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Cytidine- and guanosine-based nucleotide–lipids†

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Hybrid nucleotide–lipids composed of a lipid covalently attached to purine and pyrimidine nucleobases exhibit supramolecular properties. The novel cytidine and guanosine derivatives are promising bioinspired materials, which can act as supramolecular gelators depending on both the nucleobase and the presence of salts. These supramolecular properties are of broad interest for biomedical applications.

Introduction

Supramolecular materials derived from biological structures such as peptides,[1,2] carbohydrates,[3] or nucleosides[4] are attractive for various applications,[5,6] including green chemistry,[7,8] materials science, drug delivery,[9,10] medicinal chemistry,[11–13] tissue engineering, or regenerative medicine.[14] Nucleolipids,[15–17] which are biocompatible structures composed of a lipid covalently attached to a nucleotide, are desirable candidates for the implementation of supramolecular biomaterials as they easily engage non-covalent interactions.[18,19] Nucleotides-based lipids, in particular, are unique in that they have multiple possibilities for non-covalent interactions depending on the nature of the bases and can self-associate into stable different type of self-assembly, such as ribbons, bilayers, fibers *etc*. In previous studies, we reported the self-assembly properties of several nucleotide lipids (NLs) featuring 3′-monophosphate thymidine or adenosine head groups covalently attached to 1,2-dipalmitoyl-*sn*-glycerol.[20–22] Interestingly, biocompatible hydrogels, resulting from the self-assembly of thymidine-3′-(1,2-dipalmitoyl-*sn-glycero*-3-phosphate) (diC16-3′-dT) salts, were found to be effective soft materials for *in vivo* injection and implantation.[23]

The modulation of the polar head structure, in particular the nature of the base could influence the aggregation properties of the NLs. Therefore, we elected to design NLs with a double dipalmitoyl glycerol phosphate linked to the 3′-secondary hydroxyl of the four natural nucleosides. Indeed, the diverse hydrogen bond donor–acceptor sites in all four nucleobases (A: adenine, T: thymine C: cytosine, and G: guanine) are prone to form self-base pairing interactions that stabilize supramolecular self-assemblies.[24,25] It is therefore valuable to explore the self-assembly properties of A, C, T and G based nucleotide–lipids as supramolecular building blocks. Specifically, we report the synthesis and the physicochemical studies of a series of nucleoside-3′-monophosphate NLs featuring palmitic double chains and A, T, C, G nucleobases. Several examples of nucleoside-based amphiphiles have been reported,[26–28] however to the best of our knowledge, there are no previous examples of cytosine and guanosine nucleoside-3′-monophosphate amphiphiles.

Results and discussion

In this study, we prepared four purine and pyrimidine nucleotide–lipids *via* a phosphoramidite strategy. The supramolecular assemblies obtained with A, T, C, G nucleotide lipids either in the absence or presence of sodium chloride are reported (Fig. 1). Depending on both the conditions and the nature of the base the stabilisation of supramolecular hydrogels was observed. Likewise, as a proof of concept, *in vitro* drug release experiments show that a controlled delivery of a drug can be obtained thanks to the structure of the nucleolipid based gels.

Several strategies have been used to synthesize nucleotide lipids, including coupling reactions of monoalkyl phosphate with nucleoside and enzyme catalysis,[29] or *via* phosphoramidite synthetic pathway. The novel NLs, diC16-3′-dG **1a** and diC16-3′-dC **1b**, were synthesized using a similar approach to that used for the synthesis of diC16-3′-LNA-A[30] (see ESI, Scheme S1†). This approach uses standard procedures, routinely adopted in oligonucleotide synthesis *via* phosphoramidite chemistry in the solid phase and adapted to solution. Briefly, commercially available isobutyryl protected guanosine phosphoramidite **2a** (isobutyryl-dG-CE phosphoramidite, see ESI, Scheme S1†) and acetyl protected cytosine phosphoramidite

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