NANOLIPOSOMES: THE WHAT, WHY, AND HOW

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Introduction(EPR) Effect

Education

Family

Professional Experience

- **23 years in pharmaceutical development and manufacturing of complex parenteral formulations**
- **Formulation technologies: polymeric microparticles and nanoparticles, hydrophobic salts, liposomes, micelles, solid lipid nanoparticles**

Fun

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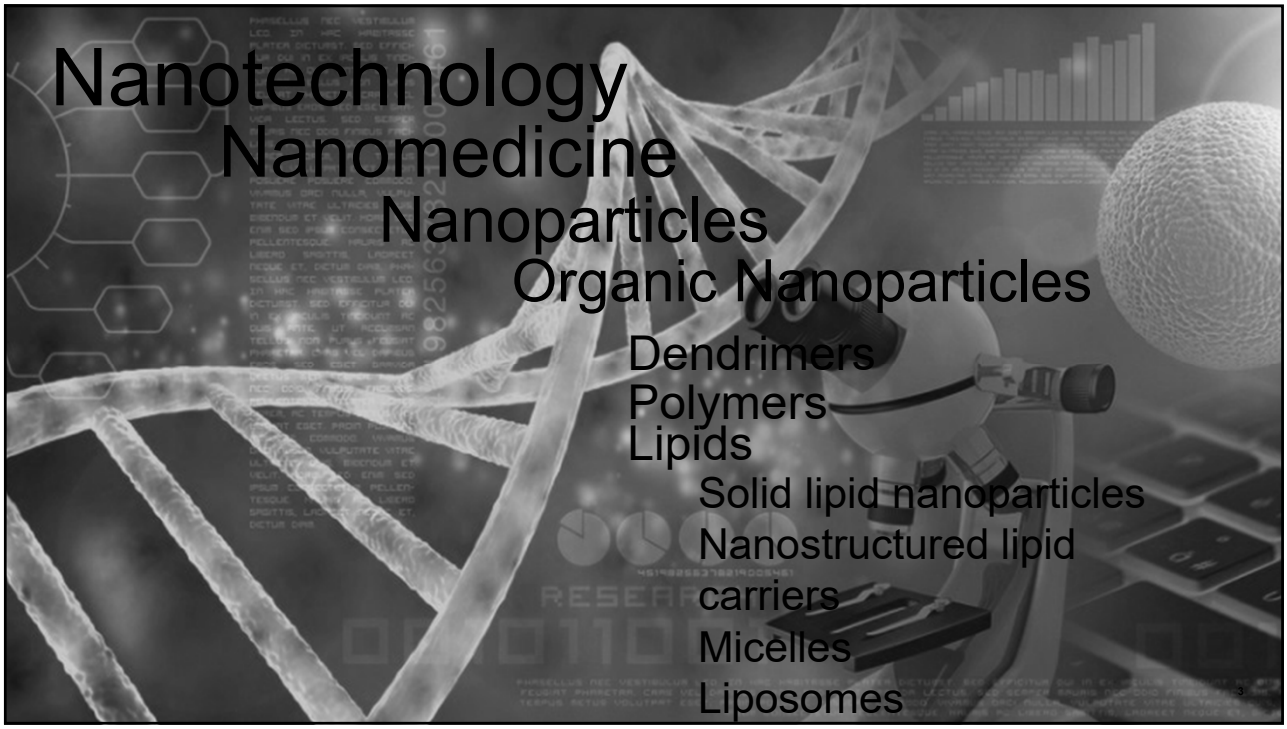

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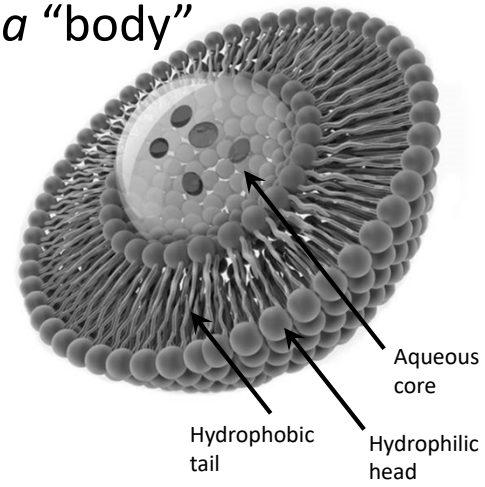
Liposome

Greek *Lipos* "fat" • *Soma* "body"

A structure consisting of one or more concentric spheres consisting of lipid bilayers surrounding an aqueous compartment. Drug molecules are entrapped in the aqueous cavity (hydrophilic drugs) or intercalated into the lipid bilayer (lipophilic drugs). PEG is often incorporated to extend circulation time. Targeting agents may be conjugated to the outside of the bilayer.



