생체 적합한 나노입자와 계면화학

Surface Chemistry in Biocompatible Nano/Colloidal Particles

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대한화장품학회/한국공업화학회 계면화학 공동 심포지움 - 9.23.2004 -

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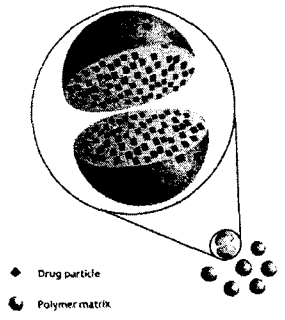
Surface Chemistry
in Biocompatible Nano/Colloidal particles



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Contents

- Colloids and Surface Chemistry
- Biocompatible and Biodegradable Materials
- Nano/microcapsules
- Self-assemblies
- Liposomes

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Colloids and Brown movement

This is the view Brown obtained in 1828, when he first recognized the cell nucleus.

John Tyndall 1828-1893
J. Tyndall first explained that the sky is blue because the different wavelengths of sunlight are scattered to different degrees by the atmosphere. Having established that there were dust particles in the air, he showed that the air contained living microorganisms.

In 1861 Thomas Graham coined the term *colloid* (which means "glue" in Greek) to describe selmi's pseudosolutions.

A. Einstein; The first paper provided a theory explaining Brownian movement, the zigzag motion of microscopic particles in suspension.

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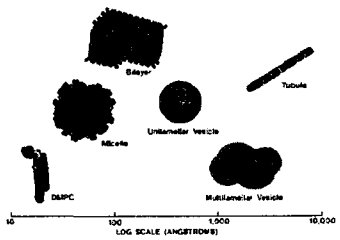
Colloids and Surface Chemistry?

□ 콜로이드(Colloid)란?
: 직경의 크기가 약 **10nm ~ 1□m**인 입자가 모인 계로서
표면적과 표면성질의 역할이 큰 시스템

□ 일반적인 입자의 크기



크기 (μm)		Example	
10^2		Sand	Pulverized coal
10^1	↑		
10^0	Mist and fog	Silt Clay	Red blood cells Paint pigment Latices
10^{-1}	↓		
10^{-2}		Colloidal silica	Coiled macromolecules Carbon black
10^{-3}		Colloid gold	Micelles

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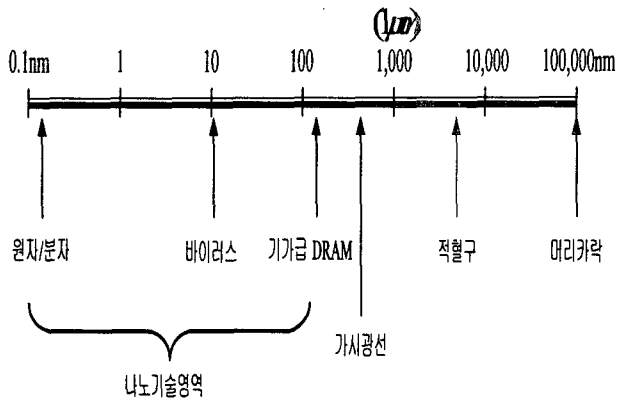
Definition of Nanotechnology

Creation of useful materials, devices, and systems through the control of matter on the nanometer-length scale and the exploitation of novel properties and phenomena developed at that scale



"There' s Plenty of Room at the Bottom."

-- Feynman, 1959

"Advances in the technologies of medicine, space, computation, and production □ and warfare □ all depend on our ability to

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Biocompatible 생체적합성

생체 이식과 부여를 목적으로 하는 물질에 대하여 과학적 방법에 따른 결과로 체내에서 조직적합성 및 혈액적합성을 갖고 있는 것

- (KFDA) -

Biocompatible materials are clearly those compatible with the biological system they are put in contact with.

In more detail, A ideally biocompatible material would cause

(1) no irritation
(2) no inflammation
(3) no foreign body response
(4) no allergic reaction
(5) no cancer

Here is a more general definition:

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application

- FDA -

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생체적합성의 대표적 평가 종류

Cytotoxicity
Cell viability
Growth, cycle

Immunocompatibility
Cytotoxic activity of
Natural Killer Cells

Blood Compatibility
- Platelet counting
- Platelet factor 4 assay
- Antithrombin III assat
- Fibrinopeptide A assay

Tissue Compatibility
- Quantitative evaluation of soft tissue of bone
- Determination of cytokines production in tissue

Infectivity
Bacterial adhesion
And growth

Genotoxicity
In vitro induced
chromatide exchange

Structural Analysis
Crystallinity degree
of biomaterials

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천연고분자 생체재료의 분류

Natural Polymers	Main Applications
Protein-based polymers	Absorbable, biocompatible, nontoxic, naturally available,
Collagen	Absorbable sutures, wound dressing, drug delivery microspheres.
Albumin	Cell and drug microencapsulation.
Poly(amino acids)	Poly(L-lysine), Poly(L-glutamic acid), Poly(aspartic acid) etc. Oligomeric drug carriers.
Polysaccharides and derivatives	
Vegetable sources	
Carboxymethyl cellulose	Cell immobilization in drug-delivery and dialysis membranes
Cellulose sulphate	Component of polyelectrolyte complexes for immunoisolation
Agarose	Supporting materials in clinical analysis
Alginate	Immobilization matrices for cells and enzymes
Carrageenan	Used for microencapsulation
Human and animal sources	
Hyaluronic acid	Excellent lubricant, potential therapeutic agent
Heparin	Candidates for ionotropic gelation and capsule formation
Microbial polysaccharides	
Dextran and derivatives	Excellent rheological properties, plasma expander, drug carrier
Chitosan and derivatives	Used in controlled-delivery systems

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합성고분자 생체재료의 분류

Synthetic Polymers	Main Applications
Aliphatic Polyesters	
Poly(lactic acid), poly(glycolic acid) and their copolymers	Used in sutures, drug-delivery systems and in tissue engineering. Biodegradable. Often copolymerized to regulate degradation time.
Poly(hydroxy butyrate), poly(e-caprolactone) and copolymers, poly(alkylene succinates), etc.	Biodegradable, a matrix for drug-delivery systems. Cell microencapsulation.
Polyamides	Sutures, dressing, haemofiltration membranes.
Polyanhydrides	Biodegradable, useful in tissue engineering.
Poly(orto esters)	Surface-eroding polymers, sustained drug delivery.
Poly(cyano acrylates)	Biodegradable, used as surgical adhesives and glues.
Thermoplastic polyurethanes	Application in drug delivery. Used in permanently implanted medical devices, catheters.
Polyethylene (low density)	Sutures, catheters, membranes.
Poly(vinyl alcohol)	Gels and blended membranes used in drug delivery.
Poly(ethylene oxide)	Highly 'biocompatible'. Used in a variety of biomedical applications.
Poly(hydroxyethyl methacrylate)	Hydrogels as soft contact lenses, for drug delivery, as skin coatings
Poly(methyl methacrylate)	Used as dental implants and in bone replacement.
Polydimethylsiloxanes	Implants in plastic surgery, orthopaedics, blood bags.
Poly(ethylene oxide-b-propylene oxide)	Amphiphilic properties; protein delivery, skin treatments.
Poly(vinyl methyl ether)	Temperature-sensitive polymer; shape-memory properties.
Poly(N-alkylacrylamides)	Temperature-sensitive gels.

