Optimisation of ultrasound-responsive niosomes for localised delivery of chemotherapy

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Introduction

- Chemotherapy is associated with significant off-target toxicity
- Ultrasound enables site-specific drug release
- Niosomes are stable, flexible and low-cost ultrasound-responsive nanocarriers

Aims of this project

- To explore the effects of cholesterol content and PEGylation on the ultrasound responsiveness of Span 60 niosomes for targeted and safe chemotherapy delivery

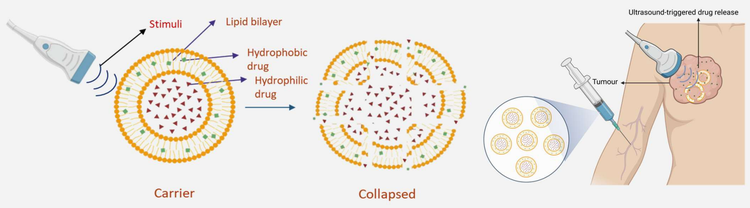

Figure 1. Ultrasound-triggered drug release from niosomal carriers

Methods

- Niosomes were prepared using varying ratios of Span 60, cholesterol and 5 mol% of PEG
- Formulations were loaded with curcumin (hydrophobic) or fluorescein sodium salt (hydrophilic) as model drugs
- Characterisation methods included
  - Particle size, polydispersity and zeta potential
  - Drug loading and ultrasound-triggered release
    - 1 MHz, 50% duty cycle, (1-3) W/cm^2 intensities, (1-5) min
  - Formulation stability
  - Formulation and ultrasound safety via haemolysis

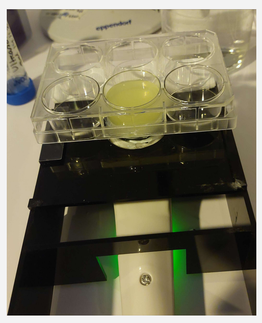

Figure 2. Ultrasound administration setup. All release and safety evaluations used cell culture wells.

Results: Baseline particle characteristics

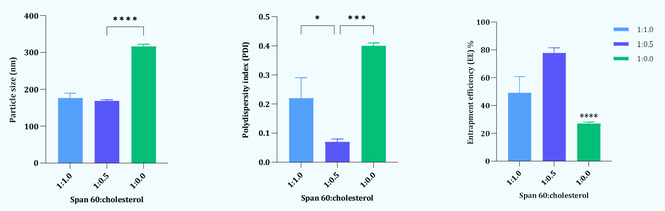

Figure 3. Effect of cholesterol on particle size (left), PDI (middle), EE% (right).

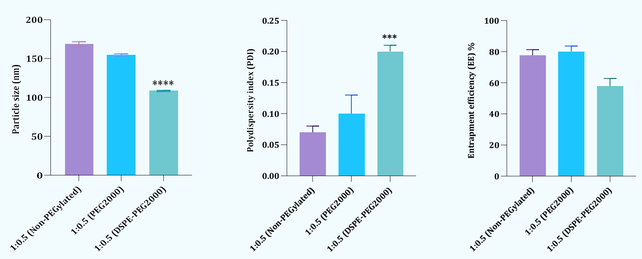

Figure 4. Characteristics of non-PEGylated and PEGylated niosomes.

Data are presented as mean ± SD (n = 3). Statistical significance was determined using one-way ANOVA as appropriate (***p < 0.001, ****p < 0.0001)

Results: Triggered drug release

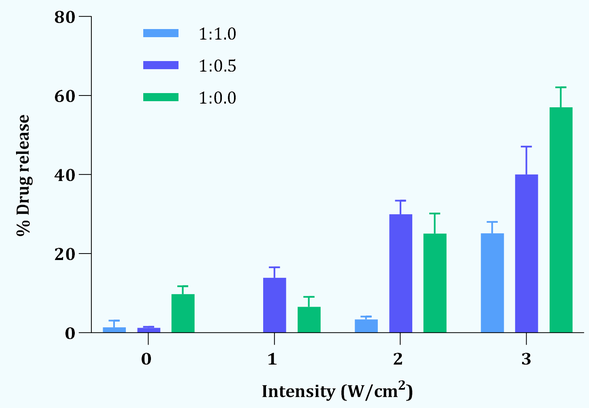

Figure 5. Ultrasound-responsive drug release across different niosomal formulations with varying Span 60:cholesterol ratios corresponding to decreasing cholesterol content (1.0-0.0)

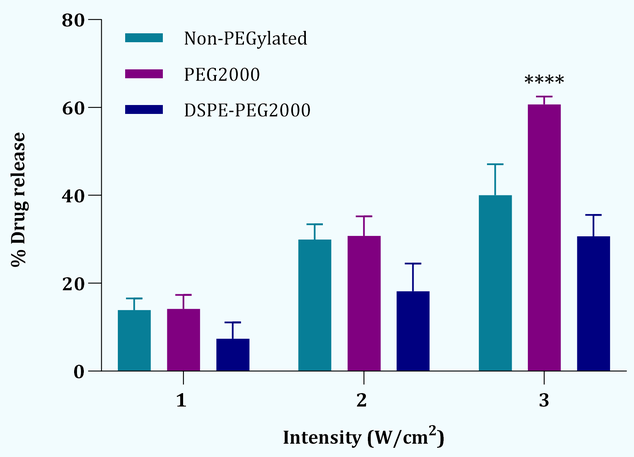

Figure 6. Triggered drug release from non-PEGylated and PEGylated niosomes at increasing ultrasound intensities for 5 min.

