	Cubosomes	50–700
4	Liposomes	10–1000
5	Polymerosomes	100–300
6	Immunoliposomes	100–150
Protein/peptide nanotubes		
1	Peptide nanotubes	1–100
2	Fusion proteins and immunotoxins	3–15
Metal nanostructures		
1	Metal colloids	1–50
2	Carbon nanotubes	1–10 (diameter) and 1–1000 (length)
3	Fullerene	1–10
4	Gold nanoparticles	100–200
5	Gold nanoshells	10–130
6	Silicone nanoparticles	
7	Magnetic colloids	100–600

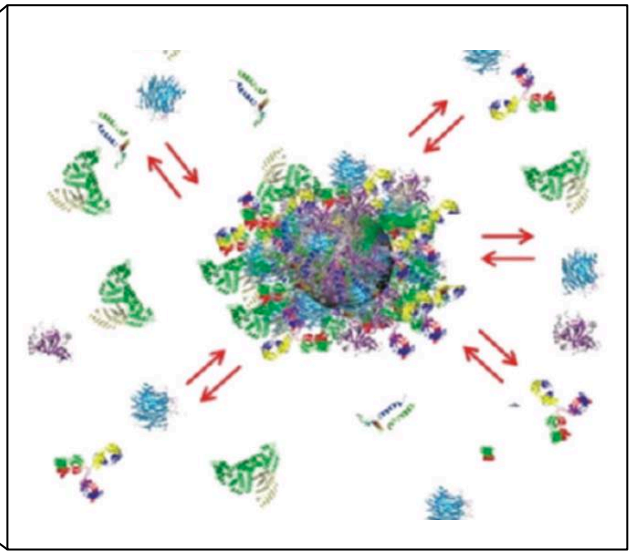
Protein Corona

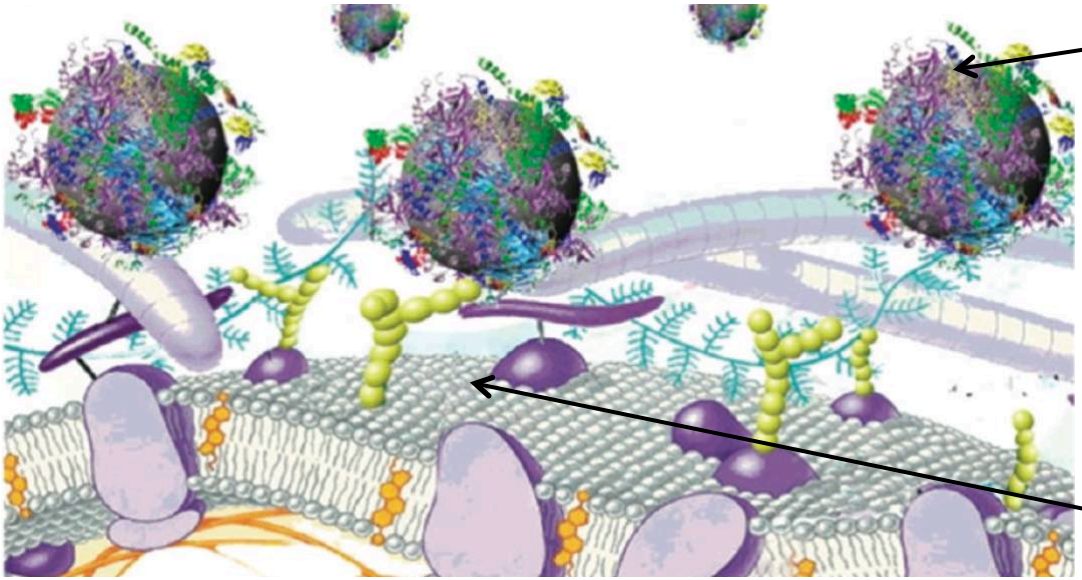
Solar eclipse

During a total solar eclipse the solar **corona** can be seen by the naked eye

What does this has to do with nanoparticles?







Peptide/Protein coated nanoparticle

Cell surface / cell membrane

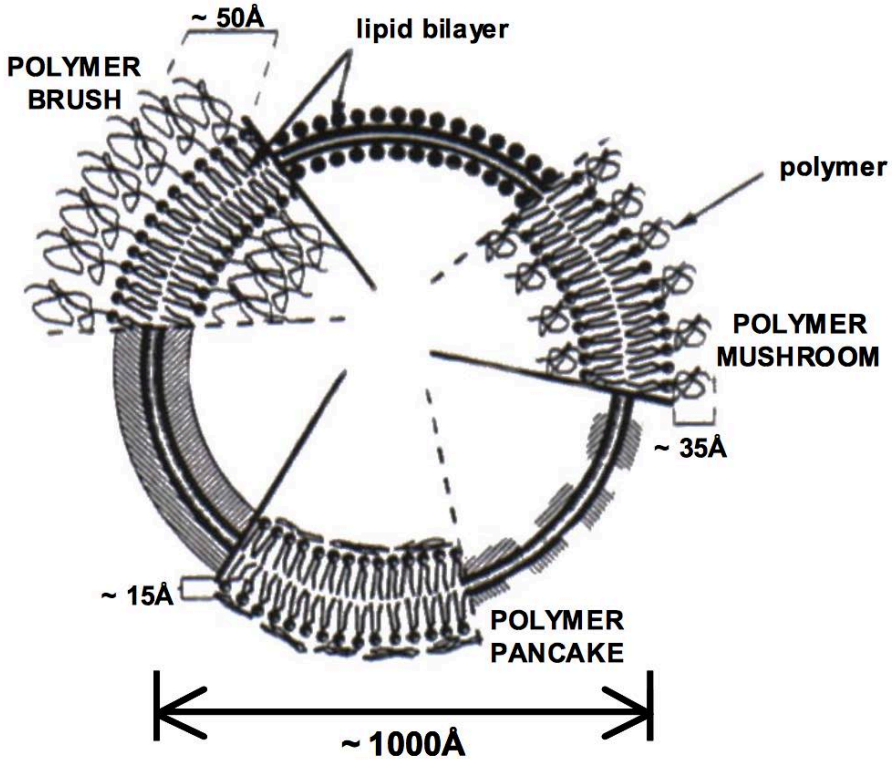
What the biological cell, organ, or barrier actually "sees" when interacting with a nanoparticle dispersed in a biological medium *likely* matters more than the bare material properties of the particle itself.

J. AM. CHEM. SOC. 2010, 132, 5761–5768

➢ Particle “stealthing”

Staying undetected by the radar system

Nanoparticle/Liposome stealthing via PEG functionalization



Staying undetected by auto-immunesystem

➢ Lecture Outline

- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using “Ceramic” Nanoparticles

➢ Types of Drug Delivery Devices

1. Diffusion Controlled Delivery Devices

- Monolithic Devices
- Membrane Controlled Devices
- Osmotic Pressure Devices
- Swelling-Controlled Devices

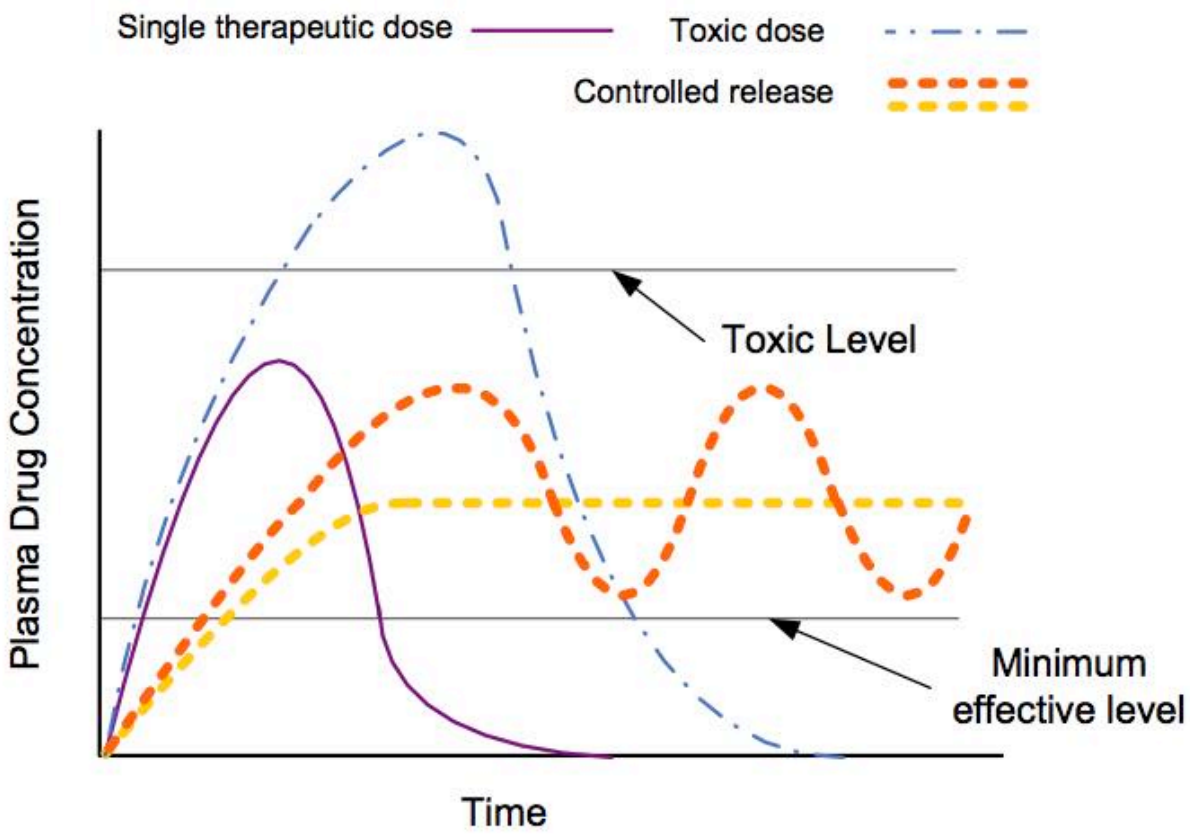
2. Chemically Controlled Approaches

- Matrix Erosion
- Combined Erosion/Diffusion
- Drug Covalently Attached to Polymer
- Desorption of Adsorbed Drug

3. Electronic/Externally Controlled Devices

- MEMS
- Superparamagnetism

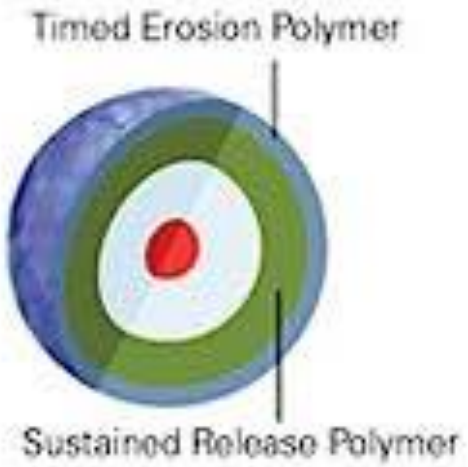
➢ Controlled drug release

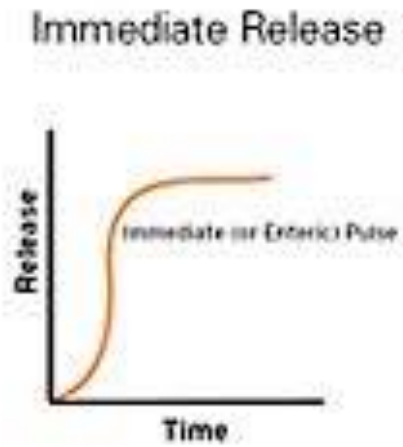


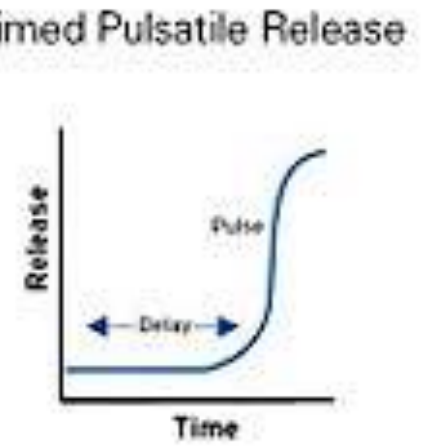
Controlled-released systems

- use less amount of drug ➔ reduce side effects
- Maintain drug therapeutic concentrations

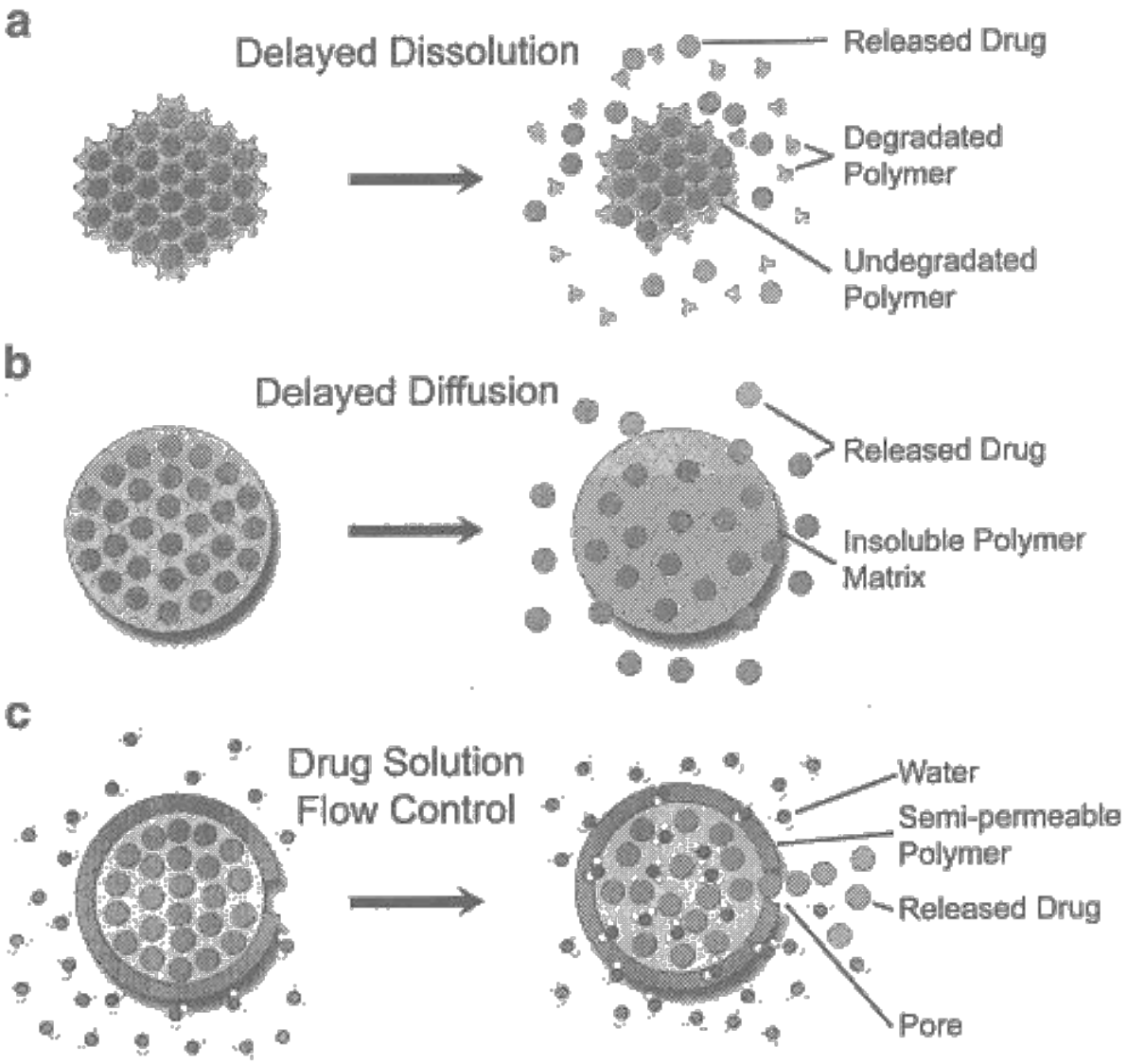
➢ Release Profiles



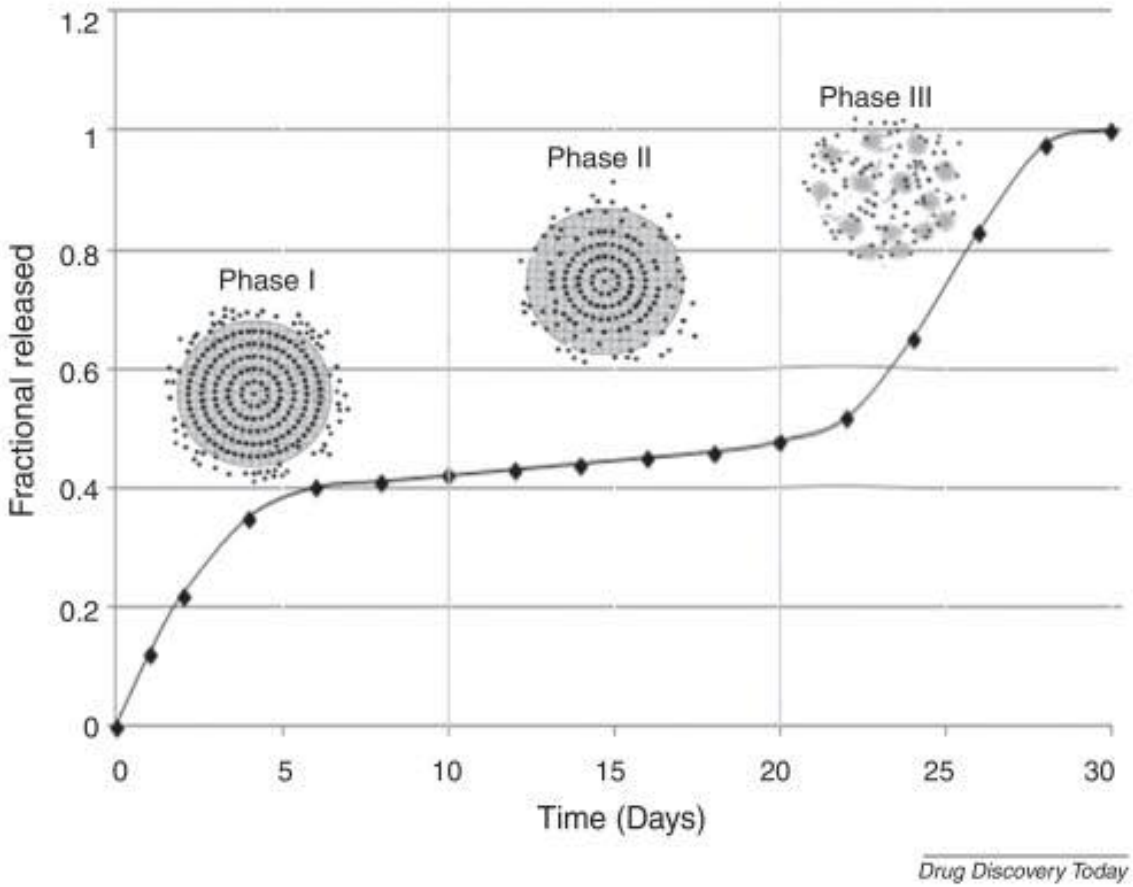




➢ Drug Release Mechanisms



➢ Burst Release



Typical triphasic release profile from poly-d,l-lactide-co-glycolide (PLGA) matrices. Phase I shows a high initial burst release, phase II is diffusion-controlled slow release and phase III is characterized by fast release owing to erosion of the polymer matrix.

