

Electrospinning of Drug Loaded Poly(ϵ -caprolactone) Nanofibers: In Vivo Evaluation of Novel Degradable Small-sized Vascular Grafts

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INTRODUCTION: Most ischaemic diseases like atherosclerosis require a revascularisation procedure. They can be treated by bypass surgery with autologous or homologous graft material but such material is not always available nor suitable^{1,2}. For this reason *in vitro* tissue engineering and biostable synthetic prostheses have been proposed, and latter are widely used. However these solutions are not fully satisfactory, especially when replacing small blood vessels ($\text{Ø} < 6\text{mm}$) where acute thrombosis and intimal hyperplasia occur³. To overcome the drawback of permanent residence of the grafts in the body we prepared biodegradable small vascular grafts composed of poly(ϵ -caprolactone) (PCL) nanofibers containing an anti-inflammatory drug. The simultaneous degradation of the graft and controlled localized drug release should favour the *in vivo* natural blood vessel reconstruction.

METHODS: PCL solutions (7.5-15%,w:v) containing dexamethasone (0-10%,w:w) were prepared in chloroform/ethanol mixtures. The solutions were electrospun (1kV/cm) and the formed nanofibers collected onto a 2mm diameter mandrel. After drying and sterilization of the grafts, their mechanical and morphological properties have been evaluated. Preliminary *in vitro* drug release studies as well as *in vivo* implantation in rats have been carried out and are still ongoing.

RESULTS: A factorial design approach was used to prepare 2mm diameter grafts having a controlled morphology mimicking the extracellular matrix and mechanical properties similar to those of native vessels. Whatever the drug loading, controlled fiber sizes are obtained with mean diameters in the range of 500nm to 2000nm, which are suitable for the use in vascular grafts. As previously described⁴, fiber diameter increases with PCL concentration while the opposite occurs for beads. In fact, beads were only found for 7.5% and 9% solutions, while no beads were detected for the 12% and 15% solutions (Fig.1). Furthermore, the mechanical properties were suitable for almost all the non loaded grafts with maximum stress values above 2MPa, value found for natural blood

vessels, and maximum strain values around 250% for the 7.5 and 9% solutions and 3-fold higher values for the 12 and 15% solutions. Dexamethasone loaded grafts showed even better mechanical properties.

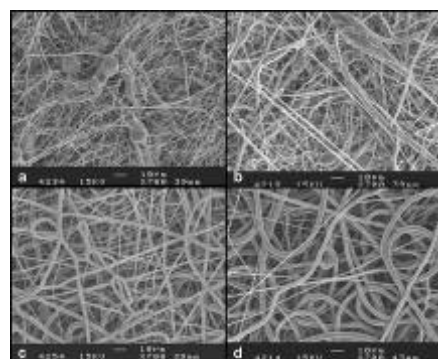


Fig.1: Influence of PCL solution concentration on fibers morphology with a) 7.5 %, b) 9%, c) 12%, and d) 15%.

Preliminary *in vivo* studies in rats followed up by angiography and histological studies have shown good patency (Fig.2a), the formation of an intima without hyperplasia (Fig.2b) and diffusion of cells without inflammation. Long term studies are under progress for *in vivo* functionality and degradability evaluations.

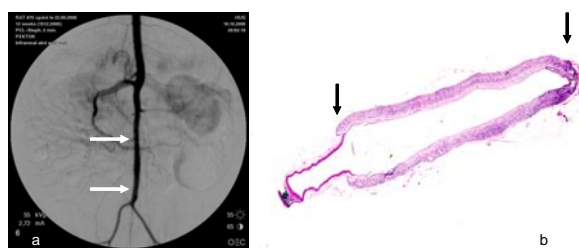


Fig.2: a) angiography and b) histological cross section of a 12 weeks implanted PCL vascular graft in rat.

DISCUSSION & CONCLUSIONS: 2mm diameter biodegradable vascular grafts made of PCL and containing dexamethasone have been successfully prepared and implanted in rats and led to promising results.

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