Co-loading Dexamethasone Palmitate in siRNA-LNPs

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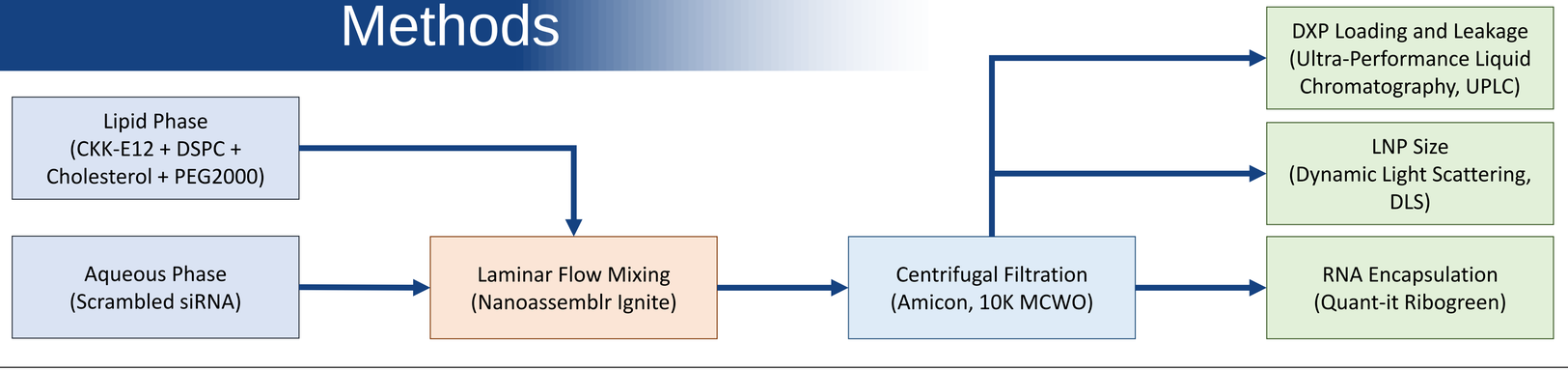
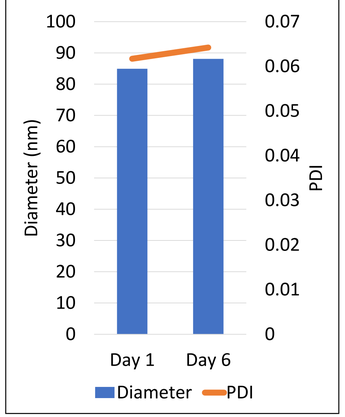
Introduction

- RNA lipid nanoparticles (LNPs) are immunostimulatory and exacerbate pre-existing inflammation
- The ionizable lipid component of LNPs signals through toll-like receptors (TLRs) to activate the NLRP3 inflammasome.
- Dexamethasone (Dex) is a clinically safe and upstream suppressor of inflammation.
- Dexamethasone palmitate (DXP) is a lipophilic precursor that metabolizes into Dex by ester cleavage in blood.

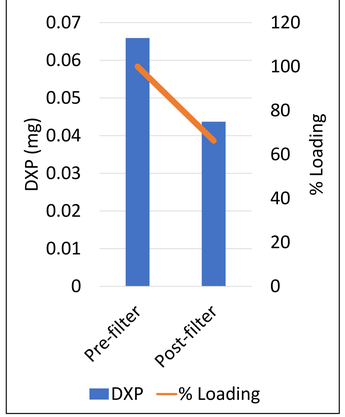
Methods



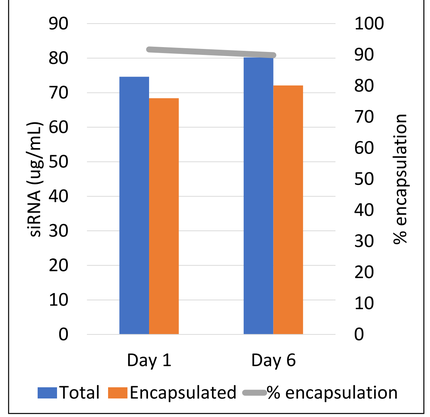
LNP Size



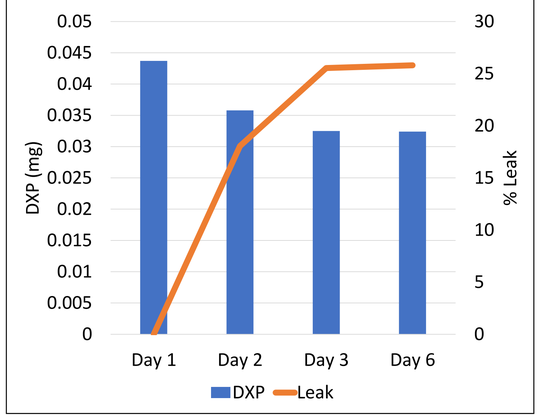
DXP Loading



siRNA Encapsulation



DXP Leakage



Hypotheses

- **DXP can be stably loaded into the lipid phase of siRNA-LNPs**
- **DXP will be retained in LNPs**

Discussion

- **LNPs formed a homogenous population of ~80 nm diameter spheres with a stable ~90% siRNA encapsulation.**
- **~66% of total DXP loaded into the LNPs and DXP leakage plateaued at ~26% over 6 days.**

Future Steps

- Evaluate inflammation suppression of LNPs in vivo
- Co-load MCC950, a specific and lipophilic, NLRP3 inhibitor

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