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# Immobilization and characterization of PLGA nanoparticles on polyethylene terephthalate cardiovascular grafts for local drug therapy of associated graft complications

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ABSTRACT

The cardiovascular graft associated complications limit the long-term patency of the graft and restrict the patient's life quality. In the present study, PLGA nanoparticles were covalently immobilized onto the woven form of crimped polyethylene terephthalate (PET, Dacron®) cardiovascular graft to treat the early thrombosis, inflammation, or bacterial infection via local delivery of therapeutic agents. PET surface was firstly functionalized to produce reactive amino groups used as anchor sites for covalent immobilization of PLGA nanoparticles by end-point technique. The functionalized surface characterized by electro kinetic analyzer showed marked negative surface potential values up to −41 mV at high pH value indicating the presence of amino groups on PET surface. The scanning electron microscopy observations of nano-coated PET showed topographic architecture of homogenously distributed monolayer of PLGA nanoparticles on the PET surfaces. Profoundly, the immobilized nanoparticles manifested stability under blood flow-mimetic conditions for 24 h. The cytotoxicity and biocompatibility of the nano-coated PET in mouse L929 fibroblasts revealed adequate biocompatibility in terms of the cellular adhesion and growth pattern without remarkable cytotoxicity.

## 1. Introduction

Polyethylene terephthalate PET (Dacron®) cardiovascular grafts displayed highly successful applications and gained a large of interest. Particularly, the woven form of crimped PET is mostly used to replace the damaged blood vessels and to cover the heart valve swing ring and vascular stent (Fig. 1) [1–4]. The proven mechanical properties and micro-porous structure of the woven form of PET grafts provide advantages for substitution of large and medium diameter vessels intended to restore the normal blood flow and the cardiac output [1–4]. However, utilization of PET grafts associates with critical complications mainly; thrombosis, inflammation, and infection leading to prolonged hospitalization, graft failure, and patients' death [1,4]. Studies suggest that the common complications after implantation showed dependency on the grafts surface properties such as hydrophobicity, porosity and electronegativity [5,6]. However, the surface modification of PET offers the opportunity to treat the main grafts-associated complications [5–7]. For instance, we previously developed several considerable techniques based on polymeric coating [8–10]. Firstly, the newly synthesized antibacterial sulfadimethoxine polyhexylene adipate-b-methoxy polyethylene oxide (SD-PHA-b-MPEO) di-block copolymer was used to limit the graft-associated infections. The initial interaction between PET graft's surface and the pathogens was prohibited and hence the biofilm formation can be avoided [8]. In the second work, the efficiency of surface modification of PET utilizing biomolecules was profoundly investigated and the initial bacterial adhesion to PET surface was also inhibited by covalent immobilization of lysozyme enzyme onto woven and knitted forms of crimped PET grafts [9]. In another embodiment, a significant improvement of biocompatibility along with remarkable resistance against fibrin and clot formation after co-grafting of heparin and collagen on PET surface were previously systematically studied [10]. The current study presents an alternative approach based on covalent immobilization of polymeric nanoparticles for local delivery of drugs at the contact surface. We take advantage of the nanoparticulate

*Abbreviations:* PET, polyethylene terephthalate; PET-$NH_2$, polyethylene terephthalate functionalized with amino group; PLGA-NPs, poly lactic-glycolic acid nanoparticles; FD-PLGA-NPs, poly lactic-glycolic acid nanoparticles loaded with fluorescein isothiocyanate labeled dextran; PET-NPs, nanoparticles immobilized-polyethylene terephthalate

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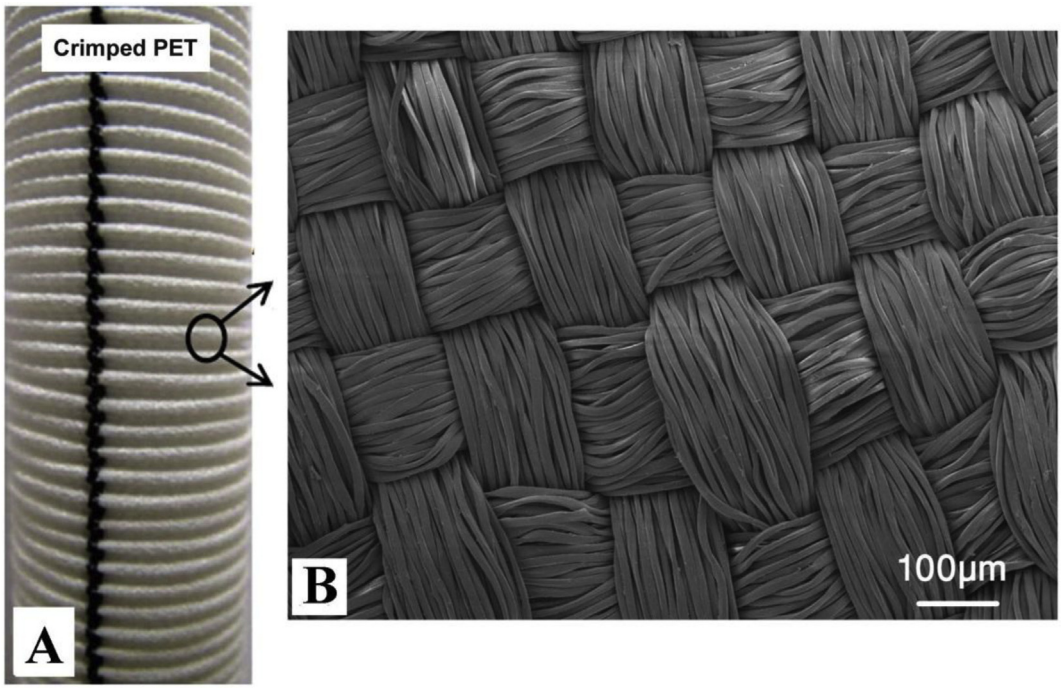


