Drug delivery with temperature sensitive liposomes

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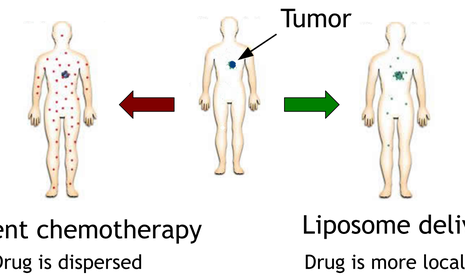
Introduction

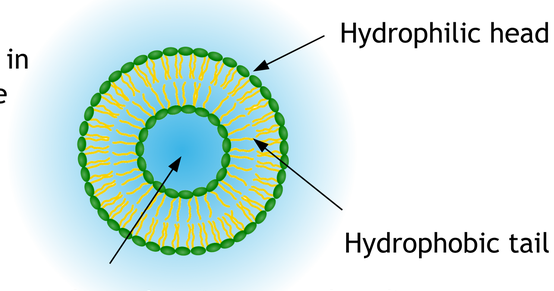
The drawbacks of standard chemotherapy treatments are well known, and are due primarily to the interaction of the drug with bodily systems outside of the targeted cancerous region. More recent treatments using liposomes (small bubbles of cell membrane material) as delivery vehicles for chemotherapeutic drugs have shown promise in reducing cardiotoxic side effects of the encapsulated drug doxorubicin. However, for delivery of the drug these formulations rely on slow leakage of the drug from within the liposome, which is indiscriminate and may impact healthy tissue as well as the targeted cancer. By using a scheme involving controlled encapsulation and release with temperature sensitive liposomes, drug delivery to cancerous sites could be much improved and adverse effects minimized.



The Liposome

➔ Composed of phospholipid bilayer

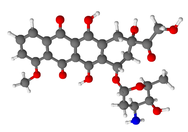
Features
- Naturally aggregates in "leaky" cancer tissue
- Releases content at approx. 40°C



Research Goals

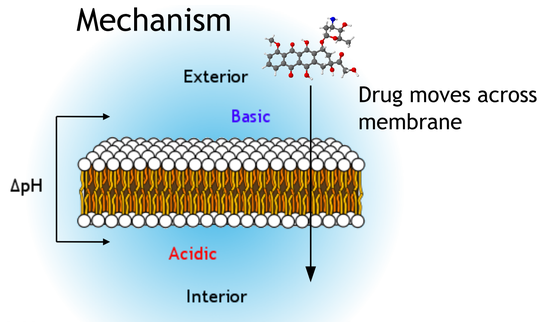
Drug Encapsulation

The Drug



Doxorubicin
(chemotherapeutic antibiotic)

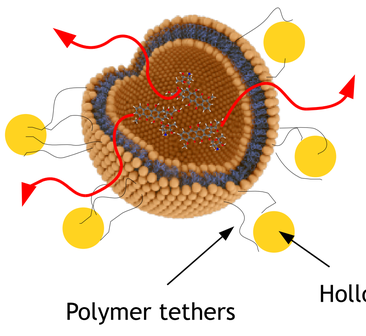
Mechanism



A difference in pH across the membrane (the pH gradient, ΔpH) facilitates encapsulation

Goals
- To determine what loading conditions yield the highest encapsulation
- To determine what method of pH gradient formation yields the highest encapsulation

Controlled Release



Mechanism
1. Nanoshells are tethered to liposome
2. Liposomes are irradiated with near-infrared laser
3. Nanoshells absorb light, and heat liposome to release temperature
4. Drug is released

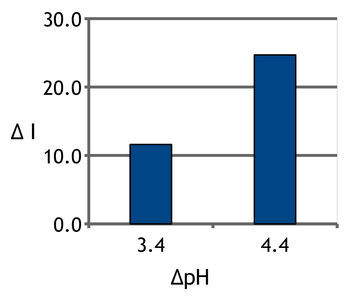
Goals
- Achieving effective enough tethering to observe significant release

