Liposomal Chemotherapeutics

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ITEMS

✓ Introduction to Nanotherapeutics and Nanomedicines
✓ Lipid based Nanotherapeutics in Nanomedicines
✓ Conclusion
✓ Future Perspective
Introduction to Nanotherapeutics


Polymeric therapeutics

Water soluble polymers, either as a bioactive itself (A) or as an inert functional part of a multifaceted construct for improved drug, protein or gene delivery (B).

Size: <25 nm

Nanocomplexes

Colloidal systems with a complex structure that consist of a polynuclear iron (III)-hydroxide core surrounded by carbohydrate polymer coatings.

Size: 20–30 nm

Nanoemulsions

Oil nanodroplets dispersed within aqueous continuous phase suitable for entrapment of hydrophobic drugs.

Size: 20–200 nm

Polymeric micelles

Supramolecular aggregates composed of amphiphilic block copolymers that self-assemble into aqueous media; inner core typically serves as a container for hydrophobic drugs.

Size: 20–80 nm

Liposomes

Vesicles composed of one or more concentric bilayers of lipid molecules (entrapping hydrophobic drugs) enclosing one or more aqueous compartments (entrapping hydrophilic drugs)

Size: >20 nm

Hydrophobic drug

Hydrophilic drug

Phospholipid

PEG

Virosomes

Reconstituted virion-like lipid bilayer vesicle that contains integrated surface glycoproteins that are derived from viruses

Size: 20–150 nm

Lipid membrane

Virus surface glycoproteins

Antigen

Nanocrystals

Nanosopic crystal of a hydrophobic parent drug

Size: 50–1,000 nm

Polymeric nanoparticle

Solid nanoparticles that consist of natural or synthetic polymers

Size: 100–1,000 nm

Polymer

Hydrophobic drug

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<thead>
<tr>
<th>Industrial perspective</th>
<th>Physician/pharmacist perspective</th>
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<tbody>
<tr>
<td>Improved utilization of costly (bio)pharmaceuticals</td>
<td>More effective and less toxic therapeutic interventions</td>
</tr>
<tr>
<td>(eg, low-dose formulation, improved drug solubility/stability, controlled drug release, improved pharmacokinetic profile, targeted drug delivery)</td>
<td>Patient-friendly drug product</td>
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<tr>
<td>Drug product reformulation by using innovative health technology</td>
<td>(eg, self-administered drug product)</td>
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<td>(eg, expanded drug lifecycle, drug reintroduction)</td>
<td>Personalized therapy</td>
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<tr>
<td>Maximizing the return of R&amp;D investments</td>
<td>Simplified therapeutic procedures</td>
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<tr>
<td></td>
<td>Providing targeted drug performance</td>
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<tr>
<td></td>
<td>Accelerating the healing process</td>
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<tr>
<td></td>
<td>Improved patient compliance/adherence</td>
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<td></td>
<td>Improved medical/pharmaceutical care</td>
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<table>
<thead>
<tr>
<th>Health care system perspective</th>
<th>Patient perspective</th>
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<tbody>
<tr>
<td>Rational prescribing</td>
<td>Reducing the frequency of dosage</td>
</tr>
<tr>
<td>Overall reduction in health care costs</td>
<td>Minimally invasive method of administration</td>
</tr>
<tr>
<td>(eg, by increasing the drug efficacy, reducing the length of in-patient care stay, reducing personal health care costs, and the effective treatment of expensive major diseases)</td>
<td>Improved therapeutic outcomes</td>
</tr>
<tr>
<td></td>
<td>Reducing adverse drug effects</td>
</tr>
<tr>
<td></td>
<td>Improved quality of life of patients</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade name</th>
<th>Company</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Liposomal amphoteracin B</td>
<td>Abelcet</td>
<td>Enzon</td>
<td>Fungal infections</td>
</tr>
<tr>
<td>Liposomal amphoteracin B</td>
<td>Ambisome</td>
<td>Gilead Sciences</td>
<td>Fungal and protozoal infections</td>
</tr>
<tr>
<td>Liposomal cytarabine</td>
<td>Depocyt</td>
<td>Pacira (formerly SkyePharma)</td>
<td>Malignant lymphomatous meningitis</td>
</tr>
<tr>
<td>Liposomal daunorubicin</td>
<td>DaunoXome</td>
<td>Gilead Sciences</td>
<td>HIV-related Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>Myocet</td>
<td>Zeneus</td>
<td>Combination therapy with cyclophosphamide in metastatic breast cancer</td>
</tr>
<tr>
<td>Liposomal IRIV vaccine</td>
<td>Epaxal</td>
<td>Berna Biotech</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Liposomal IRIV vaccine</td>
<td>Inflexal V</td>
<td>Berna Biotech</td>
<td>Influenza</td>
</tr>
<tr>
<td>Liposomal morphine</td>
<td>DepoDur</td>
<td>SkyePharma, Endo</td>
<td>Postsurgical analgesia</td>
</tr>
<tr>
<td>Liposomal verteporfin</td>
<td>Visudyne</td>
<td>Novartis</td>
<td>Age-related macular degeneration, pathologic myopia, ocular histoplasmosis</td>
</tr>
<tr>
<td>Liposome-PEG doxorubicin</td>
<td>Doxil/Caelyx</td>
<td>Ortho Biotech, Schering-Plough</td>
<td>HIV-related Kaposi’s sarcoma, metastatic breast cancer, metastatic ovarian cancer</td>
</tr>
<tr>
<td>Micellar estradiol</td>
<td>Estrasorb</td>
<td>Novavax</td>
<td>Menopausal therapy</td>
</tr>
</tbody>
</table>
Lipid based Nanotherapeutics in Nanomedicines

