Responsive release from a core-shell assembly

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Liposomal release

Leaky enough to allow release, but not so leaky that cargo is lost prematurely

- Limits range of lipids that can be used
- Poor stability

Activation allows release on demand

- Expands range of lipids that can be used (e.g. high melting lipids)
- Improves stability and reduces leakiness

\[ R \propto \frac{1}{r_a} + \frac{1}{r_b} \]
\[ \frac{1}{r_b} \propto \frac{D_K}{t} \]
\[ R \propto \frac{1}{r_a} + \frac{1}{r_b} + \frac{1}{r_s} \]
Liposome-nanoparticle assemblies (LNAs)

\[ d_{\text{NP}} < d_{\text{core}} \quad d_{\text{NP}} < \sim t_b \quad d_{\text{NP}} < d_{\text{SLB}} \]

Core encapsulated \( \rightarrow \) Bilayer embedded \( \rightarrow \) Surface decorated

Nanoparticle ‘activation’ facilitates release

- Magnetic fields – magnetic nanoparticles (e.g. \( \text{Fe}_3\text{O}_4 \))
- Light – metallic nanoparticles (e.g. \( \text{Au} \))

(B-1) Rasch et al, Nano Lett, 2010, 10
(B-2) Chen & Bothun, ACS Nano, 2010, 4
(C-1) Wu et al, J Am Chem Soc, 2008, 130
(D) Volodkin et al, Angew Chem Int Ed, 2009, 48
Magnetic nanoparticles & magnetoliposomes

• Maghemite ($\gamma$-Fe$_2$O$_3$) or magnetite (Fe$_3$O$_4$)
  – Small, single domain nanoparticles are superparamagnetic
  – Low toxicity

• Magnetic drug delivery
• Magnetic biosensing and diagnostics

\begin{align*}
\text{Permanent fields} &= \{ \text{MR image contrast agents} \} \\
\text{Alternating fields} &= \{ \text{Nanoparticle-mediated hyperthermia} \}
\end{align*}

• Responsive drug delivery

Soenen et al, *Nanomed*, 2009, 4
Nanoparticles in EMF fields (at RF)

A: **Neel relaxation.** Magnetic dipoles change direction; magnetic losses $\Rightarrow$ heat (< 10-20 nm)

B: **Brownian relaxation.** Magnetic moment does not change; frictional losses $\Rightarrow$ heat (> 10-20 nm)

$$P = \pi \mu_0 \chi_0 H_0^2 f \left( \frac{2\pi f \tau}{1 + (2\pi f \tau)^2} \right)$$

(POWER DISSIPATION PER VOLUME)

- $\mu_0$: permeability of free space
- $\chi_0$: equilibrium susceptibility, incorporates $\rho = \phi \rho_N + (1 - \phi) \rho_L$, $c_p = \phi c_{p,N} + (1 - \phi) c_{p,L}$
- $H_0, f$: field amplitude and frequency ($H =$ current $\times$ # coils per length)
- $\tau$: effective relaxation time due to Néel and Brownian relaxation

$$\frac{\Delta T}{\Delta t} = \frac{P}{c_p \rho} = \frac{SAR m_{NP}}{c_p m_v}$$

Rate of heating of a mass containing NPs

Local nanoscale heating may not be achievable

- Water is an excellent heat sink
- Bilayer thickness yields minimal heat transfer resistance

\[ \lambda \nabla^2 T + \frac{dq}{dt} = c_p \frac{dT}{dt} \]

\[ T_s - T_\infty = \left( \frac{1}{2\pi kr_p} \right) \frac{dQ_{nano}}{dt} \]

\[ T_s - T_\infty = \frac{Pr_p^2}{3k} \]

Can local heating be attained in magnetoliposomes (MLs) and measured directly using an anisotropic fluorescent probe?


