Design and development of multi wall-carbon nanotube – liposome drug delivery platforms

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According to Rowland et al., (2012):
“A Drug Delivery System (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body.”
These materials are characterized by softness (synonymous with deformability).

Nanostructured drug carriers allow for the delivery not only small-molecule drugs but also the delivery of nucleic acids and proteins.
Liposome in drug delivery:

Spherical vesicles with a phospholipid bilayer

Pharmacokinetics: efficacy and toxicity

Change the distribution and absorption

Deliver drug in desired form

Multidrug resistance

Decrease harmful side effects
Carbon nanotubes in drug delivery:

Functionalized CNTs

- Diagnosis and Imaging
  - Cancer therapy
  - Gene therapy
  - Tissue engineering
- As antioxidants
- Therapeutics
  - Biosensors
  - Enantioseparation of chiral drugs
- Extraction of chemicals

Delivery of anticancer drugs:

- Reduced toxicity
- Increased circulation period
- Active targeting
- Reduced side effects
- Controlled toxicity

Enhanced permeability and retention (EPR) effect:
Advanced drug delivery nano systems:

- Co-delivery of si-RNA and cytotoxic drugs
- Efficient cell uptake
- High drug loading
- Biomimetic molecular transport systems
- Lab-on-chip applications

- Carbon nanotubes – liposome conjugate
- Carbon nanotube – liposome supramolecular nanotrains
- Cationic liposome-multiwalled carbon nanotube hybrids

Miyako et al., 2012
Karchemchi et al., 2012
Pereira et al., 2015
Differential Scanning Calorimetry: interactions between lipid bilayers and MWCNTs

Local perturbations in the lipid structure caused by the nanotubes could lead to enhance penetration of molecular compounds across the membrane.

The membrane swells due to the presence of the nanotubes, in particular, when a bundle of nanotubes is found within the membrane. When one nanotube is parallel to the membrane and located at its center, only small structural differences are observed compared to the pristine membrane.

The pure DPPC and HSPC membranes hydrated in HPLC grade water undergo two endothermic phases: a broad low enthalpy pretransition from gel (Lβ') to rippled (Pβ') phase centered at 36.5°C and 47.9°C and a sharp-major transition from Pβ' to liquid crystal phase (Lα) at 41.9°C and 53.6°C, respectively.

Synthesis:

MWCNTs

(4:1 w/v) H₂SO₄, H₂O₂ →

(i) SO₃
(ii) (1:1 w/v) SO₃, HNO₃ →

NaHCO₃ → CN1

CN2
mixture sulfuric acid and hydrogen peroxide

the diameter is $<15$ nm.
Preparation of multi wall-carbon nanotube–liposome drug delivery platforms

Karchemski et al., 2012)
Methods:

Thermodynamic and Biophysical Characterization

- Differential Scanning Calorimetry

Physicochemical Characterization

- Dynamic and Electrophoreteric Light Scattering

Biological evaluation

- In vitro screening
Differential Scanning Calorimetry: DPPC bilayers

- The main transition temperature, which corresponds to the mobility of the acyl chains of phospholipids, remains unaffected for all the samples.
- The transition enthalpy $\Delta H_m$ decreased with the presence of MWCNTs. According to the phase transition behavior of liposomes, on heating, there is increased head group mobility and water penetration into the interfacial region of the bilayer.
- The temperature or the pretransition effect decreased and this phenomenology indicates strong interactions between the polar groups of DPPC lipid and MWCNTs.
Differential Scanning Calorimetry: HSPC bilayers

• the pretransition effect decreased and this phenomenology indicates strong interactions between the polar groups of HSPC lipid
• when nanotubes are parallel to the membrane and located at its center, only small structural differences are observed compared to pure lipid membrane
Physicochemical characteristics:

<table>
<thead>
<tr>
<th>System</th>
<th>(D_h) (nm)</th>
<th>SD</th>
<th>(\zeta)-pot (mV)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN1</td>
<td>349.0</td>
<td>10.0</td>
<td>-23.3</td>
<td>2.1</td>
</tr>
<tr>
<td>CN2</td>
<td>149.2</td>
<td>0.7</td>
<td>-21.4</td>
<td>0.1</td>
</tr>
<tr>
<td>HSPC</td>
<td>126.6</td>
<td>1.6</td>
<td>+3.5</td>
<td>0.1</td>
</tr>
<tr>
<td>DPPC</td>
<td>178.4</td>
<td>0.7</td>
<td>+3.6</td>
<td>0.1</td>
</tr>
<tr>
<td>HSPC:CN1</td>
<td>148.8</td>
<td>2.4</td>
<td>-1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>HSPC:CN2</td>
<td>196.0</td>
<td>4.2</td>
<td>-3.2</td>
<td>2.7</td>
</tr>
<tr>
<td>DPPC:CN1</td>
<td>193.6</td>
<td>2.6</td>
<td>+4.5</td>
<td>0.8</td>
</tr>
<tr>
<td>DPPC:CN2</td>
<td>282.1</td>
<td>10.6</td>
<td>+3.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- The presence of CNTs reduce the size of HSPC/DPPC mixed nanocarriers
- The \(\zeta\)-potential values of mixed nanocarriers are near zero
  - This observation indicates the effective incorporation of MWCNTs into the lipid bilayer of liposomes and absence of surface charge into mixed liposomal surface
**Fluorescence spectroscopy:**

<table>
<thead>
<tr>
<th>System</th>
<th>(I_1/I_3)</th>
<th>(I_E/I_M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSPC</td>
<td>1.42</td>
<td>0.29</td>
</tr>
<tr>
<td>DPPC</td>
<td>1.55</td>
<td>0.26</td>
</tr>
<tr>
<td>HSPC:CN1</td>
<td>1.58</td>
<td>0.59</td>
</tr>
<tr>
<td>HSPC:CN2</td>
<td>1.65</td>
<td>0.18</td>
</tr>
<tr>
<td>DPPC:CN1</td>
<td>1.37</td>
<td>0.66</td>
</tr>
<tr>
<td>DPPC:CN2</td>
<td>1.58</td>
<td>0.61</td>
</tr>
</tbody>
</table>

- \(I_1\) = 372 nm
- \(I_3\) = 383 nm
- \(I_E\) = 480 nm
- \(I_M\) = 372 nm

- ↑\(I_1/I_3\) → ↑ micropolarity
- ↑ \(I_E/I_M\) → ↑ microfluidity → ↓ microviscosity

• For mixed nanostructures the micropolarity increased.
• This may be correlated to the way that the carbon nanotubes are incorporated into the lipid tails region, which apparently results in minimum changes in the micropolarity.
• The microfluidity also increased.
Toxicity studies: *In vitro* screening:

- Low toxicity of the vast majority of the lipid/MWCNTs nanocarriers, even at high concentrations i.e. 500 μM
- The IC50 values for HSPC/MWCNTs vesicles and DPPC/MWCNTs nanocarriers are greater than 500 μM in all cases.
Conclusions:

Design and Development of advanced drug delivery systems
Interactions between the components
Acknowledgements:

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Dr. D. Chronopoulos
Thank you for your kind attention!