Bedaquiline loaded lipid nanoparticles: formulation, optimisation and in vitro assays

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ABSTRACT

Increase in antibiotic resistance is a global concern worldwide. The main objective of the NAREB European project relies on the design of novel nanotherapeutics to overcome the antibiotic resistance issues in MDR-TB and MRSA respectively.

Bedaquiline is a new drug for the treatment of MDR-TB, recently FDA-approved in 2012, but its high toxicity and its poor water solubility still hamper its therapeutic action. Considering this, Bedaquiline is therefore a good candidate for therapeutic improvement by encapsulation into biocompatible nanoparticles for a better delivery into the infected tissues. In this study, we have shown that Bedaquiline is very well encapsulated in lipid nanoparticles (LNP) with payloads up to 10% (w/w). A parallel development of neutral and cationic Bedaquiline loaded LNPs has been made with comparison of physico-chemical as well as biological features. The Cytotoxicity of the loaded particles indicated that these particles were well tolerated at desired doses. Testing with TB bacteria strains will also be presented showing that the Bedaquiline is still highly active when encapsulated, compared to the free drug. These particles have also been tested in TB-infected human macrophages in culture, indicating that cationic LNP are more active than neutral ones. Following these experiments, it was possible to select an optimal formulation for further investigation. This is now ongoing in NAREB by testing in TB-infected animal models.

Daptomycine has been discovered in 1986 and this drug could improve efficacy compared to vancomycin but still have adverse effects. The nano-encapsulation of this drug is thus a way to explore in order to improve therapeutics results against MRSA. In this study we have shown that Daptomycine is well loaded in cationic LNP whereas it is not in neutral ones. Testing with MRSA bacteria strains will also be presented showing that the Daptomycine is still highly active when encapsulated, compared to the free drug. Further investigations like drug biodistribution of encapsulated drug compared to free drug or testing in infected mice are still being carried out.

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