3.051J/20.340J

Lecture 20
Drug Delivery: Controlled Release III

Delivery Methods

1. Transdermal

Drug delivery through the skin to systemic circulation

traditional: crèmes/ointments
novel: ***controlled release patches***

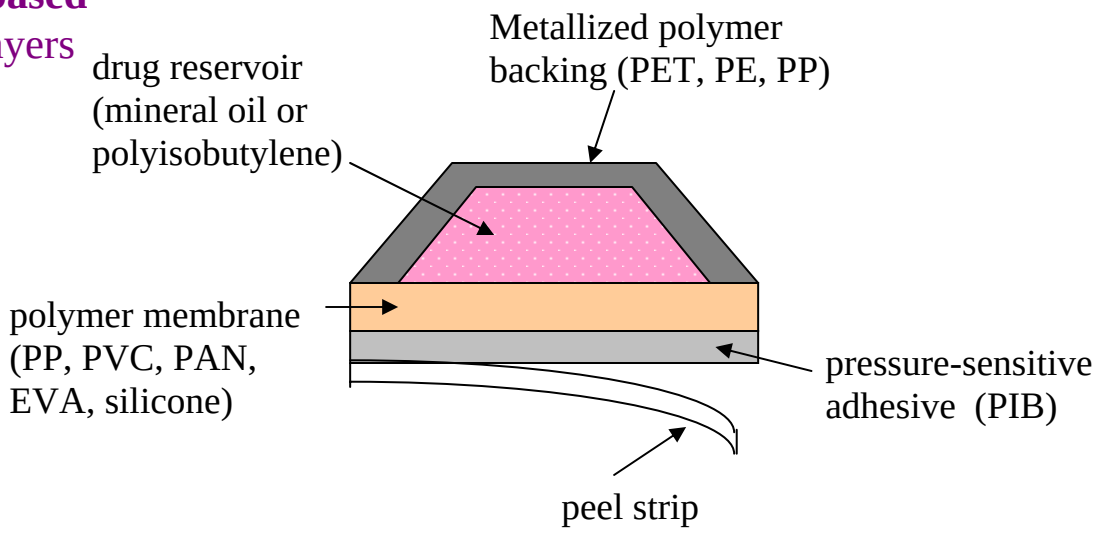
Transdermal Advantages:

- effective systemic delivery (vs. GI)
- high patient compliance
- constant rate release (membrane-based)
- easily terminated (patch removal)

Device Designs

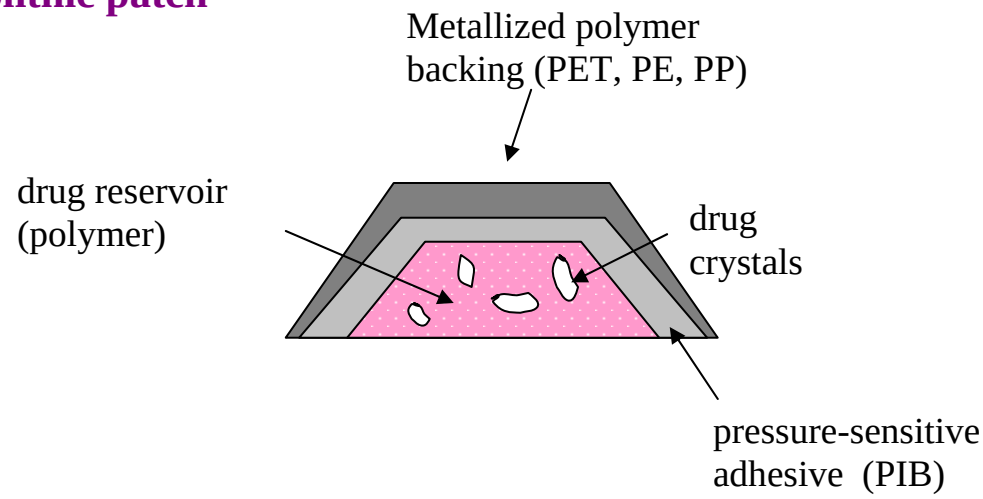
a) membrane based

laminated layers



⇒ **Release rate constant** (rate-limited by diffusion through membrane)