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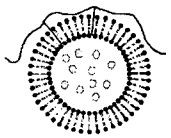
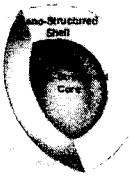
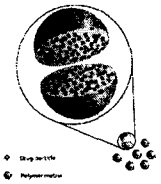
Nano/microparticle System



Nanonsphere/Microsphere



Nanoncapsule/Microcapsule

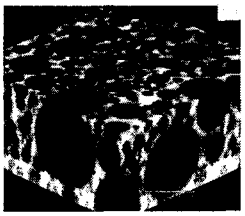


Nanoemulsion/Microemulsion

Polymeric micelles

Hydrophilic shell

Liposomes



Hydrophobic core

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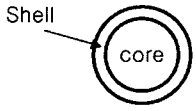
Nano/microparticle System

화장품 응용

1. 안정화
   Proteases/Keratinases[German Patent 1940105], Vitamin A palmitate [EP 316054], Mineral Oil [USP5013473]
2. 지속효과
   향 [USP4952400], 립스틱 오일[USP394571] Blushes/eye shadows의 pigment [USP532835, USP5382433]
3. 효능상승효과
   여드름 치료제, 발모 촉진 항생제, 소염제, 건선 치료제, 항진균제[USP4654354, USP5268494]
4. 자극/부작용 완화
   자외선 차단제[USP 5455048, USP5223533] 토코페롤 [Japan Patent 08259422]
5. 마찰효과
   화장 제거제 [USP3691270, USP3978240] 매니큐어 제거제[USP3686701, USP3729569]

일반 응용

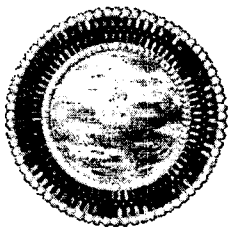
1. Carbonless copy paper
2. Oral and injected drug formulations
3. Encapsulated adhesive resin coated on automotive fasteners
4. Long-acting pesticide and herbicide products
5. Long-lasting fragrance



Continuous core/shell

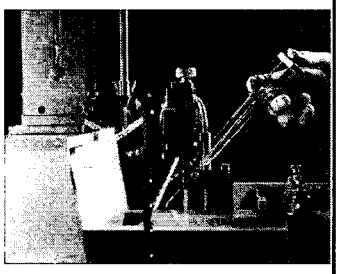
Interface Issues on Colloidal & Nanoparticles

- Size, shape & dimension
- Surface energy and charge
- Interaction & superstructure
- Function & response
- Reproducibility & self-assembly



Characterization of nanoparticles

- Particle size and shape
  Optical and electronic microscopy, diffusion, sedimentation and centrifugation gel permeation, light scattering, turbidity, x-ray, particle counters
- Size Distribution
  Average and moment, Poisson distribution Gausian distribution logarithmic distribution
- Diffusion and Brownian motion
  Fick's law, friction factor, Einstein equation
- Electrical properties
  Electrical charge, electrical double layer, potentials, zeta potential, electrophorestic retardation and relaxation



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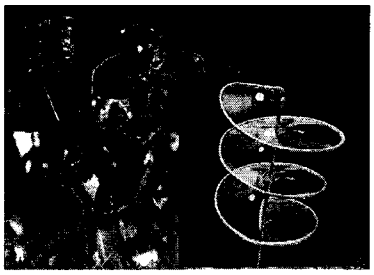
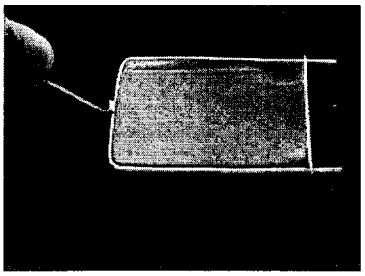
ENERGETICS

- **Gibbs Free Energy of Interface Phase**
  at constant P and T

$$dG = \sum \mu_i dn_i + d(\gamma A) + EdD + \ldots$$





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Energy and Interaction

- Cluster, nanoparticle, microparticle

  The shift of chemical bonding energy.. magnetic, optical

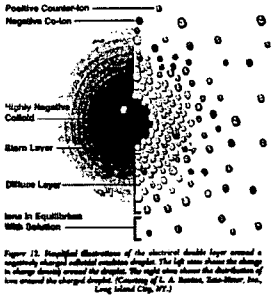
- Electrostatic interaction

  Electrical double layers, DLVO theory

- AFM (Israelachvili, 1985)

- Surface tension and size

  Young-Laplace eqn. $\Delta P = 2\gamma/r$



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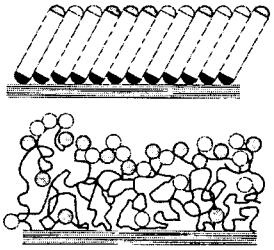
Chemical Treatment of Surface

- Surface adsorption
  - Molecular ions
  - Surfactants or adhesives
  - Polymers
  - Biomolecules
  - Particles



- Surface charge
- Surface activation

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Contact angle

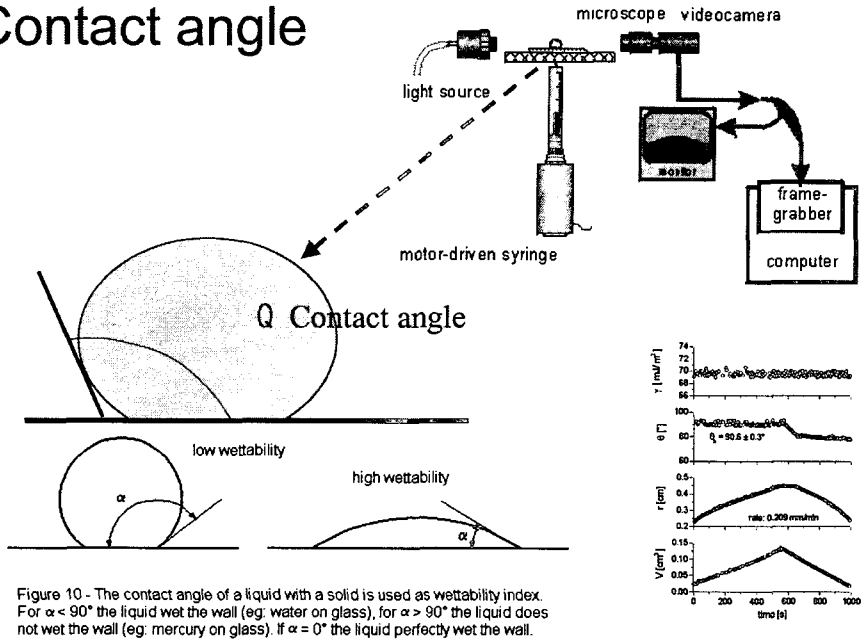


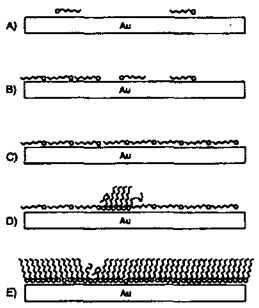
Figure 10 - The contact angle of a liquid with a solid is used as wettability index. For $\alpha < 90°$ the liquid wet the wall (eg: water on glass), for $\alpha > 90°$ the liquid does not wet the wall (eg: mercury on glass). If $\alpha = 0°$ the liquid perfectly wet the wall.