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Product	Approval year	Active Agent	Indication
Epaxal®	1993	Inactivated hepatitis A virus (strain RGSB)	Hepatitis A
Doxil®	1995	Doxorubicin	Ovarian, breast cancer, Kaposi's sarcoma
Abelcet®	1995	Amphotericin B	Invasive severe fungal infections
DaunoXome®	1996	Daunorubicin	AIDS-related Kaposi's sarcoma
Amphotec®	1996	Amphotericin B	Severe fungal infections
Ambisome®	1997	Amphotericin B	Presumed fungal infections
Inflexal V®	1997	Inactivated hemaglutinine of Influenza virus strains A and B	Influenza
Depocyt®	1999	Cytarabine/Ara-C	Neoplastic meningitis
Myocet®	2000	Doxorubicin	Combination therapy with cyclophosphamide in metastatic breast cancer
Visudyne®	2000	Verteporphin	Choroidal neovascularization
Mepact®	2004	Mifamurtide	High-grade, resectable, non-metastatic osteosarcoma
DepoDur®	2004	Morphine sulfate	Pain management
Exparel®	2011	Bupivacaine	Pain management
Marqibo®	2012	Vincristine	Acute lymphoblastic leukemia
Onivyde™	2015	Irinotecan	Combination therapy with fluorouracil and leucovorin in metastatic adenocarcinoma of the pancreas

Approved Liposomal Products

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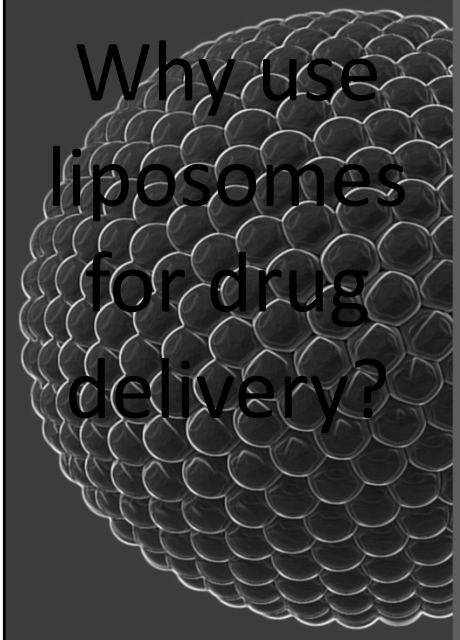
Why use liposomes for drug delivery?



- Targeting capabilities
- Improvement of efficacy
- Decreased amount of drug required
- Lower toxicity
- Reduction of side effects
- Protection of drugs (stability and reduced elimination)
- Increase circulation time
- Applicable for both hydrophilic and hydrophobic drugs
- Biocompatible, biodegradable, and non-toxic
- Large body of knowledge publicly available

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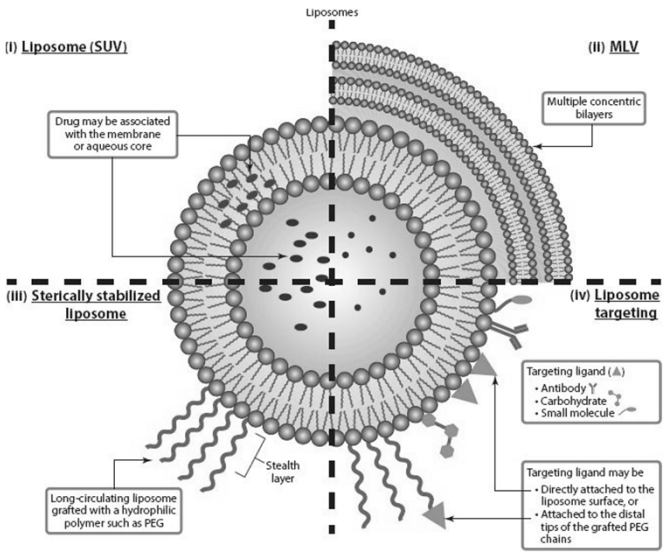

https://basicmedicalkey.com/nanotechnologies-for-drug-delivery-and-targeting-opportunities-and-obstacles/

Achieving Selective Localization of the Active at Disease Sites

- **Passive Targeting** – Drug carriers that stay in circulation for extended periods of time accumulate in pathological sites with affected and leaky vasculature via the enhanced permeability effect.
- **Active Targeting** – Use of specific ligands attached to the surface of the carrier that recognize and bind to pathological cells.

