Molecules and Particles as Nano- and Micro-scale Drug Carriers

Last time: molecular switches
Molecular railways
Proteins as motors in nanodevices

Today: nano- and micro-particle drug carriers

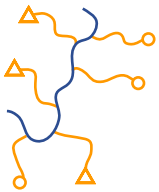
Reading:

D.A. Hammer and D.E. Discher, 'Synthetic cells- Self-assembling polymer membranes and bioadhesive colloids,' *Annu. Rev. Mater. Res*., **31**, 387-404 (2001)

T.M. Allen and P.R. Cullis, 'Drug Delivery Systems: Entering the Mainstream,' *Science* **303,** 1818-1822 (2004)

ANNOUNCEMENTS:

Carriers

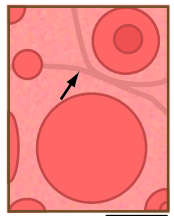


Polymer-durg conjugates

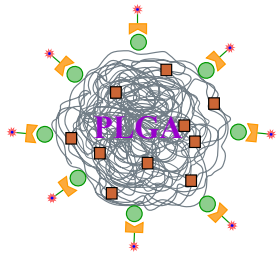
Image removed due to copyright reasons. Please see: Kakizawa, Y., and K. Kataoka. "Block Copolymer Micelles for Delivery of Gene and related compounds." Adv Drug Deliv Rev 54 (2002): 203-22.

Micelles

Vesicles
- Liposomes
- Polymerosomes

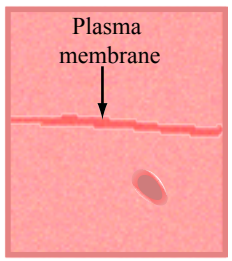


Nanoparticles



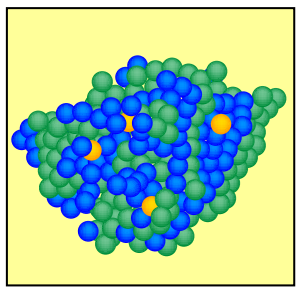
Microparticles

Biological Structures

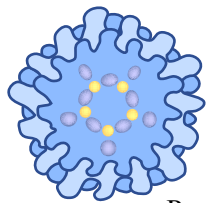


Thickness of lipid bilayer

Proteins



Viruses



Actin Fibers

Packed chromosomes

Protein Complexes

Organelles

Figure by MIT OCW.

Objectives of molecular and particulate drug carriers:

- (I) Alter pharmacokinetics
  - How long is the drug active, and at what concentration is it present?
- (II) Alter biodistribution
  - Which tissues receive drug?
    - Enhance uptake at target tissue, reduce uptake where it is not desirable
- (III) Provide drug reservoirs
  - Fewer injections, sustained level of therapeutic

Table removed due to copyright reasons.

Please see: Table 1 in Allen, and Cullis. *Science* 303 (2004): 1818.

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(1) EXTRACELLULAR BARRIERS:
Delivery of molecules to tissues from circulation, skin, or mucosal surfaces

ORAL

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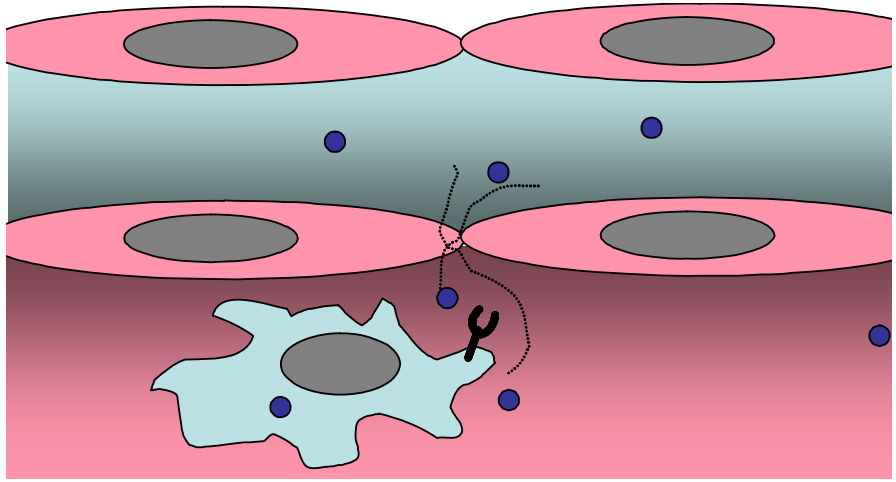
Please see Neutra, M. R, and P. A. Kozlowski. "Mucosal Vaccines: The Promise and The Challenge." *Nat Rev Immunol* 6 (2006): 148.