Response and Function of nanosystems

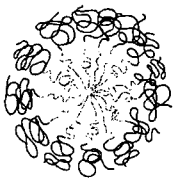
- Target sensitive
- Thermo-sensitive
- pH sensitive
- Photosensitive
- Electric (magnetic) field sensitive
- Surface force sensitive

The colloidal process:

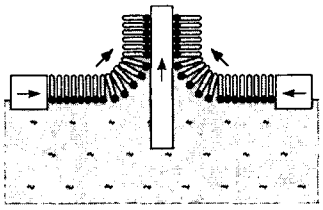
- Self assembly monolayer
- Block copolymer
- LB film



Schematics for the formation of SAM



Schematic of a block copolymer micelle



Deposition of a floating monolayer on a solid substrate

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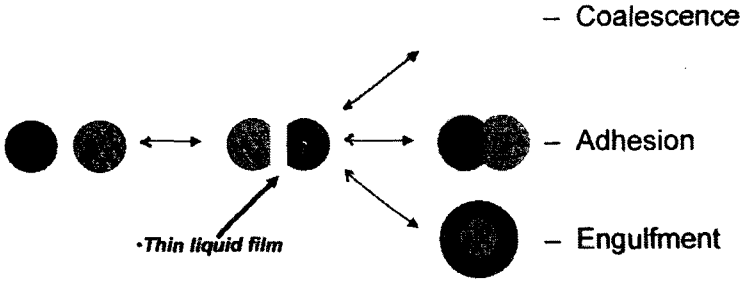
Unstable drop formation

- Coalescence: when liquids are miscible
- Adhesion : immiscible
- Engulfment : "



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Nanotech approach for DDS

Position
Shape & Size
Function
Cost

Building Blocks
Self-assembly
Architecture
Fabrication
(or replication)

LC, lipids
Copolymers
Polypeptides,
proteins

Modification
Functionalize

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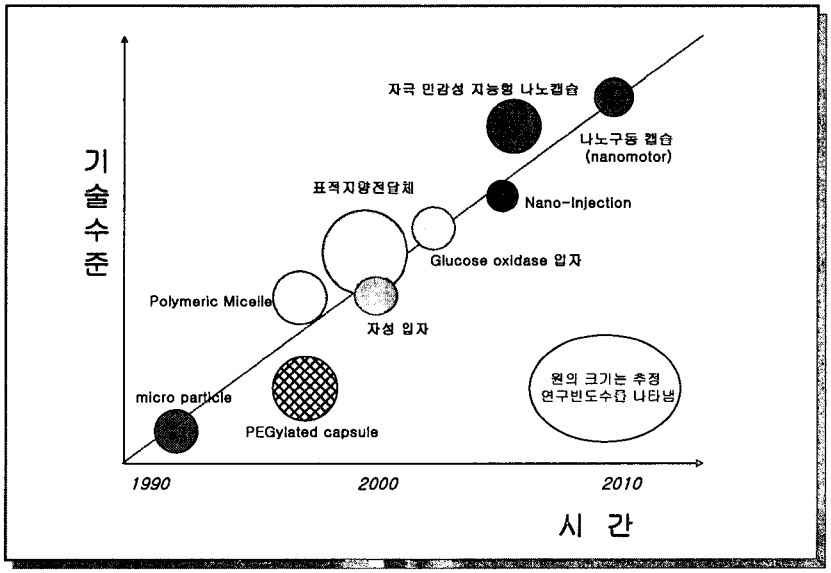
Technology Road Map



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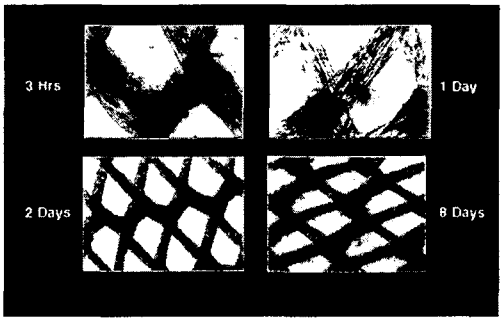
생분해성 및 생체적합성 물질
Biodegradable and Biocompatible Materials

1. 생분해성 고분자:

- ✓ Good biocompatibility, controllable biodegradability
- ✓ Relatively good processability
- ✓ The degradation time can be controlled from weeks to over a year with changes in the ratio of monomers and the processing condition.



- ✓ Poly(D,L lactide-co-glycolide) (PLGA), Polycaprolactone, etc.

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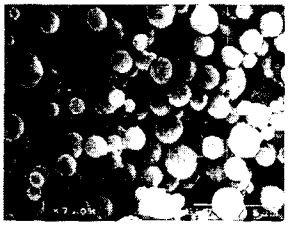
2. Polysaccharides series :

- ✓ Polymers of monosaccharides
- ✓ *May be linear or branched*
- ✓ Biodegradability, biocompatibility
- ✓ Cellulose, dextrin, hyaluronic acid, starch and alginate etc.

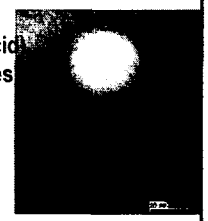


Chitosan Microsphere

Hyaluronic acid

3. Poly(amino acid)s series:

Poly(amino acid) nanoparticles



- ✓ Protein-like structure, Biodegradable
- ✓ Absence of toxicity, antigenicity and immunogenicity : biomedical polymer
- ✓ Attractive candidate for therapeutic agent delivery
- ✓ Poly(aspartic acid), Polyasparagine, Poly(L-lysine), etc.

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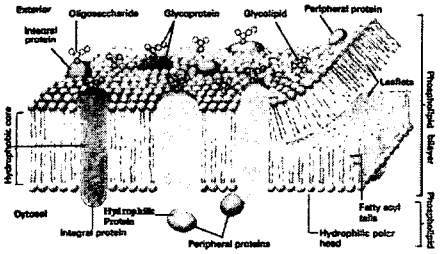
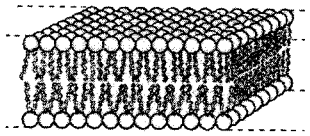
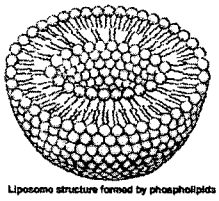
4. Lipid (Liposome): Simple Model for Cell Membrane



Simple modeling



Lipid bilayer

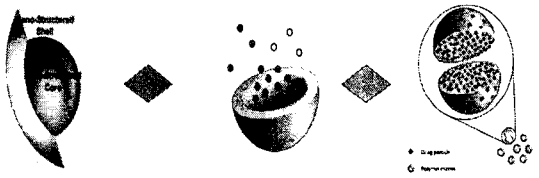


Liposome

Liposomes (lipid vesicles) are spherical, self-closed structures composed of curved lipid bilayers which entrap part of the solvent into their interior

Definition of Nano / Microcapsule

Small particles that contain an active agent or core material surrounded by a coating or shell



Classification of Nano / Microcapsules by Size

Nanocapsule/Nanosphere	*Microcapsule/Microsphere*	*Macrocapsules*
< 1 ㎛	*1 - 1000 ㎛*	*> 1000 ㎛*

Nano/Microencapsulation: Objectives and Application

Objectives	Applications
- Reduce adverse/toxic effect - Control of release of Material - Enhance material stability - Mask the taste of bitter compounds - Make liquids behavior like solids - Reduce volatility or flammability of liquid - Alter surface properties of materials	- Drug Delivery - Cosmetic - Food - Agricultural - Chemical

Release mechanism

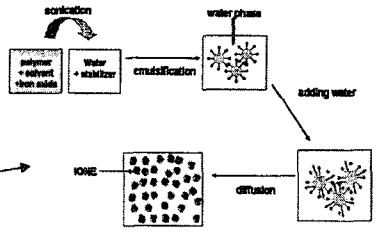
Rupture, Melting, Swelling/Dissolution, Degradation, Diffusion of solute

I. Nano/microcapsules

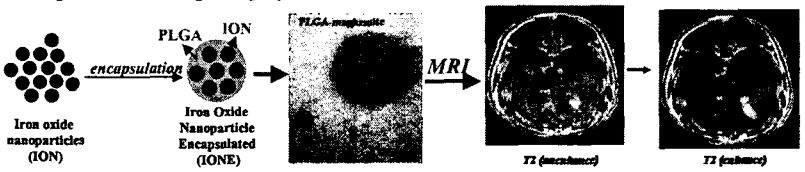
Mothod of Nano/Microencapsulation

Coacervation

- **Interfacial polymerization: emulsion, capsule wall formation**
- **In- situ polymerization**
- **Spray drying**
- **Multiple emulsion polymerization**
- **Emulsification-Diffusion Method**
- **Solvent-Evaporation Method**



- ***Encapsulation through biopolymer***



Ref. Jong-Duk Kim et al, 'Nanoparticles of magnetic ferric oxides encapsulated with PLGA and their application as MRI contrast agent', *Journal of Magnetism Magnetic Materials*, vol. 272-276, 2004, 2432.

