Mechanistic Insights into Liposomal Disassembly: Effects of Serum Proteins, Lipid Exchange on Drug Release

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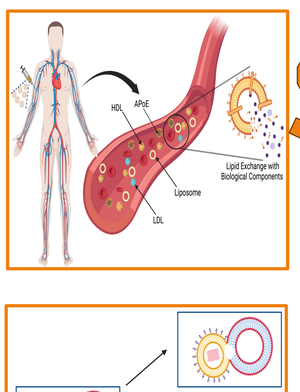
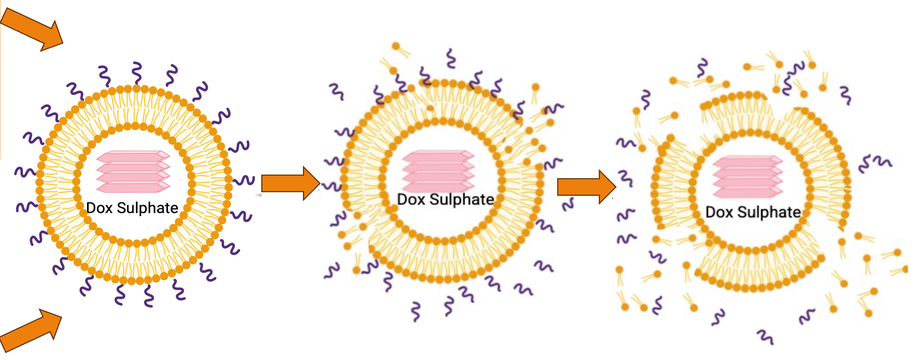
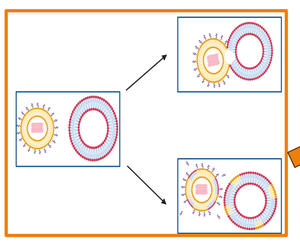
Introduction

- Caelyx (Doxil®) as the model PEGylated liposomes.
- This study examines the effects of serum protein concentrations and lipid exchange on liposomal disassembly and drug release.



1 Serum Protein Concentration

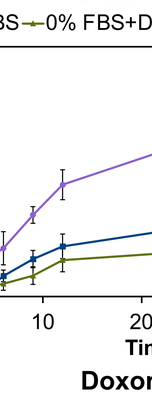




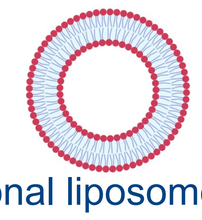
2 Lipid Exchange Mechanism

Methods

- Pharma Test Dispersion Releaser (PTDR) was used for the release study at 37ºC with 25 stirring rate.
- 300kDa MWCO membrane was used.



1 Different concentrations of FBS as release media (0,10, 50 and 90% v/v in PBS)



2 Additional liposomes into the donor phase

From the donor phase

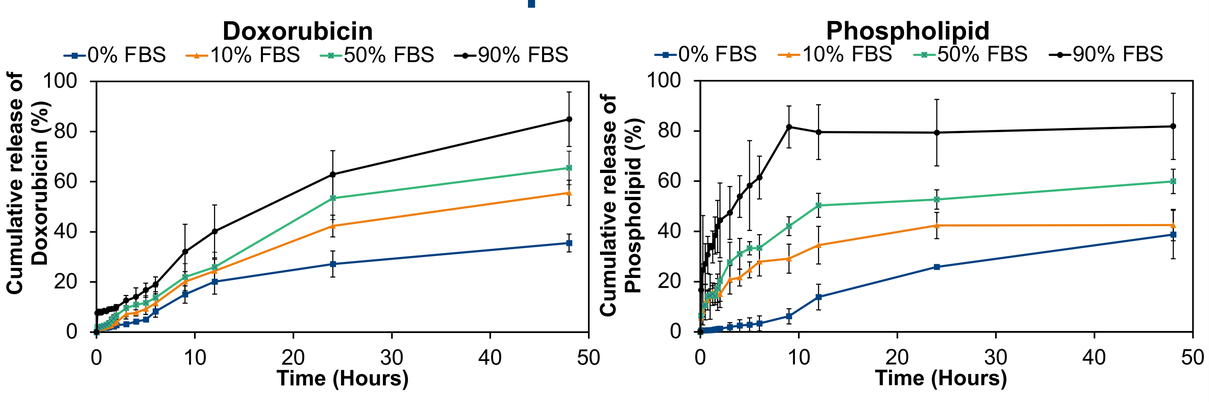
Monitoring the particle size changes over time by NTA