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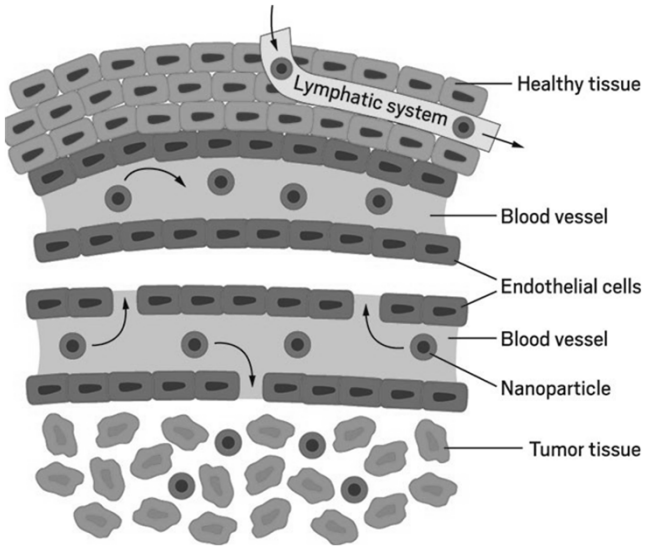

Credit: C&EN

Enhanced Permeability and Retention (EPR) Effect

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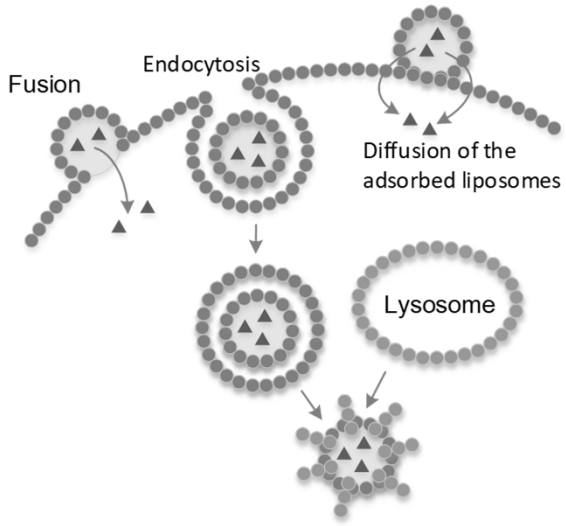

Liposome-Cell Interaction

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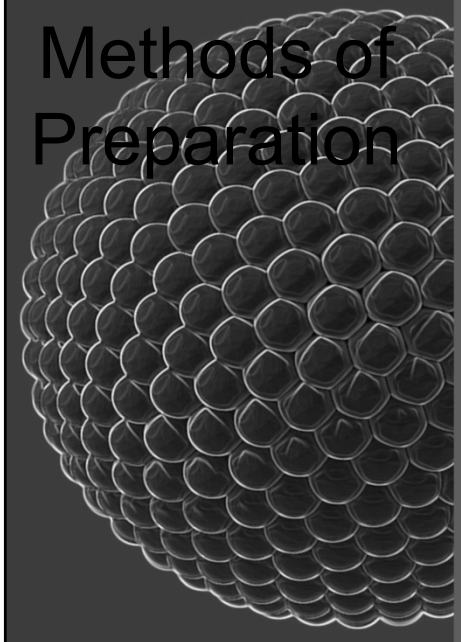

Methods of Preparation

Liposome Formation

- Mechanical Agitation
- Solvent Dispersion
- Surfactant Solubilization

Drug Loading

- Passive Loading
- Remote Loading

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Surfactant Solubilization

- Formation of mixed micelles using surfactants
- Removal of surfactant (dialysis, diafiltration)

Advantages

- Size control

Disadvantages

- Low encapsulation of water-soluble molecules
- Residual surfactant

Solvent Dispersion

- Ether Injection
  - Slow addition dissolved lipids into aqueous solution through small orifice
  - Solvent removal

