NANOLIPOSOMES: THE WHAT, WHY, AND HOW

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Introduction

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

Family

Fun

Connecting Pharmaceutical Knowledge

ispe.org
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.
Approved Liposomal Products

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

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
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.

Enhanced Permeability and Retention (EPR) Effect
Liposome-Cell Interaction

Methods of Preparation

- Mechanical Agitation
- Solvent Dispersion
- Surfactant Solubilization

Drug Loading
- Passive Loading
- Remote Loading
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

**Formation by Mechanical Agitation - Typical Process Steps**

1. Lipid hydration or solubilization
2. Sizing
3. SUV
4. Buffer exchange
5. Empty liposomes?
   - Yes
   - Concentration
   - Drug Loading
   - Buffer exchange
   - Concentration
   - Dilute to desired concentration
   - No
   - Passive Loading?
     - Yes
     - Drug solubilization
     - No

**Concentration**

**Buffer exchange**

**Drug Loading**
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)
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