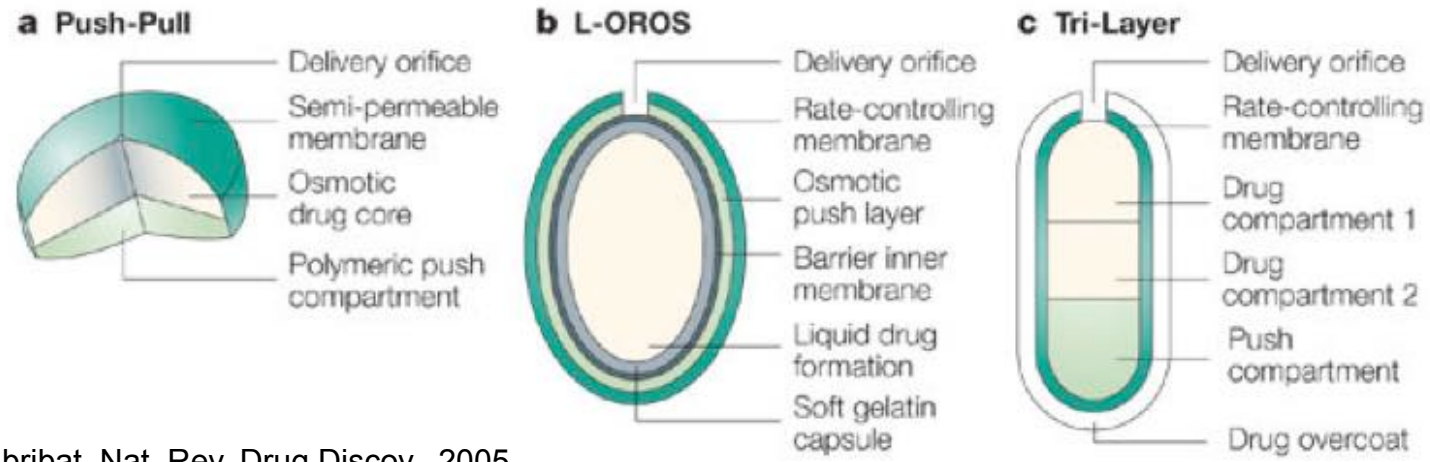
Agarwal, P.; Rupenthal, I. D. Drug Discovery Today 2013, 18, 337–349.

➢ Oral Delivery

Reservoir-based oral osmotic system (OROS™)

- Sustained release vs. immediate-release oral formulations
- Patient compliance
- Deliver drugs independently of their solubility

- Controlled-release OROS delivery system



H. Rosen, T. Abribat, Nat. Rev. Drug Discov., 2005

➢ Lecture Outline

- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using “Ceramic” Nanoparticles

➢ „Ceramic“ Nanoparticles/-carriers for Drug-Delivery/Diagnostics

metal oxide nanoparticles

- (fluorescent) silica (SiO_2)
- iron oxide (Fe_3O_4): super-paramagnetic effect

Mesoporous nanoparticles

- Pore diameters between 2 and 50 nm
- Drug loading in pores

gold nanoparticles

- radiofrequency responsive

nano-diamonds

- Planar facettes on surface
- conjugation with i.e. doxorubicin possible

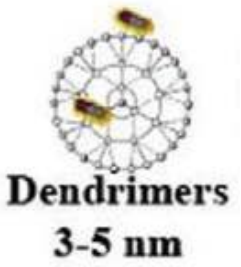
core-shell particles

- example: iron oxide core coated with mesoporous silica shell Fe_3O_4@$mSiO_2$

liposome-nanoparticle hybrids

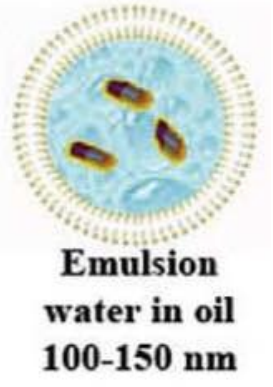
- i.e. magneto-liposome

➢ Overview: Microcapsules

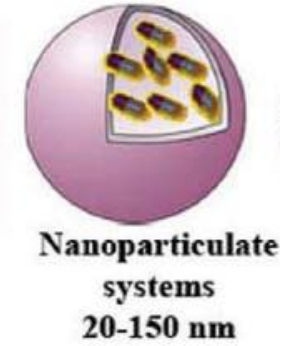


highly symmetric, spherical molecule

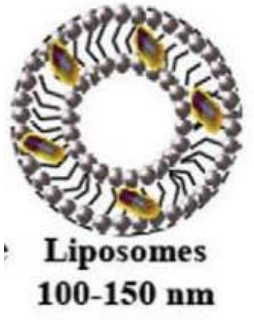
Self-Assembled cluster of surfactants



Substances encapsulated in aqueous core



(Bio)degradble particles with encapsulated substances



Vesicle composed of a lipid-bilayer (similar to micelle)

Pictures taken from: [Arruebo et al. Magnetic nanoparticles for drug delivery. nanotoday, 2(3):22-32, June 2007.]

Applications for microcapsules

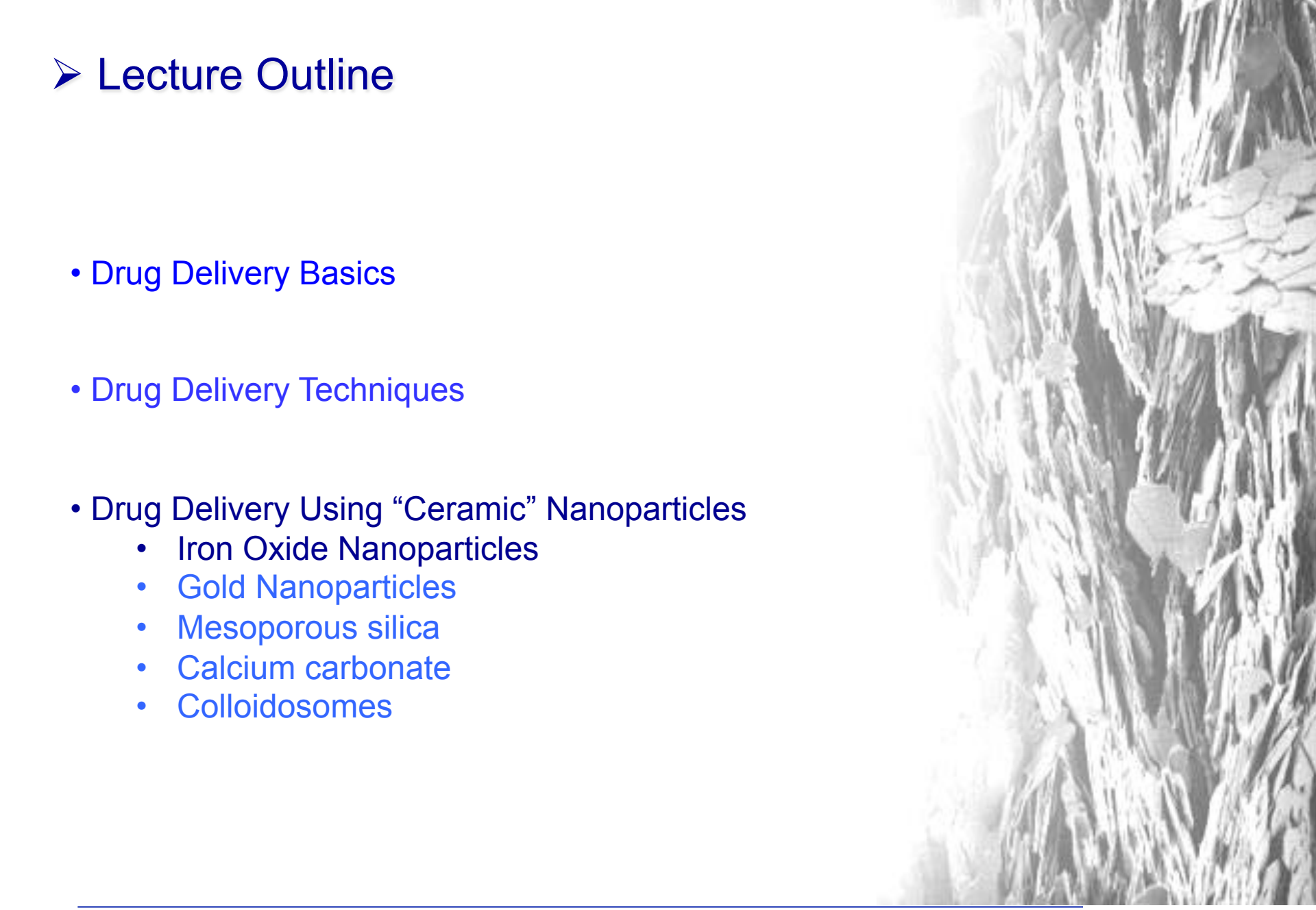
- Targeted and sustained drug delivery (medicine)
- Triggered release of pesticides (agriculture)
- Nutrition encapsulation (food industry)
- Fragrence encapsulation (cosmetic products)

Important properties

- Biocompatibility
- Controlled stability
- Tunable porosity
- Size below 500 nm for drug delivery
- “Smart” properties

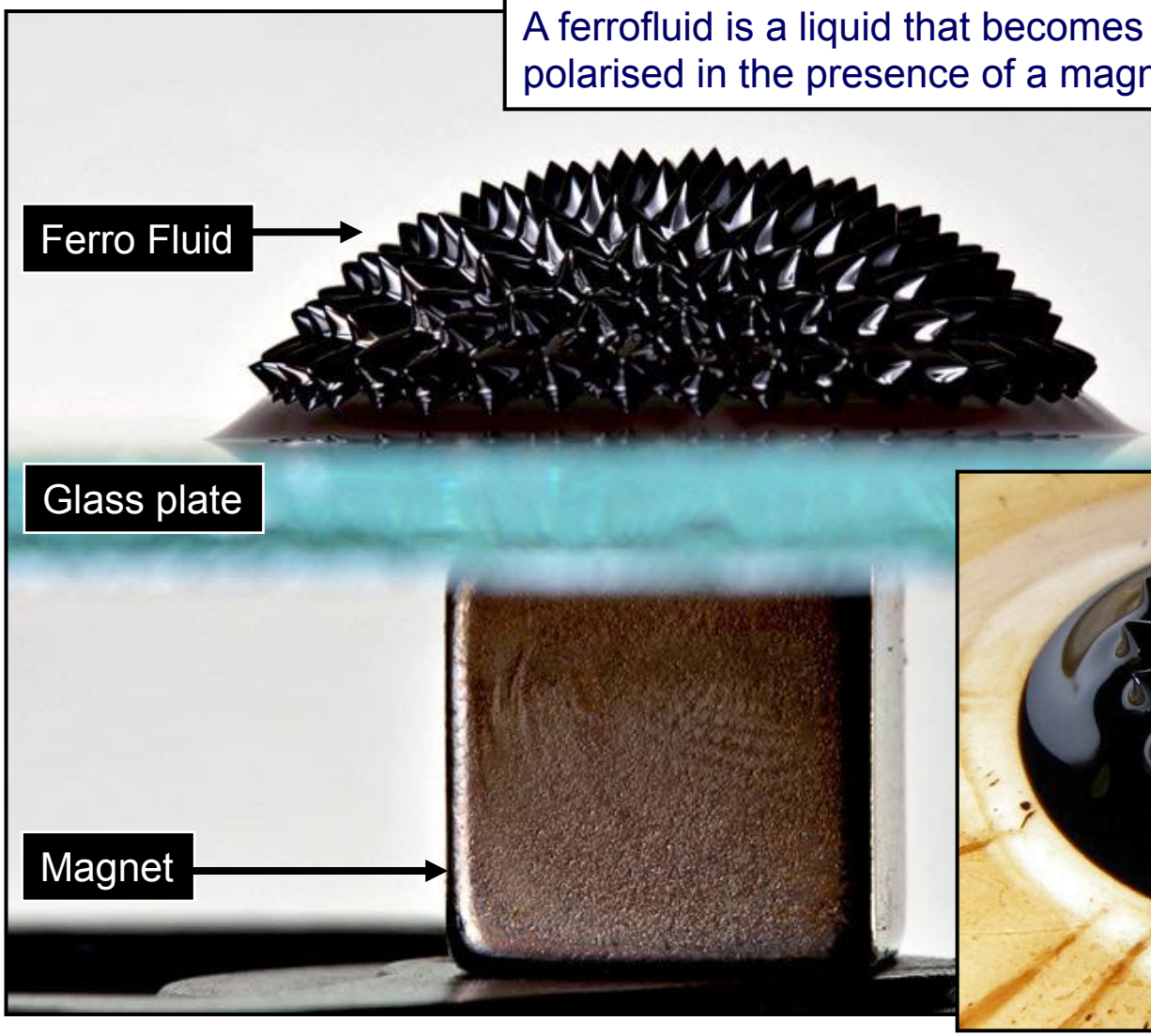
➢ Lecture Outline

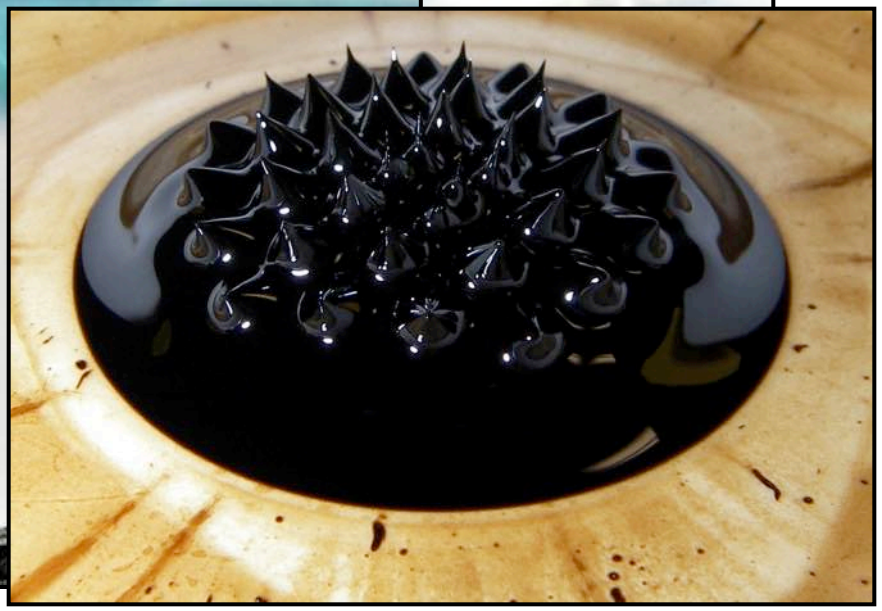
- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using “Ceramic” Nanoparticles
  - Iron Oxide Nanoparticles
  - Gold Nanoparticles
  - Mesoporous silica
  - Calcium carbonate
  - Colloidosomes



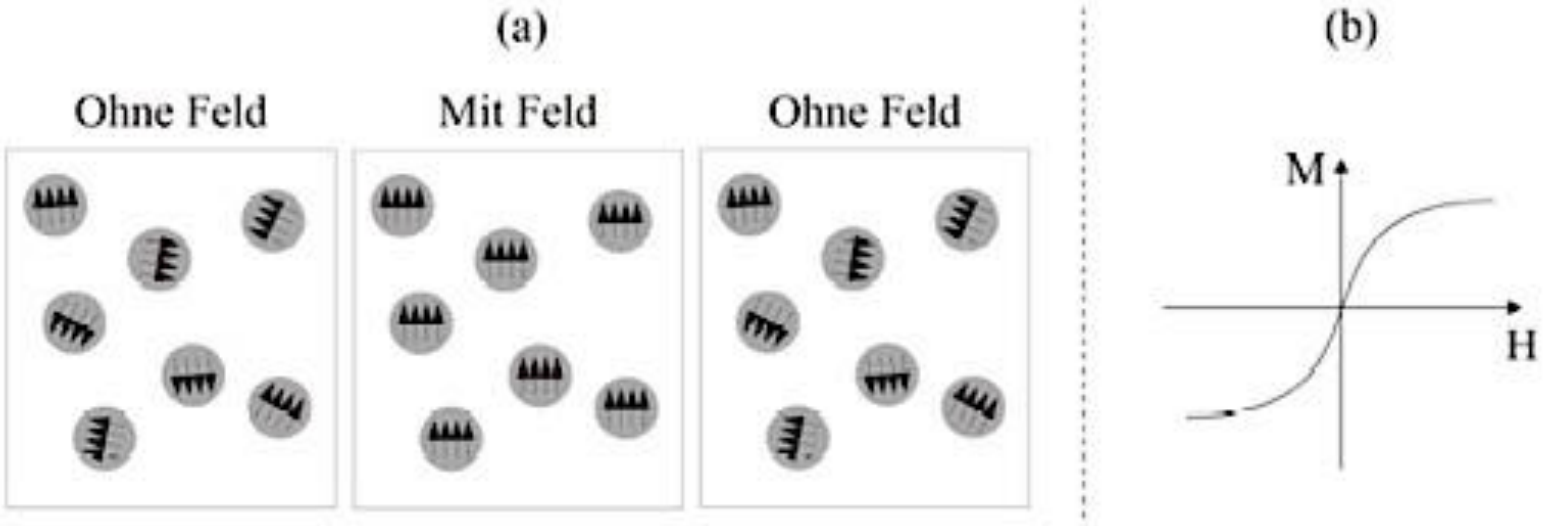
➢ Ferrofluids

A ferrofluid is a liquid that becomes strongly polarised in the presence of a magnetic field.





➢ Ferrofluids



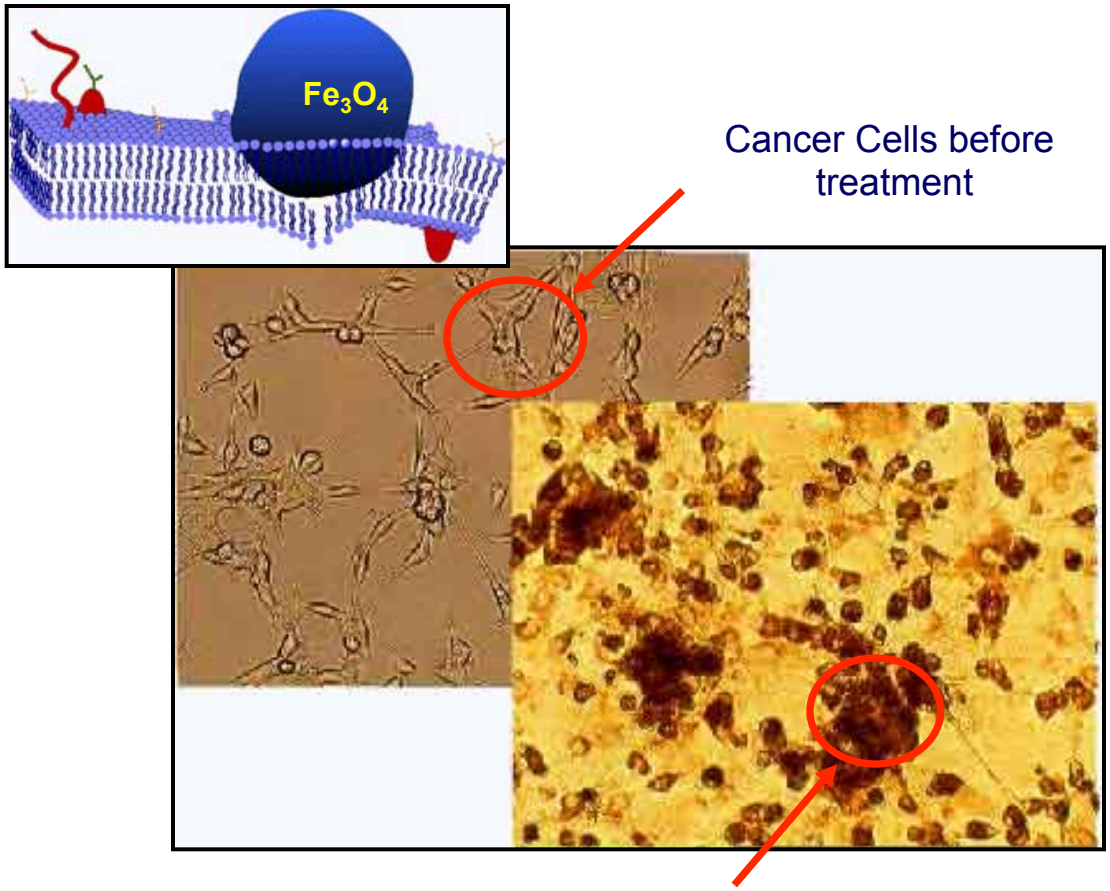
Superparamagentism:

- Particles are smaller than the magnetic domains
- Brownian motion prevents magnetic orientation of the particles
- External field ➔ orientation of ferrofluids along field lines ➔ ferromagnetism

➢ Frontiers in Science: Treatment of Cancer with Magnetic Iron Oxide Nanoparticles

The new procedure involves coating nano iron oxide particles (magnetite, Fe_3O_4, 3 – 15 nm) with an organic substance, such as the sugar glucose, and injecting them into a malignant tumor. The tumor, which has a fast metabolism and correspondingly high energy needs, greedily sucks up the little particles masquerading as sugar pellets of a sort. Healthy cells, on the other hand, show little interest.

Magnetic field heats up the nanoparticles inside the malignant tumor cells up to 45°C.