INTRAVENOUS



Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

SKIN

NASAL/LUNG MUCOSA

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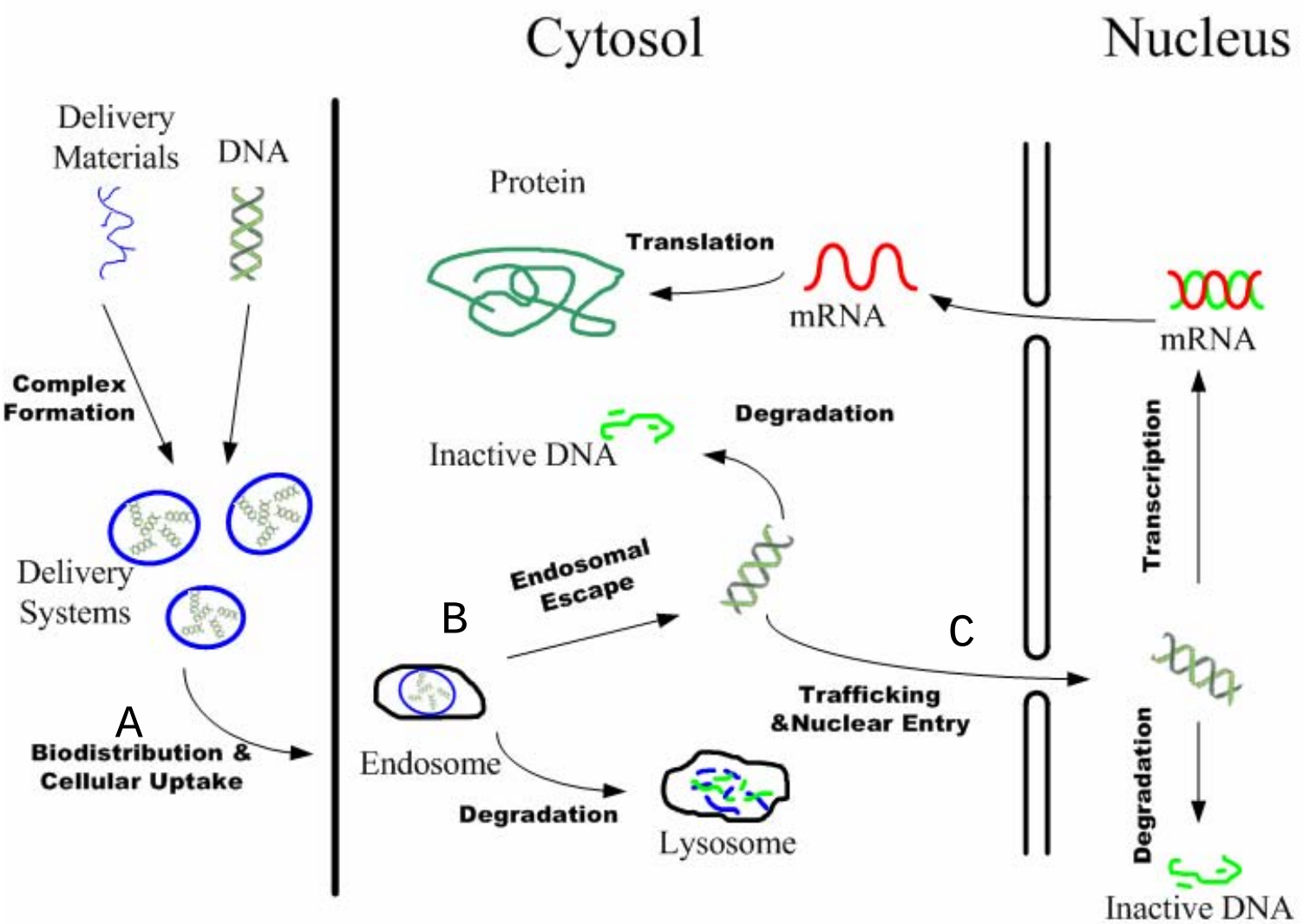
Please see Neutra, M. R., and P. A. Kozlowski. "Mucosal Vaccines: The Promise and The Challenge." *Nat Rev Immunol* 6 (2006): 148.

