COOPERATIVITY OF COMPLEXATION OF CHITOSAN OLIGOSACCHARIDES WITH SMALL INTERFERING RNA FOR GENE DELIVERY APPLICATIONS

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Abstract: Chitosan is a polycationic biopolymer used to protect and deliver small interfering RNA (siRNA) for biological applications. Chitosan prevents degradation and facilitates RNA entry into the target cells. However, the interaction between the polymer chains and the siRNA at the molecular level is poorly described since ill-defined chitosans of relatively high molecular weight are usually used to form complexes with siRNA. Here we used well-defined oligosaccharides of chitosan varying in degree of polymerization (DP) from DP=5 to DP=50 to study the role of the chitosan chain length on the thermodynamics of the complexation and the morphology of the complexes. The complexation was studied by Dynamic Light Scattering (DLS), fluorescence spectroscopy with the RiboGreen dye and Isothermal Titration Calorimetry (ITC) under various pH conditions. It was found that the chitosan chain length is a critical factor in the efficiency of the complexation. Longer chitosan chains have shown better complexation yield at various nitrogen to phosphate (N/P) ratios, illustrating the cooperative effect of the DP in complexing chitosan with siRNA. The global study provides a set of results of interest for the future design of siRNA delivery systems that must provide improved stability in the bloodstream, effective cell internalization and ease of dissociation in the cytoplasm.

[1] Alameh, M.; Lavertu, M.; Tran-Khanh, N.; Chang, C.-Y.; Lesage, F.; Bail, M.; Darras, V.; Chevrier, A.; Buschmann, M. D. Biomacromolecules 2018, 19 (1), 112–131.
[2] Bohr, A.; Tsapis, N.; Andreana, I.; Chamarat, A.; Foged, C.; Delomenie, C.; Noiray, M.; El Brahmi, N.; Majoral, J.-P.; Mignani, S.; Fattal, E. Biomacromolecules 2017, 18 (8), 2379–2388.

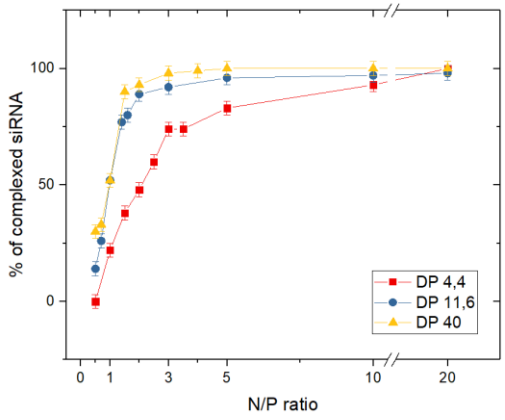

Figure 1 : Efficiency of the siRNA complexation at various N/P ratios with oligochitosans varying in DP as determined by fluorescence spectroscopy with the Ribogreen dye.