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Biodegradable nanoparticles mimicking platelet binding as a targeted and controlled drug delivery system

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ABSTRACT

This research aims to develop targeted nanoparticles as drug carriers to the injured arterial wall under fluid shear stress by mimicking the natural binding ability of platelets via interactions of glycoprotein Ib-alpha (GPIbα) of platelets with P-selectin of damaged endothelial cells (ECs) and/or with von Willebrand factor (vWF) of the subendothelium. Drug-loaded poly(D,L-lactic-co-glycolic acid) (PLGA) nanoparticles were formulated using a standard emulsion method and conjugated with glycocalicin, the external fraction of platelet GPIbα, via carbodiimide chemistry. Surface-coated and cellular uptake studies in ECs showed that conjugation of PLGA nanoparticles, with GPIb, significantly increased nanoparticle adhesion to P-selectin- and vWF-coated surfaces as well as nanoparticle uptake by activated ECs under fluid shear stresses. In addition, effects of nanoparticle size and shear stress on adhesion efficiency were characterized through parallel flow chamber studies. The observed decrease in bound nanoparticle density with increased particle sizes and shear stresses is also explained through a computational model. Our results demonstrate that the GPIb-conjugated PLGA nanoparticles can be used as a targeted and controlled drug delivery system under flow conditions at the site of vascular injury.

1. Introduction

Recent research has focused on developing nanoparticle (NP) delivery systems for drug and gene therapy to treat various cardiovascular pathological conditions (Davda and Labhasetwar, 2002; Eniola and Hammer, 2005b; Zou et al., 2005). Upon injury or under conditions like thrombosis (the formation of a blood clot), inflammation, and restenosis (the narrowing of a blood vessel), the endothelium is activated and shows an increased expression of endothelial cell adhesion molecules, like P-selectin and E-selectin, compared with normal, healthy cells (Eniola and Hammer, 2005b; Lutters et al., 2004; Sakhalkar et al., 2003; Zou et al., 2005). Specific ligand and antibodies bound to these molecules have been used for targeting therapeutic agents to the damaged endothelium. For example, E-selectin immunoliposomes loaded with the doxorubicin significantly decreased cell survival in activated ECs, but had no effect on inactivated ECs (Spragg et al., 1997). In addition, sialyl Lewis^x (sLe^x)-conjugated microparticles were shown to effectively roll on surfaces coated with purified P-selectin, similar to the rolling of leukocytes on P-selectin surfaces (Eniola and Hammer, 2005a,b). Conjugation of recombinant P-selectin glycoprotein ligand-1 (PSGL-1) to micro- or nano-particles also showed the selective adhesion of these particles to cytokine-activated endothelium *in vitro* and in animal models (Sakhalkar et al., 2003, 2005). However, a major limitation of NP delivery to the cardiovascular system is the inefficient arrest of the NPs to the vascular wall under blood flow (Blackwell et al., 2001; Lin et al., 2010).

Herein, we present a novel drug delivery system that mimics platelets binding to the injured vessel wall under physiological flow conditions. We chose glycoprotein Ib (GPIb) as the targeting ligand, because its role in platelet adhesion to the vascular wall under high shear flow conditions is well-recognized (Dong et al., 2000; Kumar et al., 2003). GPIb also serves as the targeting ligand that binds to both P-selectin that is highly expressed on damaged endothelium and von Willebrand factor (vWF), which is deposited on the luminal surface at the arterial injured site within a few minutes of injury via balloon angioplasty (Andre et al., 1997; Giddings et al., 1997). Our hypothesis is that these unique "platelet-mimicking nanoparticles" would exclusively attach to the damaged arterial wall under high shear stress conditions, increasing cellular retention and uptake of NPs.

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