Anticancer Therapy

Delivery Vehicles
- Liposomes: Biodegradable, sensitive to pH, temperature sensitive
- Metals: Gold, Iron oxide
- Polymeric: Natural, biologically active

Stealth Coating
- PEG, Poloxamer, Dextran, Silica acid derivatives
- Zwitterionic phospholipids, Polyglycerols
- Polyacrylic polymer, Polyvinyl polymer

Antibody Conjugated
- Plectin-1 + magnetofluorescence
- HER2 + superparamagnetic iron oxide
- Her2 + iron oxide

Quantum dots
- T7
- RGD - PEG

Imaging Agents

Ligands
- Antibodies: HER2, EGFR, CD19
- Affibodies: HER2, RGD, CGDK

Gene Therapy
- TUSC/FUS1
- EPS3
- EGFR miRNA
- IL-12

Legend
- Delivery vehicle
- Stealth
- Targeting moiety
- pH and Temp. sensitive
- Chemotherapeutic
- Gene therapy
- Imaging agent


<table>
<thead>
<tr>
<th>Key parameters</th>
<th>Free Drug</th>
<th>Liposome A</th>
<th>Liposome B</th>
<th>Liposome C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time (h)</td>
<td>4</td>
<td>&gt;48</td>
<td>&gt;48</td>
<td>&gt;48</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>11.3±1.3</td>
<td>112.1±8.3</td>
<td>48.7±3.4</td>
<td>267.5±16.3</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AUC$_{0-48}$ (ng·ml$^{-1}$·h)</td>
<td>23.7±4.9</td>
<td>876.6±122.9</td>
<td>220.4±58.0</td>
<td>944.8±127.1</td>
</tr>
</tbody>
</table>

Table 1
Physicochemical characterization of BEO and BEO-BF loaded liposomes. Data is presented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Average size (nm)</th>
<th>PDI</th>
<th>Zeta potential (mV)</th>
<th>Entrapment efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty-liposomes</td>
<td>177.91 ± 2.89</td>
<td>0.220 ± 0.089</td>
<td>-4.57 ± 1.76</td>
<td>-</td>
</tr>
<tr>
<td>BEO(^b)-liposomes</td>
<td>188.25 ± 2.19</td>
<td>0.230 ± 0.059</td>
<td>-2.95 ± 1.29</td>
<td>75.0 ± 2.32</td>
</tr>
<tr>
<td>BEO-BF-liposomes</td>
<td>185.14 ± 1.97</td>
<td>0.228 ± 0.062</td>
<td>-2.57 ± 1.38</td>
<td>77.0 ± 1.94</td>
</tr>
</tbody>
</table>