Surface Modification for MR molecular image

Tat-, Transferrin-, Arginine

1. Ralph Weissleder et al, MRM, 37, 885-890 (1997)
2. Ralph Weissleder et al, Nature Medicine. vol. 6, 3, (2000)
   - Transferrin – MION
3. Ralph Weissleder et al, Bioconjugate Chem., 10, 186-191, (1999)
   - Tat peptide– MION
4. Ralph Weissleder et al, Radiology. 221. 244-250. (2001)
   - Transferrin- MION for MRI contrast agent
5. Ralph Weissleder et al, Nature Biotechnology, 18, 410-414. (2000)
   - Tat peptide-derivatized magnetic nanoparticle
6. Jong-Duk Kim et al, *Journal of Magnetism Magnetic Materials*, vol. 272-276. 2432 (2004)
   - Fe_3O_4-PLGA, r-Fe_2O_3-PLGA (IONE)
7. Jong-Duk Kim et al, *31th CRS*, U.S.A., June, Proceeding 703 (2004)
   - Peptide-conjugated IONE (Tat, Arginine peptide)

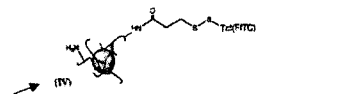
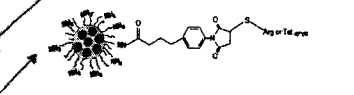
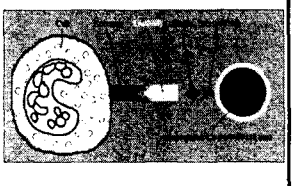
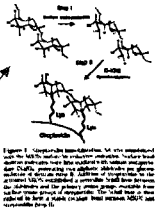


Figure 1. Synthetic scheme of superparamagnetic iron oxide-Tat peptide conjugate



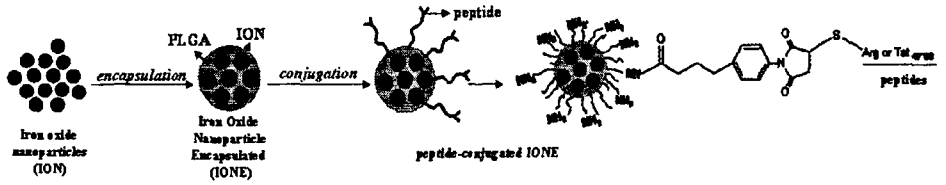


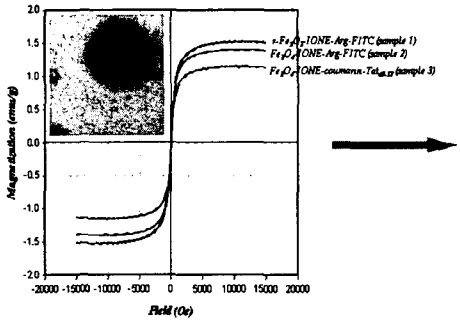


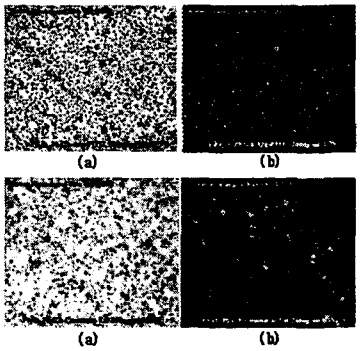
Streptavidin - biotin

1. Ralph Weissleder et al, Bioconjugate Chem., 7, 311-316, (1996)
2. Stephen Mann et al, Chem. Mater., 11, 23-26, (1999)

Surface Modification for MR molecular image







세포내로 전이된 자성입자 (a) 와 나노캡슐 (b)
(Cell line : stem cell)

Ref. Jong-Duk Kim et al, *Journal of Magnetism Magnetic Materials*, vol 272-276, 2432 (2004)
Jong-Duk Kim et al. *37th CRS*, U.S.A., June, Proceeding 703 (2004)

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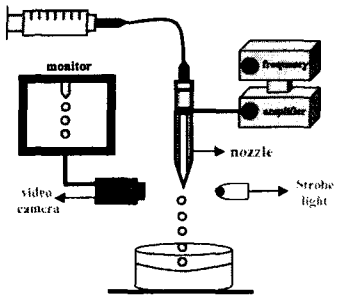
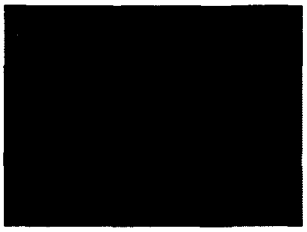
Bioadhesive Alginate-WGA Microparticles



Piezoelectric ejection process

The microparticles had avaerage diameter of 60~80 ㎛.



Encapsulation efficiency= 61.02%

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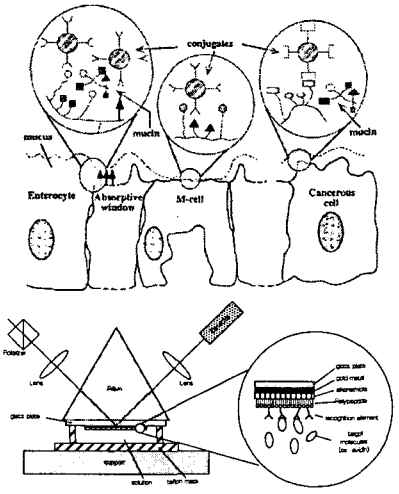
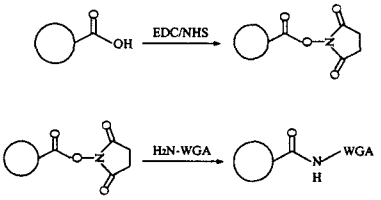
Bioadhesive Alginate-WGA Microparticles

Figure. Main possibilities of interactions mediated by ligand-receptor pairs



Preparation of WGA-microparticle conjugates



The amount of WGA bound to microparticles were about 34.3μg/mg when SGPAA microparticles, while little amount of WGA (4.3μg/mg) was bound to soluble starch microparticles. The coupling efficiency of WGA was 25.7% of initial amount of WGA.

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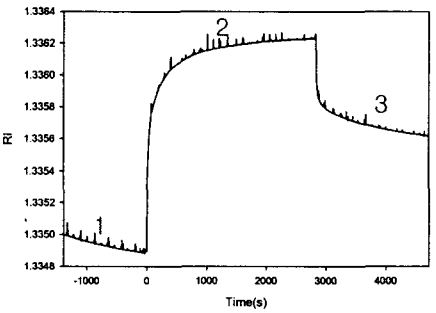
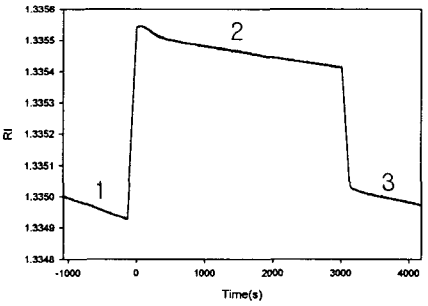
Interaction with PM immobilized SPR sensor

Alginate-WGA microparticles



Alginate microparticles



(1) The new baseline with PBS 7.4 containing 0.1 % Triton X-100
(2) The application of alginate-WGA MP and alginate MP in PBS 7.4 containing 0.1 % Triton X-100
(3) flow of PBS 7.4 containing 0.1% Triton X-100 for washing.

