# Dextran Sulfate Thin Films: A Novel Drug Delivery Platform for Drug-Eluting Balloon Applications

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**Statement of Purpose:** Peripheral artery disease (PAD) affects millions of people in the United States every year. PAD is the narrowing of blood vessels outside of heart and brain due to the deposition of atherosclerotic plaques, which restricts blood flow to the leg and several other organs. Drug-eluting balloon (DEB) is used to treat the blockage by opening the artery and delivering an anti-proliferative drug to inhibit the growth of smooth muscle cells (SMCs) thereby reducing the chances of artery re-narrowing [1, 2]. However, 80% of drug coated on the balloon is lost in the blood stream. This will not only causes systemic toxicity but also results in insufficient delivery of drug to the diseased site [1]. Hence, there is a need to use a temporary drug carrier to avoid drug loss in the blood stream and then to release clinically relevant drug dose at the diseased site. In this study, we investigated the use of dextran sulfate (DS) films for delivering paclitaxel (PAT) for DEB applications. PAT containing DS films were thoroughly characterized for their physicochemical properties, mechanical properties, drug loading and release, and SMC inhibitory capacity.

**Methods:** Dextran sulfate polymer films were prepared using a solvent casting method. A polymer-drug solution was prepared with 25 w/v % of DS, 10 w/w % of glycerol (plasticizer), and 0.27 w/w % of PAT in a solvent mixture of deionized water (di-$H_2O$) and 10 v/v % of ethanol. The solution was stirred overnight, poured in a petri-dish, and then transferred to a vacuum oven at 50 ˚C and maintained under vacuum of -20 Hg. The samples were taken out of the oven after 30 h and cut into 1 cm × 1 cm specimens. DS films prepared without PAT loading were used as controls. The PAT loaded DS films (PAT-DS) and control DS films (Ctrl-DS) were characterized using SEM, FTIR spectroscopy, and DSC to determine the morphology, chemical composition, and thermal properties, respectively. The mechanical properties were determined using a tensile tester. The *in vitro* drug release at different time points (15 sec, 30 sec, 1 min, 2 min, and 5 min) in PBS/tween-20 solution was measured using a HPLC. A $15 \times 10^3$ density of SMCs were grown in a 24-well plate for 24 h. The cells were then treated with Ctrl-DS and PAT-DS films. The viability and proliferation of cells after 1, 3, and 5 days of treatment with control and PAT containing DS films were investigated using resazurin fluorometric assay. The morphology of the cells was examined using fluorescence microscopy (FM).

**Results:** SEM images showed that both Ctrl-DS and PAT-DS films had smooth surfaces. There were no PAT crystals formed inside the DS films as evident from the cross-sectional images (Fig 1). DSC spectra indicated that PAT was molecularly dispersed in DS films. The FTIR spectra of surfaces and cross-sections of PAT-DS films showed no signs of chemical linkage formed between PAT and DS. This indicated that the drug was physically incorporated into the DS film. Both Ctrl-DS and PAT-DS films showed an excellent elongation making them suitable for DEB applications (Fig 2A). Fig 2B shows the amount of PAT released at different time points. The total amount of PAT loaded was 137 ± 29 µg/cm$^2$. Out of this, only ~10% of the drug was released within 1 min. This was followed by ~30% and ~60% of the drug released between 1-2 min and 2-5 min, respectively. This indicated that DS could prevent early drug loss and then deliver maximum amount of drug at the desired site. Both Ctrl-DS and PAT-DS films inhibited SMCs on days-1, 3, and 5 (Fig 3A). The PAT-DS films showed maximum inhibitory effect on SMCs (Fig 3B). The FM images showed that SMCs were well grown with a typical spindle shaped morphology in Ctrl-Wells (Fig 4A). The cells in Ctrl-DS and PAT-DS treated wells were significantly lesser in number with an uncharacteristic discoid shape (Fig 4B,C). The inhibitory effect of PAT-DS was significantly greater than that of the Ctrl-DS films.

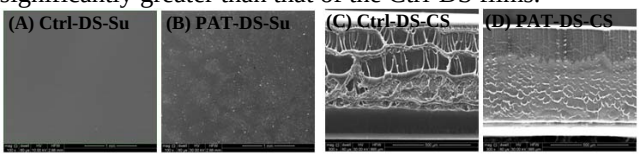


Fig 1: SEM images of surface (Su) and cross-section (CS) of control (A,C) and PAT incorporated (B,D) DS films.

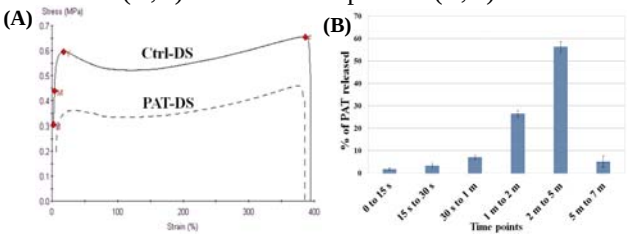


Fig 2: Mechanical properties of DS films (A), and percentage of PAT released from PAT-DS films (B).

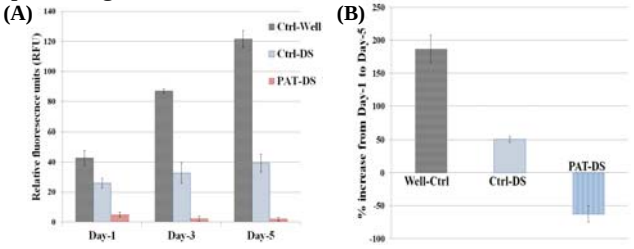


Fig 3: Viability and proliferation of SMCs (A), and % proliferation of SMCs from day-1 to 5 (B).

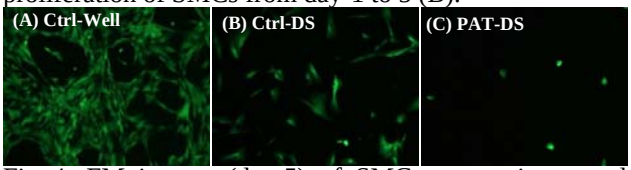


Fig 4: FM images (day-5) of SMCs grown in control wells (A), Ctrl-DS (B), and PAT-DS (C).

**Conclusions:** This study demonstrated dextran sulfate as a suitable temporary drug delivery carrier for delivering paclitaxel for drug-eluting balloon applications.

**References:** [1] Waksman R. Circ Cardiovasc Intervent. 2009;2:352-358. [2] Loh J P. J Am Coll Cardiol Intv. 2012; 5(10):1001-1012.