

Delivery of Protein Pharmaceuticals

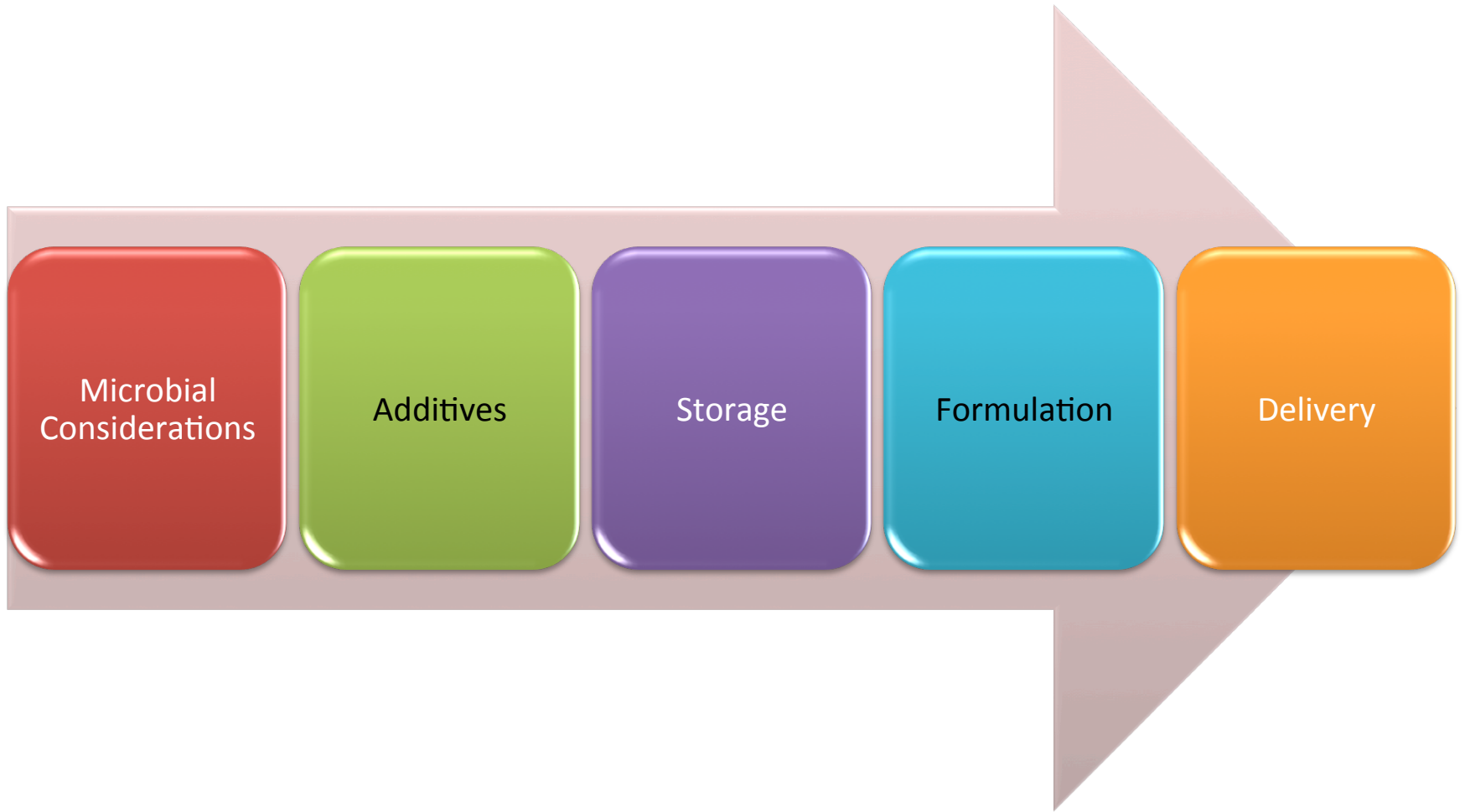
Dr. Aws Alshamsan
Department of Pharmaceutics
Office: AA87
Tel: 4677363
aalshamsan@ksu.edu.sa

Objectives of the Lecture

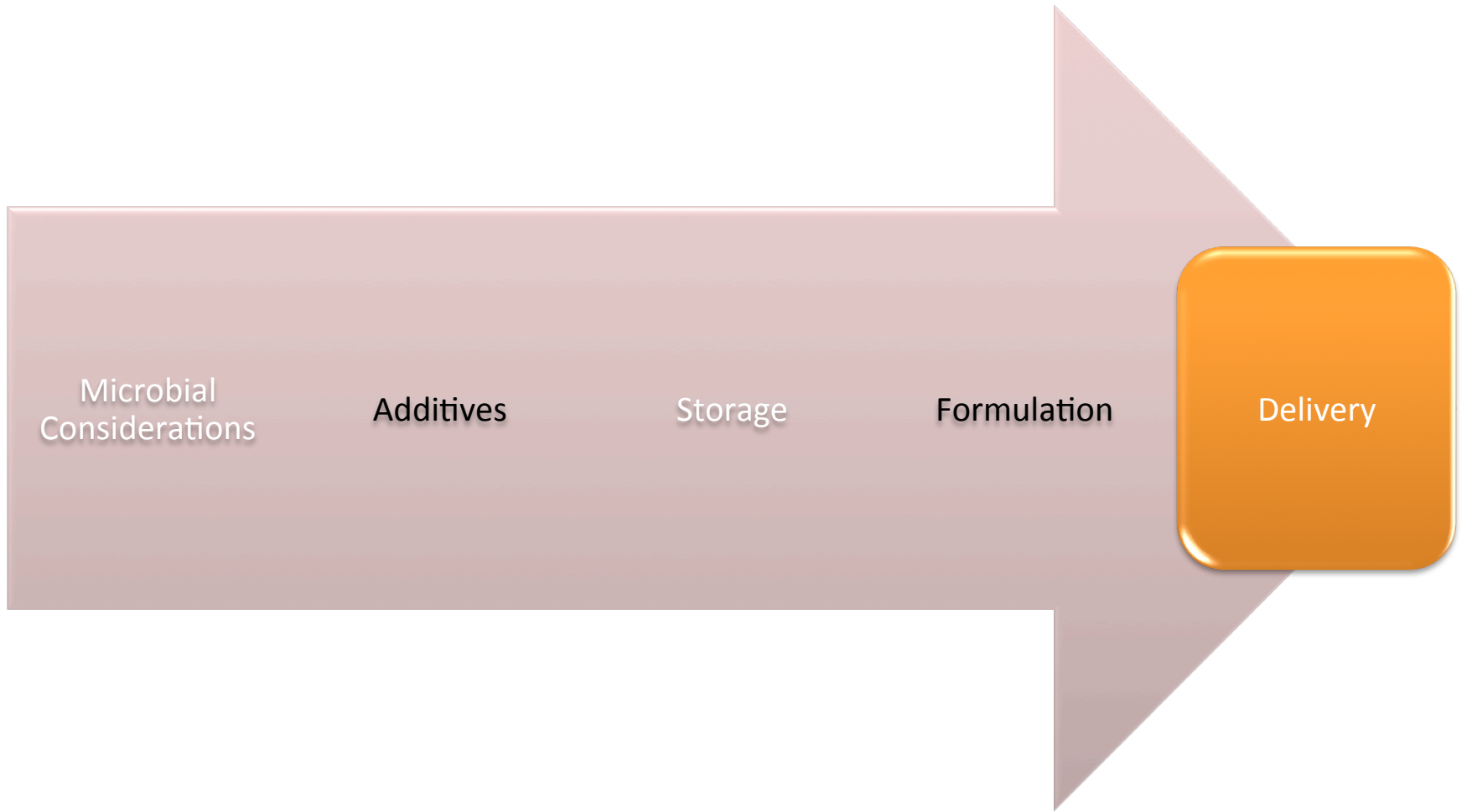
By the end of this lecture you will be able to:

1. Describe techniques for optimal protein formulation
2. Realize the importance of delivery systems for protein pharmaceuticals
3. Compare different delivery methods

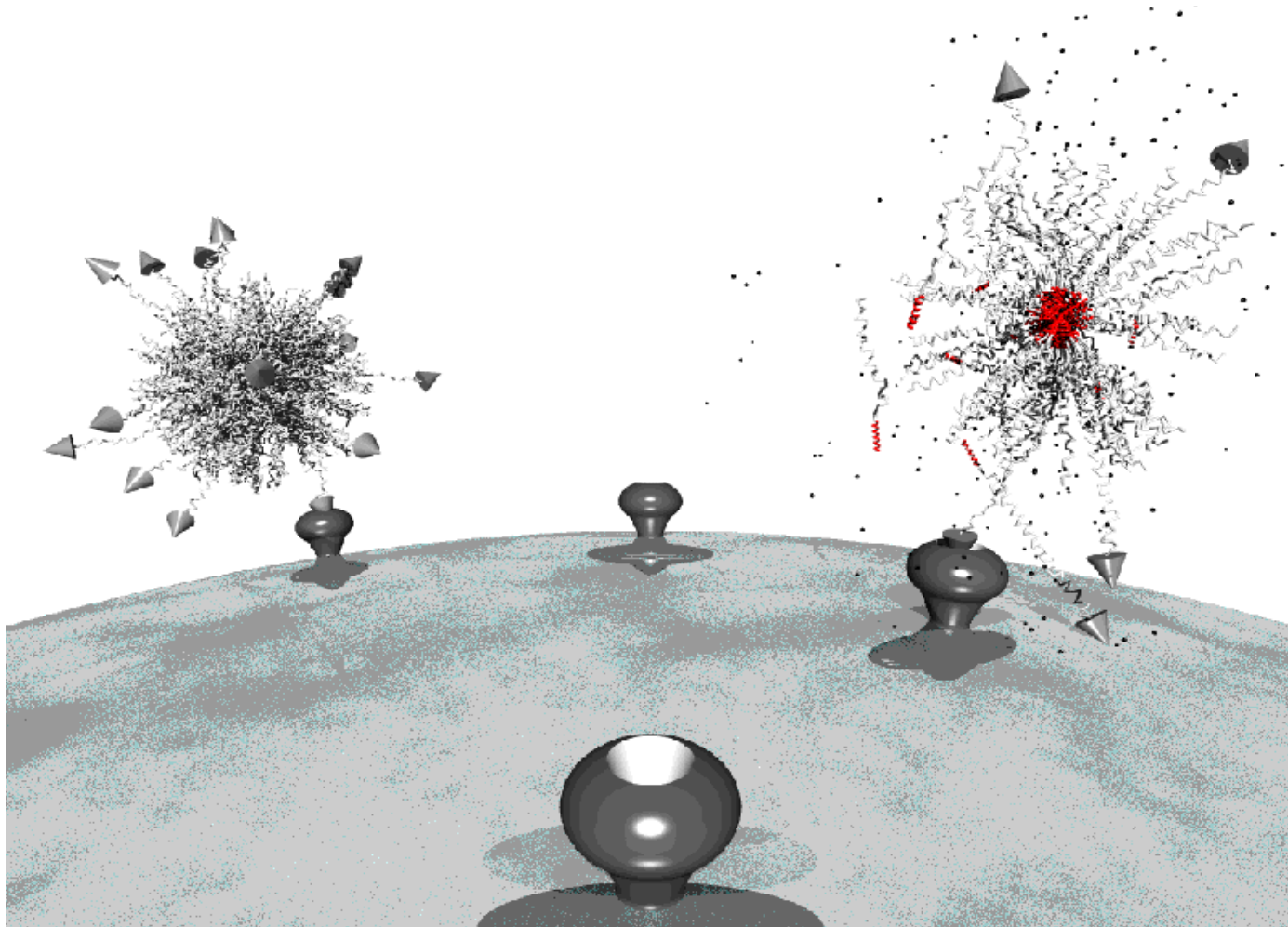
Solving the problems



Solving the problems

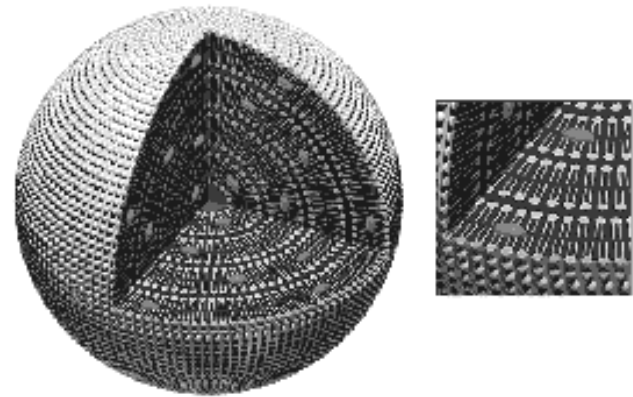
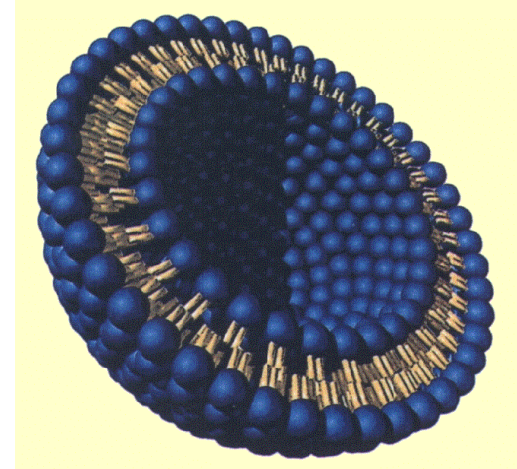