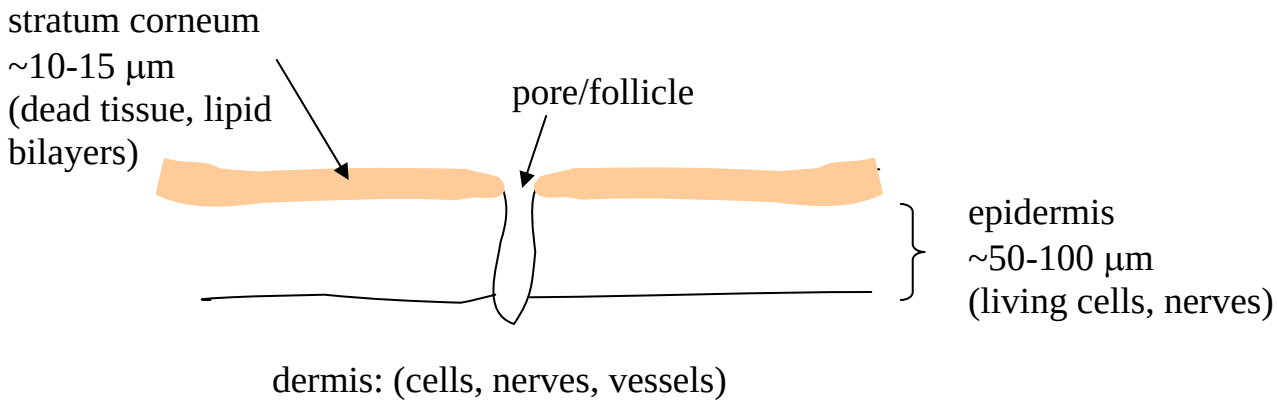
b) monolithic patch



⇒ $C_0 >> C_S$ Drug dissolution in polymer matrix controls release rate

Disadvantages to Transdermal Delivery

a) low skin permeability to drugs



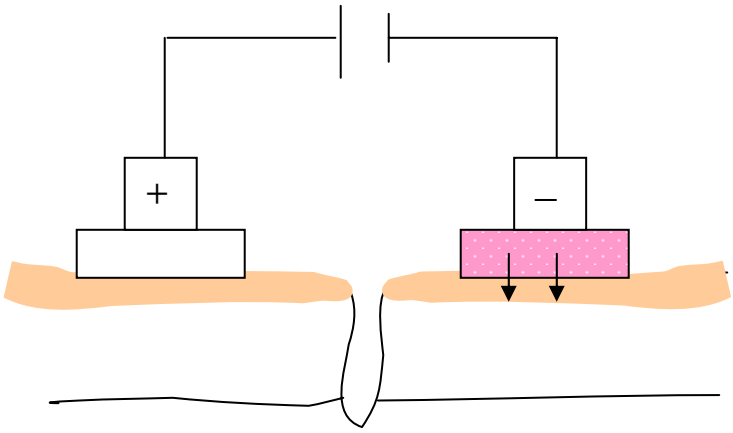
- Stratum corneum is hydrophobic – limits drug penetration
- Epidermis is hydrophilic
- Main entry to vasculature via pores (small % of surface)