12 nm Fe₃O₄
67% encap.
317 nm dia.
In situ heating via membrane order, $\langle r \rangle$

1 kW, 330 kHz, 250 A

Cannot distinguish between local and bulk temperatures at the fluorescence time scale
An approach inspired by biology

Brownian and Neel relaxation

Transmembrane proteins
hydrophobic core and hydrophilic ends

\[ E_{\text{stretch}} \propto \kappa_a \]
\[ E_{\text{bend}} \propto \kappa_b \]

\( d = 6.5 \text{ nm} \)


Y. Chen, A. Bose, G.D. Bothun, ACS Nano 2010, 4(6), 3215-3221
Bilayer-embedded SPIO nanoparticles

5 nm maghemite ($\gamma$-Fe$_2$O$_3$) stabilized in chloroform with oleic acid (Ocean NanoTech)

Solvent phase
Dipalmitoylphosphatidylcholine (DPPC)
SPIO NPs (as received and washed)

DIUF water

emulsification

REV at 50 $^\circ$C
450 mbar, 20 min
300 mbar, 20 min
200 mbar, 10 min

DPPC

1 - 10 mM DPPC
DPPC/NP
2 - 25,000:1 (0.5 mM, 0.08 mg/ml Fe$_2$O$_3$)
3 - 10,000:1 (1.2 mM, 0.19 mg/ml)
4 - 5,000:1 (2.4 mM, 0.38 mg/ml)
Structure and embedment via cryo-TEM

DPPC/NP
25,000:1
ϕ_{NP/L} = 0.002

DPPC/NP
10,000:1
ϕ_{NP/L} = 0.005

DPPC/NP
5,000:1
ϕ_{NP/L} = 0.01

Scale bars = 200 nm
Embedded NPs exist partially as aggregates
Effect of SPIO NPs on DPPC phase behavior

Experiments conducted at 0.1 mM DPPC using a TA Instruments Nano DSC

<table>
<thead>
<tr>
<th>L/N ratio</th>
<th>$\Delta H_m$ (KJ/mol)</th>
<th>$\Delta T_{m,1/2}$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34.3</td>
<td>1.2</td>
</tr>
<tr>
<td>25,000:1</td>
<td>35.7</td>
<td>3.8</td>
</tr>
<tr>
<td>10,000:1</td>
<td>37.2</td>
<td>3.5</td>
</tr>
<tr>
<td>5,000:1</td>
<td>41.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Controlled release from dMLs

25 °C

CF Leakage (fraction)

Time (s)

Total release

(1) DPPC
(2) DPPC/NP = 25,000:1
(3) DPPC/NP = 10,000:1
(4) DPPC/NP = 5,000:1

diffusing probe (carboxyfluorecein)
lipid bilayer
Enhanced stability & non-invasive

![Graph showing initial leakage rate vs. mM Fe₂O₃ with and without heating.]

- w/ heating, optimum
- w/o heating, stabilization

![Bar graph showing CF leakage (%).](DPPC/NP = 10,000:1, 30 min heating, Hf < 4.85x10⁵ kA m⁻¹ s⁻¹)
Thermomechanical leakage mechanism

\[ \tau_N \sim 1 \times 10^{-9} \text{s} \]
\[ \tau_B \sim 4 \times 10^{-7} \text{s} \]

w/ aggregation, \( \tau_N \) decreases
\( f^{-1} \sim 3 \times 10^{-6} \text{s}, \text{Neel + Brownian} \)

L/N = 5,000:1
Before heating

L/N = 5,000:1
After heating, 250 A
Conclusions

- Small hydrophobic nanoparticle “triggers” can be embedded in lipid bilayer membranes to control liposomal release
  - May overcome stability limitations and poor cargo delivery
- Release achieved at non-invasive EMF conditions
  - Transient burst-release mechanism

- Restructuring due to embedment
- Functional and stabilizing lipids
- Cytotoxicity (w/o PEG-lipid shown)
Bothun Lab & Collaborators

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