Targeted Micelles



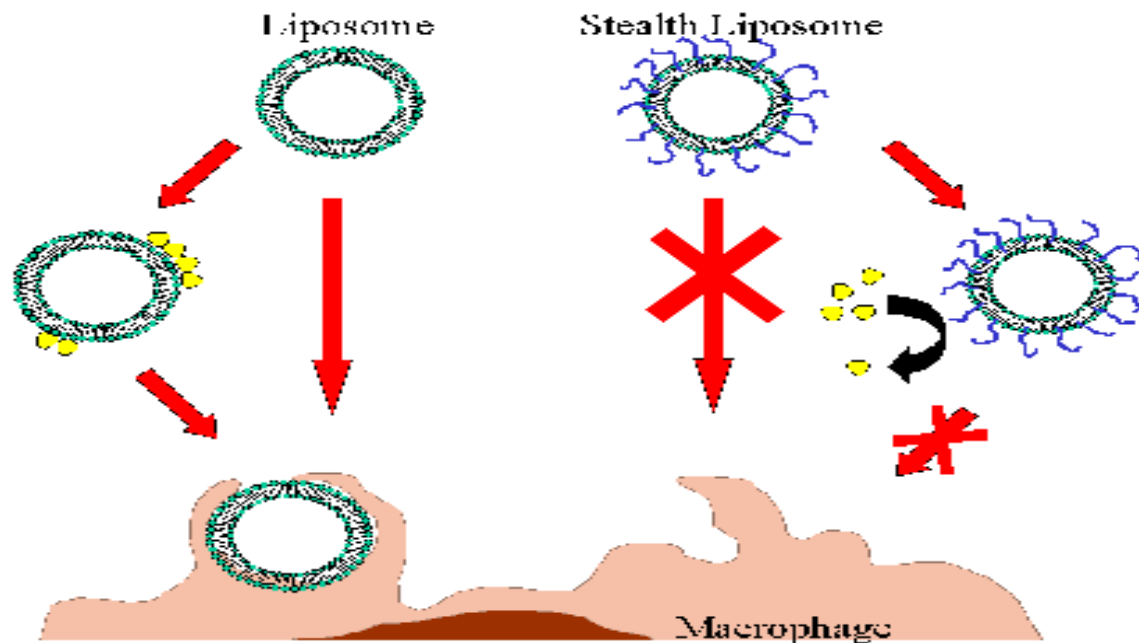
Liposomes

- **Phospholipid bilayer**
- **Aqueous core**
- **80-100nm in size**
- **Biocompatible**
- **Uni- or Multilamellar**
- **Could be easily functionalized**

