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# The fate of squalene-based nanoparticles in biological medium: interactions with serum albumin

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## Introduction

Although squalene-based drug nanoparticles have already shown their efficiency *in vivo*, little is actually known of their stability and fate in biological medium. Here, through *in vitro* physico-chemical characterizations we assess the evolution of Squalene-Adenosine nanoparticles (SqAd NPs) in presence of bovine serum albumin (BSA), the main protein component of plasma.

## Methods

The NPs were prepared by nanoprecipitation of SqAd conjugate monomers solubilized in ethanol into an aqueous solvent. After ethanol removal, the NPs were mixed with phosphate buffer saline (PBS) and BSA. The NPs structure and stability was assessed by small angle neutron scattering (SANS) and cryo-transmission electron microscopy (cryoTEM). The nature of the interaction between SqAd and BSA was more specifically characterized by circular dichroism analysis, measurement of the fluorescence quenching of BSA and isothermal titration calorimetry (ITC).

## Results

*Colloidal stability of the nanoparticles* – While SqAd NPs quickly aggregate in PBS, they are shown to be stable in presence of BSA. SANS measurements can be fitted by a distribution of spherical particles. Additionally, in presence of BSA, a decrease of the NP radius and of the volume fraction is observed. Likewise, cryoTEM observations of Sq-Ad NPs with BSA show a shift of the size distribution.

*Spectroscopic characterization of the SqAd – BSA interaction* – In presence of SqAd NPs, the CD spectrum of BSA is modified, indicating a change in secondary conformation, in particular a decrease in the  $\alpha$ -helix content. Likewise, the BSA fluorescence is quenched, showing the formation of a complex. Further characterization by ITC indicates an enthalpy-driven exothermic interaction.

## Discussion

The colloidal stability of SqAd NPs is enhanced in presence of BSA. However, a significant decrease of radius is observed suggesting an extraction of the SqAd from the NPs. The spectroscopic analyses indeed show a specific interaction between the SqAd monomers and BSA. These results may have implication in the uptake and transport of bioactive squalenoid monomers *in vivo*. Indeed, they suggest that if the

NPs act as a convenient reservoir to inject bioactive SqAd molecules, they are partly disassembled in the biological medium while the resulting monomers are carried along by serum albumin.