Fast-curing Nitric Oxide-releasing Poly(diol citrate)

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Introduction
The delivery of nitric oxide (NO) has important applications in medical therapies such as in revascularization procedures. We have previously reported the synthesis of biodegradable nitric oxide-releasing poly(diol citrate) (PDC) elastomers for potential use in implantable devices or extracorporeal devices\textsuperscript{1, 2}. We propose to develop an injectable drug-eluting biodegradable stent that will polymerize in the body and mold to the contour of the freshly angioplastied artery. This approach is referred to as the injectable polymerizable biodegradable stent (IPBS). The objective of this study was to synthesize an IPBS pre-polymer that can be fast cured in less than 3 minutes and release NO.

Materials and Methods
All chemicals were purchased from Sigma-Aldrich. Fresh porcine aortas were obtained from local slaughter house (Park Packing Company). The methacrylated poly(diol citrate) prepolymers (MA-POC and MA-PDDC) were prepared by polycondensation of citric acid with 1,8-octanediol or 1,12-dodecanediol followed by the coupling reaction with 2-aminoethyl methacrylate. The poly(diol citrate) elastomers were synthesized via UV-polymerization of methacrylated prepolymers in ethanol. 2-hydroxy-2-methylpropiophenone was used as an initiator. The polymers were characterized by NMR, FTIR, GPC, viscosity measurements and mechanical tests. The in vitro biocompatibility of polymers was assessed via cell culture with human umbilical vein endothelial cells. In vitro degradation rate was tested by measuring the mass loss of materials after incubation in pH7.4 PBS buffer at 37°C. Diazoeniumdilatated diethylenetriamine as an NO donor was incorporated into the polymeric matrix via blending before curing. Griess reaction was used to detect the NO release under physiological conditions.

Results and Discussion
A series of methacrylated poly(diol citrate) with different molecular weights and different compositions were synthesized. Increasing the citric acid contents during the polycondensation could yield the prepolymers with the lower viscosity and the higher functionality. The cross-linked poly(diol citrate) networks could be obtained via photo-polymerization of prepolymers within 3 minutes upon UV irradiation. The films could be formed on glass, Teflon, and the wall of porcine aortas. The tubular stent could be formed by inflating the balloon of catheter to cast the prepolymer in silicone tubing. The resulting materials are biodegradable (Fig.1) and have high tensile strength and elongation (Fig.2). The hydrated polymers (incubated in Milli-Q water for 8hrs) were more elastic than the corresponding dry polymers. Mechanical and degradation characteristics of polymers could be optimized by altering chemical composition, cross-linking density and molecular weight of prepolymers. Cell compatibility was confirmed by the viability and proliferation of endothelial cells on the polymers (Fig.3). All NO donor-containing polymers (films or coatings on the wall of blood vessel) released NO for at least 2 days (Fig.4). NO releasing rate could be controlled by the hydrophilicity of the polymers.

Conclusions
Biodegradable and biocompatible NO-releasing polymeric elastomers with differing mechanical properties were synthesized via photo-polymerization of methacrylated poly(diol citrate) prepolymers within 3 minutes. This biomaterial will be applied for the development of an IPBS.

References