$k_d=6.924\times10^{-8}\ s^{-1}$

$k_a=2.440\times10^{-7}\ g^{-1}Ls^{-1}$

$K=k_a/k_d=3.523 g^{-1}L$

$k_d=3.605\times10^{-8}\ s^{-1}$

$k_a=5.752\times10^{-8}\ g^{-1}Ls^{-1}$

$K=k_a/k_d=1.60 g^{-1}L$

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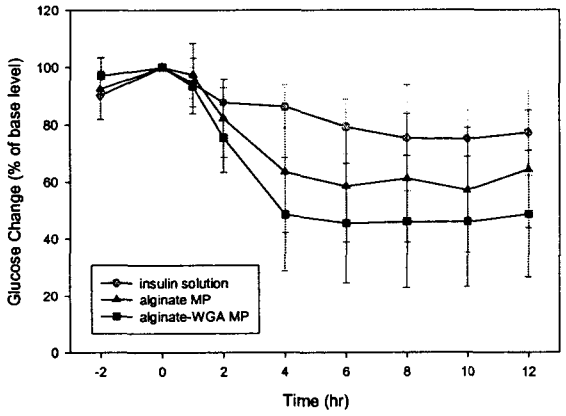
In vivo studies



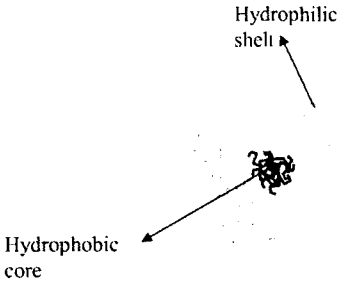
Oral administration

Following formulations were administered to rats orally: (1)control insulin solution (insulin dose 50 IU/kg), (2)alginate MP (insulin dose 50 IU/kg), (3) alginate-WGA MP (insulin dose 50 IU/kg).

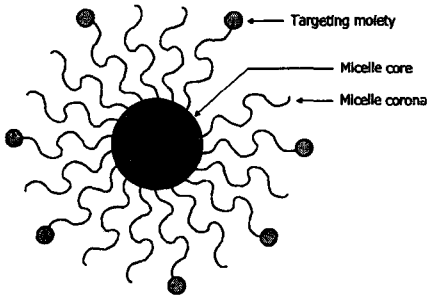
Measurement of glucose level

Blood samples were collected from tail vein at -2(2h before oral administration), 0,1,2,4,6,8,10,12h and glucose level was measured by Glucotrend II (Roche, Germany).

II. Self-assemblies



Self-assembly of Amphiphilic Polymers in aqueous solution



Key Physical Parameters
Surface density of hydrophilic chains
Charge
Hydrophilicity
Block length
Derivatization (targeting moiety)

Factors Affected
Biodistribution
Pharmacokinetic Parameters
Biocompatibility
Steric Stability
Specificity
Surface Adsorption to Proteins
Adhesion to Biosurfaces

- § Hydrophobic core : solubilizes hydrophobic molecules
- § Hydrophilic shell : make entire assembly water soluble
- § Nanoparticles : colloidal particles ranging in size from 10 to 1000nm
- § Self-assembly of polymeric amphiphiles
  - Block copolymer
  - Graft copolymer
  - Hydrophobically modified water-soluble polymer : bile salt, hydrophobic polymers, phospholipid, alkyl chain
- § Advantage
  - Nanosize
  - Higher surface/volume ratio
  - Drug targeting

Graft copolymer systems

Comb-like polymer

Macromonomers containing a functional polymerizable chain

Polystyrene-graft-Poly(methyl methacrylate)

M. Matsuda et al. Macromolecules.19, 2253 (1986)

Polyisoprene-graft-Polystyrene

P. Kratochvil et al. Makromol. Chem., 190. 2967 (1989)

Poly(acrylic acid)-graft-polystyrene

S.E. Webber et al, Macromolecules. 31. 1773 (1998)

Eisenberg group for "crew-cut" micelle

Macromolecules. 30, 1001 (1997)

Poly(L-lysine)-graft-PLGA

T.G. Park et al, J. Controll. Rel. 82, 159 (2002)

Block copolymer systems

Poly(lactic acid)-b-poly(ethylene glycol)

Poly(lactic-co-glycolic acid)-b-PEG

R. Langer et al, Science. 263, 1600 (1994)

Poly(L-leucine-b-L-glutamate)

Poly(ethylene oxide-b-caprolactone)

S. Wang et al, Macromolecules. 32, 590 (1999)

Poly(styrene-b-ethylene oxide)

Poly(styrene-b-sulfonated isoprene)

Y. Morishima et al, Langmuir. 15, 454 (1999)

Poly(ethylene glycol)-b-Poly(aspartic acid)

Poly(ethylene glycol)-b-Poly(L-lysine)

K. Kataoka, Macromolecules. 28, 5294 (1995)

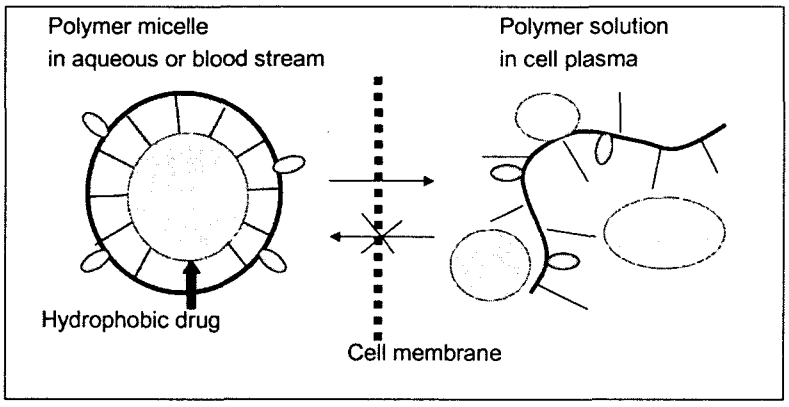
아미노산 유도체를 이용한 나노입자 시스템

(Self-aggregates of hydrophobically modified poly(amino acid)' derivatives)

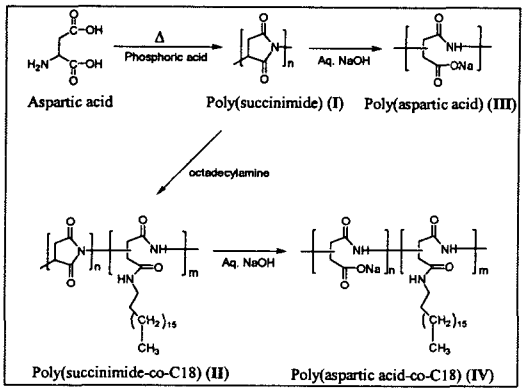
- [1,2]Poly(aspartic acid)-g-alkyl chains (PAsp-g-alkyl)
- [3]Poly(asparagine)-g-poly(carprolacone) (PAsn-g-PCL)
- [4]Poly(2-hydroxthyethyl aspartamide)-g-dehydrocholic acid(PHEA-g-DHA)
- [5]Proteinoid-g-cholesterol (Chol-TP)

[1]H.S. Kang, M.S. Shin, J. –D. Kim, J. W. Yang, Polym. Bull. 45 (2000) 39-43
[2]H.S. Kang, S.R. Yang, J.-D. Kim, S.H. Han, I.S. Chang, Langmuir 17 (2001) 7501-7506
[3]J. H. Jeong, H.S. Kang, S.R. Yang, J.-D. Kim, Polymer 44 (2003) 583-591
[4]S.R. Yang, J.H. Jeong, K. Park, J.-D. Kim, Coll. & Polym. Sci. 281(2003),852-861
[5]S.K. Bae, J. D. Kim, J. Biom. Material Research 24 (2002) 282-290

Design concept of polymer micelle



Poly(α,β-aspartic acid) modified with long alkyl chains



(PAsp-g-alkyl)

Degree of substitution

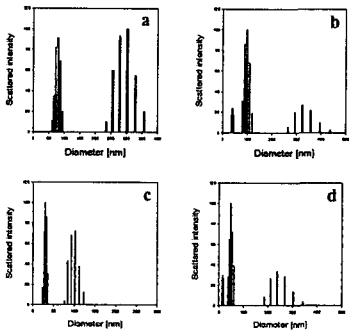
Grafting mole % (DS) was determined by ^{1}H-NMR and elemental analysis.