Primary Method: Fluorescence Spectroscopy
- Fluorescence of doxorubicin is measured before and after lysing liposomes with detergent
- From this, a change in intensity (ΔI) is calculated, and related directly to the amount of drug encapsulated within the sample

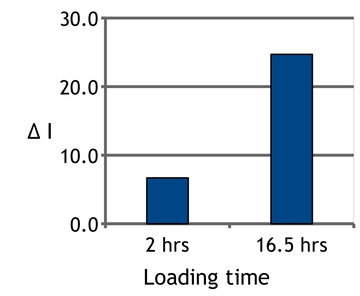
Preliminary Results: Encapsulation

➔ Change in fluorescence intensity (ΔI) is indicative of how much drug was encapsulated

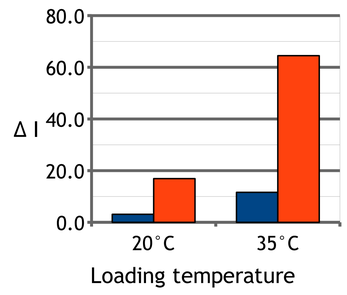
Increased pH Gradient



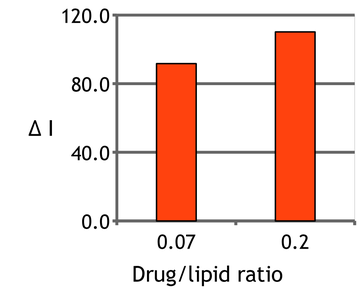
Increased Loading Time



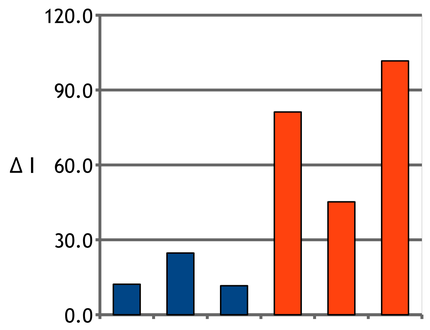
Increased Loading Temperature



Increased Drug/Lipid Ratio



Method Comparison



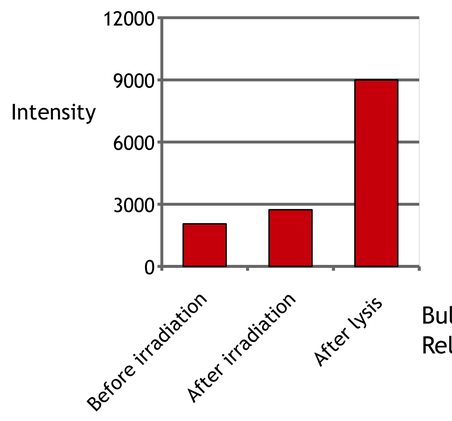
Two loading schemes used

- Double buffer method
  - Manually established pH gradient
- Ion gradient method
  - Passively established pH gradient

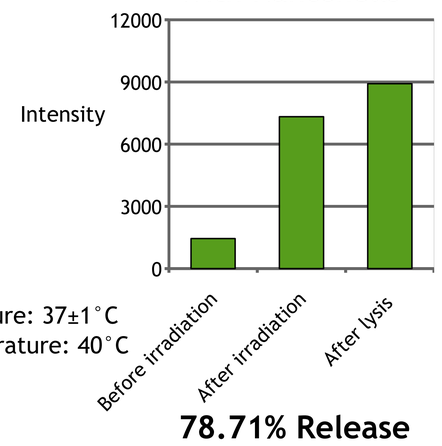
Preliminary Results: Release

➔ Loaded liposomes irradiated with near-infrared laser

Without Nanoshells



With Nanoshells



Bulk Temperature: 37±1°C
Release Temperature: 40°C

78.71% Release

Conclusions

Encapsulation

Increases in encapsulation seen when:
- pH gradient is increased
- Loading time is increased
- Loading temperature is increased
- Drug to lipid ratio is increased
- Ion gradient loading shows to be much more efficient

Release

- Significant release observed with nanoshells
- This suggests relatively effective nanoshell tethering

Future Work

- Leakage measurement
- Comparative release with different tethering methods
- More encapsulation data, specifically loading time