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(2) INTRACELLULAR BARRIERS: Intracellular drug delivery

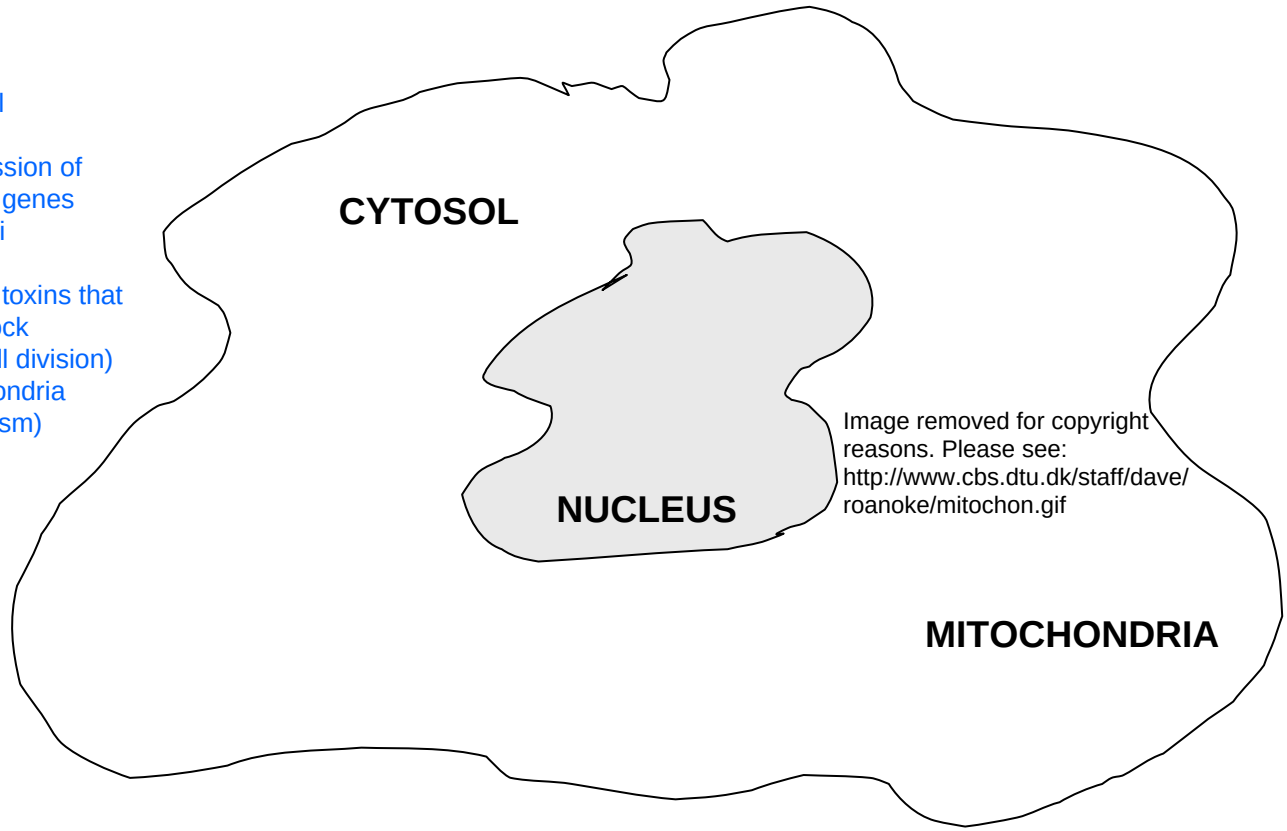


Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(2) INTRACELLULAR BARRIERS: Intracellular drug delivery

Applications requiring delivery of molecules to intracellular compartments:

- Vaccines
  - MHC restriction of T cell
- Gene delivery
  - Plasmid DNA for expression of missing/foreign genes
- Anti-sense therapy, siRNA/RNAi
- Therapeutic molecules
  - Intracellular toxins (e.g. toxins that bind DNA to block transcription/cell division)
  - Drug delivery to mitochondria (affect metabolism)



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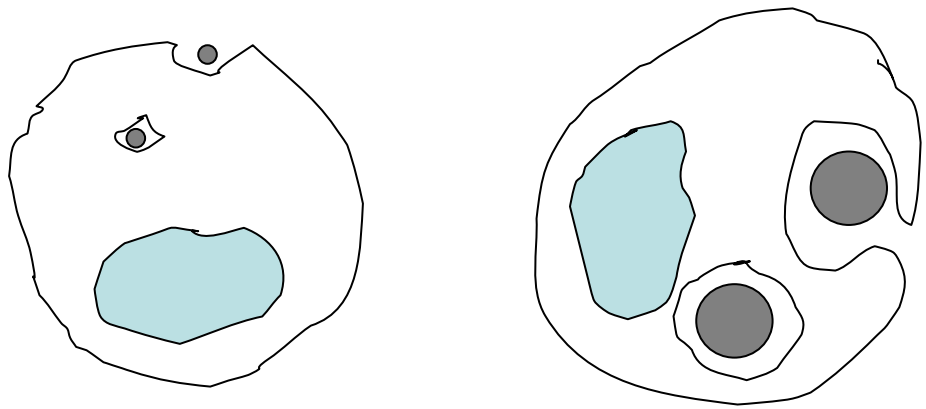
Objectives of nano- and micro-carriers:
(1) protection of cargos from premature degradation