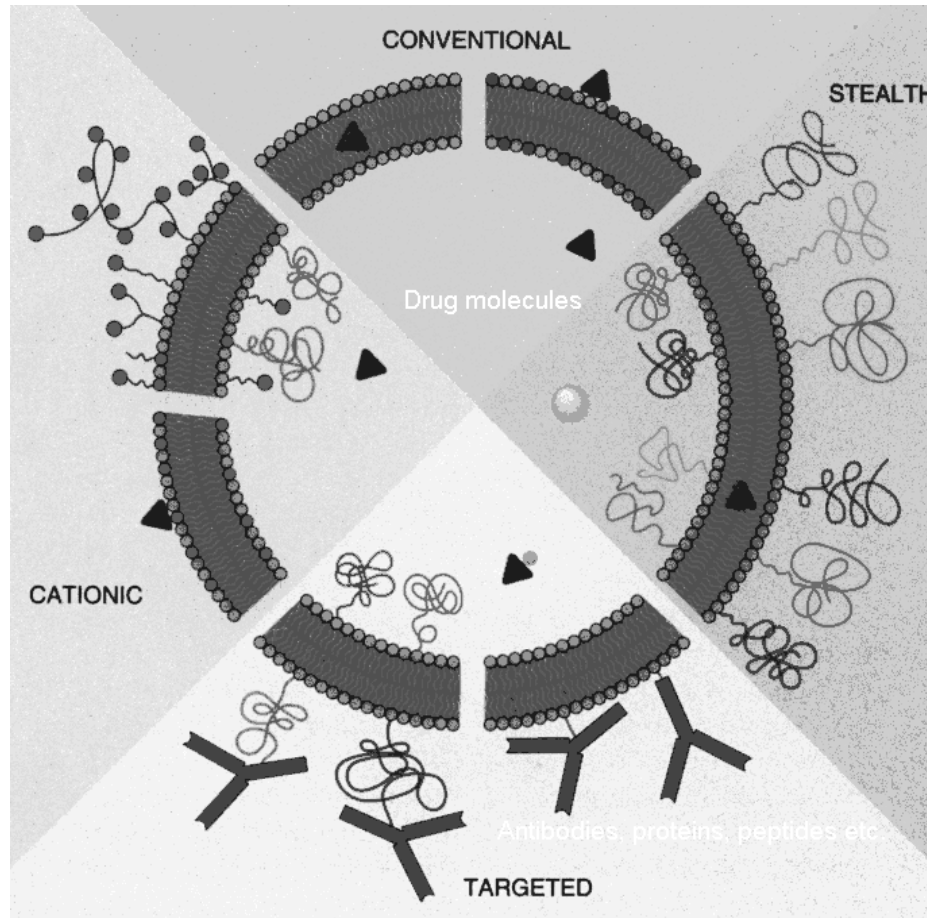


Liposomes

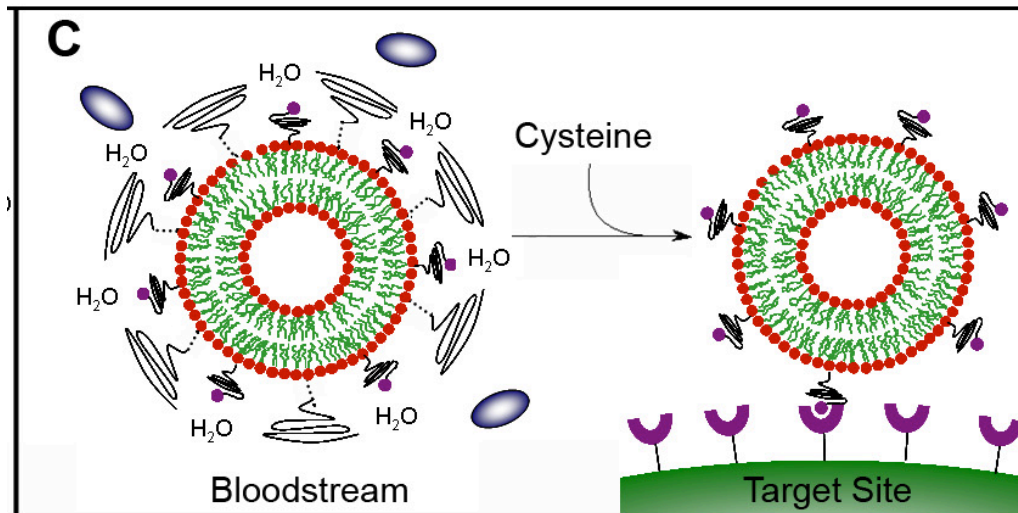
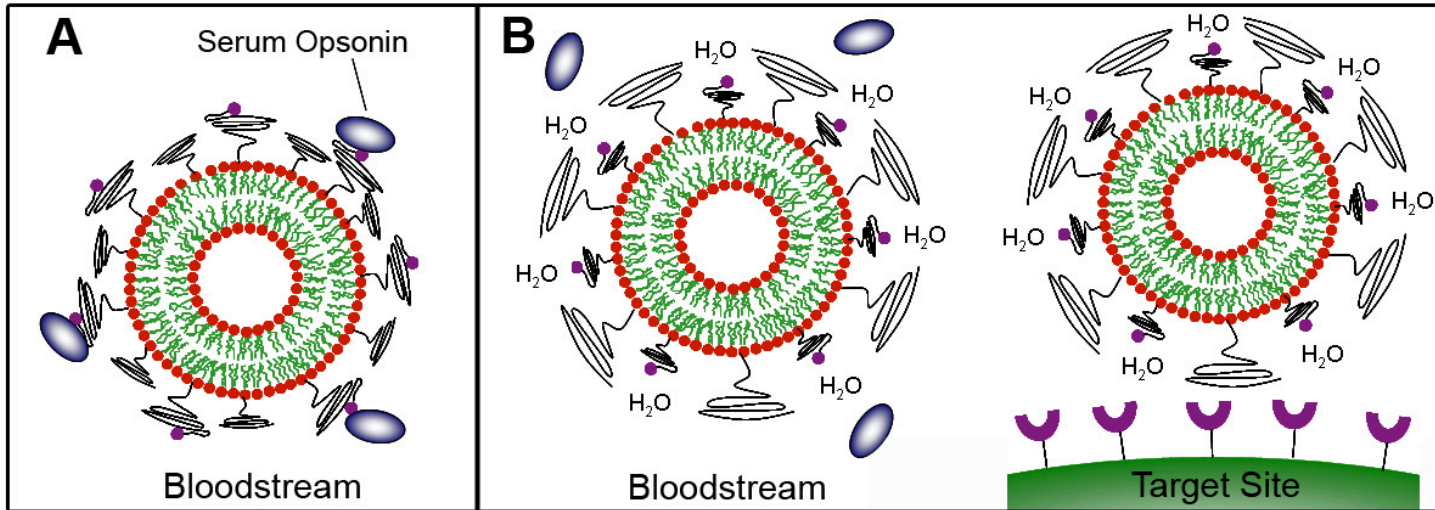
- Preferential retention in leaky vasculature e.g. cancer
- Easily uptaken by macrophages
- Overcome by Stealth property (PEGylation)



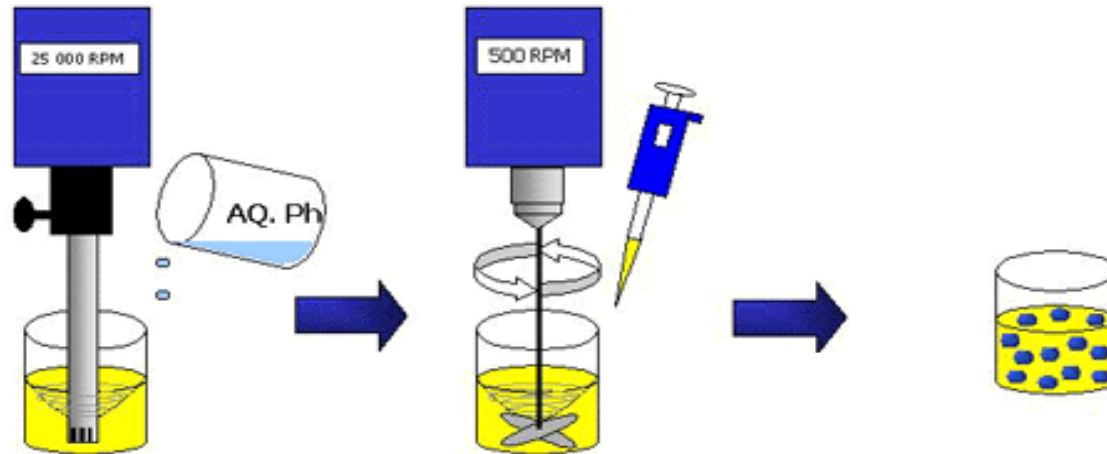
Liposomes



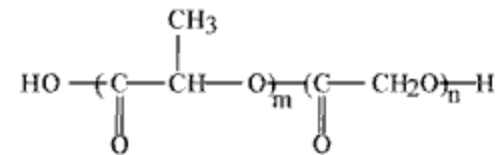
Liposomes



Microspheres and Nanoparticles



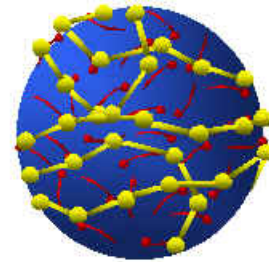
- Encapsulation of a protein or peptide inside a porous particle
- Constructed of Biodegradable, Biocompatible polymer
 - PLGA (FDA approved)



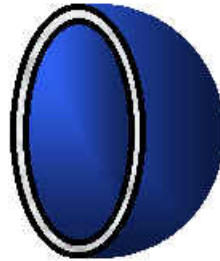
Chemical structure of PLGA polymer.
The "m" component represents lactic acid and "n" component represents glycolic acid.