Methods to enhance permeability:

i) penetration enhancers "shield" interactions, i.e., amphiphiles (traditional crèmes: H_2O/oil + lipids)

ii) iontophoresis – mild electrical current (0.5mA/cm^2) applied to skin at delivery site increases penetration rate of charged therapeutic agents

ex., Vyteris lidocaine transdermal delivery

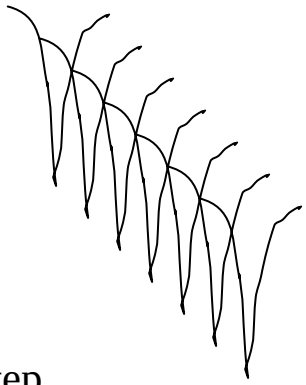


E-field drives charged drugs thru skin

iii) microneedles – penetrate the stratum corneum or epidermis

iv) ultrasound

ex., 3M hollow plastic needle system for vaccine delivery (L>100 μm)

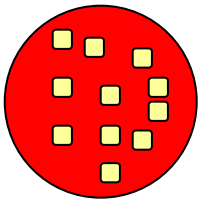


b) drugs bind to skin – desorption becomes rate-limiting step

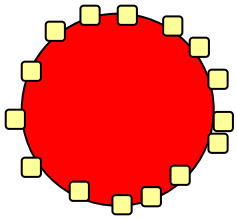
c) allergic reaction—triggered by adhesive

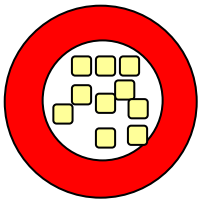
2. Colloidal Drug Delivery vehicles

Spherical particles of polymers or lipids with dispersed, adsorbed, covalently bound or encapsulated therapeutic agents

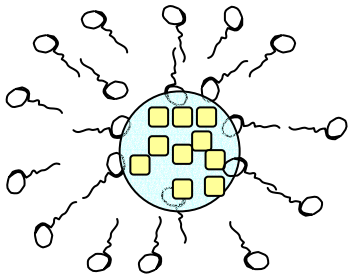


nanospheres/
microspheres





nanocapsules/
microcapsules



liposomes

Administration Routes

a) Oral

- **released drug is absorbed in small intestine**
- **phagocytosis of delivery vehicles (dia. < 10μm) in small intestine via M-cells (lymphatic tissue) of Peyer's patches**

Advantages: - patient acceptance
- convenient

Issues: - poor uptake—rapidly metabolized
- chemical instability in GI tract

b) Subcutaneous injection

- **phagocytosis, deposition in lymph nodes (dia. < 10μm)**
- **particles collect at injection site (dia. > 30μm)**

Advantages: - patient can administer
- does not require digestion (nauseated patients)

Issues: - poor distribution to target
- local tissue irritation/toxicity

c) Intravenous administration

- **systemic circulation for dia. < 4 μm (smallest capillary)**
- **interaction with reticular endothelial system (RES)**
- **phagocytosis in liver, spleen, lungs, lymph nodes**

Advantages: - effective systemic treatment
- does not require digestion

Issues: - short circulation times
- low penetration of endothelial lining of vasculature (requires dia. < 5nm)

Types of Vehicles

a) Nanospheres (10nm-1μm)/microspheres (1-10μm)

Drug is dissolved or dispersed in a polymer matrix, or adsorbed to polymer bead surface