Advantages
- High encapsulation
- Continuous processing possible

Disadvantages
- Broad size distribution
- Exposure to solvents
- Residual solvents
- Long production times

- Ethanol Injection
  - Rapid addition of dissolved lipids into aqueous solution through small orifice
  - Solvent removal

Advantages
- Simple, gentle
- High yields

Disadvantages
- Solubility limitations
- Dilute = Large volumes
- Low encapsulation
- Removal of ethanol

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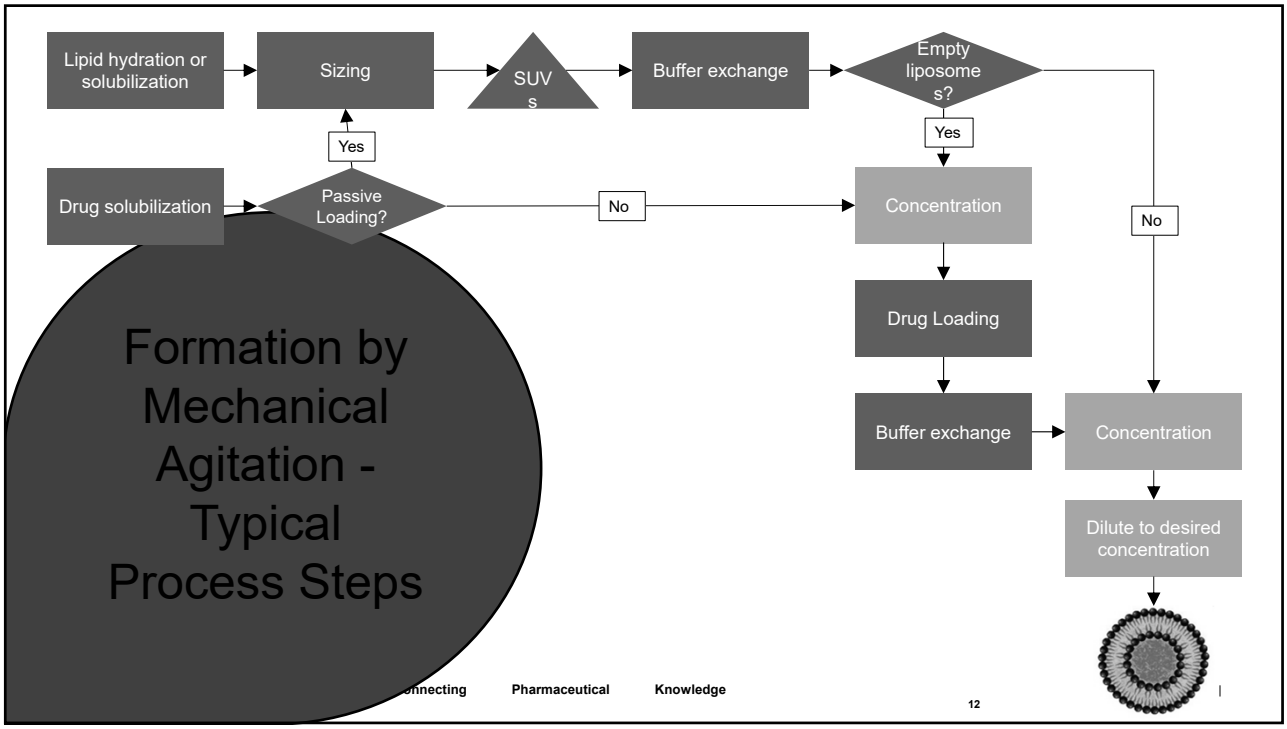

