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Niosomes based on synthetic cationic lipids for gene delivery: the influence of polar head-groups on the transfection efficiency in HEK-293, ARPE-19 and MSC-D1 cells †

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We designed niosomes based on three lipids that differed only in the polar-head group to analyze their influence on the transfection efficiency. These lipids were characterized by small-angle X-ray scattering before being incorporated into the niosomes which were characterized in terms of pK_a, size, zeta potential, morphology and physical stability. Nioplexes were obtained upon the addition of a plasmid. Different ratios (w/w) were selected to analyze the influence of this parameter on size, charge and the ability to condense, release and protect the DNA. *In vitro* transfection experiments were performed in HEK-293, ARPE-19 and MSC-D1 cells. Our results show that the chemical composition of the cationic head-group clearly affects the physicochemical parameters of the niosomes and especially the transfection efficiency. Only niosomes based on cationic lipids with a dimethyl amino head group (lipid **3**) showed a transfection capacity when compared with their counterparts amino (lipid **1**) and tripeptide head-groups (lipid **2**). Regarding cell viability, we clearly observed that nioplexes based on the cationic lipid **3** had a more deleterious effect than their counterparts, especially in ARPE-19 cells at 20/1 and 30/1 ratios. Similar studies could be extended to other series of cationic lipids in order to progress in the research on safe and efficient non-viral vectors for gene delivery purposes.

1. Introduction

Gene therapy has become one of the main areas of interest for scientists, because it focuses on the possibility of delivering a normal functioning gene into the cell in order to have a therapeutic effect.[1] However, the efficient delivery and expression of genes into cells is not as easy as it seems. The entry of the DNA into cells and the protection of the genetic material against enzymatic digestion before reaching the nucleus are two important factors that may clearly hamper this process. Other factors to be considered in the development of effective gene carriers include the intracellular trafficking and the subsequent entry into the nucleus in order to obtain the desirable results.[2]

Basically, there are two main gene carrier systems: viral and non-viral vectors. Viral vectors rely on the use of viruses as carriers due to their natural ability to insert genetic material into the cells. However, some serious concerns such as immunogenicity, oncogenicity and the high cost of production jeopardize their use in human beings.[3] On the other hand, non-viral vectors based on cationic lipids or polymers offer a safer way to deliver genetic material, as they exhibit lower risk of antigen-specific immune and inflammatory responses. Moreover they are cheaper and easier to elaborate, and the size of DNA inserted is theoretically unlimited.[4] However, non-viral vectors are less effective than viral vectors as gene carriers. Therefore, research on the design of safe and effective novel non-viral vectors merits special attention from the research community.

Niosomes are non-ionic surfactant vesicles with a bilayer structure that have been effectively used to vectorize many kinds of drugs.[5,6] Unfortunately, these outcomes have not been the same for gene therapy purposes where their use is still limited; however some promising results have been recently reported in the literature for retinal gene delivery purposes.[7] Therefore, research on niosomes as non-viral vectors represents a challenging topic to be further developed.

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