\(^a\) Polydispersity index.
\(^b\) Bergamot essential oil.
\(^c\) Bergamot essential oil bergaptene-free.
Table 2: Plasma pharmacokinetic parameters of GEM and its inactive metabolite, 2',2'-difluorodeoxyuridine, after a single intravenous administration in CB-17 SCID-mice.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>$t_{1/2}$ (h)</th>
<th>$C_{max}$ (µg/ml)</th>
<th>$T_{max}$ (h)</th>
<th>$V_d$ (ml)</th>
<th>AUC (µg/ml h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free GEM</td>
<td>1.0 ± 0.12</td>
<td>0.55 ± 0.07</td>
<td>0.5 ± 0.1</td>
<td>181.81 ± 0.09</td>
<td>0.666 ± 0.034</td>
</tr>
<tr>
<td>L-GEM*</td>
<td>8.0 ± 0.26</td>
<td>0.51 ± 0.01</td>
<td>1.0 ± 0.1</td>
<td>444.44 ± 0.13</td>
<td>5.171 ± 0.029</td>
</tr>
<tr>
<td>Metabolite from GEM</td>
<td>4.0 ± 0.24</td>
<td>1.25 ± 0.05</td>
<td>0.5 ± 0.2</td>
<td>80.00 ± 0.20</td>
<td>10.260 ± 0.086</td>
</tr>
<tr>
<td>Metabolite from L-GEM*</td>
<td>10.0 ± 0.39</td>
<td>1.57 ± 0.08</td>
<td>2.0 ± 0.1</td>
<td>72.46 ± 0.11</td>
<td>23.302 ± 0.076</td>
</tr>
</tbody>
</table>

* All data of pharmacokinetic parameters have a statistical significance ANOVA $P < 0.001$ with respect to free GEM and metabolite from GEM.

a, panel a shows the body distribution of SLs after *in vivo* injection in liver and blood; b, panel b shows the body distribution of SSL(4)s after *in vivo* injection in liver and blood.

Nude SKID mice bearing MDA-MB-231 breast cancer bone metastasis cells treated by using Dox hydrochloride-loaded SSLs. The anticancer treatment is carried out for 5 weeks. Images are acquired per week. Animals are injected i.v. during the treatment. 5 animals per groups is used during the experiments. Key legends: A) PBS solution (control); B) empty SSLs; C) Doxorubicin hydrochloride; D) Doxorubicin hydrochloride-loaded SSLs.

Quantification of tumor development and body weight in Nude SKID mice bearing MDA-MB-231 breast cancer bone metastasis cells treated by using Dox hydrochloride-loaded SSLs. Key legends: (●) PBS buffer solution; (▼) Empty SSLs; (■) Doxorubicin hydrochloride; (◇) Doxorubicin hydrochloride-loaded SSLs. 5 animals per groups is used during the experiments.

Physicochemical Properties

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Size/nm</th>
<th>PDI</th>
<th>ζ/mV (-)</th>
<th>EE/%</th>
<th>LED/μg/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Lip</td>
<td>106.2 ±1.1</td>
<td>0.093 ± 0.016</td>
<td>10.2 ± 0.6</td>
<td>62.2 ± 1.6</td>
<td>58.4 ± 3.5</td>
</tr>
<tr>
<td>E-Lip</td>
<td>114.7 ± 1.5</td>
<td>0.044 ± 0.028</td>
<td>10.7 ± 0.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RE-Lip₁</td>
<td>116.6 ± 1.3</td>
<td>0.064 ± 0.016</td>
<td>11.8 ± 1.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RE-Lip₂</td>
<td>96.1 ± 0.6</td>
<td>0.158 ± 0.009</td>
<td>9.3 ± 1.1</td>
<td>—</td>
<td>—</td>
</tr>
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</table>

Conclusion

✔ Liposomes can significantly enhance the anticancer efficiency of chemotherapeutics for the treatment of solid and blood-borne tumors.

✔ Liposomes can increase the circulation time, decrease side effects, enhance tumor accumulation and overcome drug resistance of chemotherapeutics.

✔ Liposomes improve pharmacokinetic and biopharmaceutical features of chemotherapeutics.

✔ Liposomes provide a customized chemotherapy in innovative Nanomedicine.

✔ Liposomes are therapeutic tools for chemotherapeutic treatment.
Future Perspective

✔ Many more liposomal chemotherapeutics will gain clinical approval in the near future.

✔ Overcome the potential toxicity arising from the presence of PEG on liposomal surface.

✔ Overcome the high production costs in comparison with conventional cytotoxic agents.

✔ Improve the number of Clinical Trails using liposomal chemotherapeutics.

✔ Customize Selective Liposomal Chemotherapeutics.
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