Degree of substitution	Mole ratio (succinimide unit / ODA)	DS by ^{1}H-NMR	Weight fraction of alkyl groups
0	100/0	0 %	0 %
2%	98/2	0.7 %	1.6 %
5%	95/5	2.8 %	6.3 %
8%	92/8	5.1 %	11.1 %
10%	90/10	8.8 %	18.3 %

Self-aggregation

Degree of substitution	Mole ratio (succinimide unit / ODA)	Elution time (min)[1]	Number-average mean diameter
0	100/0	28.97	-
2%	98/2	28.63	77.4nm
5%	95/5	29.02	31.1nm
8%	92/8	29.12	28.0nm
10%	90/10	29.18	25.7nm

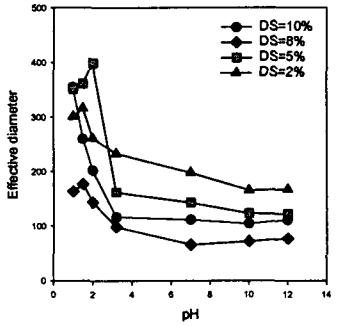
1. Determined by size exclusion chromatography (Waters 626 system with Ultrahydrogel Linear and Ultrahydrogel 120 columns, 0.1M $NaNO_3$ at the flow rate of 0.5 ml/min)

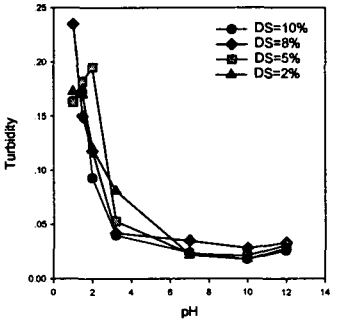


The size of self-aggregates decreases in PBS solution (concentration: 1%) as DS increases

- Degree of substitution of octadecyl group
  (a) : DS=2%, (b) : DS=5%
  (c) : DS=8%, (d) : DS=10%

pH-dependence I





Diameters of micelles are unchanged in most physiological conditions, but increased near pH 2, because of the surface charge of backbone polymers.

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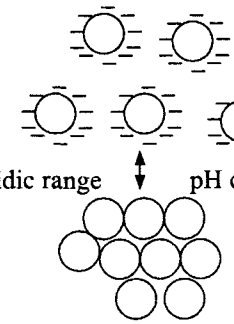
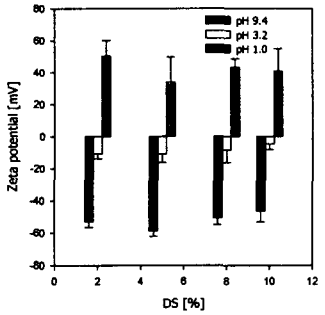
pH-dependence II

Neutral & basic range



Acidic range ↕ pH change



In physiological condition, micelles are well dispersed because the surface potentials are negative, but near pH 2, zeta- potentials are close to zero for most DS and the micelle dispersion are destabilized, indicating DLVO theory applicable. Also, the chain stiffening would be expected by the dehydration due to discharge.

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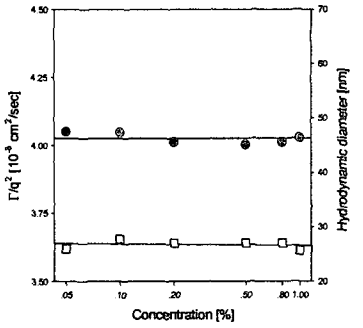
Concentration effect

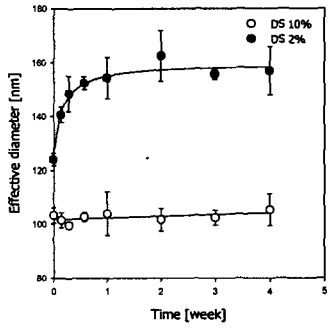
- Formation of the inner hydrophobic domains by self-association
- Stable aggregate system by octadecyl groups as a role of crosslinker and anionic charge repulsion

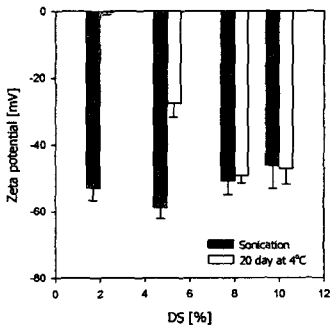
  - Diffusion coefficient is obviously independent of the concentration.
  - The size of primary aggregates was maintained constant.
  - Diffusion coefficient at infinite dilution : 4.025×10^{-8} cm²/sec



Diffusion coefficient (□) and diameter of primary aggregates (○) of PASP-C18 (DS=10%) as a function of the concentration (temperature : 25°C, detection angle : 90°)

Time stability of PAsp-C18





Aggregates of 2% DS were loosely formed and reconstituted to a thermodynamically stable configuration as time lapsed, while that of 10% DS were stably maintained. As it swells, the surface charge disappears.

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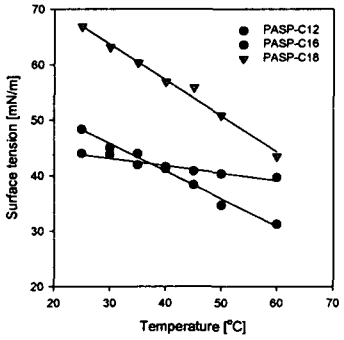
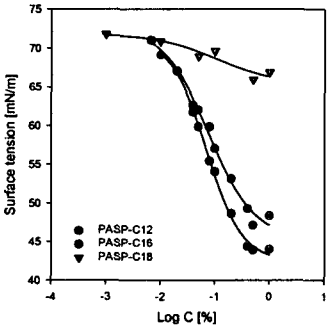
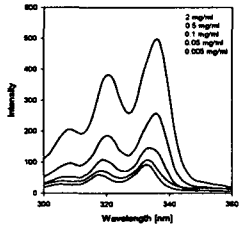
Surface tension

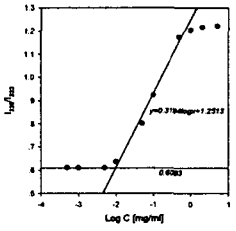




Graft copolymers of PAsp-C18 exist as aggregates rather than at the air-water interface to lower surface tension, while those of C12 and C16 not only form aggregates, but also exist at the air-water interface.

Formation of hydrophobic domains





As the polymer concentration increased, the intensity of shifted band increased. The plot of ratio of I336/I333 vs concentration gives a sharp change indicating the formation of aggregation, called CAC(critical aggregation concentration) corresponding to the CMC(critical micellization concentration).