Microspheres and Nanoparticles

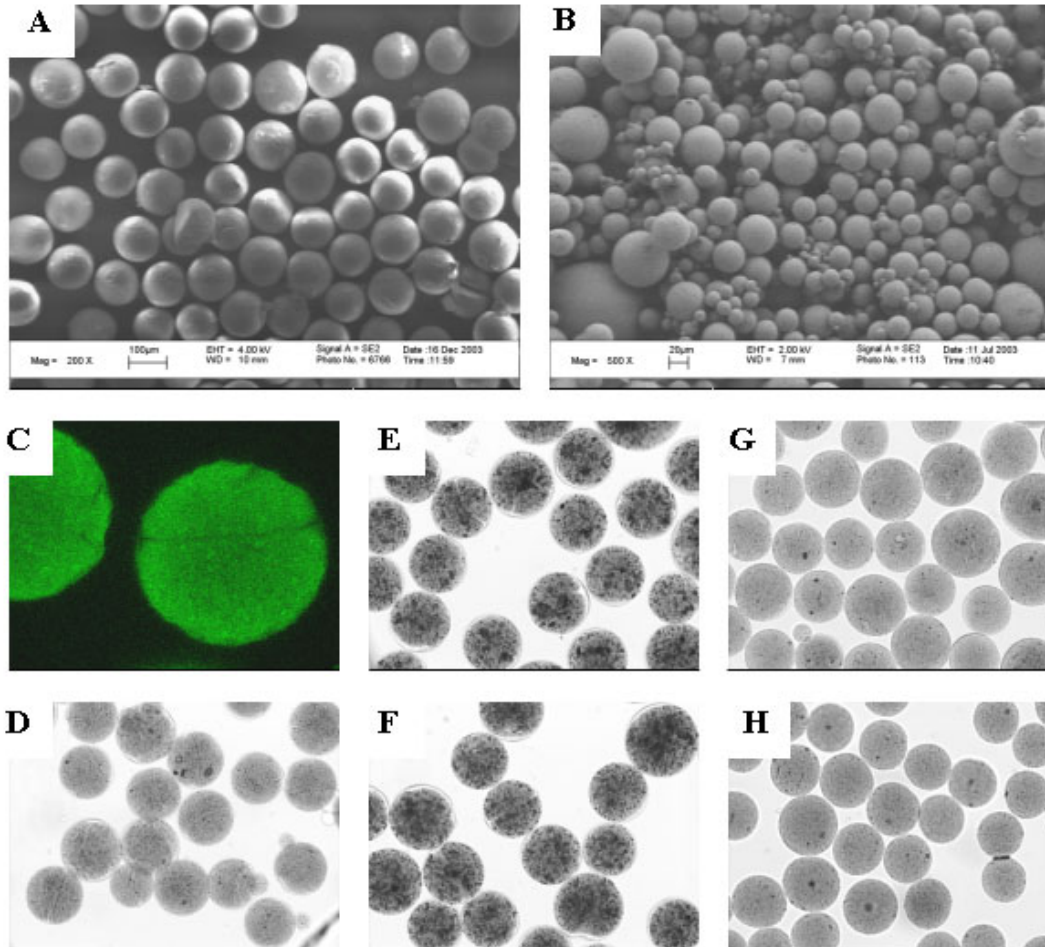
Nanosphere



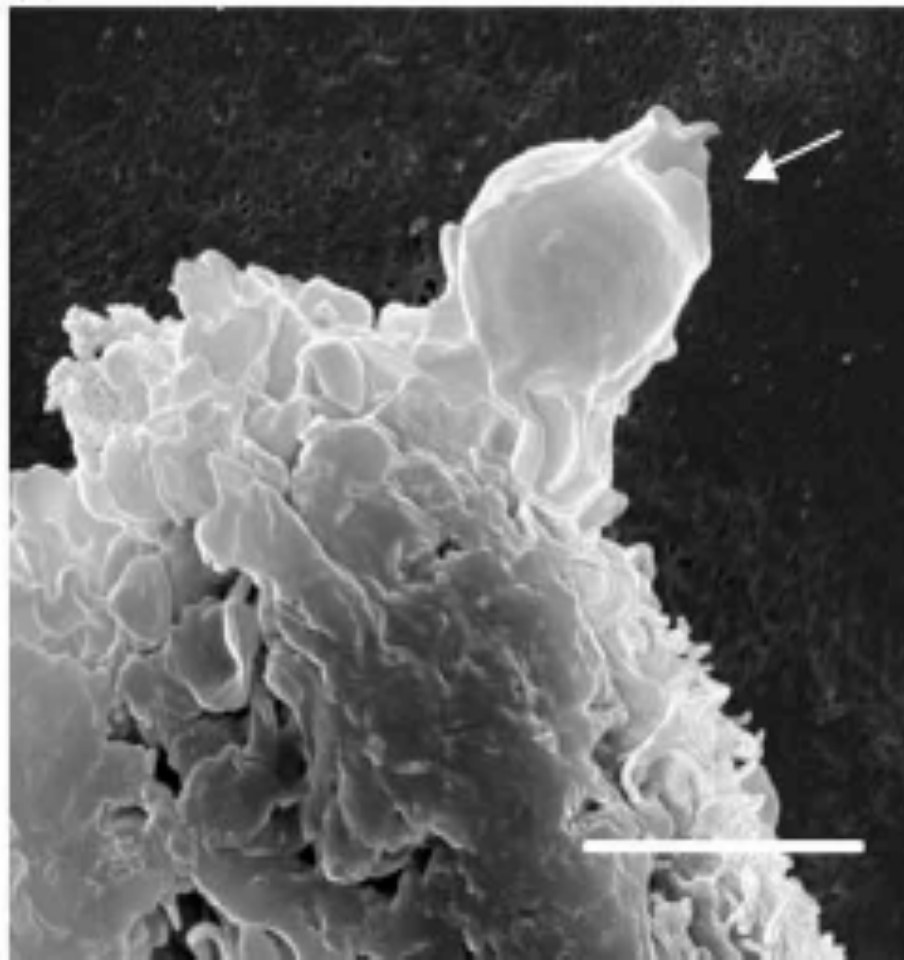
Nanocapsule



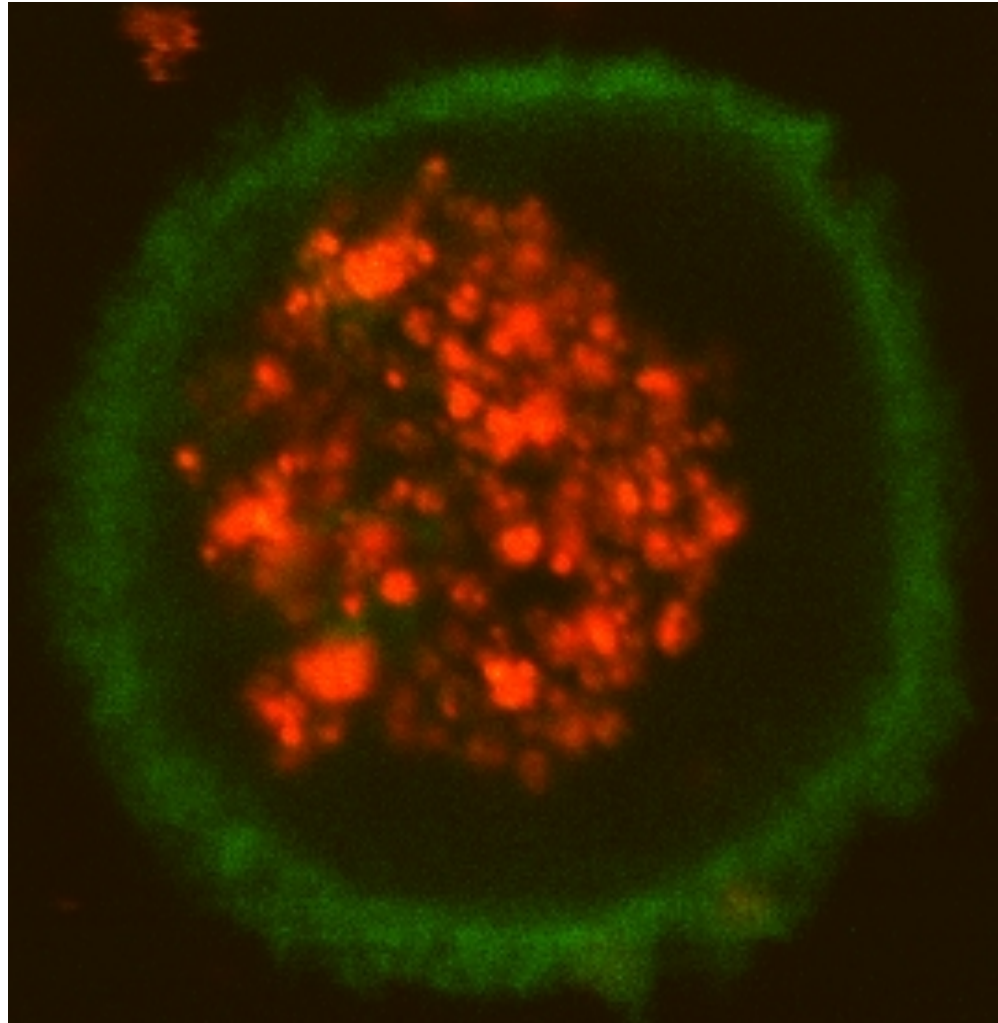
Microspheres and Nanoparticles



Polymeric Nanoparticle Uptake by Human DCs: SEM image

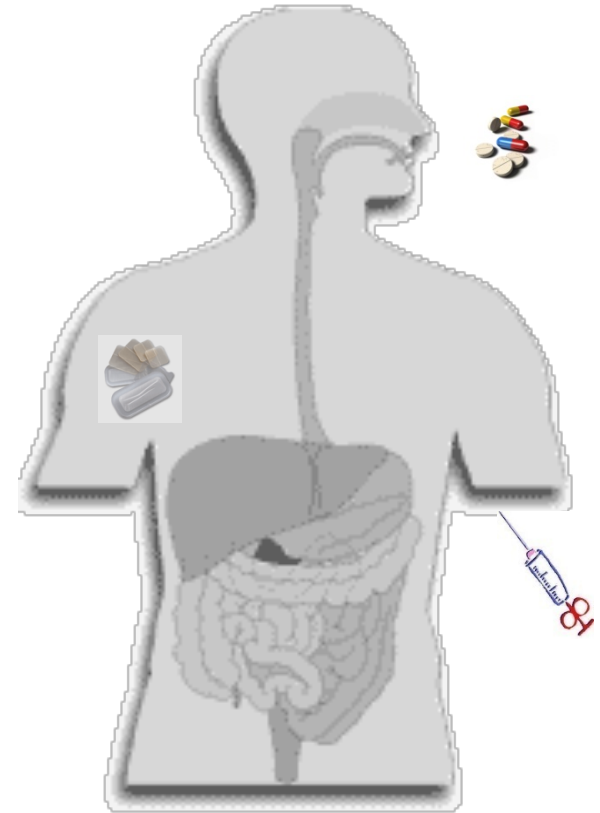


Polymeric Nanoparticle Uptake by Human DCs: Confocal Image



Protein Delivery

- Drugs could be administered by several routes:
 - Parenteral (injections)
 - Transdermal
 - Oral



Parenteral



Action 8: Withdrawing clear insulin. (Photo by Rick Brady.)

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Action 9: Withdrawing modified insulin. (Photo by Rick Brady.)

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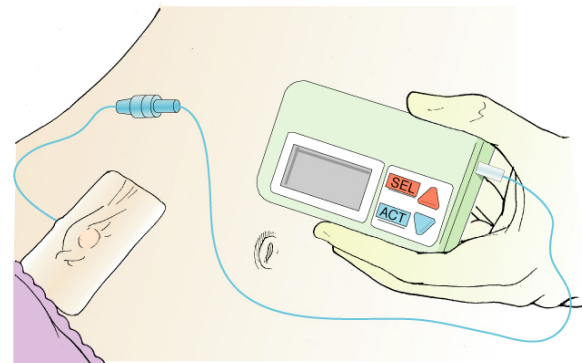


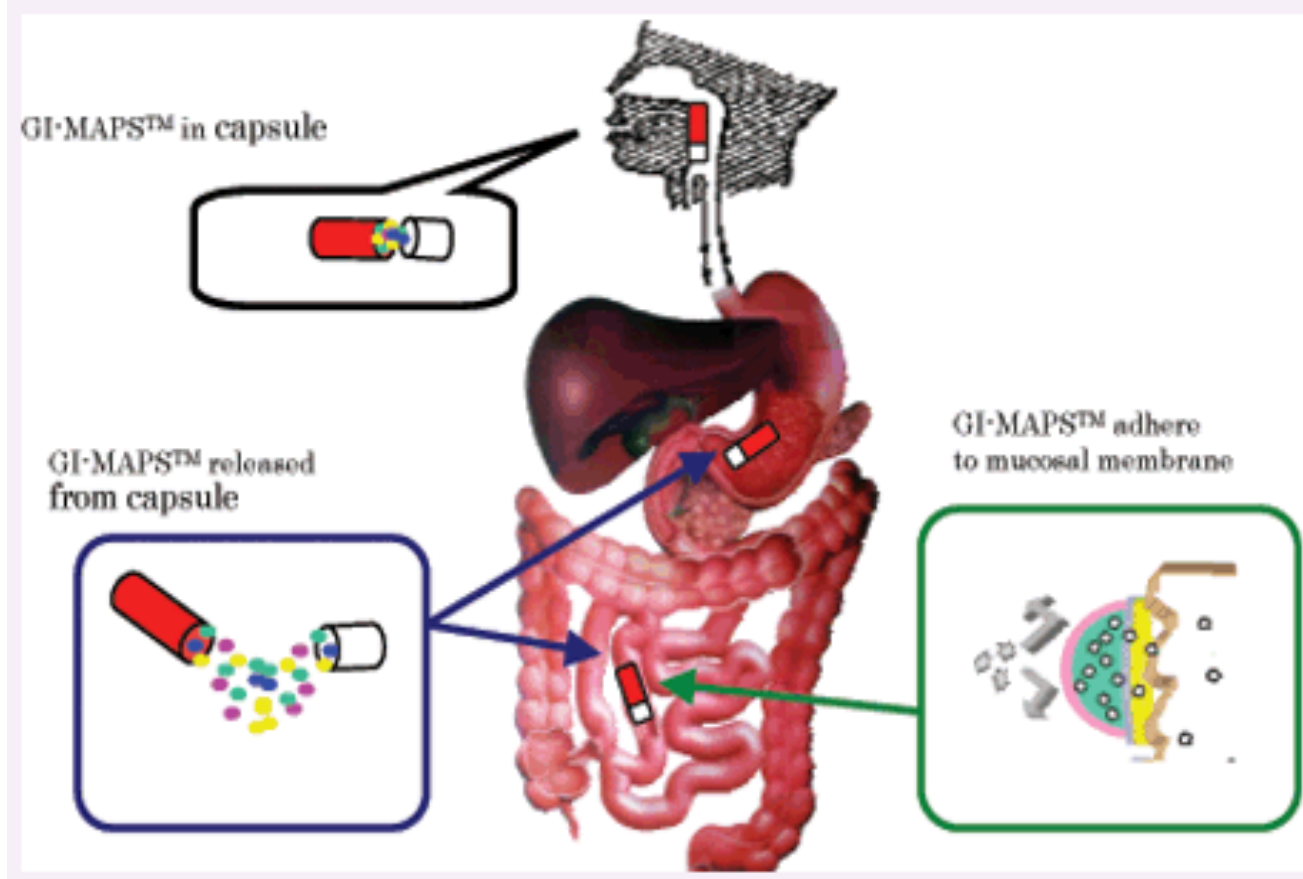
Figure 29-8 Patient wearing insulin pump.

