# Local Delivery of Modified Paclitaxel-Loaded Poly(ε-caprolactone)/Pluronic F68 Nanoparticles for Long-Term Inhibition of Hyperplasia

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**ABSTRACT:** The purpose of this research is to test the possibility of localized intravascular infusion of didodecyldimethylammonium bromide (DMAB)-modified paclitaxel-loaded poly(ε-caprolactone)/Pluronic F68 (PCL/F68) nanoparticles to achieve long-term inhibition of hyperplasia in a balloon-injured rabbit carotid artery model. Paclitaxel-loaded nanoparticles were prepared by modified solvent displacement method using commercial poly(lactide-*co*-glycolide) (PLGA) and self-synthesized PCL/F68, respectively. DMAB was adsorbed on the nanoparticle surface by electrostatic attraction between positive and negative charges to enhance arterial retention. Nanoparticles were found to be of spherical shape with a mean size of around 300 nm and polydispersity of less than 0.150. The surface charge was changed to positive values after the DMAB modification. The *in vitro* drug release profile of all nanoparticle formulation showed a biphasic release pattern. Drug release from DMAB-modified PCL/F68 nanoparticles (DPNP) was significantly slower than DMAB-modified PLGA nanoparticles (PGNP). After 90 days, DPNP group showed very significant inhibition of neointimal proliferation ($p < 0.01$), and PGNP group yielded significant inhibition of neointimal proliferation ($p < 0.05$), when compared with drug-free nanoparticles group. In conclusion, local delivery of paclitaxel-loaded DMAB-modified PCL/F68 nanoparticles was proven an effective means of long-term inhibition of hyperplasia in the rabbits.  J Pharm Sci 98:2040–2050, 2009

**Keywords:** nanoparticles; polymer synthesis; biodegradable polymers; polymeric drug delivery systems; controlled release; drug effects

## INTRODUCTION

Restenosis, the re-obstruction of an artery following an interventional procedure such as percutaneous transluminal balloon angioplasty (PTA) or stenting, remains a major limitation to the success of these interventional procedures.[1] This process is characterized by intimal hyperplasia and vessel remodelling.[2] Intimal growth results from vascular smooth muscle cell (VSMC) migration and proliferation into the media followed by the formation of extracellular matrix.[2,3] Thus, inhibiting the neointimal hyperplasia after vascular interventions is critical to the efficacy of interventional treatment.

Since systemic drug administration is inefficient in the prevention of restenosis and induces severe side effects,[4] the focus has recently been

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shifted to the local drug delivery systems. Several local drug delivery systems for prevention of restenosis are under investigation. Stent-based local delivery of a drug (drug eluting stent, DES) has been successful in the clinic.[5–7] However, its efficacy and safety has not been confirmed in all clinical settings, especially with respect to treating in-stent restenosis (ISR). There is growing concern that the drug concentration is highest at the stent struts, where healing is most important. On the other hand, incomplete inhibition of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES.[8] Moreover, a large number of coronary lesions cannot be treated with stents, mainly because they occur in small or tortuous vessels.[9] Hence, other methods for prevention of restenosis beyond DES are necessary. Among them, the most promising method to reduce VSMC growth and neointimal formation is the local administration of drug-loaded nanoparticles using drug delivery catheters.[2,10]

Colloidal drug carrier systems based on biodegradable polymer provided a local release and sustained retention of the drug in the arterial wall.[2,11–17] In previous studies, Levy and colleagues[13–15] demonstrated an efficient intravascular localization of drug-loaded nanoparticles in the arterial wall, and effectiveness for inhibition of restenosis in animal models. However, a low efficiency of nanoparticle retention in the arterial wall when delivered *in vivo* through an infusion catheter was noted.[18] Thus, there is a great need for nanoparticle modification to enable this novel pharmaceutical formulation to practically benefit clinical applications. Previous studies by Song et al. demonstrated modification of drug-loaded nanoparticles with DMAB, fibrinogen, and heparin/DMAB could greatly enhance arterial retention in various animal angioplasty models.[13–15,19,20] Among them, the DMAB surface modification was demonstrated most effective and produced at least sevenfold greater arterial drug levels in comparison to the unmodified nanoparticles.[19,20] Surface modification of nanoparticles with DMAB changed the negative surface charge of unmodified nanoparticles to positive surface charge. The cationic nature of surface modified nanoparticles probably increased ionic interactions with the negatively charged glycosaminglycan enriched arterial wall, thus facilitating their arterial uptake and retention. In addition, since DMAB is a mild surface-active agent, it could transiently change the permeability of the arterial vasculature and facilitate nanoparticle internalization into the arterial wall.[21]

Poly(lactide) (PLA), poly(D,L-lactide-*co*-glycolide) (PLGA), and poly(caprolactone) (PCL) are FDA-approved biodegradable polymers, which are used most often in the literature of drug delivery. Previous studies by our group have demonstrated that DMAB modified paclitaxel-loaded PLGA nanoparticles as local delivery system provide an effective means of inhibiting proliferative response to vascular injury in the rabbits.[16] However, the efficiency was observed only 28 days, and the long-term effects of this formulation were unknown. Thus, DMAB modified drug-loaded PCL/F68 nanoparticles were prepared in the present study in order to obtain long-term therapeutic effects in animal model. PCL degrades much slower than other known biodegradable polymers, which makes it very suitable for making long-term drug delivery devices.

Pluronic F68 is a FDA approved excipient under the trade name of Poloxamer 188. It is both water and organic solvent soluble. It has been used in pharmaceutical formulations primarily as emulsifier.[22] In this study, Pluronic F68 was incorporated into PCL as a pore-forming agent and drug releasing enhancer. Previous studies by our group have demonstrated the amount of F68 blended into PCL affected the microspheres morphology and controlled paclitaxel release.[23] In addition, commercial grade Pluronic F68 has been reported to exhibit hemorrheological, antithrombotic, and neutrophil-inhibitory properties, presumably via hydrophobic interaction with surface of blood cells, vascular endothelial cells, and/or alteration of plasma protein properties (particularly fibrinogen, soluble fibrin, and albumin).[24] Experimental and clinical studies have confirmed that intravenous administration of Pluronic F68 is of significant benefit in the management of myocardial infarction, in which Pluronic F68 reduces reocclusion and ameliorates reperfusion injury.[25]

Paclitaxel has several properties that make it a good candidate for local drug therapy of excessive arterial smooth muscle cell proliferation in restenosis after balloon angioplasty or stent implantation. These properties have been tested *in vitro*, in animal models, and in clinical studies.[26,27] Some of paclitaxel formulations (e.g., paclitaxel-eluting stents) even have been approved for clinical treatment of restenosis. However, the drawbacks of DES described above limited its application. Thus, in this research we investigate the hypotheses that a novel paclitaxel-loaded