Processing Methods: Emulsion-based

- **Emulsion polymerization with drug dispersion**

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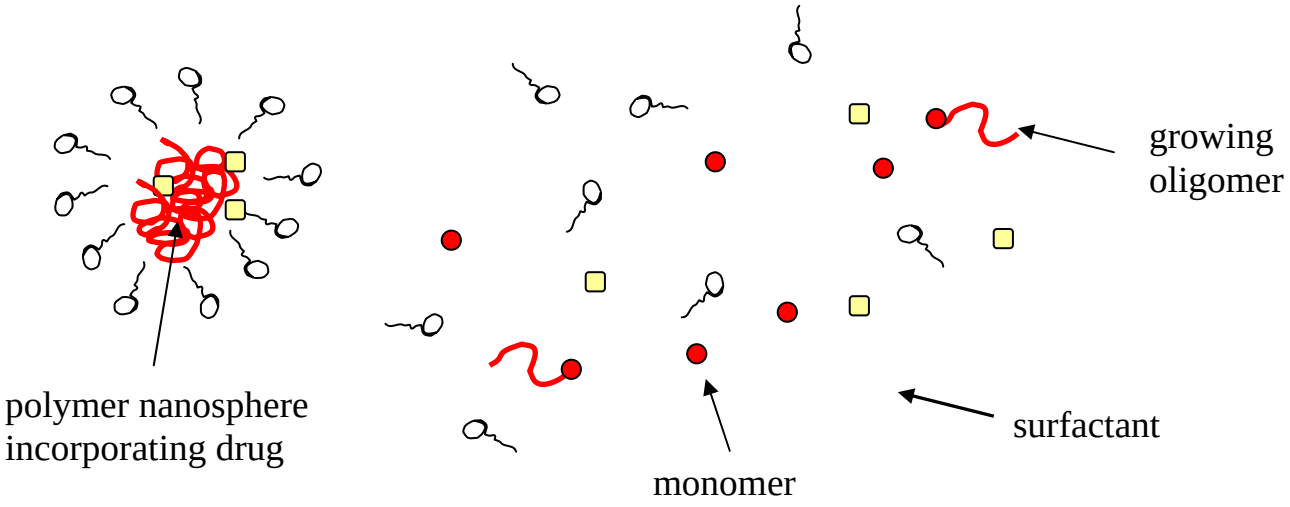


Growing polymer chains are immiscible in solvent

- Micelles form, incorporating the polymer and drug

- Can be aqueous or organic based synthesis, depending on polymer and therapeutic agent

- Examples: polyacrylamide/antigen vaccines, biodegradable poly(alkyl cyanoacrylate)/doxorubicin chemotherapeutics PMMA/antigen vaccines (influenza, HIV)

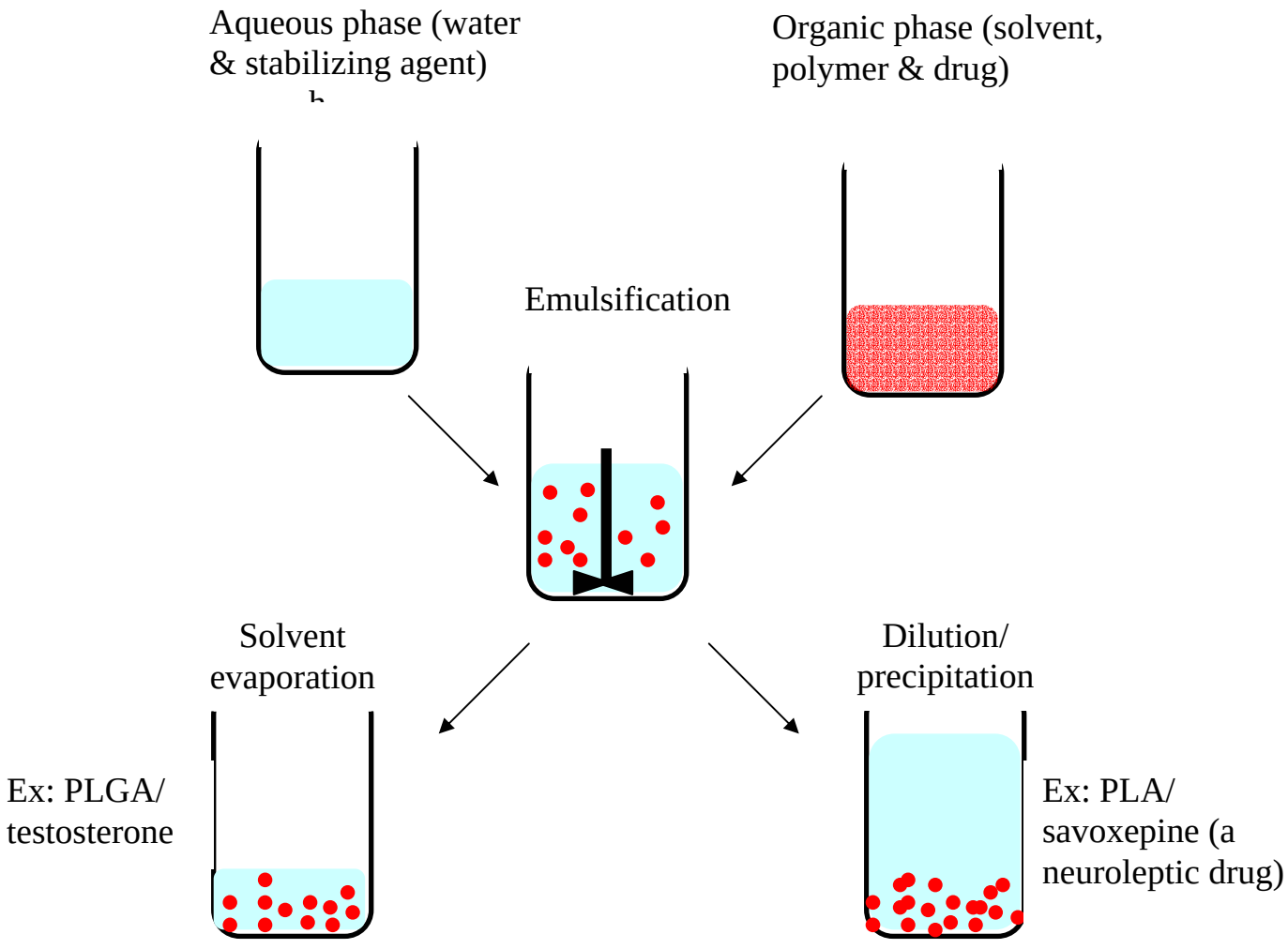
- **Emulsification of polymer and drug**