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Parenteral Delivery

- Route of delivery for 95% of proteins
- Allows rapid and complete absorption
- Allows smaller dose size (less waste)
- Avoids first pass metabolism
- Avoids protein “unfriendly zones”
- Problems with overdosing, necrosis
- Local tissue reactions/hypersensitivity
- Everyone hates getting a needle

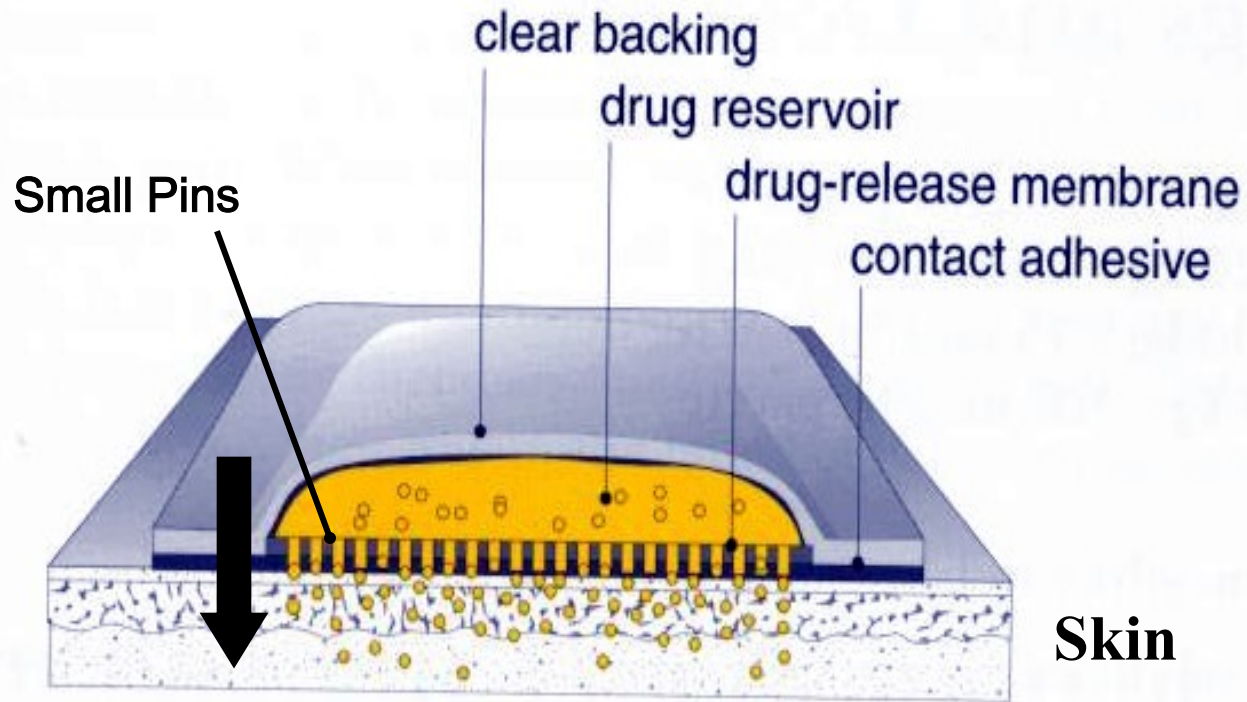
Oral (GI-MAPS[®])



Transdermal Patches

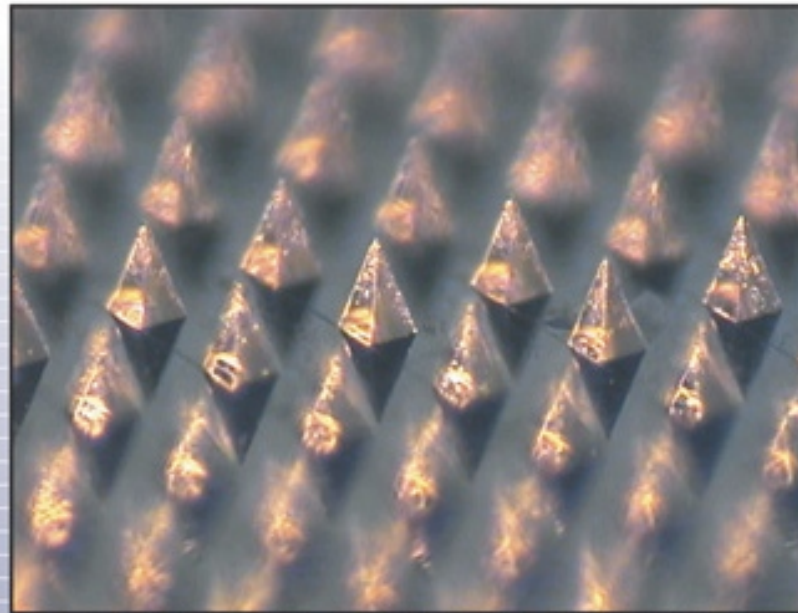
- Proteins imbedded in a simple matrix with appropriate additives
- Patch is coated with small needles that penetrate the dermal layer
- Proteins diffuse directly into the blood stream via capillaries
- Less painful form of parenteral drug delivery

Transdermal patch



Close-up of Patch Pins

A photomicrograph of an array of microneedles in 3M's Microstructured Transdermal System.