COMPOUND	APPLICATION	EXAMPLE HALF-LIVES IN CIRCULATION	REFERENCES
Short peptides (5-20 amino acids)	Vaccine epitopes, ligands for drug targeting, peptide drugs	2 min., 5 min, 2 hrs	*J. Biol. Chem*. **48**, 48503 (2002); *J. Pharm. Sci*. **81**, 731 (1992)
Cytokines (polypeptides typically 5-20 KDa)	Regulation of tissue physiology (e.g., growth factors), disease treatment (e.g., interferon-α)	**IFN-α** 3-8 hrs **interleukin-6** 2.1 min **tumor necrosis factor** 3 min	*Nat Rev Drug Discov* **2**, 214-21 (2003)

EXTRACELLULAR CLEARANCE:

INTRACELLULAR CLEARANCE:



Protection of DNA from DNAses

Abbott laboratories anti-TNF antibody for treatment of Rheumatoid arthritis: 40 mg every 2 weeks… (active at nM conc.)

Objectives of nano- and micro-carriers: (2) Avoiding the immune system

(I) Opsonization:

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Please see: http://medtech.cls.msu.edu/ISL/immunology/opsonize.htm

Internalization is also triggered by complement
Protein adsorption can trigger opsonization (via exposure of un-natural epitopes)

(II) anti-drug/carrier antibody production:

- B cells binding to a foreign protein, drug, or particle can be triggered to produce antibodies against the drug or carrier
- Even human proteins provided in non-physiological contexts may elicit antibodies (e.g., DNA)

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Please see: Abbas, A. K., and A. H. Lichtman. *Cellular and Molecular Immunology*. San Diego, CA: Elsevier, 2005. ISBN: 1416023895.

Objectives of nano- and micro-carriers:
(3) targeted delivery to select tissues or cells