  - Preformed polymer dissolved in volatile organic solvent (ex., chloroform, methylene chloride, ethyl acetate)

  - Organic solution is mechanically dispersed in aqueous phase containing surfactant or stabilizer, forming an emulsion

  - Drug incorporated in organic (if lipophilic) or aqueous (if hydrophilic) phase, or later adsorbed

  - Nanoparticles recovered by evaporation of organic solvent or precipitation through dilution with water



- Matrices: PLA, PGA, PLGA, PCL (polycaprolactone), PHB (poly(hydroxybutyrate)), polyorthoesters (acid sensitive)

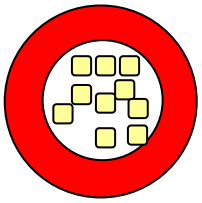
Influences on Nanosphere Release/Degradation Rate

- **Molecular weight**
- **Crystallinity**
- **Diameter**
- **Water permeability**
- **T_g**
- **pH Sensitivity**

b) Nanocapsules/microcapsules

Drug or drug dispersion in matrix is enclosed by a polymer membrane/outer layer

What is the advantage of this approach?



Processing Methods:

- **Interfacial polymerization of polyamides**

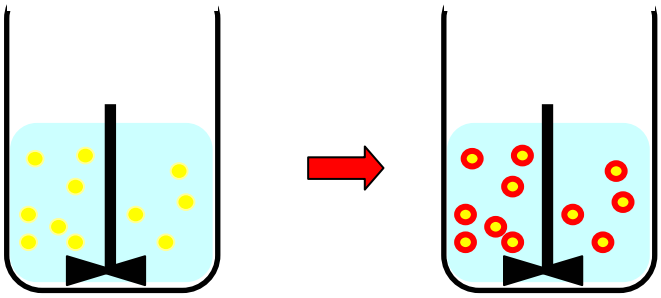
  - Emulsion formed with acid dichloride monomer & drug in dispersed oil phase, diamine monomer in water phase