Exubera (Inhaled Insulin)

- Exubera, a dry-powder form of insulin, is inhaled with a special device similar to an asthma inhaler
- Exubera normalized blood sugar levels as well as injections did
- Patients taking inhaled insulin also reported greater satisfaction and quality of life (for 18+ only)
- About 1/5 study subjects developed a mild cough with inhaled insulin
- Product pulled in Oct. 2007



Pfizer

Oral (Oralin/Oral-Lyn) by GENEREX

the rapidmist™ device
(click for cutaway view)

**It is not oral, it is
buccal**



THE CANISTER



THE RAPIDMIST DEVICE

Oral Insulin (Oralin/Oral-lyn)



- Buccal aerosol delivery system developed by Generex (Approved in Ecuador and India)

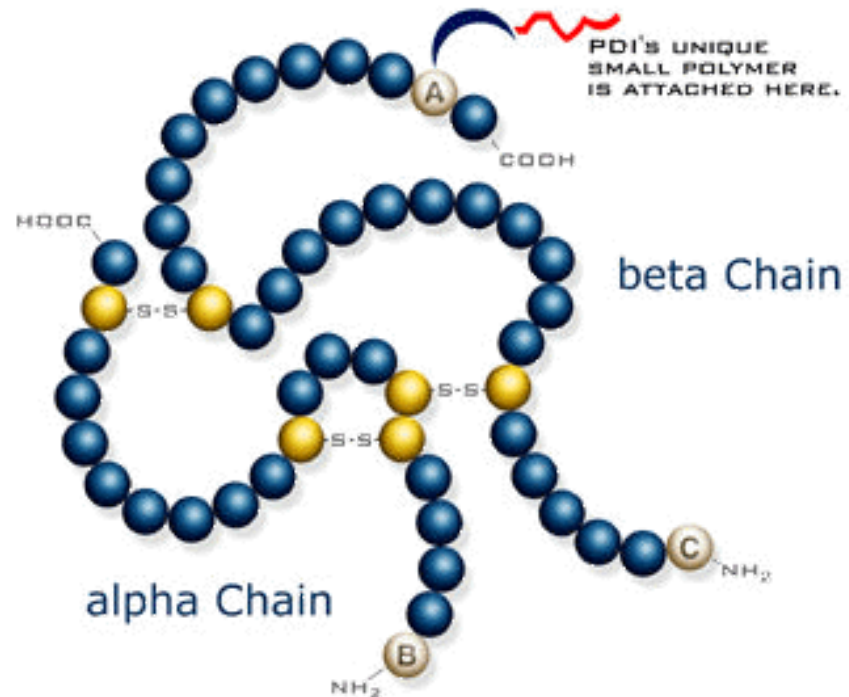
Oral Insulin (Oralin/Oral-lyn)

- Insulin is absorbed through thin tissue layers in mouth and throat
- Insulin is formulated with a variety of additives and stabilizers to prevent denaturation on aerosolization and to stabilize aerosol particles

Oral insulin by NOBEX

- Conjugate the lysine residue with amphiphilic oligomer
- Alkyl chain + PEG
- Enhance stability in vivo
- Hydrolysis of oligomer release the native structure
- Phase II clinical trial (2004)

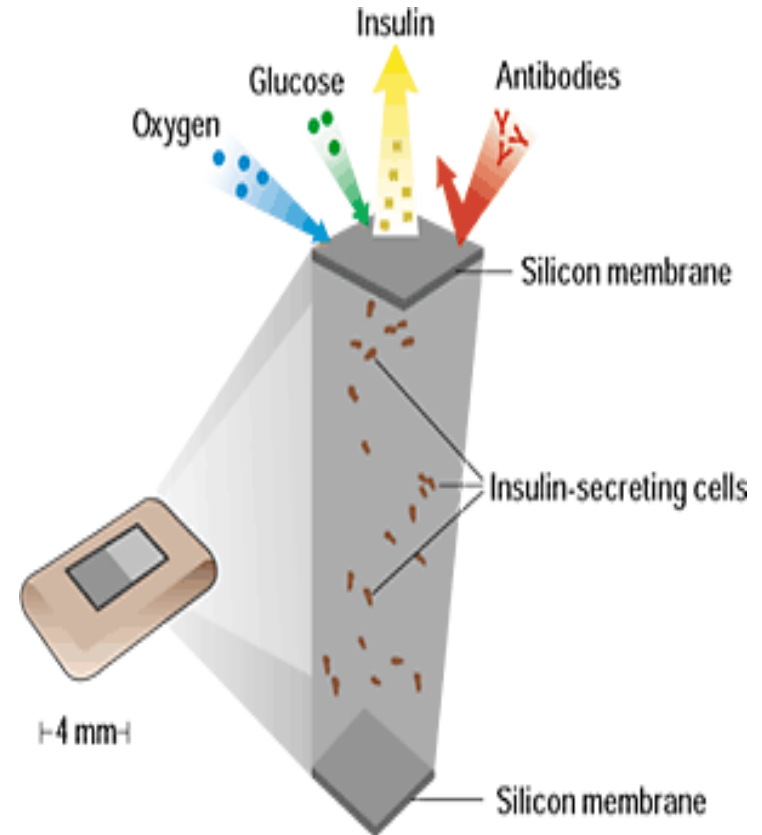
An Example:
Recombinant Human Insulin Conjugate



Future Delivery

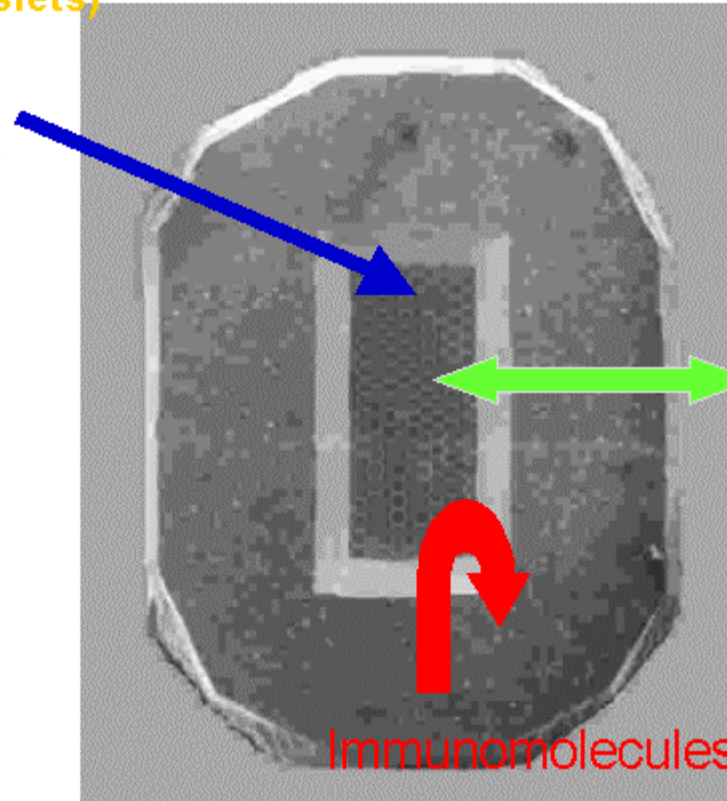
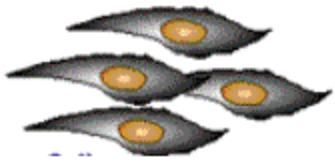
Future Delivery (Biocapsule)

- Encapsulation of insulin-secreting cells (insulinoma)
- Immune components physically excluded
- Glucose molecules pass freely
- Insulin is secreted in response to glucose



Biocapsules

Hormone-secreting cells
(i.e. pancreatic islets)



Insulin,
glucose,
oxygen

Immunomolecules

Now you are able to:

- ✓ Describe techniques for optimal protein formulation
- ✓ Realize the importance of delivery systems for protein pharmaceuticals
- ✓ Compare different delivery methods