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Preparation, characterization, cytotoxicity and transfection efficiency of poly(DL-lactide-co-glycolide) and poly(DL-lactic acid) cationic nanoparticles for controlled delivery of plasmid DNA

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Abstract

The objective of this study was to investigate the effect of formulation parameters (i.e. polymer molecular weight and homogenization speed) on various physicochemical and biological properties of cationic nanoparticles. Cationic nanoparticles were prepared using different molecular weights of poly(DL-lactide-co-glycolide) (PLGA) and poly(DL-lactic acid) (PLA) by double emulsion solvent evaporation at two different homogenization speeds, and were characterized in terms of size, surface charge, morphology, loading efficiency, plasmid release, plasmid integrity, cytotoxicity, and transfection efficiency. Cationic surfactant, cetyltrimethylammonium bromide (CTAB), was used to provide positive charge on the surface of nanoparticles. Reporter plasmid gWIZ™ Beta-gal was loaded on the surface of nanoparticles by incubation. Use of higher homogenization speed and lower molecular weight polymer led to a decrease in mean particle size, increase in zeta potential, increase in plasmid loading efficiency, and a decrease in burst release. The nanoparticles displayed good morphology as evident from scanning electron micrographs. In vitro cytotoxicity study by MTT assay showed a low toxicity. Structural integrity of the pDNA released from nanoparticles was maintained. Transfecting human embryonic kidney (HEK293) cells with nanoparticles prepared from low molecular weight PLGA and PLA resulted in an increased expression of beta-galactosidase as compared to those prepared from high molecular weight polymer. Our results demonstrate that the PLGA and PLA cationic nanoparticles can be used to achieve prolonged release of pDNA, and the plasmid release rate and transfection efficiency are dependent on the formulation variables.

Keywords: Poly(DL-lactide-co-glycolide) (PLGA); Poly(DL-lactic acid) (PLA); Cationic nanoparticles; Plasmid DNA (pDNA); Cytotoxicity; Transfection efficiency

1. Introduction

The turn of the century has seen enormous progress being made in the field of gene therapy. This strategy has been explored in the treatment of gene related disorders such as cystic fibrosis (Alton and Geddes, 1995; Griesenbach et al., 2004), severe combined immunodeficiency syndrome (Otsu and Candotti, 2002; Cavazzana-Calvo et al., 2005), cancer (Zwiebel et al., 1993; Kashani-Sabet, 2004), cardiovascular diseases (Shah and Losordo, 2005), and AIDS (Strayer et al., 2005; Vanniasinkam and Ertl, 2005). Several thousand patients have been involved in clinical trials going on all over the world with majority focusing on cancer (66%), followed by monogenic diseases (8.7%), and vascular diseases (8.7%) (http://www.wiley.co.uk/genetherapy/clinical/). The basic concept of gene therapy is that human diseases may be treated by the transfer of genetic material into specific cells of a patient in order to correct or supplement the defective gene. Though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge (Wiethoff and Middaugh, 2003).

In order to enhance gene therapy, specialized design features are required for delivery vector to overcome extracellular and intracellular barriers, and ensure efficient DNA delivery to the nucleus (Wiethoff and Middaugh, 2003; Lechardeur and Lukacs, 2002). The vectors used for gene delivery are broadly classified as viral and non-viral vectors. Viral vectors account for about 75% of the clinical protocols currently in opera-

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