[Jordan A, et al. The effect of thermotherapy using magnetic nanoparticles on rat malignant glioma. J Neuro-Oncol. 2006]

[www.ccnanochem.de, UK Charite (Berlin)]

➢ SPIONs in clinical trials or available on the market

Product	Company/Developer	Coating Agent	Application	Targeting Moiety	Use
Feridex/ Endorem	AMAG Pharma, Inc.	Dextran	Liver tumors	None	Imaging
Ferumoxytol	AMAG Pharma, Inc.	Polysorbito carboxy methyl ether	CNS tumors	None	Imaging
Resovist®	Bayer Schering Pharma AG	Carboxydextran	Liver metastasis; colon cancer	None	Imaging
SPION	Sun , Ranganathan, Feng 2008	PEG/Dextran	Breast cancer	Folic Acid	Imaging
SPION	Kohler *et al.*, 2005	3-(aminopropyl) trimethoxysilane	Brain tumors	Methotrexate	Imaging and treatment
SPION	Sun, Lee, Zhang, 2008	PEG	Brain tumors	Chlorotoxin	Imaging and treatment
SPION	Wang *et al.*, 2008	PEG	Prostate cancer	A10 RNA aptamer	Imaging and treatment
SPION	Leuschner *et al.*, 2006	Chorionic gonadotropin	Breast cancer	LHRH	Imaging
SPION	Kikumori *et al.*, 2009	Liposome	Breast cancer	Anti-HER2 antibody	Imaging
SPION	Chen *et al.*, 2009	Dextran	Breast cancer	Herceptin	Imaging
USPION	Jiang *et al.*, 2009	3-(aminopropyl) trimethoxysilane	Lung cancer	RGD	Imaging

CNS, central nervous system; PEG, poly(ethylene glycol); LHRH, luteinizing hormone releasing hormone; RGD, arginine-glycine-aspartic acid.

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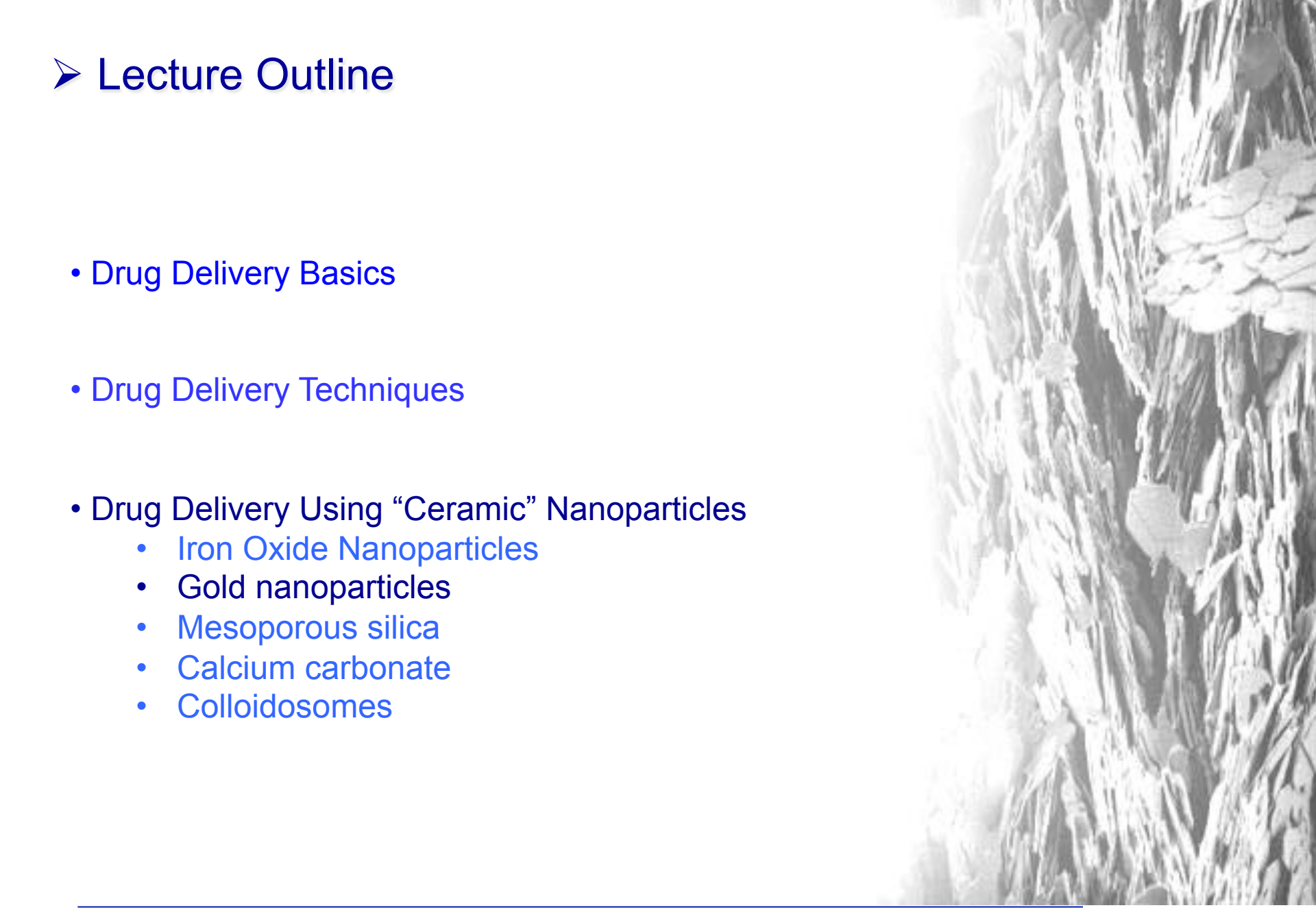
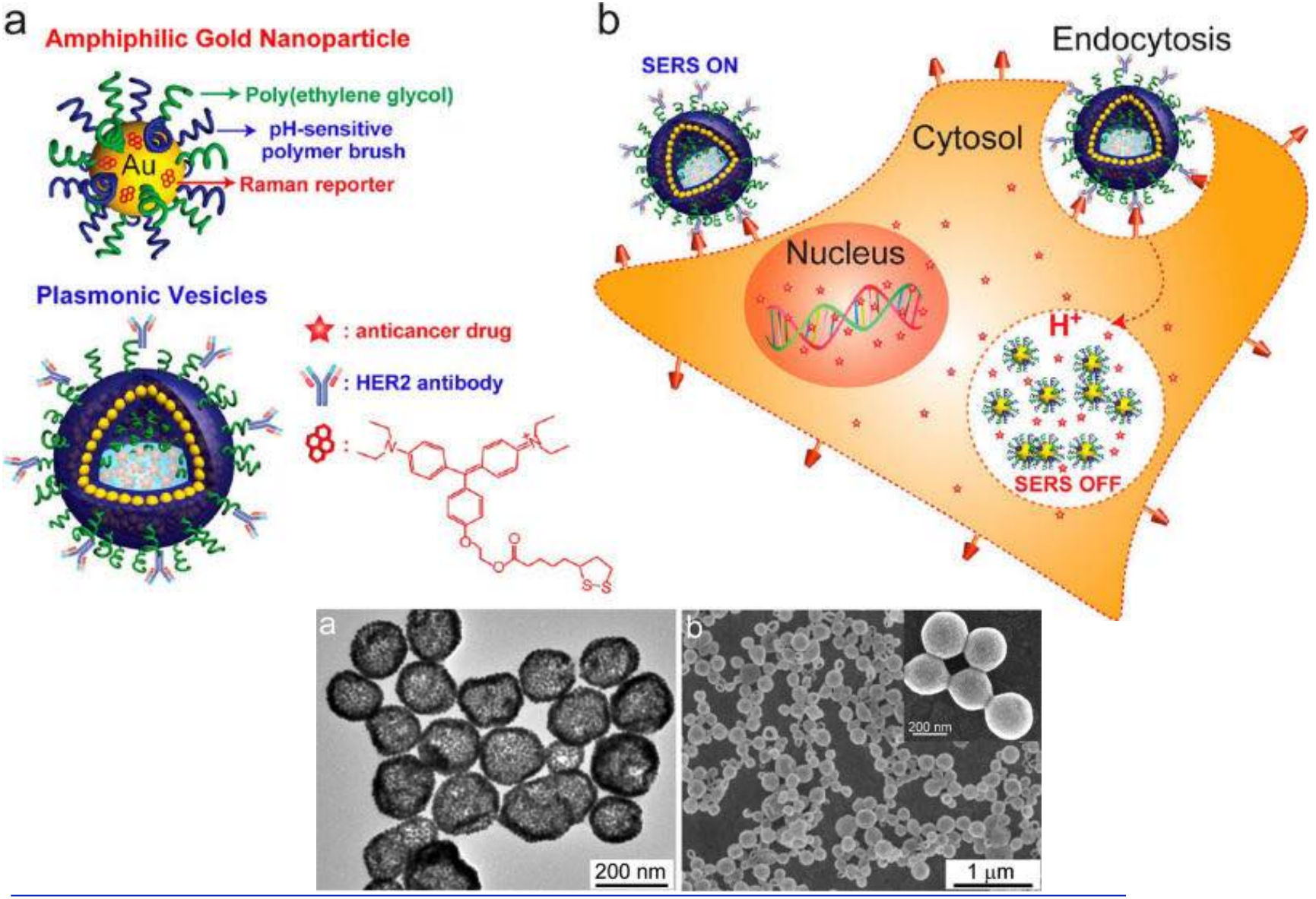
  - Calcium carbonate
  - Colloidosomes

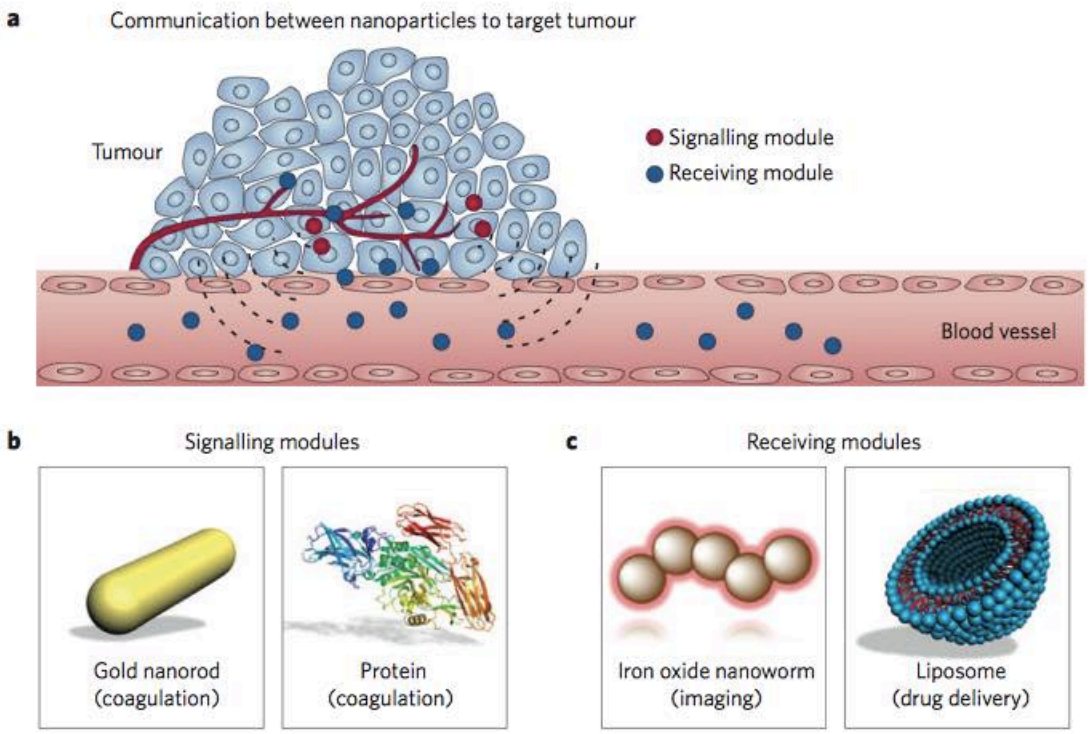


➢ Gold-NP: Plasmonic coupling effect and drug delivery



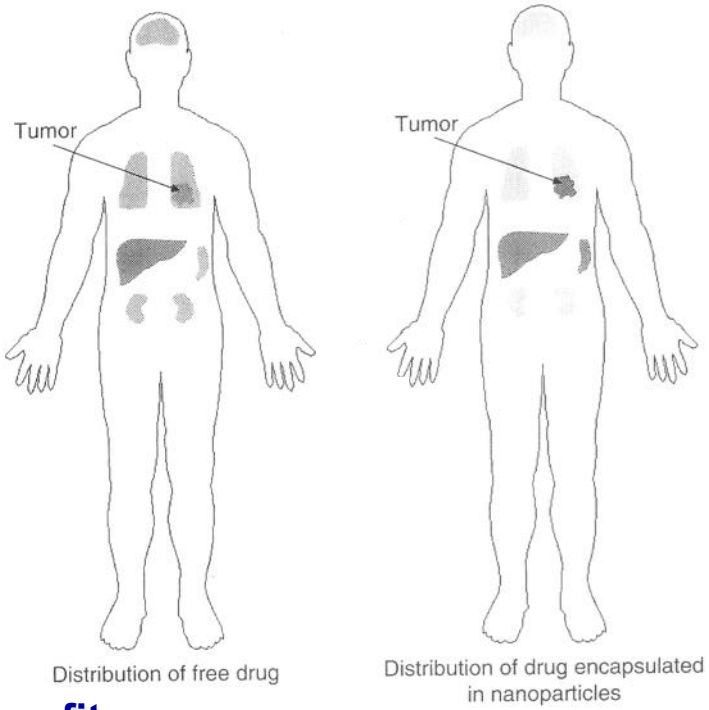
➢ Microcapsules in Cancer Therapy

Targeted drug delivery and theragnostics



Wang, Y.; Brown, P.; Xia, Y. *Nat Mater* **2011**, *10*, 482–483,
Von Maltzahn, G.; et al. *Nat Mater* **2011**, *10*, 545–552.

Local drug concentration control



Benefits

+ higher local drug concentration
+ less side effects
+ more effective therapy

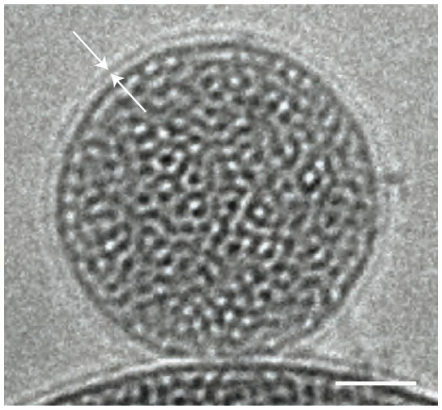
[Monika Schäfer-Korting. Drug Delivery. Handbook of Experimental Pharmacology. Springer, 2010.]

Still missing ➡ **Universal and simple microencapsulation technique that creates capsules with multiple properties.**

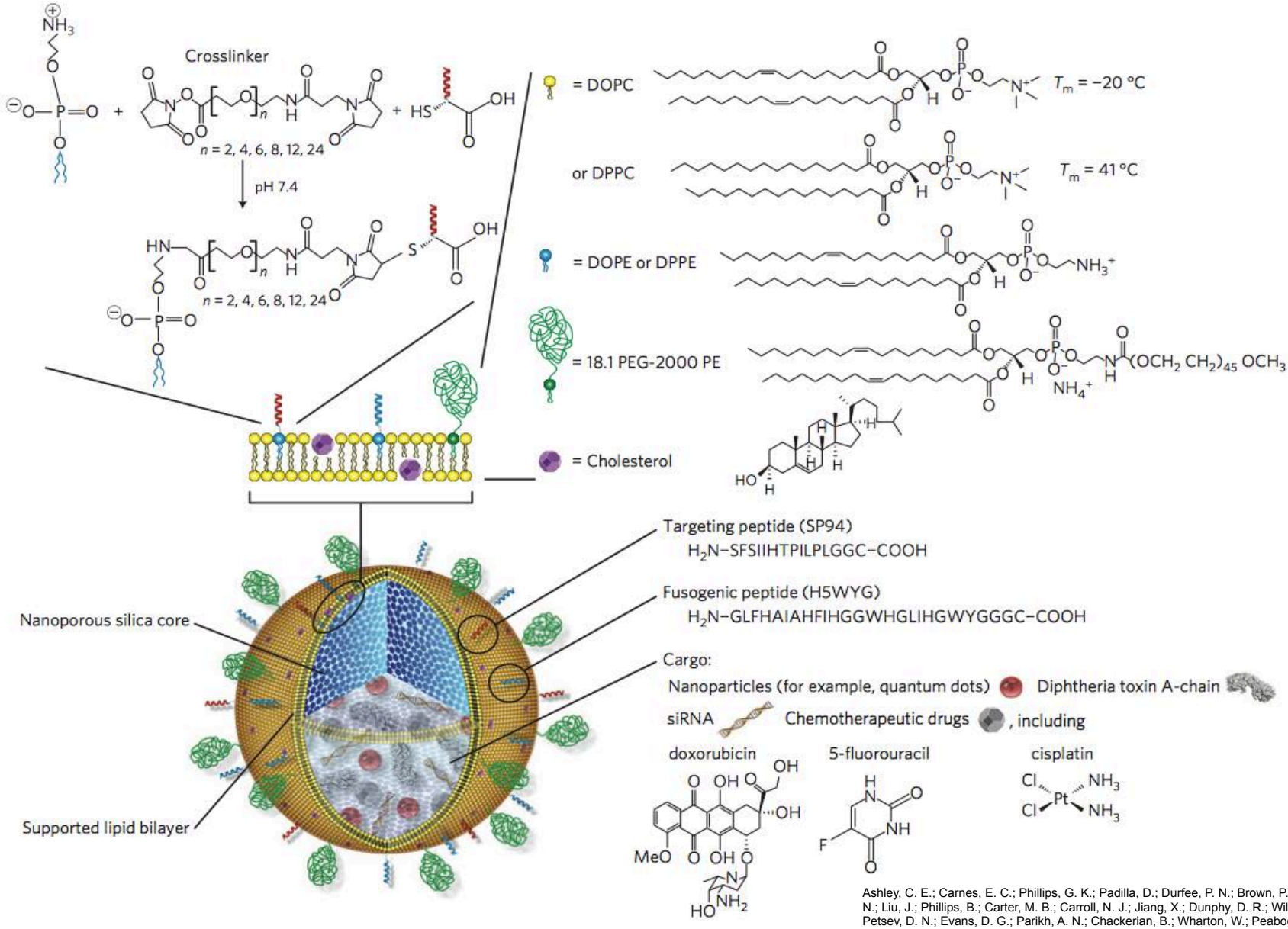
➢ Lecture Outline

- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using Ceramic Nanoparticles
  - Iron Oxide Nanoparticles
  - Gold nanoparticles
  - Mesoporous silica
  - Calcium carbonate
  - Colloidosomes

➢ One Nanoparticle, One Kill



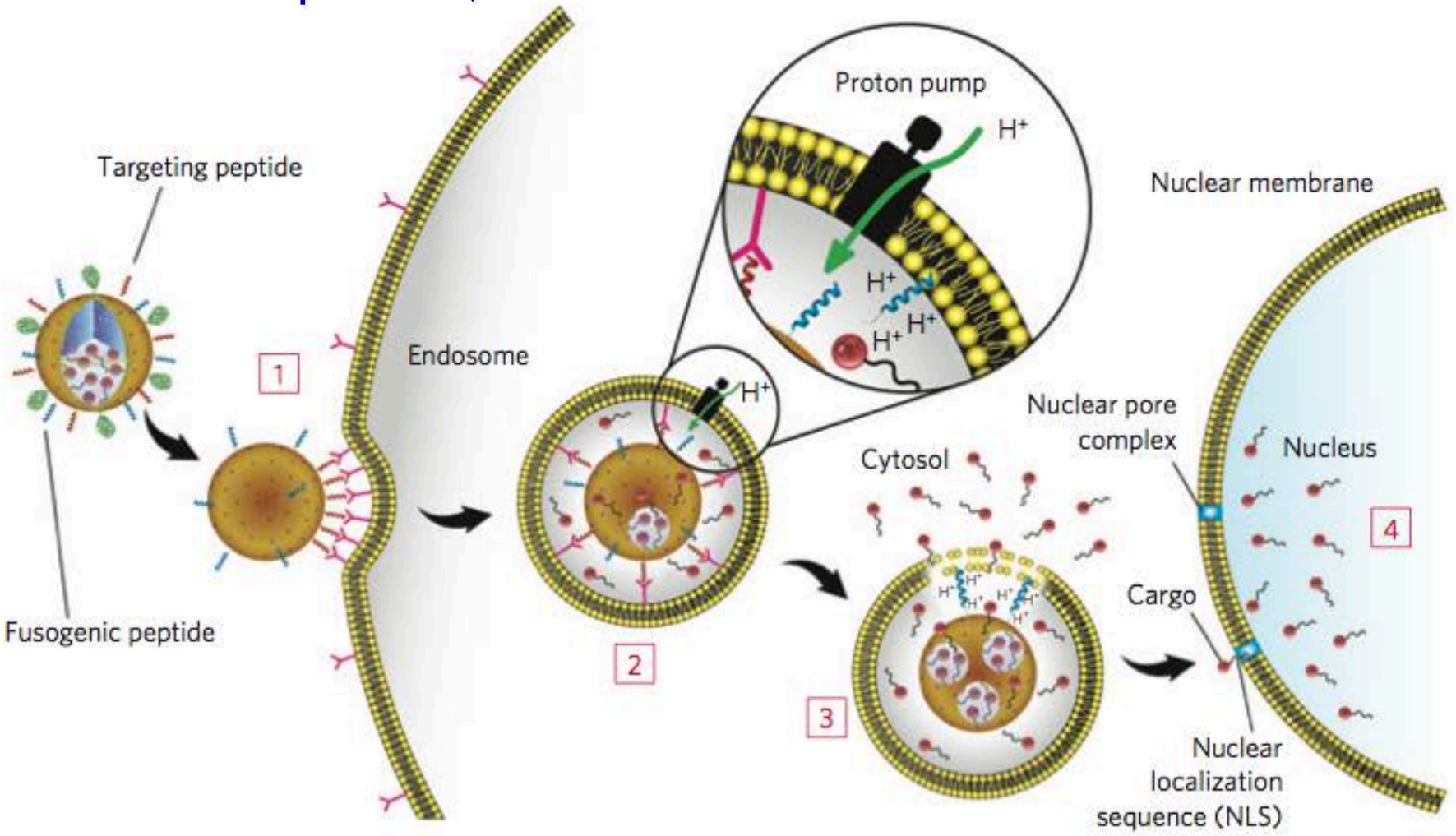
Ashley, C. E.; Carnes, E. C.; Phillips, G. K.; Padilla, D.; Durfee, P. N.; Brown, P. A.; Hanna, T. N.; Liu, J.; Phillips, B.; Carter, M. B.; Carroll, N. J.; Jiang, X.; Dunphy, D. R.; Willman, C. L.; Petsev, D. N.; Evans, D. G.; Parikh, A. N.; Chackerian, B.; Wharton, W.; Peabody, D. S.; Brinker, C. J. Nat Mater 2011, 10, 389–397.