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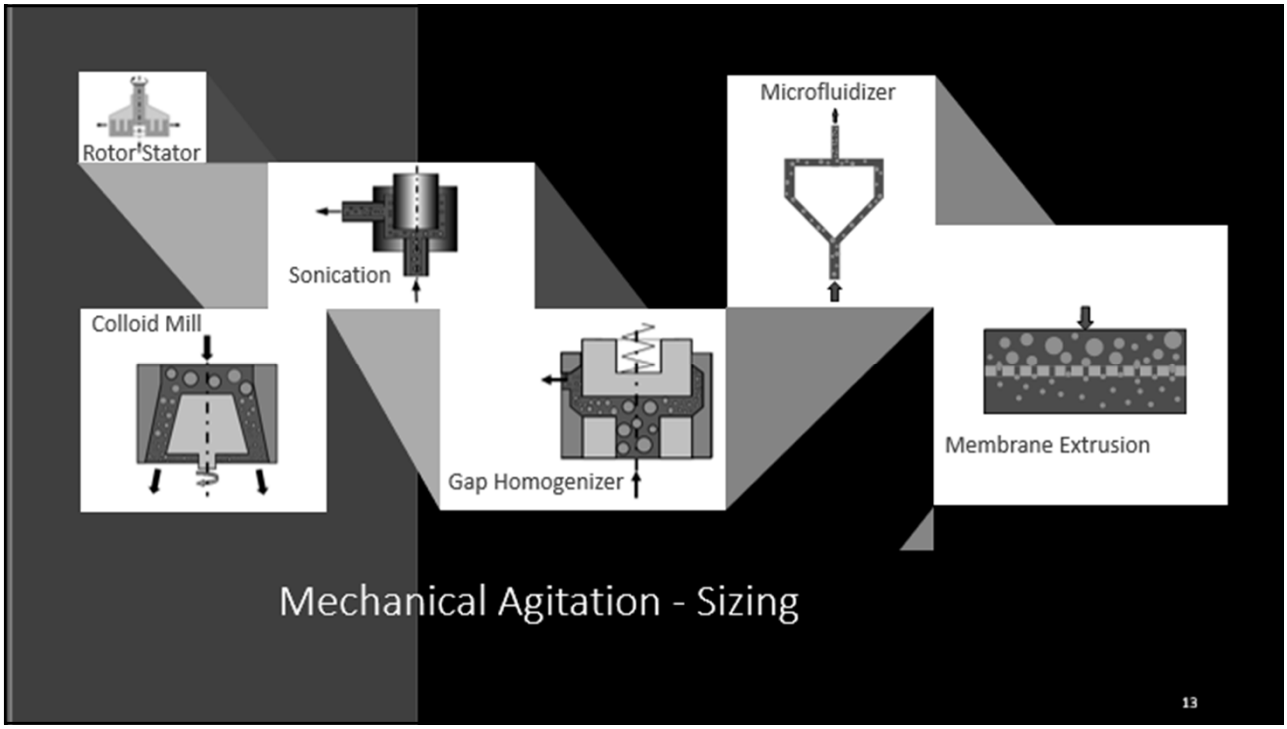

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Disadvantages

- High production costs
- Temperature sensitivity (manufacturing and storage)
- Stability
- Characterization
- Control of release rate
- Sufficient drug loading
- Biological barriers (e.g., skin, blood-brain barrier)

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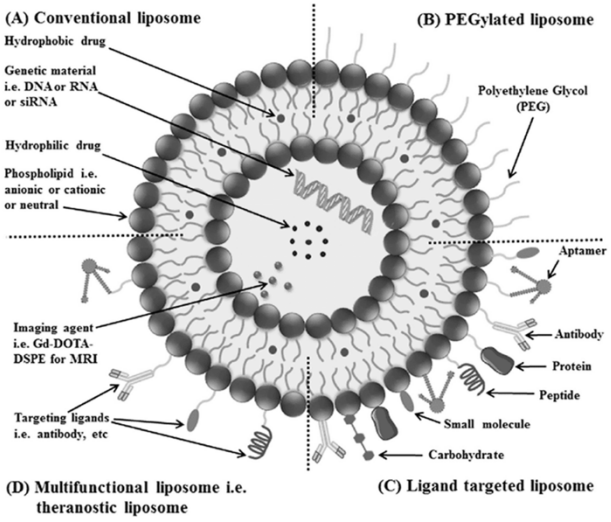

Summary

Consider nanoliposomal formulations IF:

- Parenteral route of administration
- Desire/need targeting capabilities
- High value or highly toxic active
- Protection of drugs (stability and reduced elimination)
- Increase circulation time

Figure reference: Riaz, Muhammad & Zhang, Flora & Congcong, Lin & Wong, Ka & Chen, Xiaoyu & Zhang, Ge & Lu, Aiping & Yang, Zhijun. (2018). Surface Functionalization and Targeting Strategies of Liposomes in Solid Tumor Therapy: A Review. International Journal of Molecular Sciences. 19. 195. 10.3390/ijms19010195.

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