Aggregation number

Degree of Substitution	PAsp-C18 2%	5%	8%	10%
N_{alkyl}[1]	0.88	3.5	6.4	11.0
N_{Pasp}[2]	16.8	10.7	6.2	4.0
Aggregation N_{alkyl}[3]	14.8	37.6	39.4	44.4
Aggregation N_{Pasp}[4]	25.5	52.7	45.4	36.1
N_{domain}[5]	1.5	4.9	7.3	9.0

1 : Experimentally determined number of alkyl chains per one polymer chain
2 : Number of polymer chains required to form one hydrophobic microdomain
3 : Aggregation number of alkyl chains per one hydrophobic microdomain
4 : Aggregation number of polymer chains per one aggregate
5 : Number of hydrophobic microdomains per one aggregate

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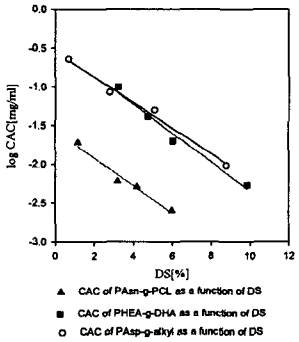
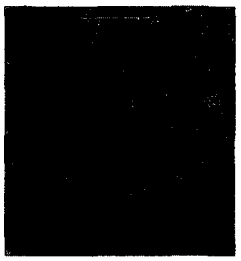
아미노산계 초미세 나노입자

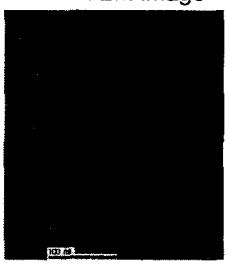
Critical aggregation concentration



TEM image

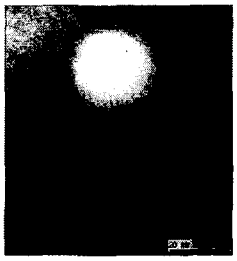


PHEA-g-DHA



PAsn-g-PCL

Figure shows the CAC of three poly(amino acid) graft copolymer of PAsp-g-alkyl, PHEA-g-DHA and PAsn-g-PCL. In fact, the CACs of PAsn-g-PCL are as small as 1/10 of the others. Since the PCL side chain forms crystalline phase, it is expected that the graft copolymer may have the small CAC.

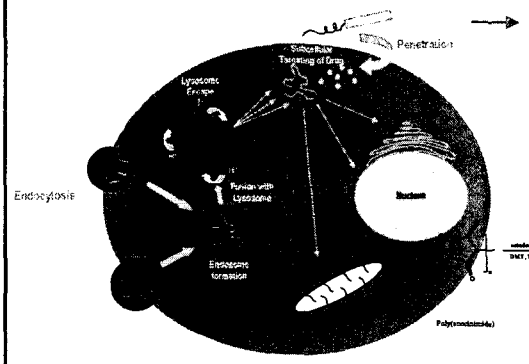


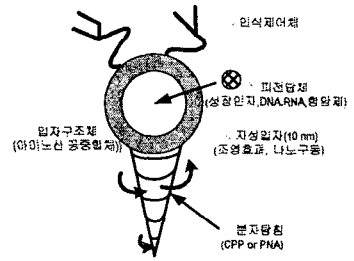
PAsn-g-PCL

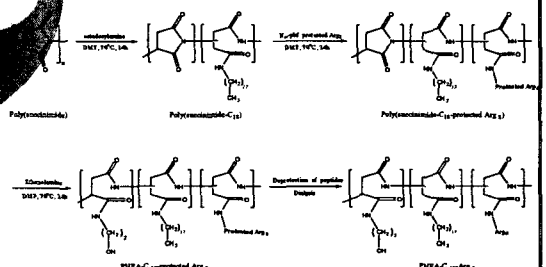
연구목표: 나노 닥터의 구현

Intracellular delivery carrier
(PHEA-g-alkyl-Arg_8)

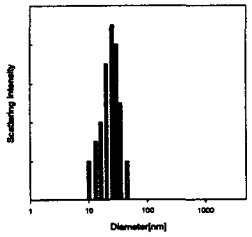
Transport of macromolecules into cell



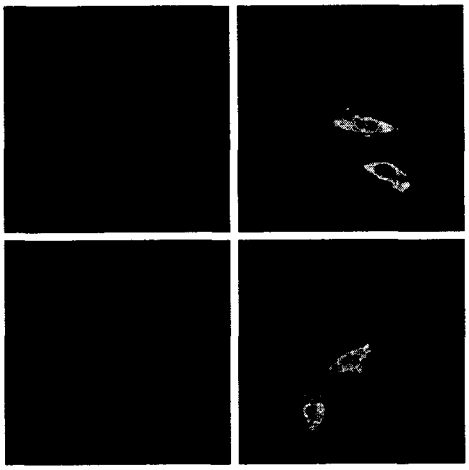




Intracellular delivery carrier (PHEA-g-alkyl-Arg_8)

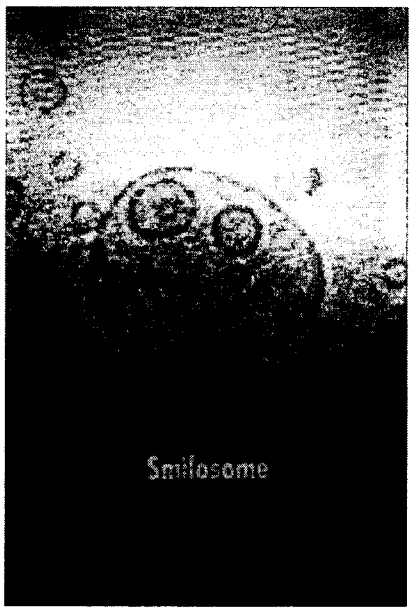


Size distribution of PHEA-C_{18}-Arg_8

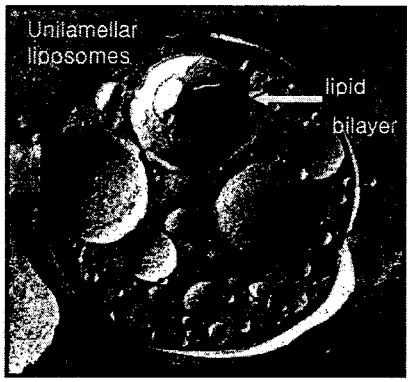


Confocal laser scanning microscopy images of HeLa cells after incubations with 50μg/ml of (a)control polymer(PHEA-C_{18}-FITC) at 37°C for 1h (b)PHEA-C_{18}-Arg_8-FITC at 37°C for 1h (c)control polymer(PHEA-C_{18}-FITC) at 4°C for 1h (d) PHEA C_{18}-Arg_8-FITC at 4°C for 1h

III. Liposome



Shape of Liposome



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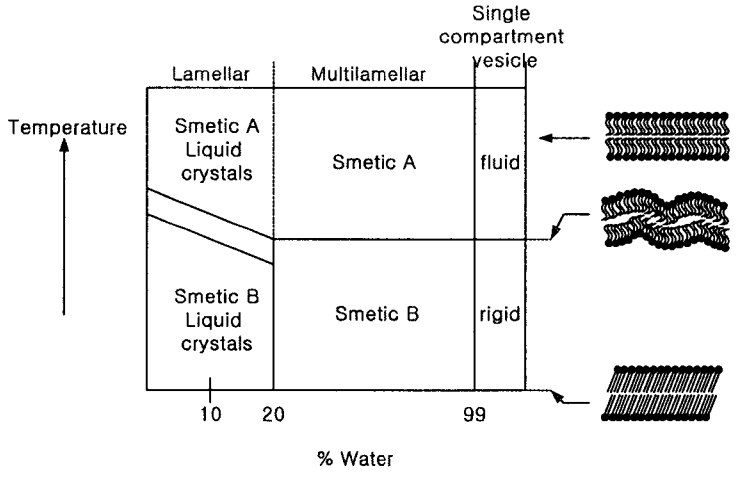
Phase transition