Sketch ligand-mediated binding and uptake on cells

OVERVIEW OF MOLECULAR/PARTICULATE DRUG CARRIERS: STRUCTURE, SYNTHESIS, PROPERTIES

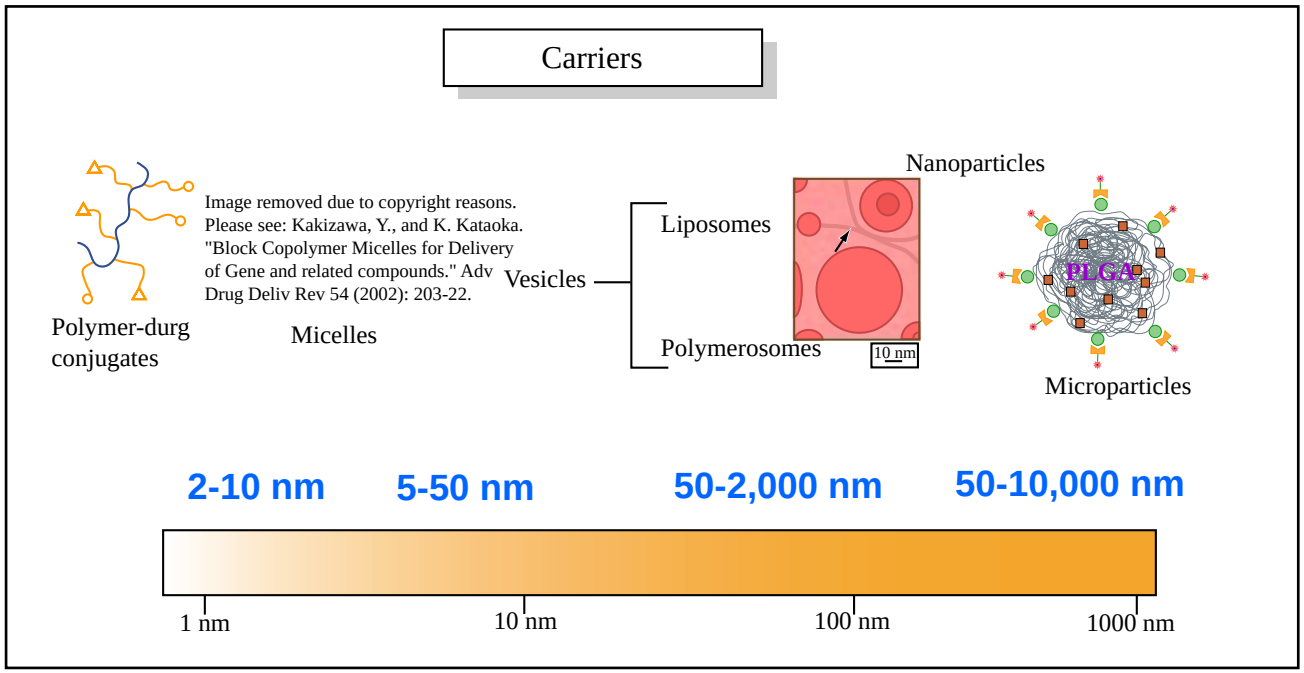

Figure by MIT OCW.

Polymer pro-drugs and markers

Role of polymeric carriers:

1. Control solubility of drug
2. Multivalency

    - High avidity binding to low-affinity receptors for detection/delivery
      Cooperative binding – $2^{nd}/3^{rd}$, … binding event is facilitated by initial ligation
    - Potent delivery on a per-molecule basis

3. Aid penetration of tissues

4. ‘stealth’ functions

Polymer pro-drugs and markers

Architecture of polymeric carriers:

SKETCH FROM ADV MATER 1995 REVIEW

1. Requires water-soluble backbone
   e.g., PEG, dextran, PHEMA

2. Drug may need to be selectively released
   nonspecific- hydrolysis of side chains
   triggered release- localized to specific microenvironment
      pH
      enzyme recognition

Polymer pro-drugs and markers

Endosomal enzyme-sensitive marker:
Fluorochromes quenched until enzyme clips backbone

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Please see: Weissleder, et al. *Nat Biotech* 17, 375 (1999).

Pro-Ile-Cys(Et)-Phe-Phe-Arg-Leu

cathepsin D substrate

Polymer pro-drugs and markers

Cell-activated polymer-fluorochrome conjugates for *in vivo* tumor imaging:

Sketch leaky tumor vasculature, conjugate uptake concept

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Please see: Weissleder, et al. *Nat Biotech* 17, 375 (1999).

Micelle carriers

Cargo-loaded micelles via polyion association:

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Please see: Figure 5 in Kakizawa, Y., and K. Kataoka. "Block Copolymer Micelles for Delivery of Gene and Related Compounds." *Adv Drug Deliv Rev* 54 (2002): 203-22.

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Please see: Kakizawa, Y., and K. Kataoka. "Block Copolymer Micelles for Delivery of Gene and Related Compounds." *Adv Drug Deliv Rev* 54 (2002): 203-22.

Micelle drug carriers

Attachment of cargo molecules to core block of micelle:

Figure removed due to copyright restrictions.

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Limitations:

Unstable at high dilution
Low cargo capacity

Further Reading

1. Torchilin, V. P. PEG-based micelles as carriers of contrast agents for different imaging modalities. *Advanced Drug Delivery Reviews* **54**, 235-252 (2002).
2. Weissig, V. & Torchilin, V. P. Drug and DNA delivery to mitochondria. *Adv Drug Deliv Rev* **49**, 1-2 (2001).
3. Kakizawa, Y. & Kataoka, K. Block copolymer micelles for delivery of gene and related compounds. *Adv Drug Deliv Rev* **54**, 203-22 (2002).
4. Torchilin, V. P. PEG-based micelles as carriers of contrast agents for different imaging modalities. *Adv Drug Deliv Rev* **54**, 235-52 (2002).
5. Harris, J. M. & Chess, R. B. Effect of pegylation on pharmaceuticals. *Nat Rev Drug Discov* **2**, 214-21 (2003).
6. Park, S. & Healy, K. E. Nanoparticulate DNA packaging using terpolymers of poly(lysine-g-(lactide-b-ethylene glycol)). *Bioconjug Chem* **14**, 311-9 (2003).
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8. Li, Y. et al. PEGylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. *J Control Release* **71**, 203-11 (2001).
9. Stolnik, S., Illum, L. & Davis, S. S. Long Circulating Microparticulate Drug Carriers. *Advanced Drug Delivery Reviews* **16**, 195-214 (1995).
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12. Halperin, A. Polymer brushes that resist adsorption of model proteins: Design parameters. *Langmuir* **15**, 2525-2533 (1999).