Note: Data are presented as mean ± SD (n = 3). Statistical significance was determined using two-way ANOVA as appropriate (****p < 0.0001)

Results: Temperature increment

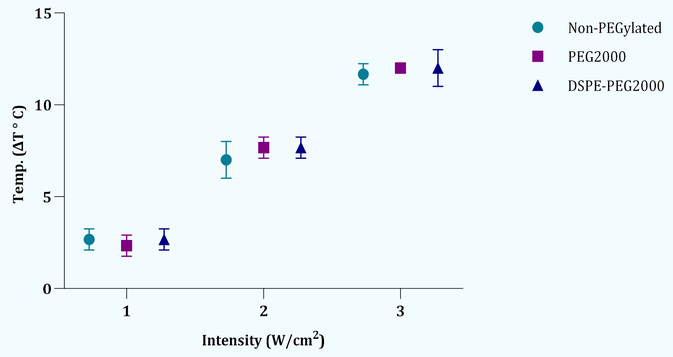

Figure 7. Ultrasound-induced temperature increment with different formulations at increasing ultrasound intensities for 5 min

Results: Haemolysis with and without US

Table 1. Haemolysis results for non-PEGylated and PEGylated niosomes at three different concentrations.

Concentration (µg/mL)	500	250	125
Non-PEGylated	Variable	Safe	Safe
PEGylated	Variable	Safe	Safe

Table 2. Haemolysis results for different ultrasound intensities and administration times. A 50% duty cycle was used in all cases.

Intensity	1 min	2 min	3 min	4 min	5 min
1 W/cm^2	Safe		Safe		Safe
1.5 W/cm^2		Variable	Variable		Variable
2 W/cm^2	Safe	Variable	Unsafe		Unsafe
2.5 W/cm^2					
3 W/cm^2	Safe	Variable	Unsafe		Unsafe

Results: Haemolysis (formulation + ultrasound)

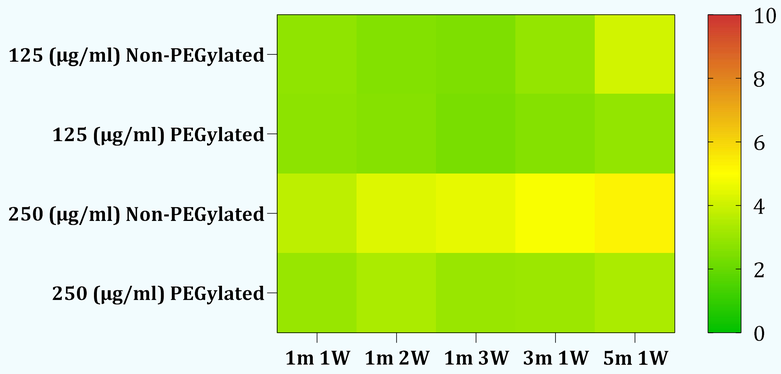

Figure 10. Heatmap showing percent haemolysis for non-PEGylated and PEGylated formulations subjected to various ultrasound treatments

Colour bar represents haemolysis percentage (0-10%).

Results: Stability studies

Table 3: Stability studies of Non-PEGylated vs PEGylated (PEG2000) formulation over a 28-day period

Formulation	Non-PEGylated		PEGylated	
Storage period	Day 0	Day 28	Day 0	Day 28
Size (nm)	165.6 ± 0.8	500.0 ± 284.2 ***	170.6 ± 4.0	171.5 ± 5.3
PDI	0.15 ± 0.04	0.54 ± 0.37 **	0.20 ± 0.06	0.20 ± 0.05
Zeta (mV)	- 17.5 ± 1.6	- 16.8 ± 3.3	- 19.3 ± 1.2	- 17.8 ± 1.9
EE (%)	80.6 ± 5.1	69.1 ± 4.0	77.4 ± 6.8	62.4 ± 17.4

Conclusion

- Increasing cholesterol enhanced particle stability but reduced US responsiveness
- PEGylation with PEG2000 preserved particle size and surface charge while significantly enhancing US responsiveness at higher intensities
- PEGylation with DSPE-PEG2000 reduced particle size to (108.4 ± 0.6 nm), neutralised the surface charge, and reduced particle US sensitivity
- Temperature increases were dependent on ultrasound intensity and exposure duration
- Safe operating conditions were identified as niosome concentrations of ≤250 µg/mL and ultrasound exposure for 1 min at 1-3 W/cm² or for 3 min at 1 W/cm² establishing operational parameters for future translational studies

Future directions

Formulation and ultrasound safety via human dermal fibroblast viability assay

Contact details

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