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Oligoalkylamine Modified Poly(Amidoamine) Generation 4.5 Dendrimer for the Delivery of Small Interfering RNA

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Abstract : In recent years, the discovery of small interfering RNAs (siRNAs) has got great attention for the treatment of cancer and other diseases. However, the therapeutic efficacy of siRNAs has been faced with many drawbacks because of short half-life in blood circulation, poor membrane penetration, weak endosomal escape and inadequate release into the cytosol. To overcome these drawbacks, we designed a non-viral vector by conjugating polyamidoamine generation 4.5 dendrimer (PDG4.5) with diethylenetriamine (DETA)- and tetraethylenepentamine (TEPA) followed by binding with siRNA to form polyplexes through electrostatic interaction. The result of 1H nuclear magnetic resonance (NMR), 13C NMR, correlation spectroscopy, heteronuclear single–quantum correlation spectroscopy, and Fourier transform infrared spectroscopy confirmed the successful conjugation of DETA and TEPA with PDG4.5. Then, the size, surface charge, morphology, binding ability, stability, release assay, toxicity and cellular internalization were analyzed to explore the physicochemical and biological properties of PDG4.5-DETA and PDG4.5-TEPA polyplexes at specific N/P ratios. The polyplexes (N/P = 8) exhibited spherical nanosized (125 and 85 nm) particles with optimum surface charge (13 and 26 mV), showed strong siRNA binding ability, protected the siRNA against enzyme digestion and accepted biocompatibility to the HeLa cells. Qualitatively, the fluorescence microscopy image revealed the delocalization (Manders' coefficient 0.63 and 0.53 for PDG4.5-DETA and PDG4.5-TEPA, respectively) of polyplexes and the translocation of the siRNA throughout the cytosol to show a decent cellular internalization and intracellular biodistribution of polyplexes in HeLa cells. Quantitatively, the flow cytometry result indicated that a significant ($P < 0.05$) amount of siRNA was internalized by cells treated with PDG4.5-DETA (68.5%) and PDG4.5-TEPA (73%) polyplexes. Generally, PDG4.5-DETA and PDG4.5-TEPA were ideal nanocarriers of siRNA in vitro and might be used as promising candidates for in vivo study and future pharmaceutical applications.

Keywords : non-viral carrier, oligoalkylamine, poly(amidoamine) dendrimer, polyplexes, siRNA
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