Ashley, C. E.; Carnes, E. C.; Phillips, G. K.; Padilla, D.; Durfee, P. N.; Brown, P. A.; Hanna, T. N.; Liu, J.; Phillips, B.; Carter, M. B.; Carroll, N. J.; Jiang, X.; Dunphy, D. R.; Willman, C. L.; Petsev, D. N.; Evans, D. G.; Parikh, A. N.; Chackerian, B.; Wharton, W.; Peabody, D. S.; Brinker, C. J. Nat Mater 2011, 10, 389–397.

Figure 1 | Schematic illustration of the nanoporous particle-supported lipid bilayer, depicting the disparate types of therapeutic and diagnostic agent that can be loaded within the nanoporous silica core, as well as the ligands that can be displayed on the surface of the SLB. Targeting and fusogenic peptides are chemically conjugated to phosphatidylethanolamine (DOPE or DPPE), present in the SLB at 1–5 wt%, by a heterobifunctional crosslinker with a PEG spacer arm ($n = 24$). The SLB, composed of either fluid (DOPC) or non-fluid (DPPC) zwitterionic phosphatidylcholine lipids with 30 wt% cholesterol, is further modified with 5 wt% PEG-2000 PE to enhance colloidal stability and decrease nonspecific interactions.

➢ One Nanoparticle, One Kill



DOPC protocells (1) bind to HCC with high affinity owing to recruitment of SP94 targeting peptides (magenta) to the cell surface, (2) become internalized by receptor-mediated endocytosis and (3) release their cargo into the cytosol on endosome acidification and protonation of the H5WYG fusogenic peptide (blue). (4) Cargos modified with an NLS are transported through the nuclear pore complex and become concentrated in the nucleus.

➢ Lecture Outline

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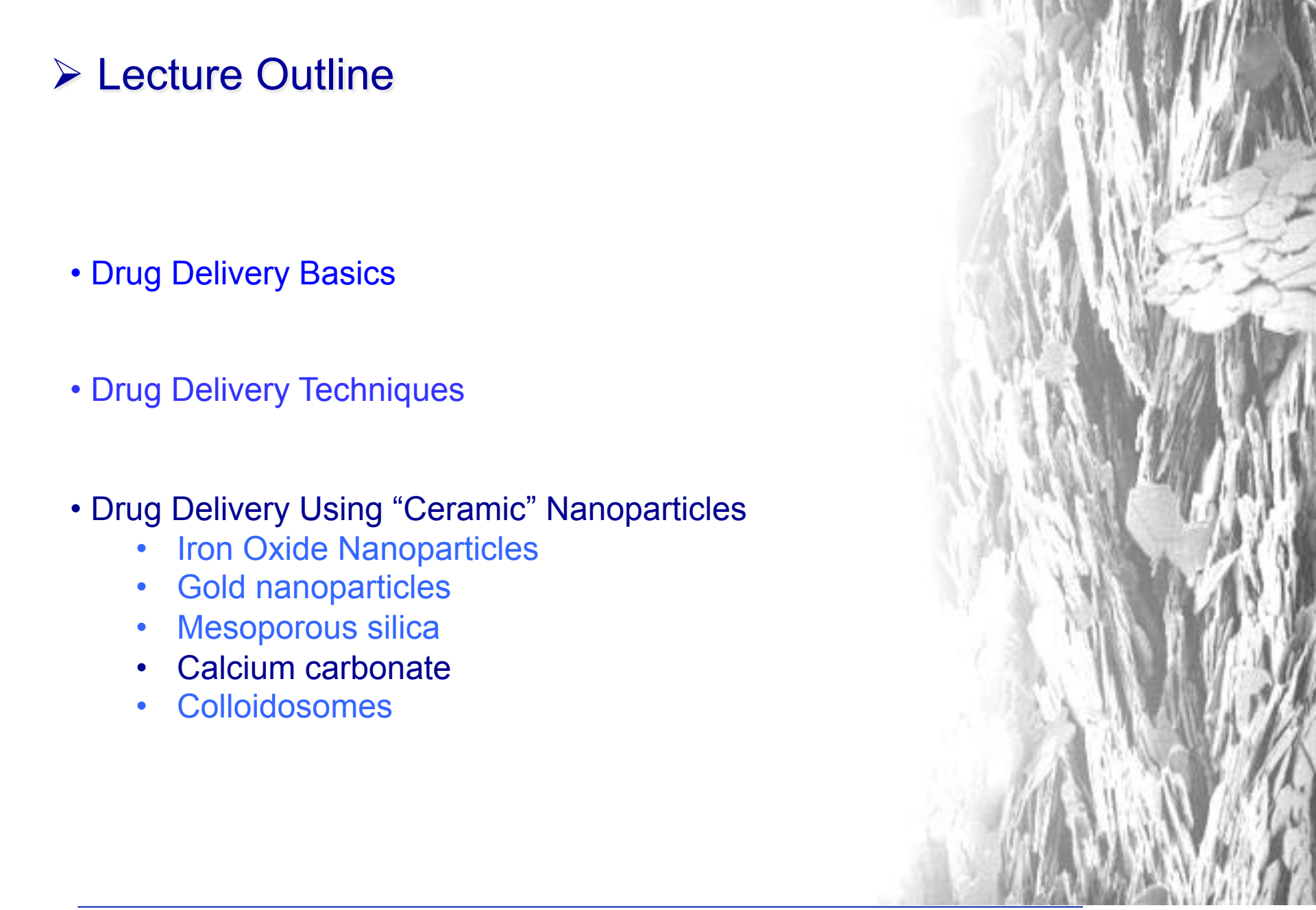
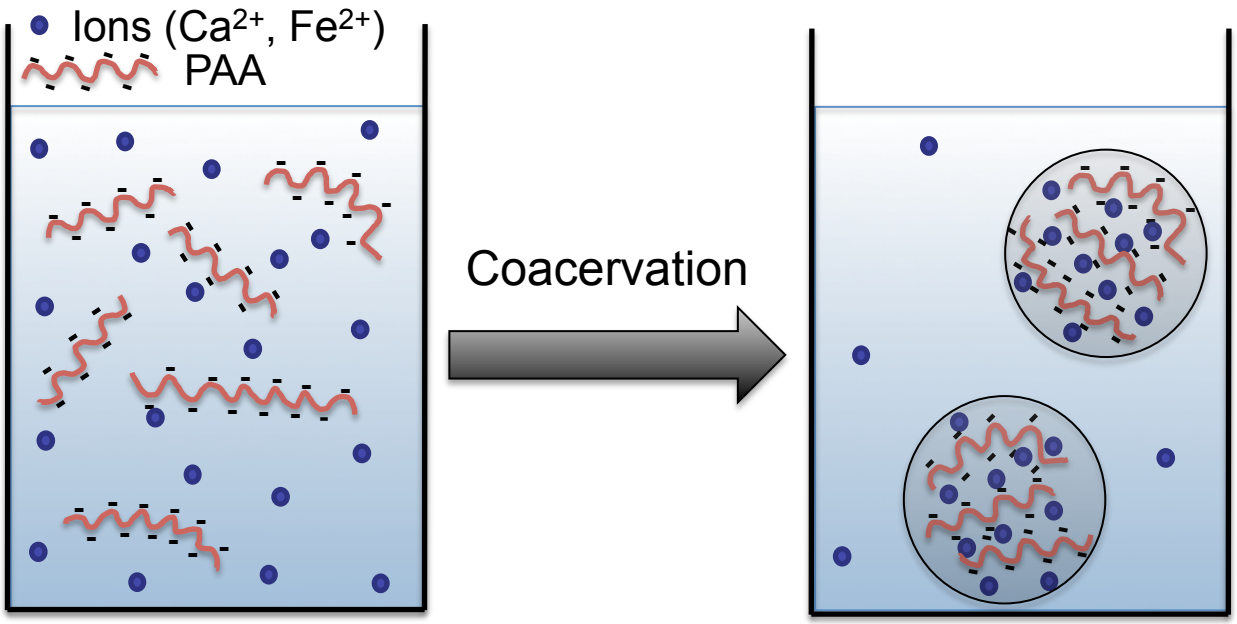
- Drug Delivery Using “Ceramic” Nanoparticles
  - Iron Oxide Nanoparticles
  - Gold nanoparticles
  - Mesoporous silica
  - Calcium carbonate
  - Colloidosomes



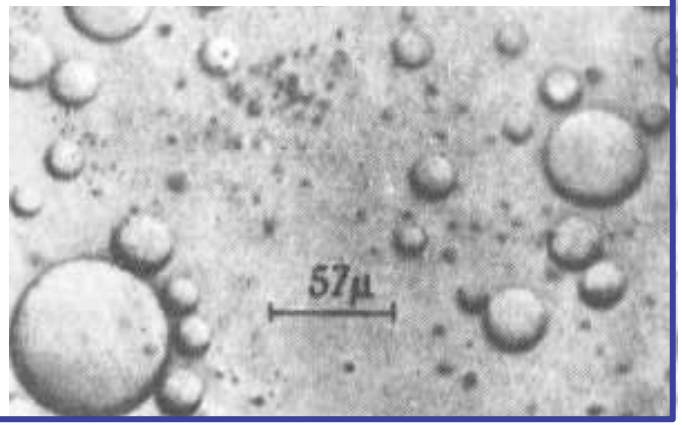
Coacervation



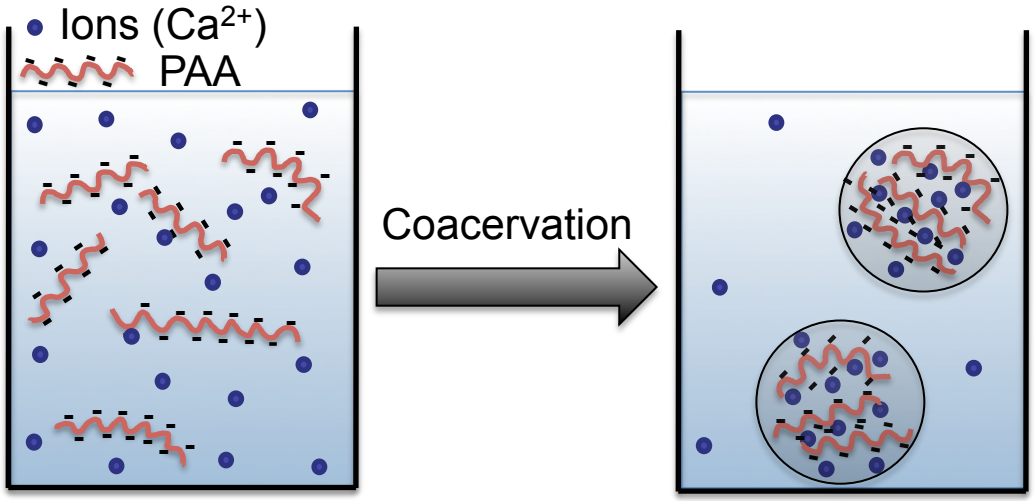
Coacervation:

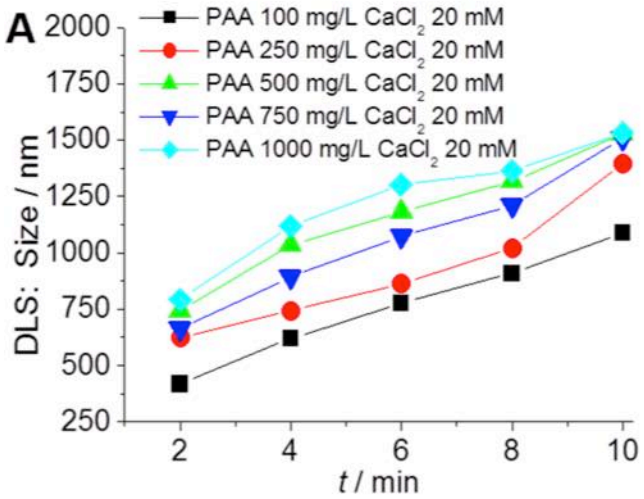
- Demixing or liquid-liquid phase separation of lyophilic colloids into a two-phase system.
- Driving force: electrostatic interaction, entropy
- Classic system: gelatin + gum arabic

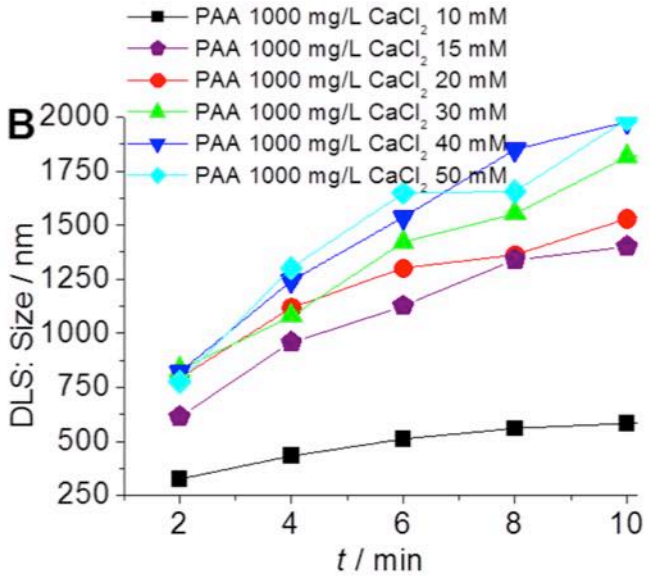
Bungenberg de Jong, H.; Kruyt, H. In *Proc. K. Ned. Akad. Wet*; 1929; Bd. 32, 849–856.



Coacervation



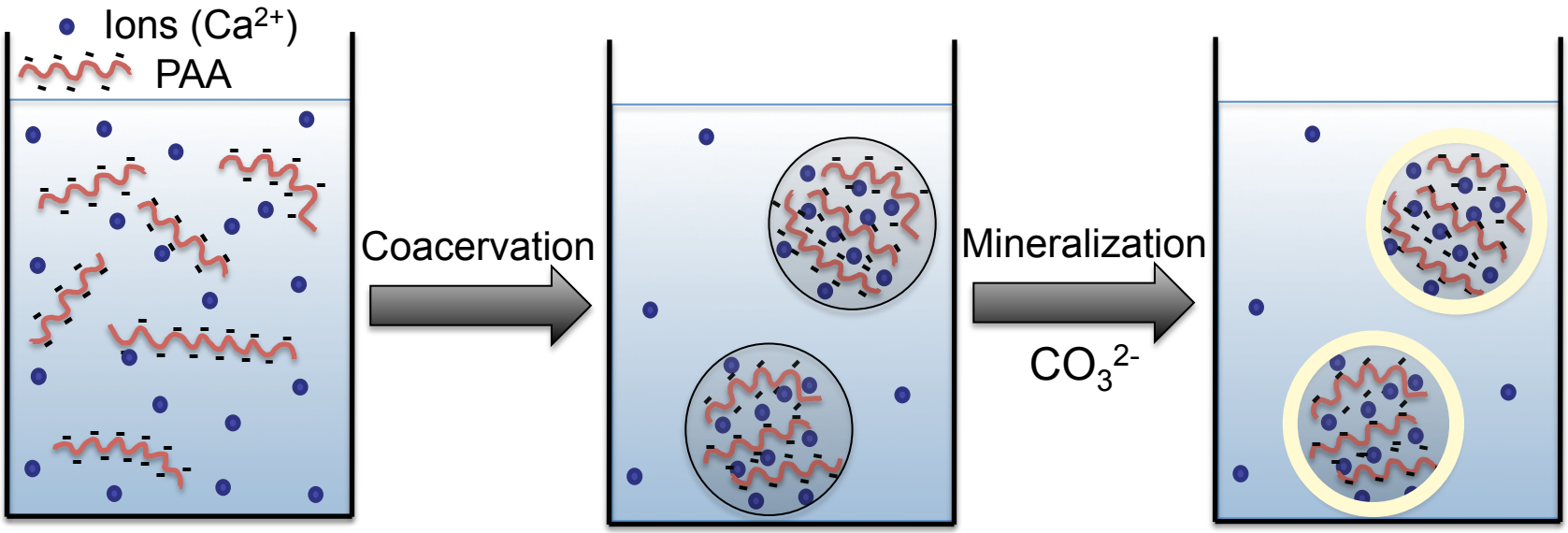


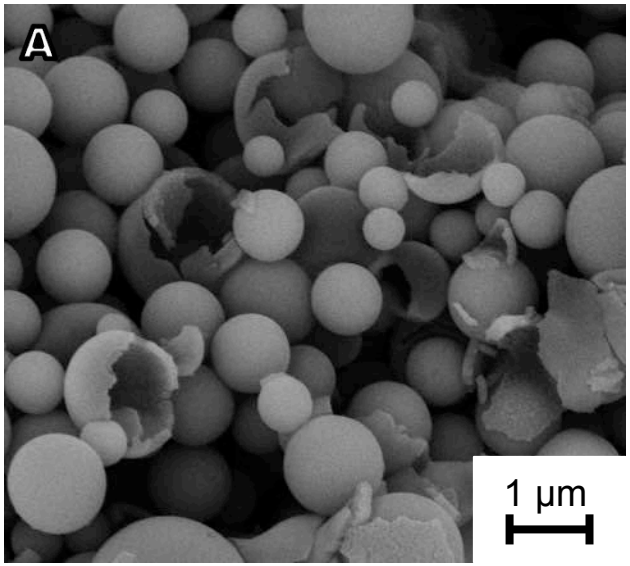


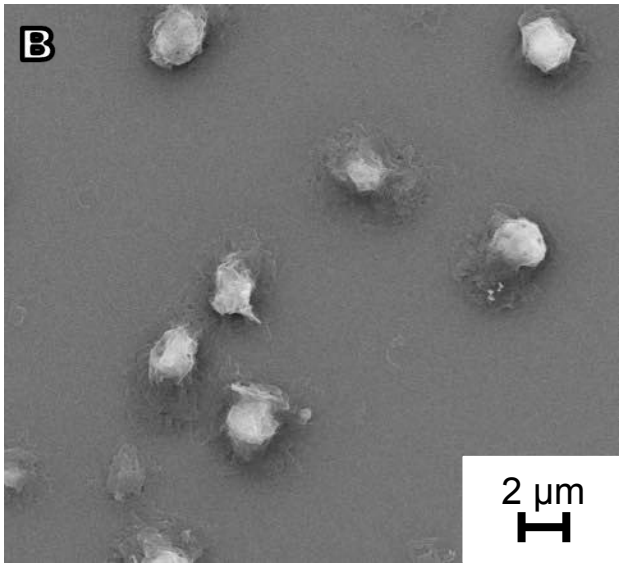
(A) DLS results as a function of the PAA concentration (B) DLS results as a function of the $CaCl_2$ concentration

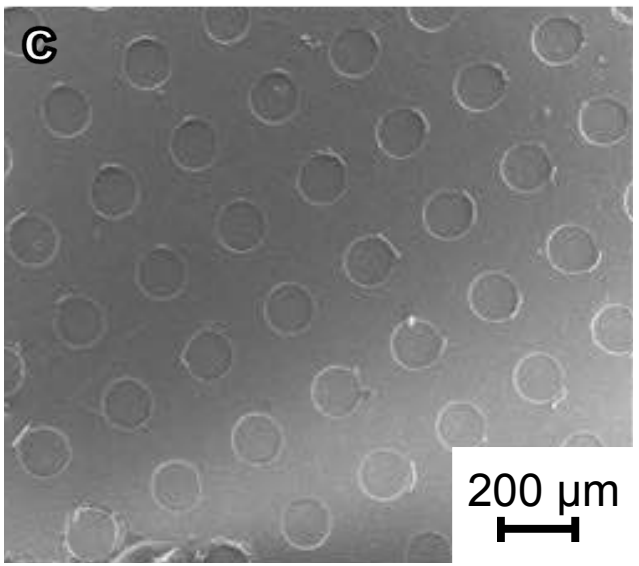
Kaempfe, P.; Lauth, V. R.; Halfer, T.; Treccani, L.; Maas, M.*; Rezwan, K. JACE 2013, 3, 736–742.