Schematic representation of a phospholipid-water-temperature diagram

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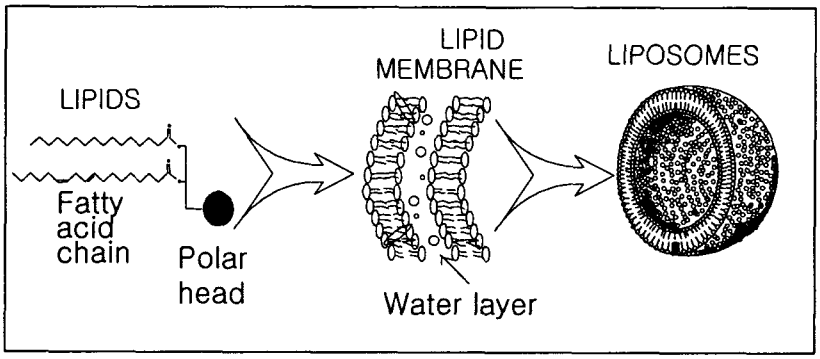
Formation of liposomes in an aqueous medium



Advantage of Liposomes as Drug Carrier

-Non-toxic, Biodegradable
- Reduction in allergic and immunological reaction
- Controlled drug release
-Controllable in preparation
(Entrapment, Loading, Size, etc)

Disadvatages

-Stability

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전자 현미경 사진

SEM (Etching)	TEM (Negative staining)
Liposomal suspension --> Freezing ---> *Etching* ---> *Coating wih C/Pt*	Liposomal suspension + Heavy Metal ---> *Air drying*
	
X 1000, 10-20 ㎛	115000, 0.2-0.5 ㎛

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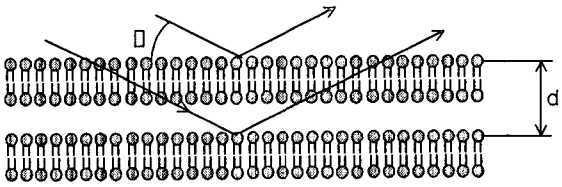
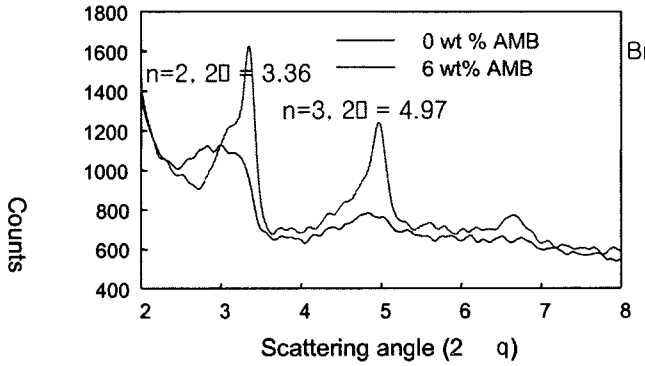
X-ray Diffraction





Bragg's Law

$n\lambda = 2d \sin\theta$

$\lambda = 1.5418$ Å

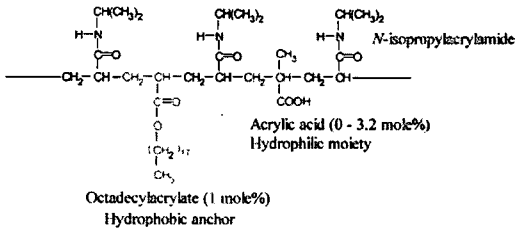
n=2, 2θ = 3.356

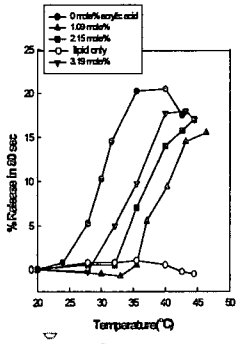
n=3, 2θ = 3.356

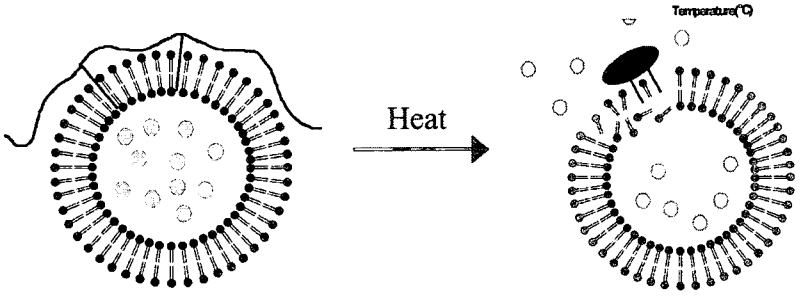
d = 53 Å

Stimuli-sensitive functions

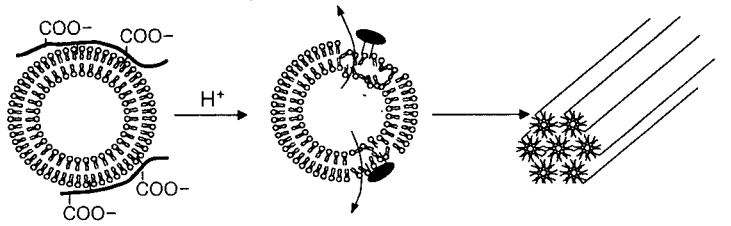
1. Temperature-sensitive Liposomes







2. pH-sensitive liposomes



Liposomes coated with Poly(NIPAM-co-MAA) at B.T and neutral pH

low pH
v/la = 1 (PC)

v/la > 1
(Unsaturated PE)

v/la = 1 (PC)	Stable lamellar	H^+	Stable lamellar	Remains intact → Liposomes
v/la > 1 (Unsaturated PE)	Stable lamellar	H^+	Unstable	Changes to → Hexagona II

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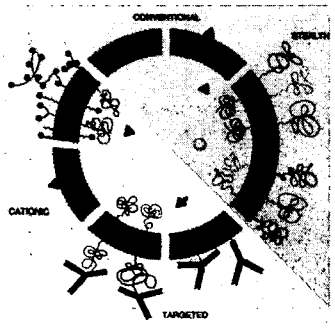
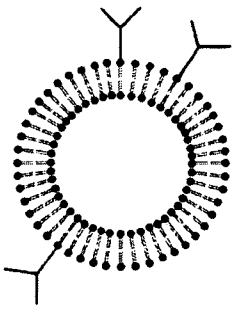
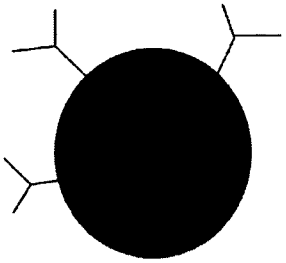
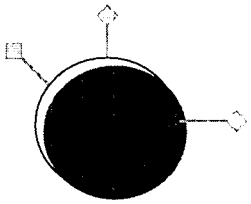
Target-sensitive Liposome









Ligand-Receptor Interaction

- ❖**Lock-and-key model**
- ❖**Hydrogen bonding**에 의한 구조인식
- ❖**Hydrophobic interaction**에 의한 결집체 형성

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Summary

- Surface chemistry is the most important science for nano and colloidal dimension systems.
- Biocompatible materials can be used for nano and colloidal systems of foods, cosmetics and pharmaceutics.
- Surface energy is the key factor for formation of shape, size, interaction and structure.
- System response can be implanted by modifying the surface of nano/micro-systems.
- Microcapsule, self-assembly, and liposome can be used for specific carriers.

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