**Fig. 1.** Photograph (A) and SEM micrograph (B) of woven form of crimped PET graft. The multifilament PET threads in woven form are fabricated in an over-and-under pattern. The crimped technique, shown in the photographic picture, is utilized to increase the flexibility, distensibility, and kink-resistance of grafts.

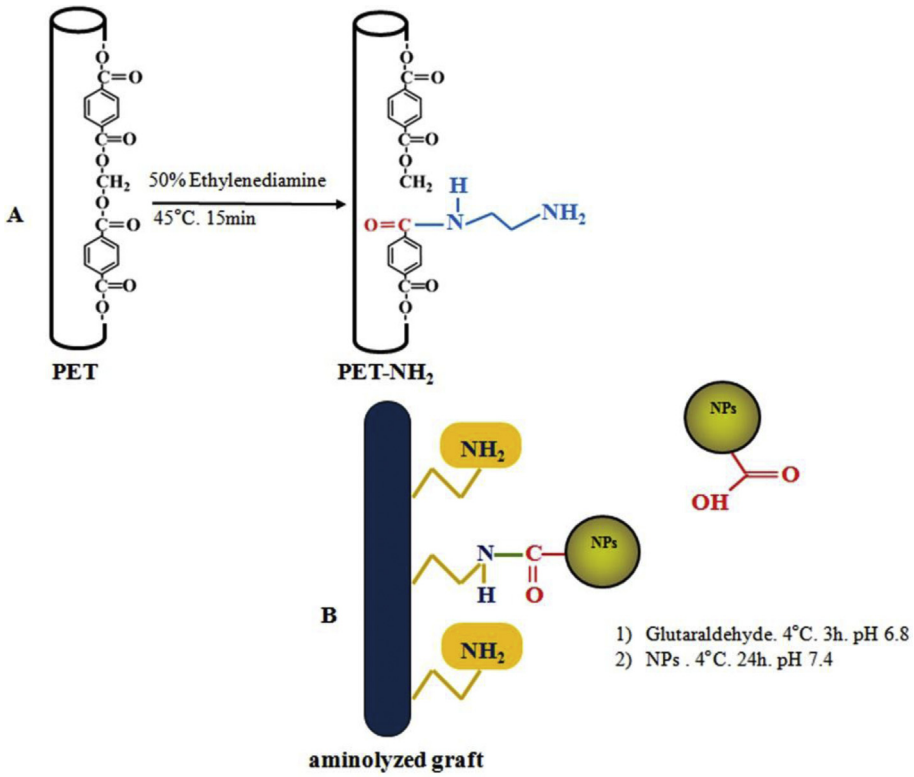


**Fig. 2.** Schematic illustration of the surface aminolyzation process of the woven form of crimped polyethylene terephthalate PET graft (A) and the covalent immobilization of PLGA nanoparticles on the aminolyzed PET surface (B). The intrinsic ester linkages within PET structure were selectively cleaved by aminolyzation reaction to produce functional amino groups on the surface (PET-$NH_2$). Subsequently, amide bonds were formed upon reaction of the created amino groups on PET-$NH_2$ and the intrinsic carboxyl groups on PLGA nanoparticles using the cross-linker glutaraldehyde.

system over other approaches such as biodegradability, compatibility, improvement of drug stability, and alleviation of drug adverse effects along with the controlled release of the entrapped drug [11–14]. In order to modify the surface of PET, the previously established aminolyzation reaction using the wet-chemical reaction technique was performed [15,16]. Consequently, the previously prepared poly lactic-glycolic acid PLGA nanoparticles were covalently immobilized through amide bond formation. The modification process was completed in two main steps as schematically illustrated in Fig. 2. In the first step, the intrinsic ester linkage within PET structure was selectively cleaved by aminolyzation reaction to produce reactive amino group on the surface, which was confirmed using an electro kinetic analyzer. In the second step, the reactively charged amino groups were used for covalent immobilization of PLGA nanoparticles. The immobilized nanoparticles were tested for stability under blood flow-mimetic conditions and the nano-coated PET was observed subsequently under scanning electron