Coacervation: $CaCO_3$ Microcarriers

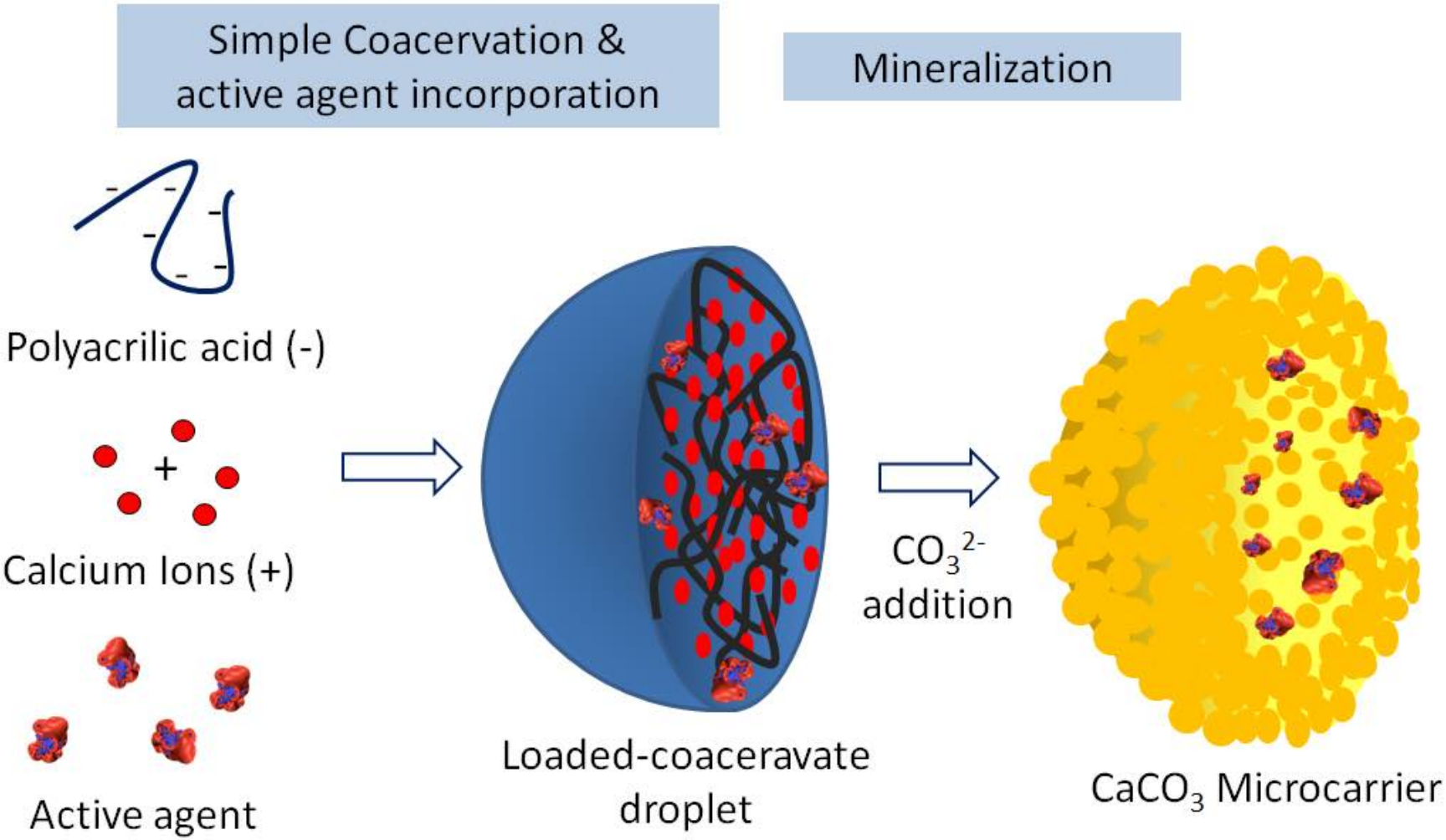








➢Coacervation: $CaCO_3$ Microcarriers



➢Coacervation: $CaCO_3$ Microcarriers

Amount of BSA incorporated in $CaCO_3$ microcarriers

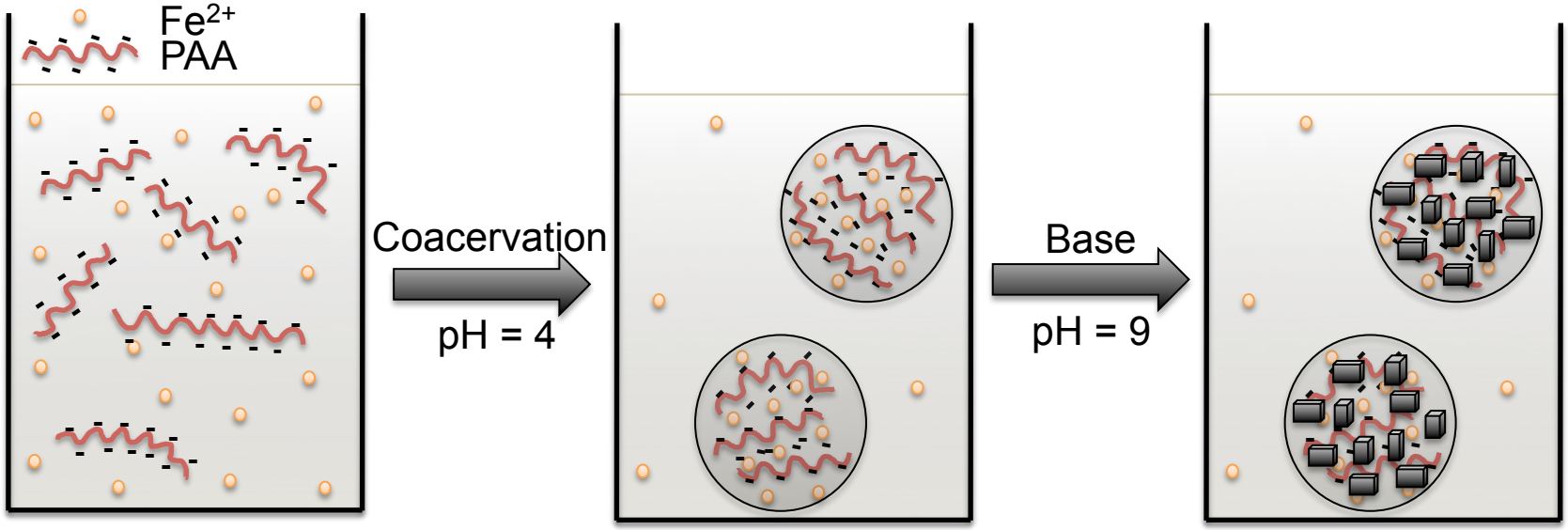
	ug BSA per mg CaCO3				Efficiency (%)			
			25 min. complexation				25 min. complexation	
	0,5 g/L BSA		0,5 g/L BSA		0,5 g/L BSA		0,5 g/L BSA	
Sample	pH 7	pH 10	pH 7	pH 10	pH 7	pH 10	pH 7	pH 10
700.12.12	0.00	0.31	0.00	0.02	0.00	1.48	0.00	0.05
1400.12.12	1.50	2.18	0.00	1.55	9.78	18.87	0.00	5.56
1900.12.12	0.65	1.68	0.00	0.00	2.59	10.52	0.00	0.00

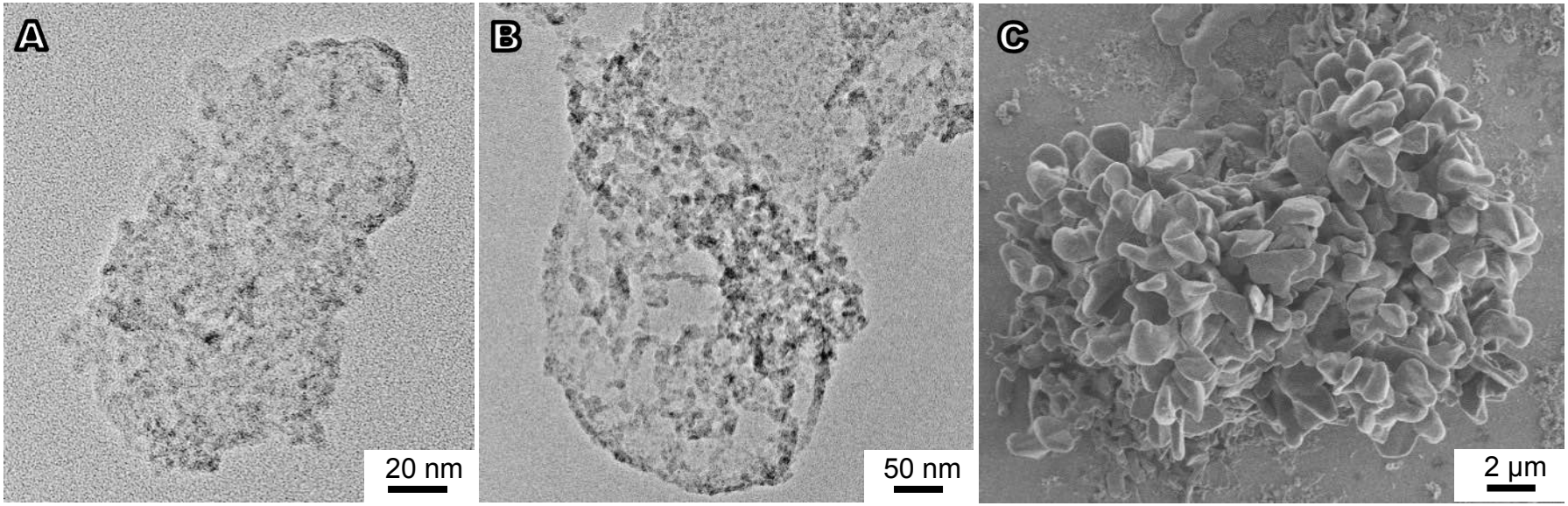
PAA concentration

Ca^{2+} concentration

CO_3^{2-} concentration

Coacervation: Magnetite Microspheres



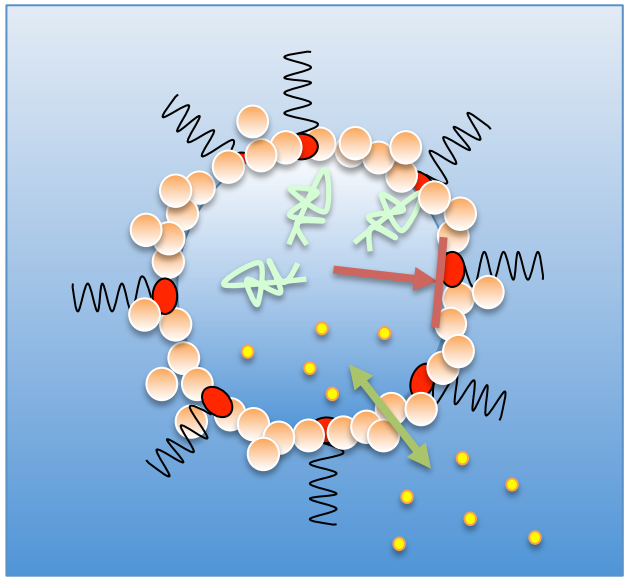


➢ Lecture Outline

- Drug Delivery Basics
- Drug Delivery Techniques
- Drug Delivery Using “Ceramic” Nanoparticles
  - Iron Oxide Nanoparticles
  - Gold nanoparticles
  - Mesoporous silica
  - Calcium carbonate
  - Colloidosomes

➢ Colloidosomes: Overview

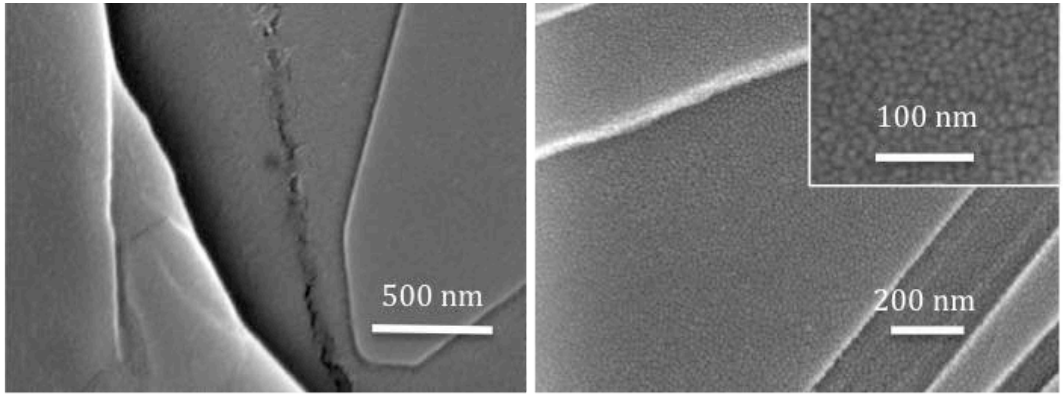
Definition:
Microcapsules with nanoparticle shells



Advantages:
- Tunable porosity ➔ selective permeability
- Range of possible building blocks
- Tunable size
- Monodisperse

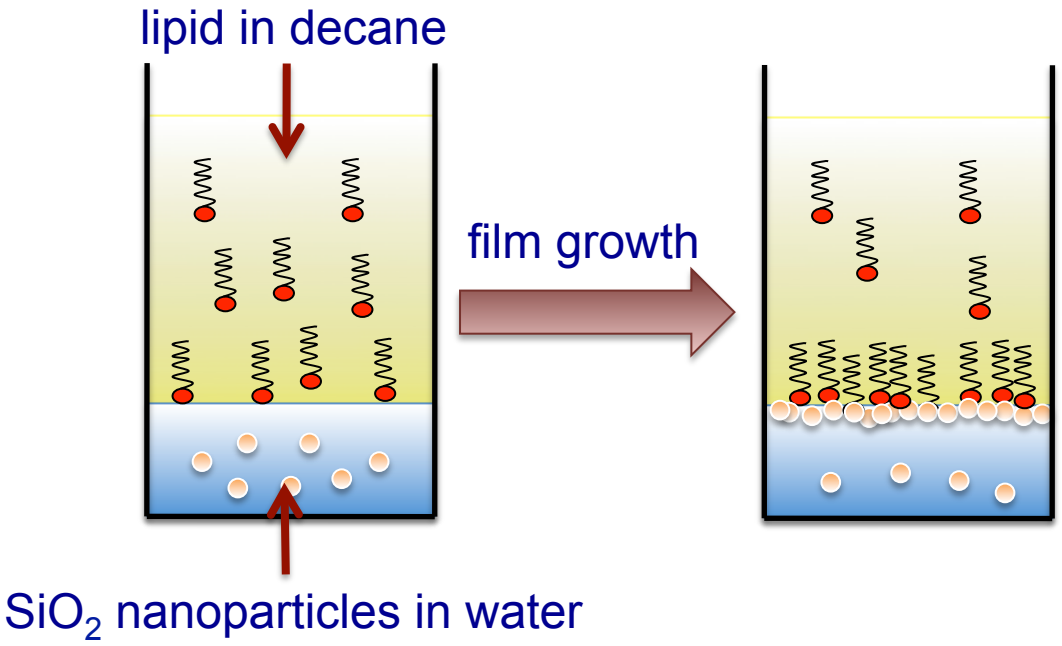
Known methods:
- Based on polymer beads that are sintered at elevated temperatures
- Additional polymers for gelled cores or reinforced shells
- Huge colloidosomes (10 – 100 µm)

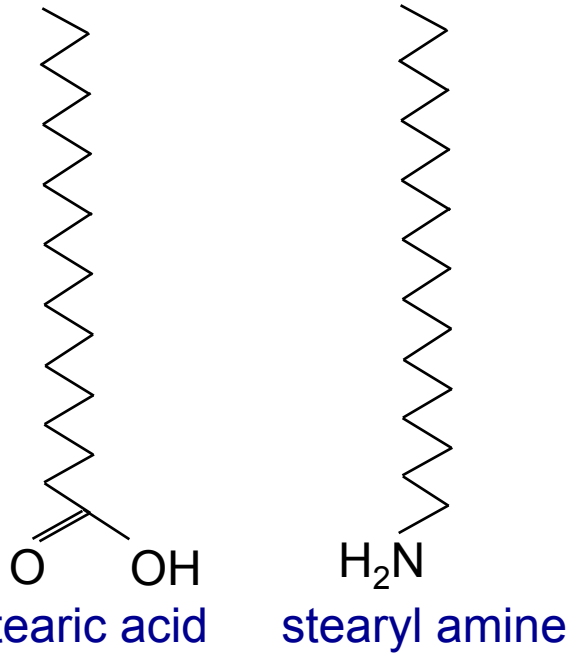
Surfactant stabilized Thin-Films



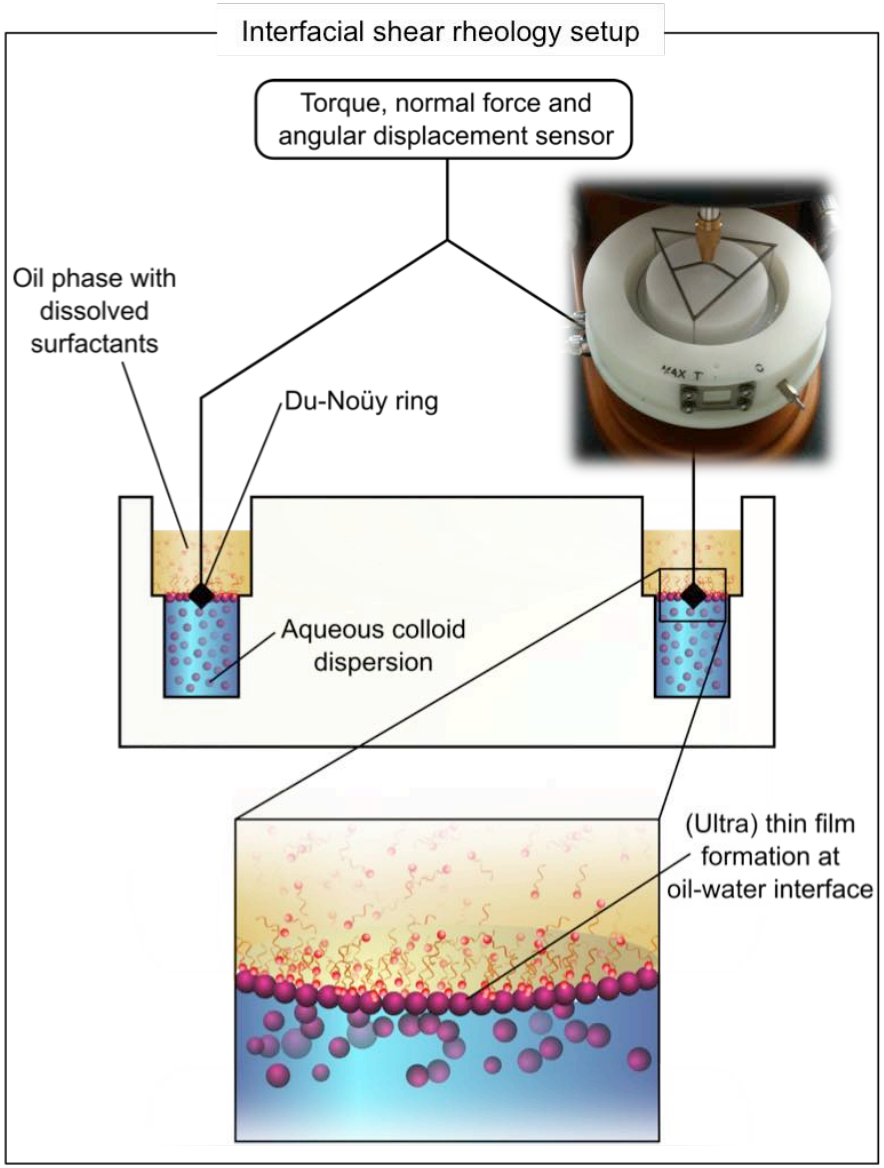
- Surfactant stabilized nanoparticle thin films
- Idea derived from biomimetic $CaCO_3$ thin films

Maas, M.; Ooi, C. C.; Fuller, G. G. Langmuir 2010, 26, 17867–17873.