  - monomers migrate to oil/water interface and polymerize by condensation reaction, encapsulating the drug

$$NH_2\text{-}R\text{-}NH_2 + R'(COCl)_2 \rightarrow (ClCO)\text{-}R'\text{-}CONH\text{-}R\text{-}NH_2 + HCl$$

amide bond

  - trichlorides and triamines added as crosslinking agents



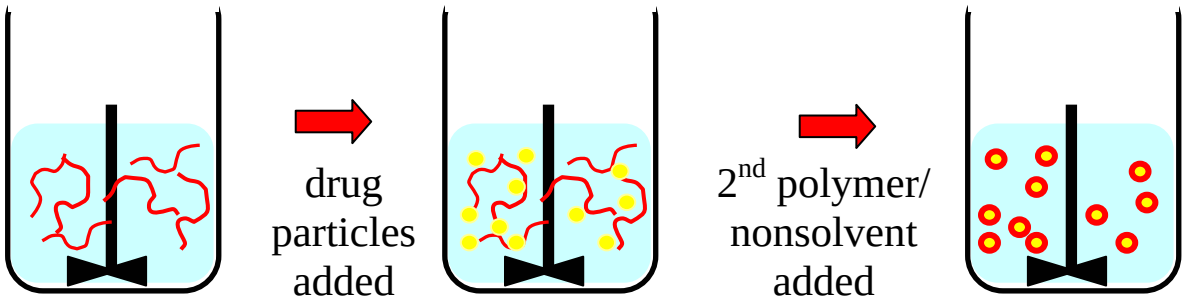
- **Interfacial Coacervation**

  - encapsulating polymer dissolved in organic phase

  - drug particles are added to organic solution

  - a second polymer immiscible with the first (or other nonsolvent) is added to suspension, inducing phase separation

  - encapsulating polymer precipitates onto the drug particle surfaces, forming a capsule

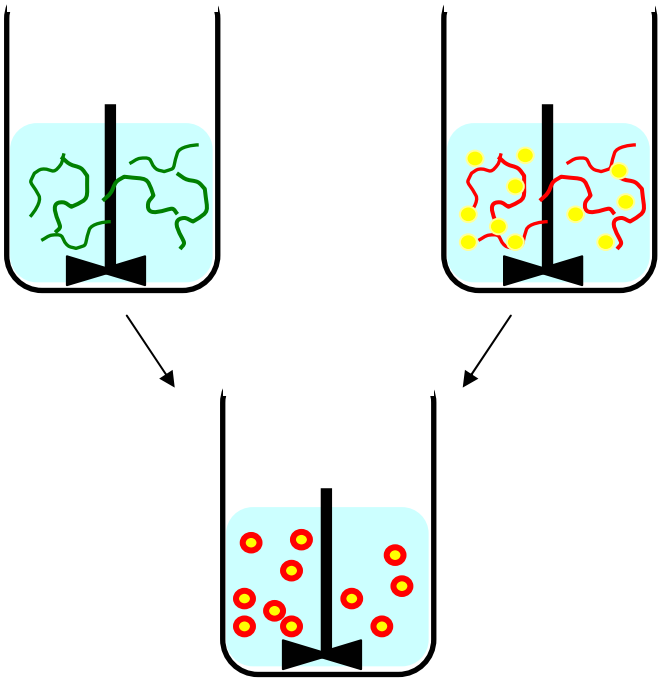


- **Complex Coacervation**

  - two solutions of oppositely charged polyelectrolytes are prepared, one containing drug dispersion