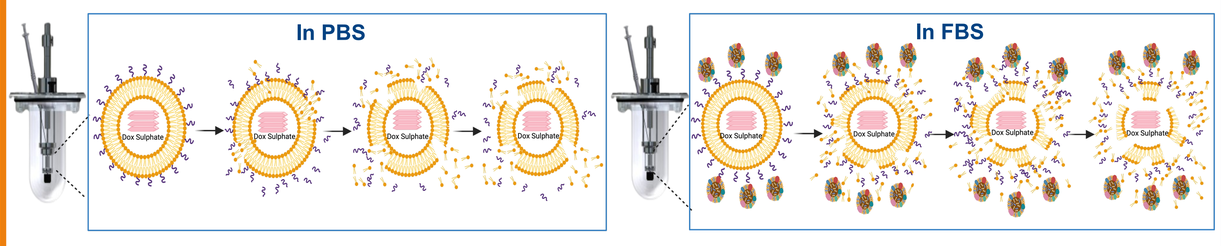
From the acceptor phase

Quantitative analysis of drug and phospholipid by HPLC and LCMS respectively

Results

Effect of serum protein concentrations





In PBS, both the drug and phospholipid exhibited slow initial release, followed by a slightly increase in release, before reaching a plateau.

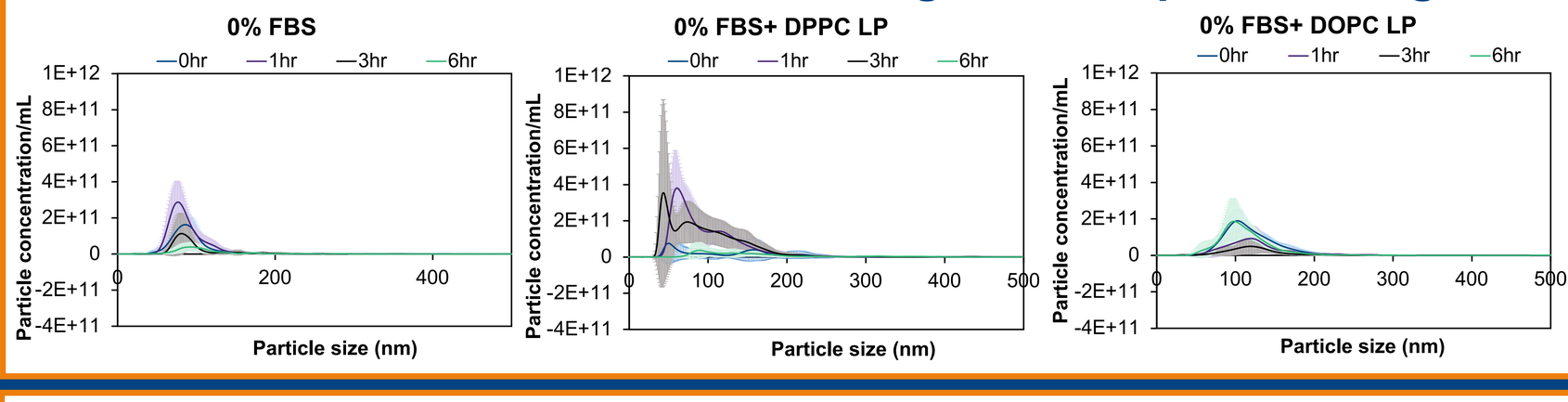
In FBS, increasing serum concentration accelerates both phospholipid and doxorubicin release. Phospholipid release exhibited a rapid initial phase followed by a plateau, whereas doxorubicin release displayed a slower initial phase, possibly due to a lag time associated with dissolution of doxorubicin sulphate crystal, followed by an accelerated release after 6 hours, and a final plateau.

Lipid exchange study

DPPC LP and DOPC LP were employed to investigate lipid exchange. In PBS, the presence of **DPPC LP significantly reduced release**, whereas **DOPC LP enhanced release**.

In contrast, **no significant lipid exchange effect** was observed **in the presence of serum proteins.**

Particle size changes from lipid exchange study by NTA



DPPC LP increased particle size distribution, suggesting **lipid exchange** mediated **liposome fusion**, resulted in **reduced release**. In contrast, particle size distribution remained stable in only PBS or with DOPC LP, with only a decrease in particle concentration, indicating phospholipid release.

Conclusion

- Phospholipid and drug release increased in an **FBS concentration-dependent manner**, indicating serum-mediated liposome destabilization and enhanced lipid transfer.
- Additional liposomes in the donor phase modulated the release profiles of both drug and phospholipid, suggesting that **lipid exchange influences release kinetics.**
- The particle size distribution data are consistent with **lipid exchange and vesicle-vesicle interactions** (e.g., lipid transfer and transient hemi-fusion), which depend on the membrane properties and the phase transition of the interacting liposomes.

References

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