➢ Thinfilms: Interfacial Shear Rheology



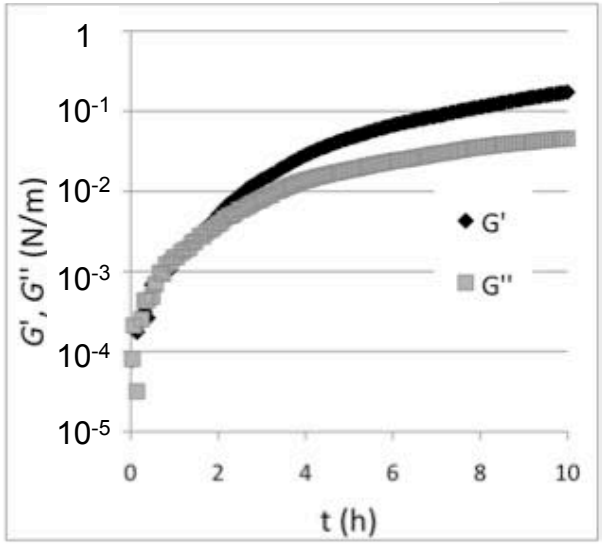
2D double Couette shearing system
TA instruments DHR3 rheometer

G': storage module ➔ elastic properties
G'': loss module ➔ viscous properties

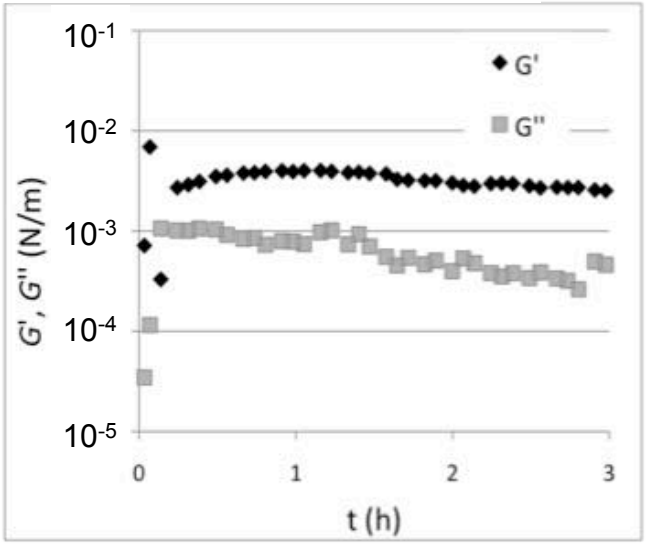
Method to quantify thin-film growth,
Important for microcapsule studies

➢ Interfacial Shear Rheology of the decane/water interface

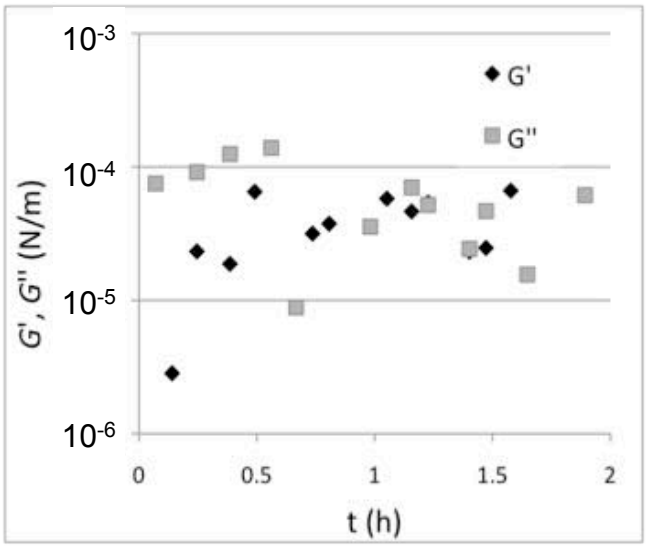
a) SiO_2 + stearic acid



b) SiO_2 + stearyl amine



c) SiO_2 + stearyl alcohol

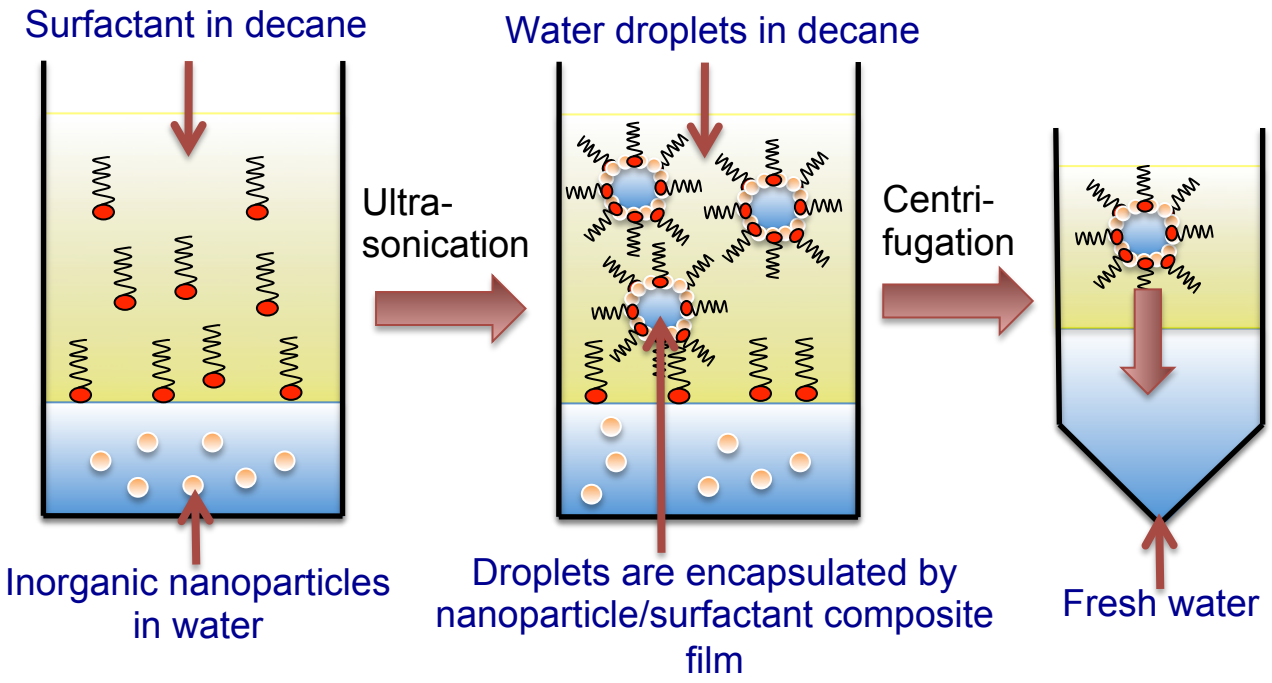


Time tests of films grown at the interface between

a) **SiO_2** (pH 10) in water + 1 mM **stearic acid** in decane,
b) **SiO_2** (pH 10) in water + 1 mM **stearyl amine** in decane,
c) **SiO_2** (pH 10) in water + 1 mM **stearyl alcohol** in decane.

Maas, M.; Ooi, C. C.; Fuller, G. G. Langmuir 2010, 26, 17867-17873

Colloidosomes

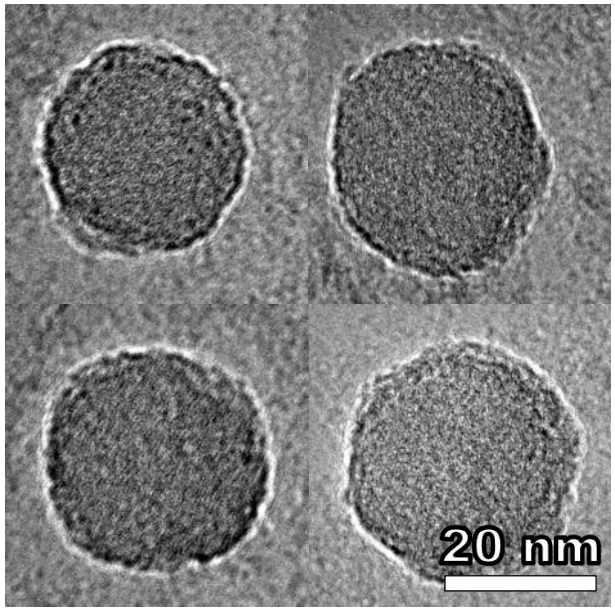


Colloidosome assembly works best with nanoparticles and surfactants with the same charge!

SiO_2 + stearic acid
Al_2O_3 + stearyl amine

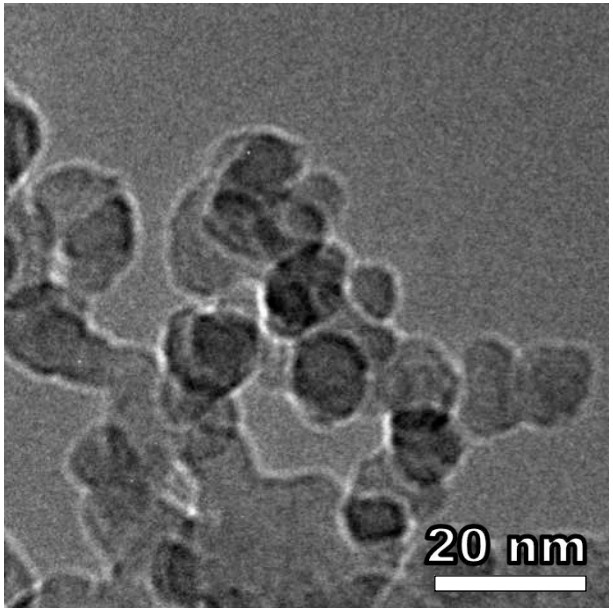
TEM Characterization of Colloid Particles

SiO_2 (LudoxTMA)



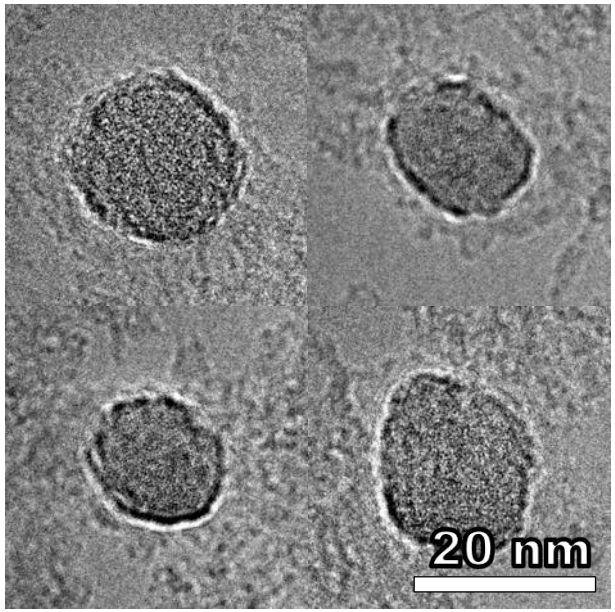
- uniform & mostly spherical
- no agglomeration
- d = 22 nm
- ζ-Potential = -24 mV

Al_2O_3 (AluC)

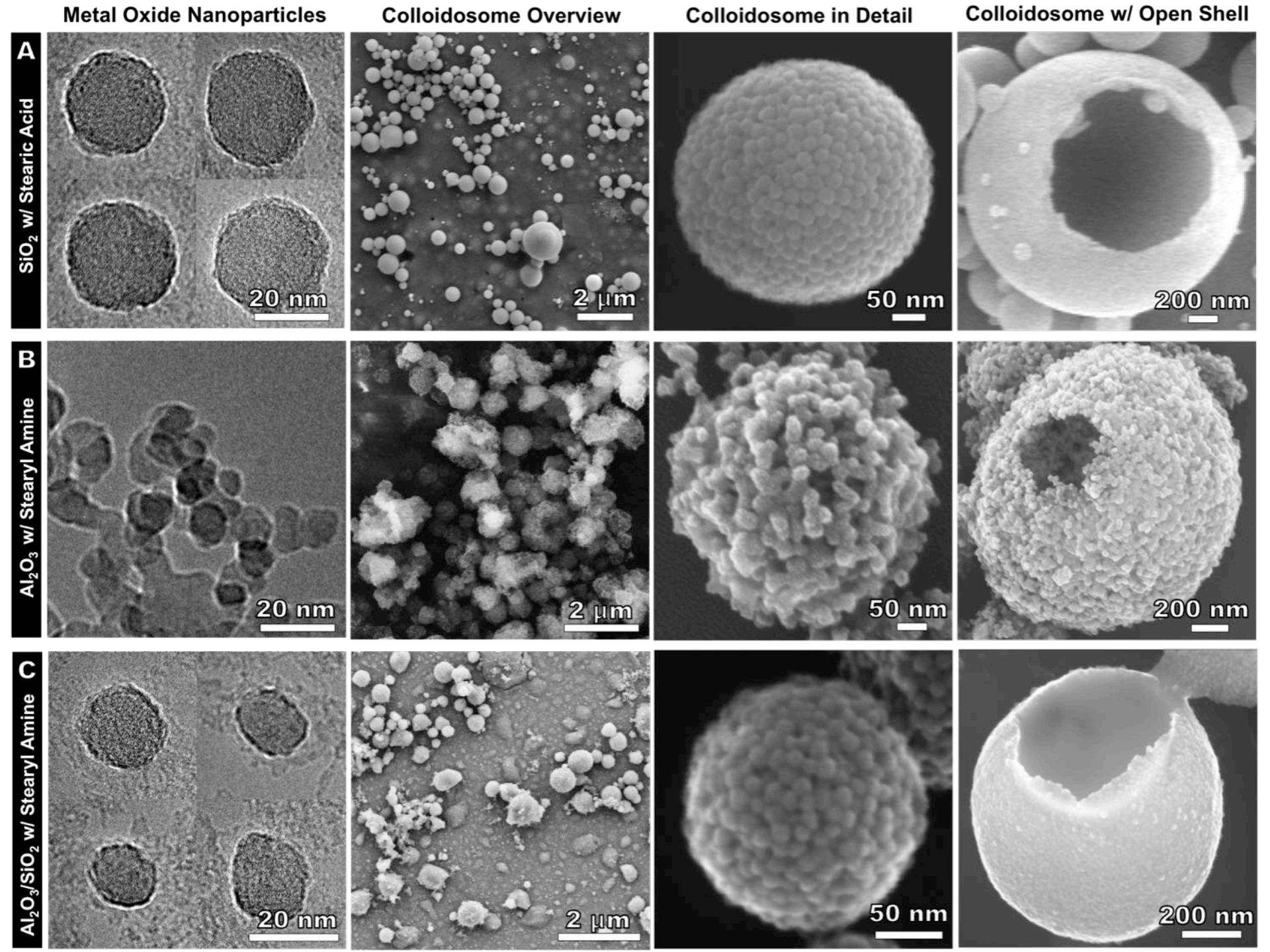


- varying shapes
- strong agglomeration
- d = 13 nm
- ζ-Potential = +30 mV

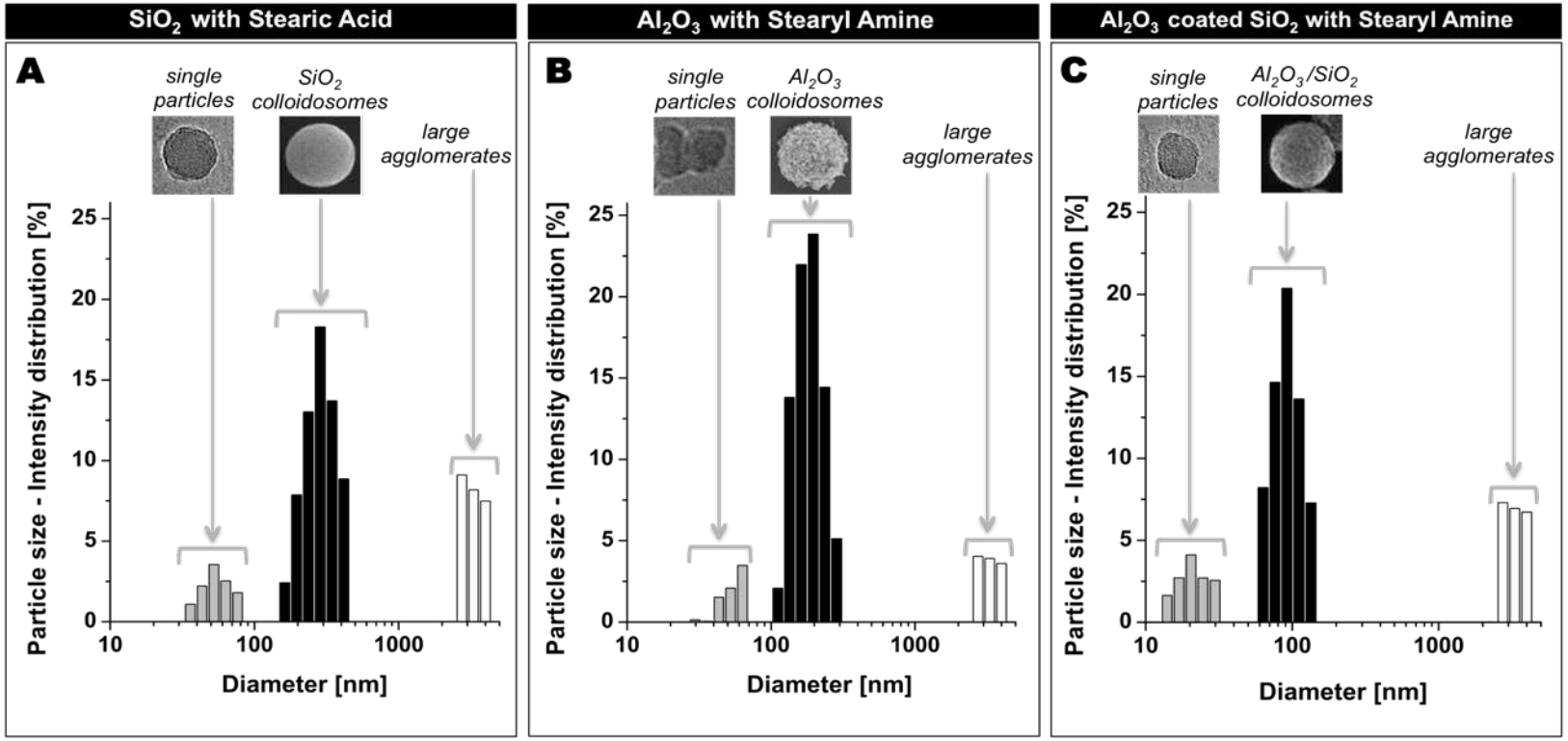
Al_2O_3 coated SiO_2 (LudoxCL)



- mostly spherical
- no agglomeration
- d = 15 nm
- ζ-Potential = +25 mV


Metal Oxide Nanoparticles
Colloidosome Overview
Colloidosome in Detail
Colloidosome w/ Open Shell
A
SiO2 w/ Stearic Acid
20 nm
2 µm
50 nm
200 nm
B
Al2O3 w/ Stearyl Amine
20 nm
2 µm
50 nm
200 nm
C
Al2O3/SiO2 w/ Stearyl Amine
20 nm
2 µm
50 nm
200 nm

Colloidosomes: Dynamic Light Scattering

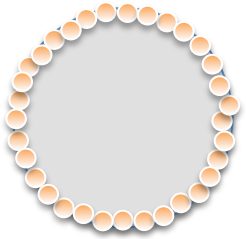


Metal Oxide	Average particle diameter (nm)	Average colloidosome diameter (nm)	Zeta potential (mV)
SiO_2	25 ± 4	420 ± 160	-40 ± 2
Al_2O_3	12 ± 3	230 ± 60	+43 ± 11
Al_2O_3 coated SiO_2	17 ± 3	200 ± 140	+75 ± 6

SEM & TEM studies of internal Capsule structure

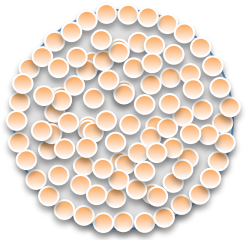
Are Capsules hollow or filled with particles?