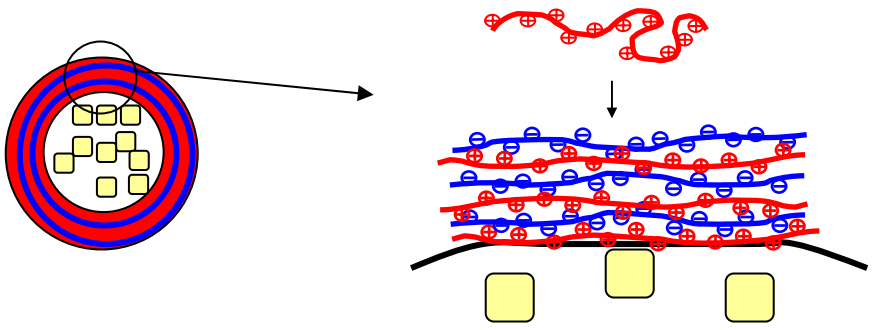
  - addition of second polyelectrolyte to first results in complexation and precipation onto drug particles

  - Examples: gelatin (-) and gum arabic (+), alginate (-) and chitosan (+)



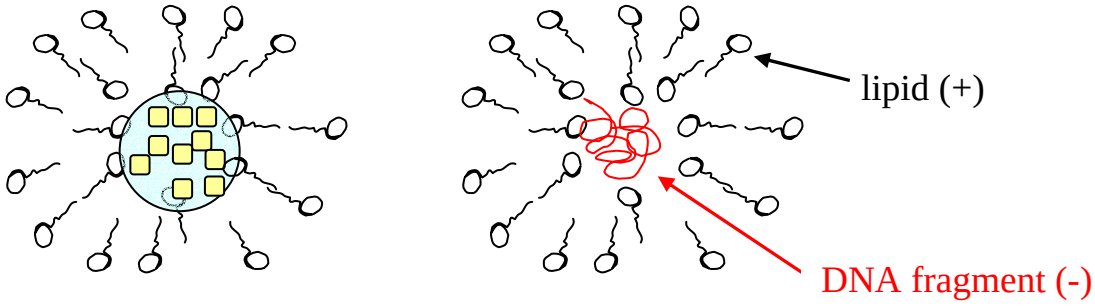
- **Polyelectrolyte Multilayers (recent)**

  - alternate adsorption of polyanions and polycations onto drug-containing particles



c) Liposomes

Drug encapsulated in spherical phospholipid bilayers/vesicles



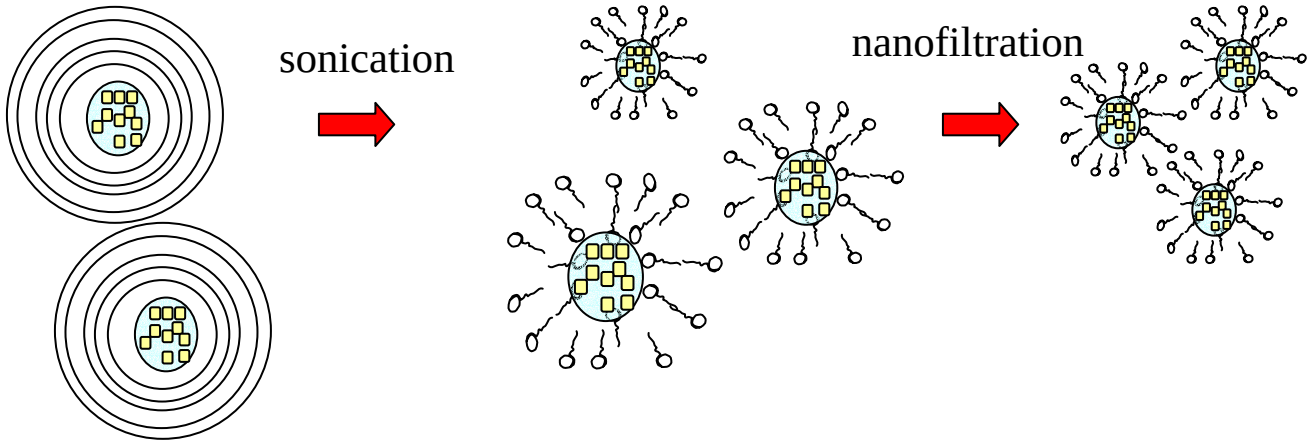
Processing Method:

- Water-in-oil emulsion formed of aqueous drug solution, amphiphiles, and volatile organic phase

- Evaporation of organic solvent—lipids deposit around aqueous microdroplets, forming vesicles

- Ultrasound conversion to unilamellar vesicles

- nanofiltration to control size distribution



Therapeutic Agents:

- bacterial, viral, parasitic antigens (vaccines)
- DNA, DNA fragments (gene therapy)
- chemotherapeutic agents

Targeted Therapy Mechanisms:

- liposome collection in RES (lymph nodes, liver, lungs)
  Common metastatic sites of cancers

- incorporation of lipid-bound MAbs for targeting chemotherapy

  $\Rightarrow$ "MAGIC BULLET"

Ex. MAb for mouse pulmonary endothelial cell surface proteins used to target metastatic lung cancer

- Incorporation of lipid-bound peptides
  Receptor-mediated endocytosis

- Engineer liposome structure to mimic red blood cell membrane
  Drug-targeting to regions of high capillarity (ex., tumors, inflammation sites)

- DNA vaccines
  Immunogen or antigen encoded in DNA, cells take up in nucleus

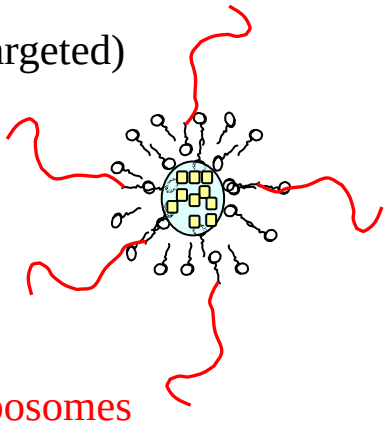
  In clinical trials: cystic fibrosis, melanoma

Liposome Advantages:

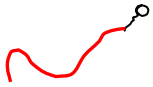
- low toxicity
- uptake by endocytosis (can fuse with cell wall)
- high transfection efficiency (gene therapy)

Issues:

- short circulation time due to phagocytosis (non-targeted)



Strategies to enhance circulation time:



- decrease size
- increase bilayer rigidity
- incorporate PEO-amphiphiles

⇒ "STEALTH" Liposomes

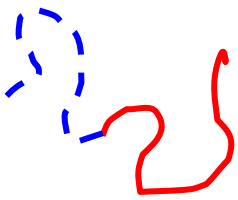
- liposome instability
  - poor mechanical stability
  - phospholipids easily hydrolyzed (ester linkages)

⇒ drug leaching

Strategy to enhance stability:

polymer vesicles from amphiphilic block copolymers

⇒ "Polymersomes"



What is a disadvantage of this strategy?

- denaturation of therapeutic proteins
    - in processing: shear forces, solvents, T
    - *in vivo*: secondary interactions, pH variations

Example Liposome Products

Product	Agent	Use
AmBisomes	amphotericin B	systemic fungal infection
DOX-SL	doxorubicin	chemotherapy
DaunoXome	daunorubicin	Karposi's sarcoma
Epaxal-Berna	inactive hepatitis A	vaccine

3. Externally Controlled Implantable Pumps

Enable doctor/patient control of:

- Delivery dosage
- Flow rate
- Dosage schedule

Examples

SynchroMed Infusion System (Medtronic)

- percutaneously refillable reservoir
- lithium battery-operated peristaltic pump

- magnetic telemetry link for computer control
- FDA approved for chemotherapeutic agents, morphine sulfate

Programmable Implantable Medical System (PIMS) (Johns-Hopkins)

- percutaneously refillable reservoir
- solenoid-based pump
- being developed for insulin delivery for diabetes

Photo of PIMS removed for copyright reasons.

References

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Biomaterials Science: An introduction to materials in medicine, B.D. Ratner et al., eds., Academic Press, NY 1996.