Case 1



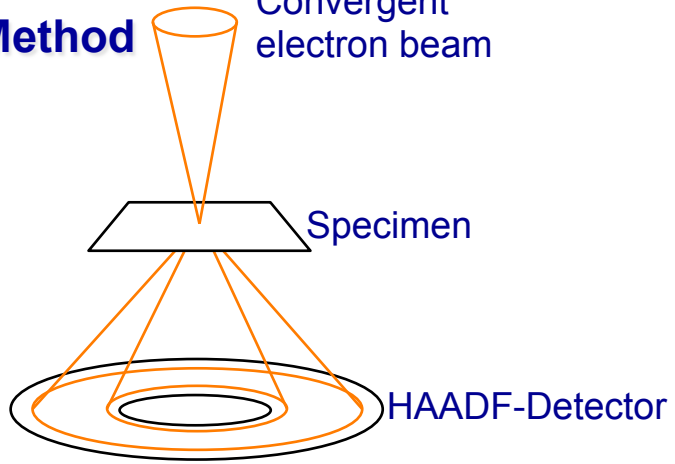
Hollow capsule

Case 2



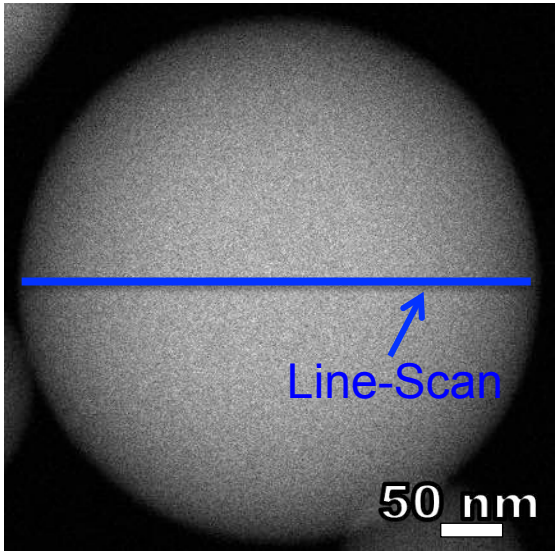
Particle filled capsule

STEM-Method

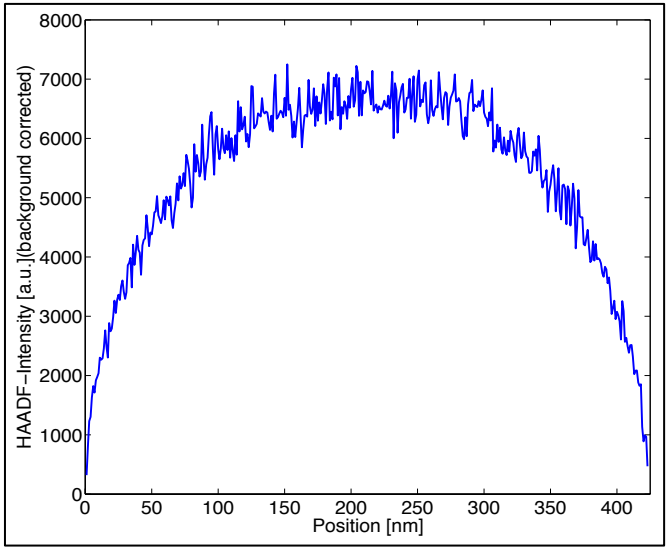


HAADF intensity increases homogenously with increase in specimen thickness

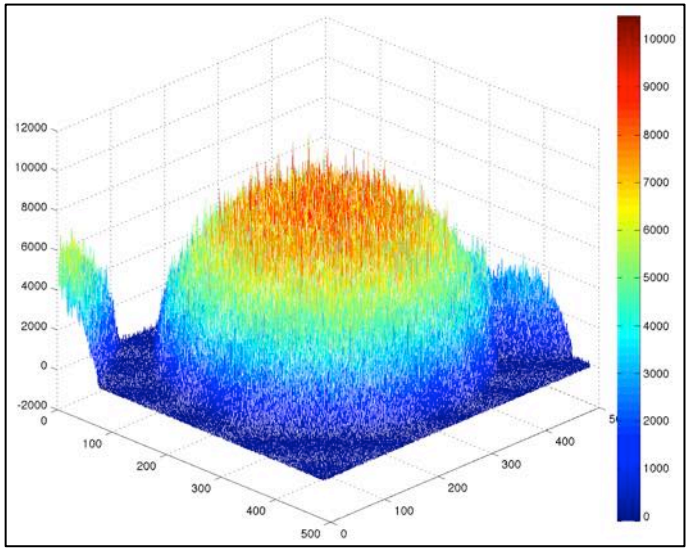
SiO_2-Particle (full)



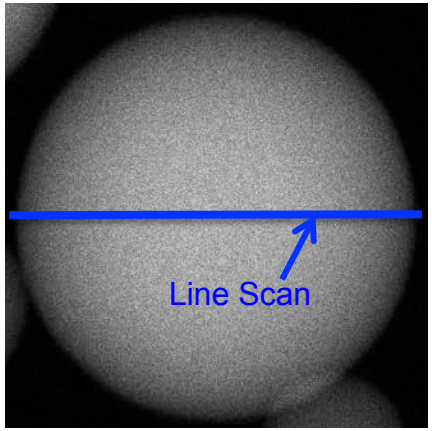
HAADF line scan

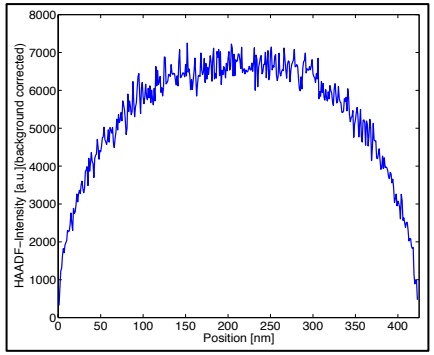


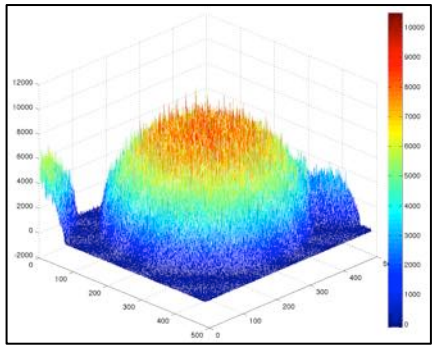
HAADF surface plot



SiO_2-Particle (full)

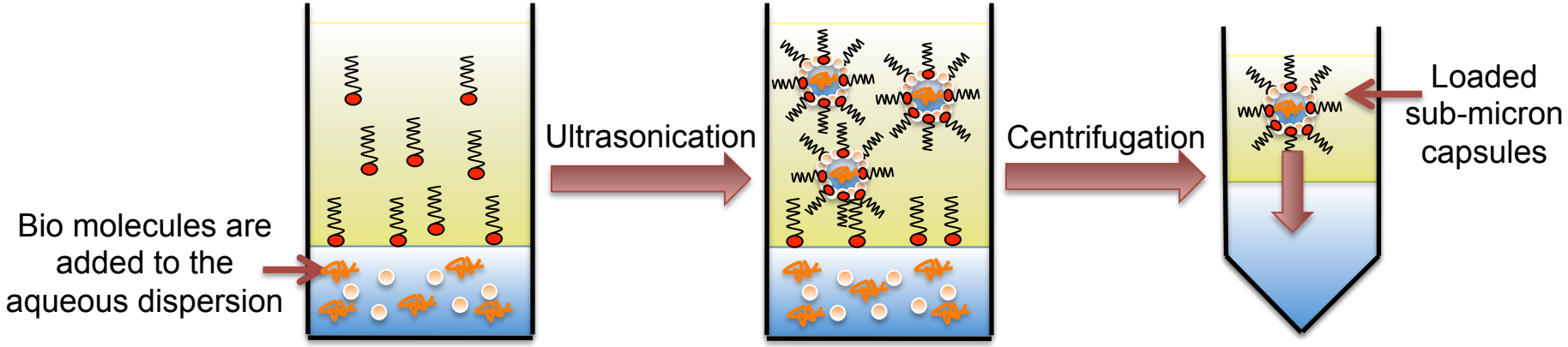




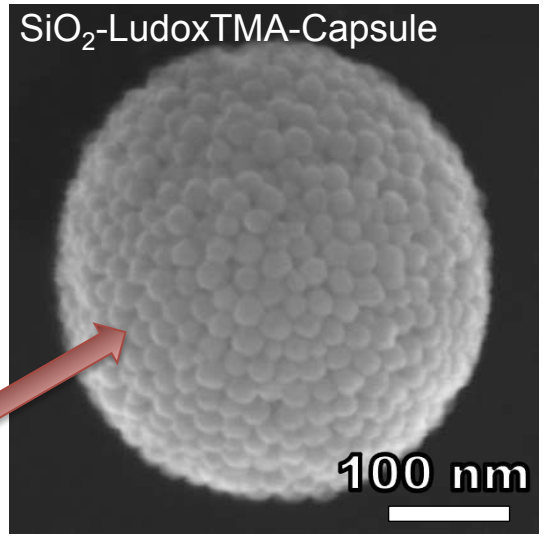


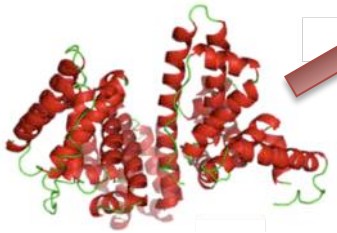
Advanced CERAMICS

Capsule loading with Proteins (Preparation)



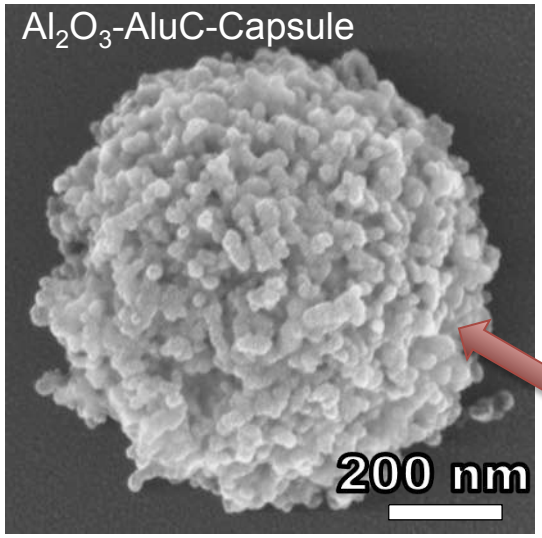
negative ζ-Potential



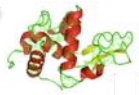


FITC-Bovine Serum Albumin

- m(BSA) = 66.5 kDa
- Dimension: 14x4x4 nm^3
- Charge at pH = 7: **- negative**
- IEP: pH 4.7



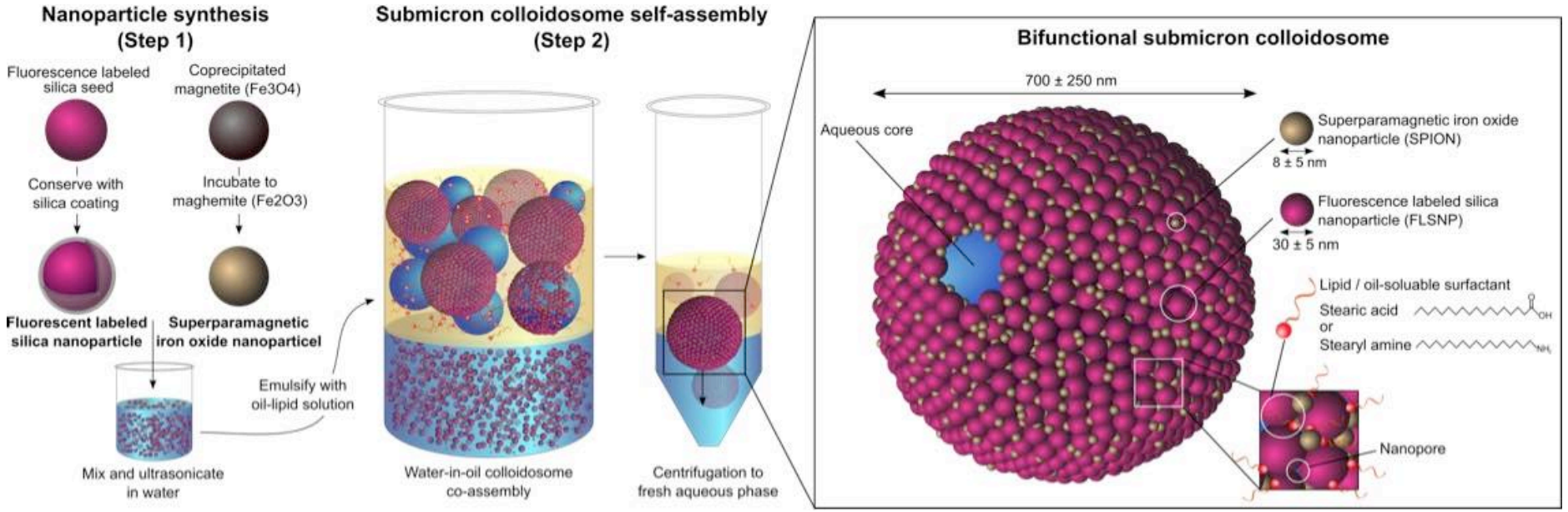
positive ζ-Potential



Lysozyme

- m(Lysozyme) = 14.3 kDa
- Dimension: 5x3x3 nm^3
- Charge at pH = 7: **+ positive**
- IEP: pH 11

➢ Multifunctional Colloidosomes

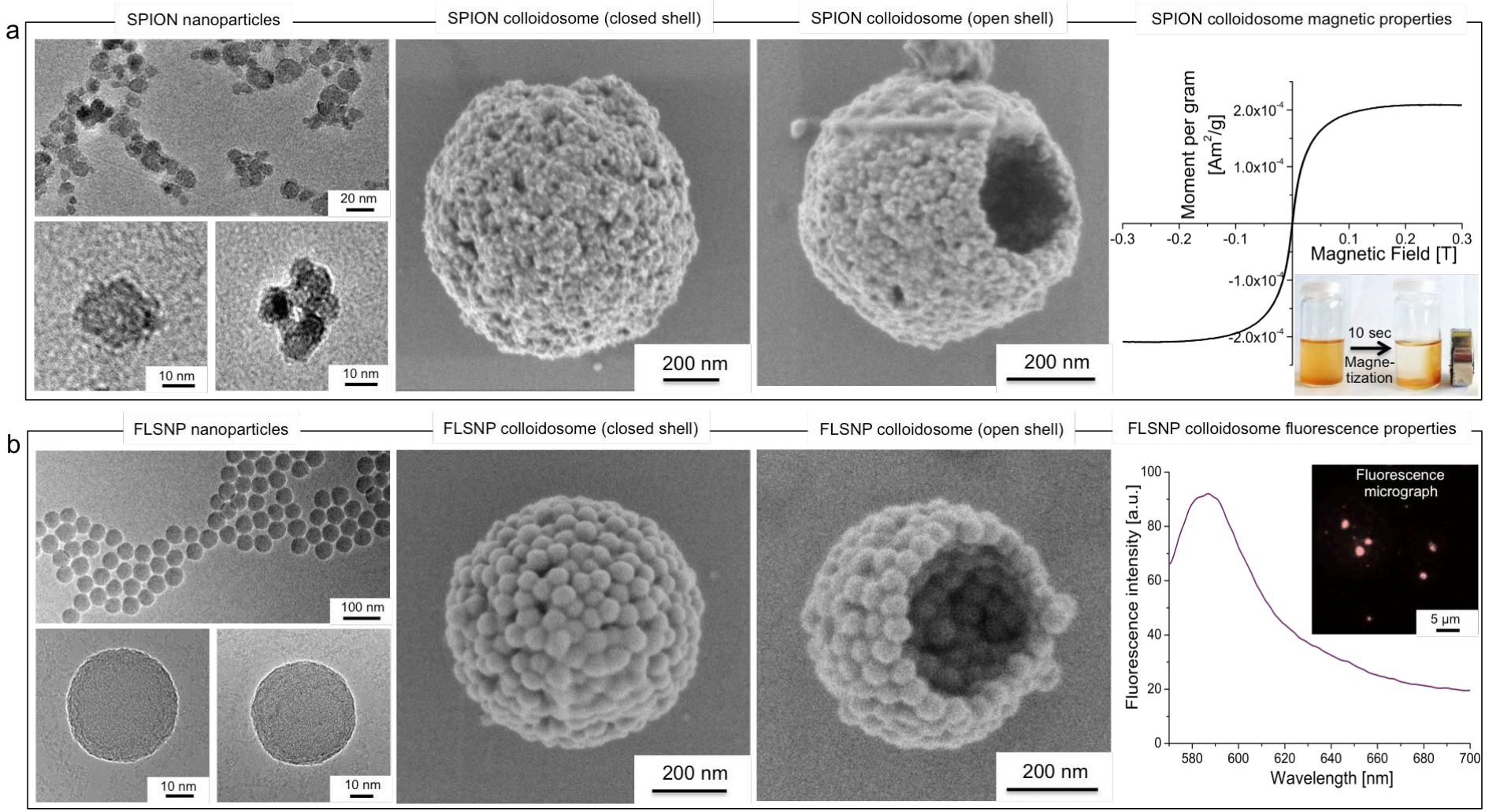


Multifunctional Colloidosome

Properties:

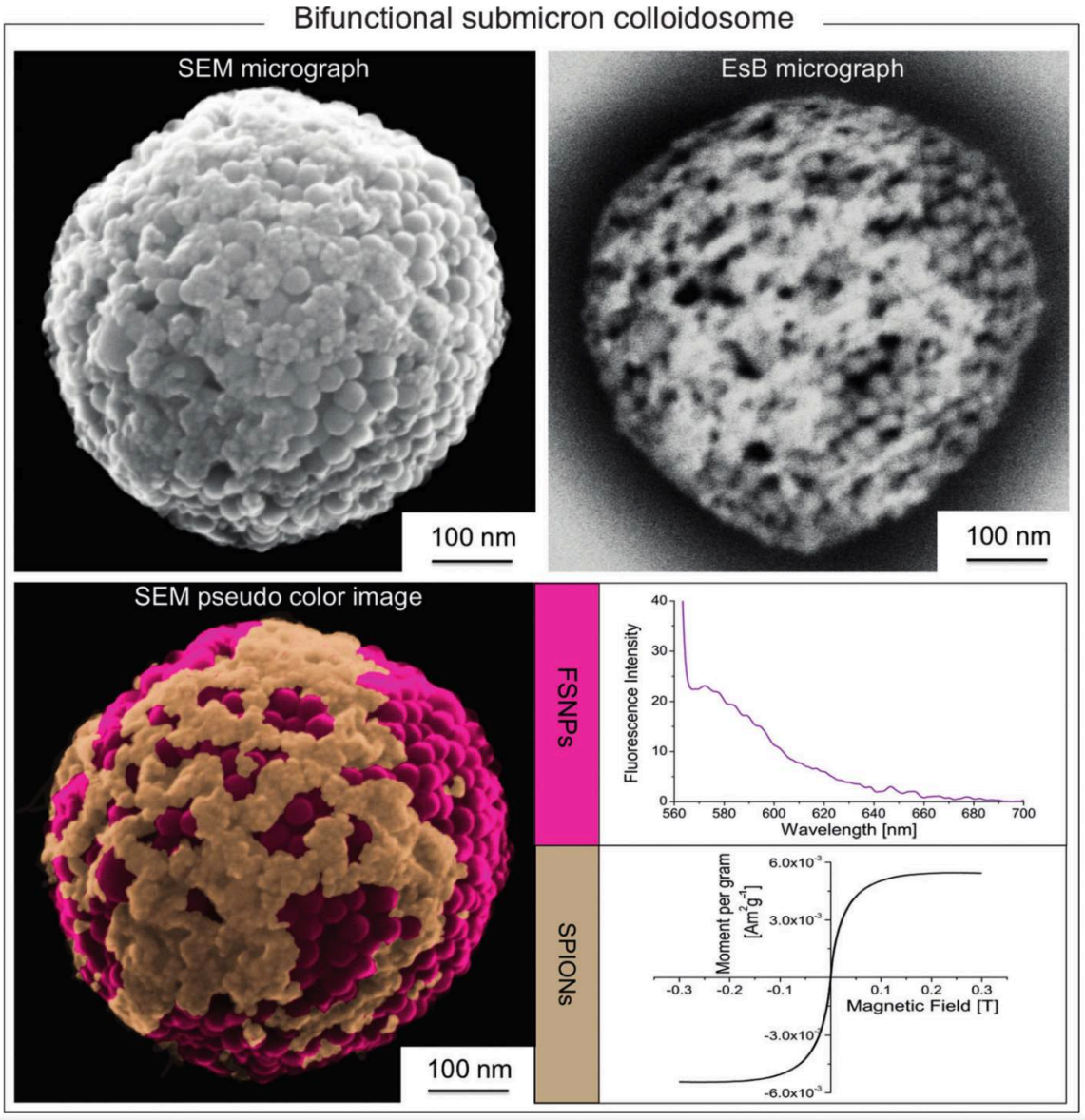
- Submicron Capsule based on different types of nanoparticles with distinct properties
- Building block system (easily integrate other nanoparticles types)
- Submicron size
- (Protocell like structure)

Superparamagnetic and Fluorescent Colloidosomes



- a: Superparamangetic submicron colloidosomes
- b: Fluorescent submicron colloidosomes

➢ Co-Assembled Multifunctional Colloidosome



Multifunctional Colloidosome

Properties:

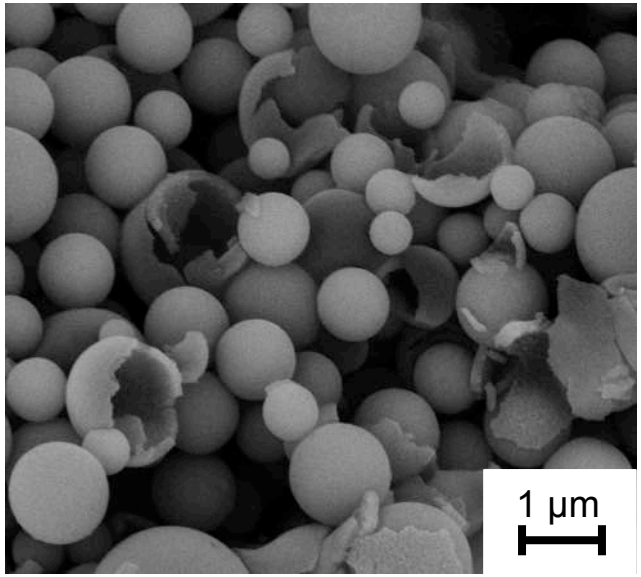
- Submicron Capsule based on different types of nanoparticles with distinct properties
- Building block system (easily integrate other nanoparticles types)
- Submicron size

➢ Summary

Coacervation-Mediated Mineralization

Advantages:

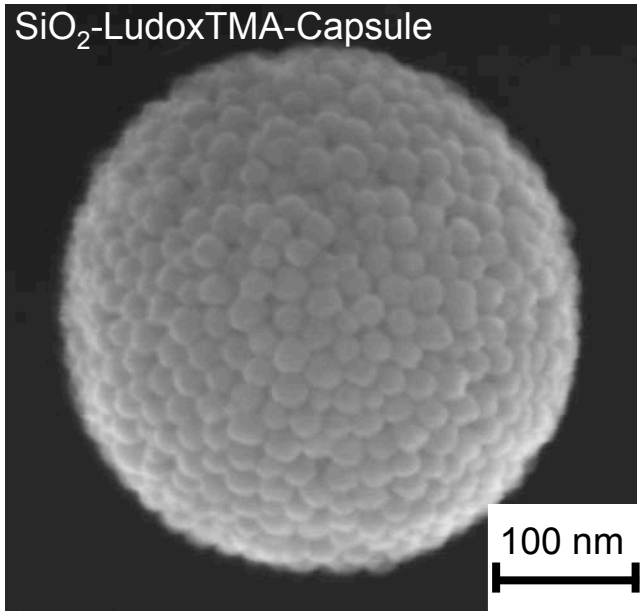
- Biocompatibility
- One-pot-process
- Tunable size (200 nm – 2 µm)



Colloidosome Formation

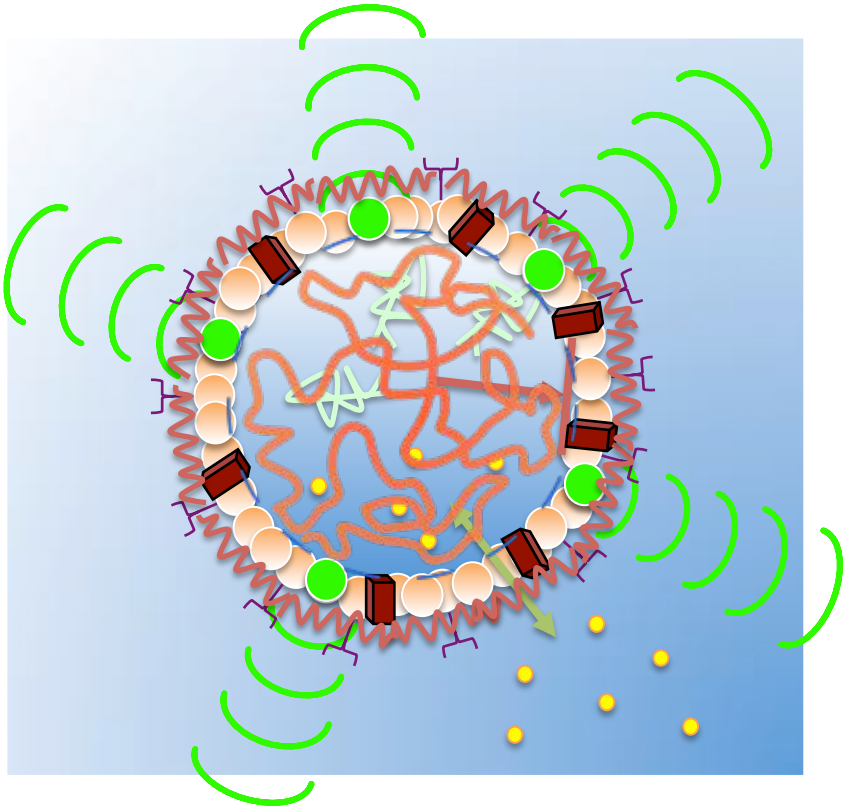
Advantages:

- Range of possible building blocks
- Tunable porosity ➔ selective permeability
- Submicron size



Outlook

Lego system for microcapsule design



- inorganic nanoparticle shell
- large molecule active agents: proteins
- small molecule active agents: growth factors, antibiotics
- superparamagnetic nanoparticles for mobility, triggered release and diagnostics
- fluorescent nanoparticles for diagnostics
- polymer/coacervate core for structural tuning, controlled porosity
- functionalized nanoparticles as receptors
- protein/polymer corona for tuned biological interaction

➢ Outlook

A versatile platform for functional submicron capsules for theragnostics:

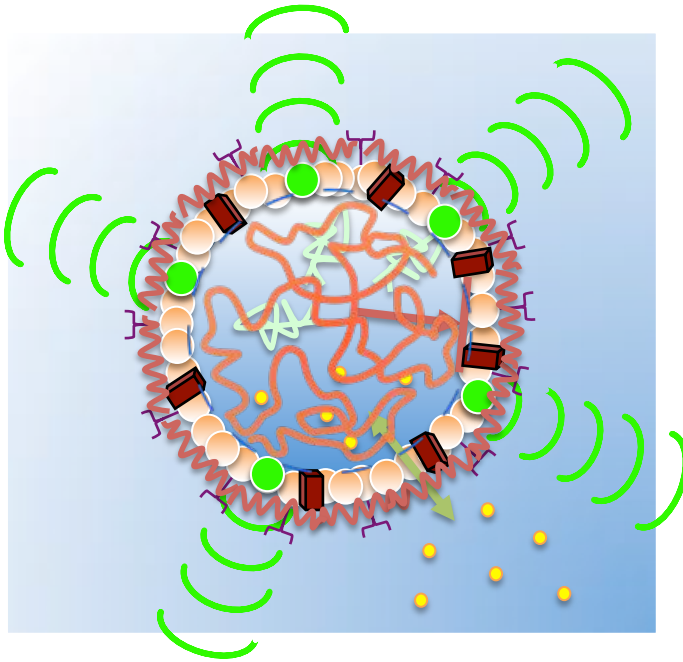
- Inorganic nanoparticle framework
- Functional building blocks
- Shell reinforcement via mineralization
- Self-assembly processes under mild conditions
- Various strategies: colloidosome route, coacervation route

Basic research:

- nanoparticle/protein interactions in interfacial films
- multicomponent thin films
  - ➔ interfacial shear rheology
  - ➔ LB-trough studies
- biomimetic mineralization of $CaCO_3$, CaP and Fe_3O_4

Related projects:

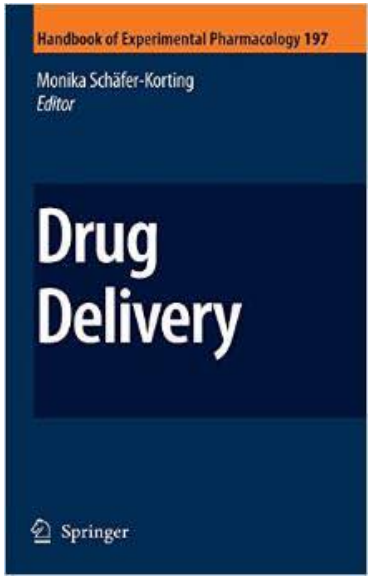
- micromolding
- porous ceramics
- nanofibers



➢ Course Outline „Bioceramics”

1. Introduction: Applications, Goals and Challenges
2. A short Introduction to Proteins and Cells
3. Ceramics at the Biology Interface: Fundamental Interactions
4. Characterization of Biomolecule Adsorption
5. Bones and Teeth: Composites of Ceramics and Proteins
6. Ceramics for Orthopedic and Dental Implants: Alumina and Zirconia
7. Scaffolds for Bone Tissue Engineering: Calciumphosphates
8. Scaffolds for Bone Tissue Engineering: Bioglass® and Glass-Ceramics
9. Drug Delivery Using Ceramic Nanoparticles
10. Biomineralization
11. Biomimetic Materials
12. Student Talks on Selected Topics
13. Summary

➢ Further reading



Drug delivery, Handbook of Experimental Pharmacology 197, Monika Schaefer, Springer Verlag, 2010 (this one is highly suggested)

Design of Controlled Release Drug Delivery Systems, Xiaoling Li, McGraw-Hill, 2006

Characterization of Nanoparticles Intented for Drug Delivery, Springer Protocols, Methods in Molecular Biology, 2011

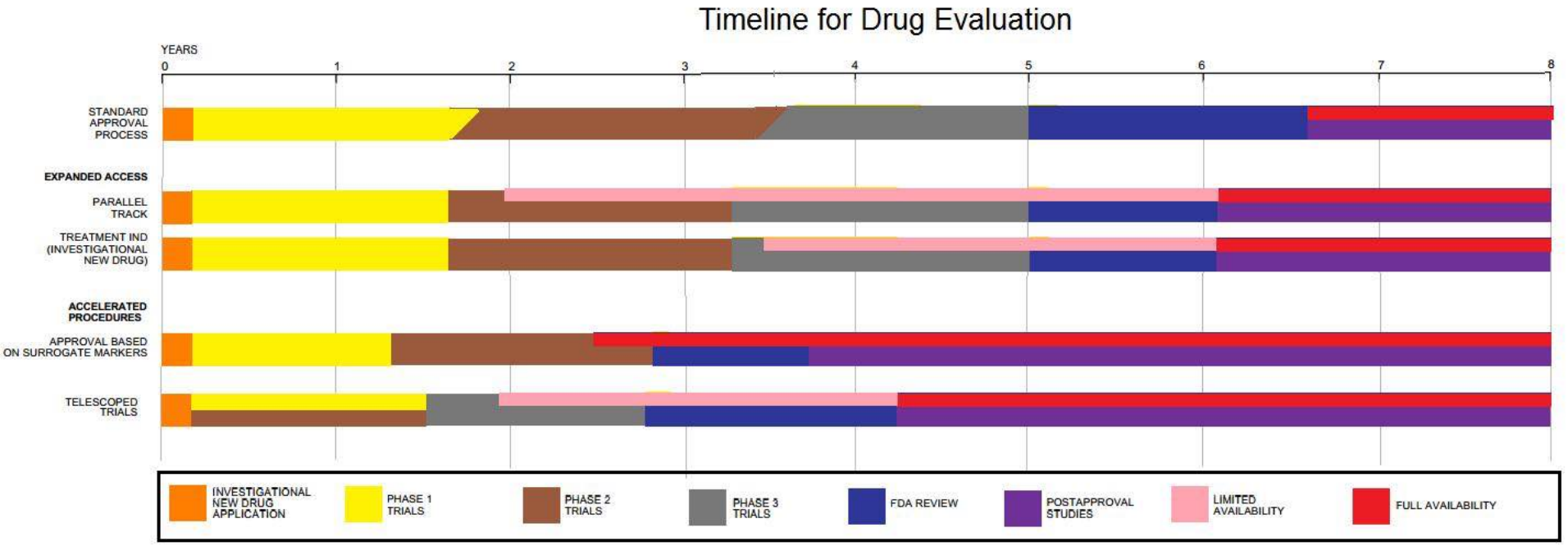
Nanoparticle Technology for Drug Delivery, Ram Gupta, Drugs and the Pharmaceutical Sciences Vol 159, 2006

44 marketed Nano-delivery products

Product	Generic	Formulation	Indication	Manufacturer
Abraxane	Paclitaxel	Polymeric nanoparticles	Cancer chemotherapy	Celgene
Abelcet	Amphotericin B	Liposomal formulation	Fungal infections	Elan/Alkermes, Enzon, Cephalon
Adagen	Adenosine deaminase	PEGylation	Enzyme replacement therapy	Enzon, Sigma-Tau
AmBisome	Amphotericin B	Liposomal Formulation	Oral and perioral infections	Astellas/Gilead Sciences
Amphotec	Amphotericin B	Liposomal Formulation	Oral and perioral infections	Three Rivers Pharmaceuticals/ALZA
Avinza	Morphine sulphate	nanocrystal formulation	Moderate to severe pain	Elan/Alkermes, Pfizer
Copaxone	Glatiramer acetate	Copolymer of lglutamic acid, lalanine, l-tyrosine and l-lysine)	Multiple sclerosis	Teva Pharmaceuticals
Curosurf	Poractant alfa	Liposome	Neonatal respiratory distress	Chiesi Farmaceutici SpA
DaunoXome	Daunorubicin	PEGylated liposome Formulation	Cancer chemotherapy	Gilead Sciences
DepoCyt	Cytarabine	Sustained-release Liposomes	Cancer chemotherapy	SkyePharma/Enzon
Depodur	Morphine sulphate	Liposome	Pacira Pharmaceuticals	Pacira Pharmaceuticals
Diprivan	Propofol	Liposomes	Induction of anesthesia	AstraZeneca
Doxil/CaelyX	Doxorubicin	PEGylated liposome Formulation	Cancer chemotherapy	ALZA/ OrthoBiotech/ Schering Plough
Elestrin	Elestrin Estradiol gel	Phosphate nanoparticles	Menopausal symptoms	BioSante
Elyzol	Metronidazole	Dental gel	Parodontitis Camurus	Camurus
Emend	Aprepitant	Nanocrystal Formulation	Anti-emetic	Merck & Co+ Elan/Alkermes
Epaxal	Hepatitis A vaccine	Virosome technology	Prevention of Hepatitis A infection	Berna Biotech
Episil	Bioadhesive barrier	Fluidcrystal	Oral pain	Sinclair/Teva
Estrasorb	Estradiol gel	Micellar Nanoparticles	Menopausal symptoms	Novavax/Espirit Pharma
Focalin XR	Dexmethylphen idate hcl	Nanocrystals	ADHD	Novartis Élan/Alkermes
Fosrenol	Lanthanum carbonate	Inorganic Nanoparticles	End-stage renal disease	Shire
Genexal PM	Paclitaxel	Polymeric micelles	Cancers	Samyang

Product	Generic	Formulation	Indication	Manufacturer
Indaflex	Indomethacin	Solid/lipid nanoparticles	Osteoarthritis	AlphaRx
Inflexal V	Subunit influenza vaccine	Virosome	Influenza prophylaxis	Crucell
Invega Sustenna	Paliperidone	Nanocrystal	Antipsychotic	Janssen
Macugen	Pegaptanib	Pegylated anti-vegf aptamer	Age-related macular degeneration	OSI Pharmaceuticals/ Pfizer
Myocet	Doxorubicin citrate complex	Liposome encapsulated	Cancer chemotherapy	Cephalon/Zeneus Pharma/ Sopherion Therapeutics
Megace ES	Megestrol acetate	Nanocrystal formulation	Cancer therapy	Elan/Alkermes+Par+Bristol-Myers Squibb
MuGard	Hydrogel mouth rinse	Nanogel	Head and neck cancers	Access Pharma
Naprelan	Naproxen	Nanocrystal formulation	Arthritis, gout	Elan/Alkermes
Nanoxel	Paclitaxel	Polymeric nanoparticles	Cancer chemotherapy	Dabur Pharma
Neulasta	Filgrastim	Pegylation	Neutropenia	Amgen
Oncospar	Oncospar PEG-Lasparaginase	Pegylation	Cancers	Enzon/Schering-Plough
Pegasys	Peginterferon alfa 2a	Pegylation	Hepatitis B, hepatitis C	Roche/Nektar
PegIntron	Peginterferon alfa 2b	Pegylation	Chronic hepatitis C	Schering-Plough
Rapamune	Sirolimus	Nanocrystal formulation	Immunosuppression	Wyeth Élan/Alkermes
Renagel	Sevelamer hcl	Poly (allylamine) resin	Hyperphosphatemia in hemodialysis	Genzyme
Salinum	Potassium, magnesium, chlorine	Oral liquid	Xerostomia	
Somavert	Pegvisomant	Polymer protein conjugate	Acromegaly	Pfizer
Ritalin LA	Methylphenidate Hcl	Pulsatile release Nanocrystal formulation	ADHD	Elan/Novartis
Survanta	Beractant	Liposome encapsulated	Neonatal respiratory distress	Abbott
Tricor	Fenofibrate	Nanocrystal formulation	Lipid reduction	Abbott Élan/Alkermes
Triglide	Fenofibrate	Nanocrystal formulation	Lipid reduction	SkyePharma/ First Horizon Pharmaceuticals/Sciele Pharma
Verelan/ Verelan PM	Verapamil	Elan's SODAS Multiparticulate technology	Hypertension	Elan/Alkermes Schwarz

Source BCC Research


Timeline for Drug Evaluation
YEARS
0
1
2
3
4
5
6
7
8
STANDARD APPROVAL PROCESS
EXPANDED ACCESS
PARALLEL TRACK
TREATMENT IND (INVESTIGATIONAL NEW DRUG)
ACCELERATED PROCEDURES
APPROVAL BASED ON SURROGATE MARKERS
TELESCOPED TRIALS
INVESTIGATIONAL NEW DRUG APPLICATION
PHASE 1 TRIALS
PHASE 2 TRIALS
PHASE 3 TRIALS
FDA REVIEW
POSTAPPROVAL STUDIES
LIMITED AVAILABILITY
FULL AVAILABILITY