

## Local Delivery of Paclitaxel Using Infusion Balloon Catheters

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**Statement of Purpose:** Drug-coated balloons are commonly used to treat peripheral vascular diseases. However, a large amount of drug is lost in the blood stream even before the balloon is taken to the diseased site.<sup>1</sup> This results in insufficient amount of drug delivered at the diseased site. In this study, we are showing the use of infusion balloon catheters as an alternative way to locally deliver drugs with any dose that is required for the treatment. Infusion balloon catheters (Atrium ClearWay RX) are made up of microporous PTFE material. Once the balloon is taken to the desired site, it is inflated by allowing the drug solution to pass through the balloon. This causes the drug solution to be infused out through the micropores of the balloon and is delivered at the diseased site. Hence, the infusion balloon provides an excellent flexibility for the clinicians to choose any type and dose of drug that are needed for the treatment. A patient-specific therapy is also possible using infusion balloons. In this study, paclitaxel (PAT) was infused through the balloons using several different types of excipients including cremophor, abraxane, urea, contrast agent, and saline solution (control). The in vitro drug release and the effect of infused solutions on smooth muscle and endothelial cell growth were studied. Also, the in vivo drug uptake was studied in a rabbit model.

**Methods:** ClearWay Atrium Infusion RX balloons (2 x 20 mm) were used in this study. The balloon surfaces were characterized using scanning electron microscopy (SEM) for determining the pore size, shape, and density. The real-time images of solutions infusing out through the balloon were captured using a CCD camera. A solution of PAT in cremophor, abraxane, urea, contrast agent, and saline solution was prepared at a concentration of 0.1 mg/mL. Then, a 15 mL of each of the prepared solutions was infused through the balloon for 5 mins at 3 mL/min. The amount of PAT delivered was determined using high performance liquid chromatography (HPLC). Also, an extensive cleaning procedure using ethanol and deionized water was carried out to retrieve any PAT physically adsorbed inside the balloon without infusing out. For in vitro cell culture experiments, 0.25 mL of the infused solutions was individually treated with human aortic smooth muscle cells (SMCs) and human aortic endothelial cells (ECs). The cell viability and proliferation were measured using resazurin assay while the cell morphology was imaged using a phase contrast microscope. For in vivo studies, once the solutions were infused, the animals were sacrificed and the arteries were harvested to examine tissue uptake of the drug by histology. A one way ANOVA was used to determine any statistical significant differences at  $p < 0.05$ .

**Results:** SEM images showed 2  $\mu\text{m}$  to 50  $\mu\text{m}$  sizes of irregularly shaped pores were randomly present on the balloons (Fig 1A). CCD images showed how the solution infuses out through the porous balloon (Fig 1B).

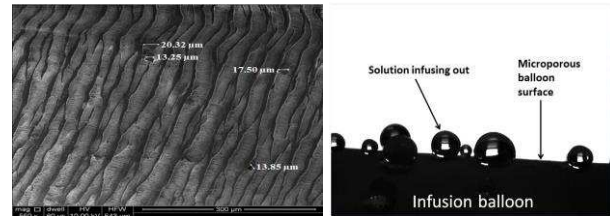


Fig 1. SEM image of the infusion balloon surface (A) and CCD image of solution infusing out (B).

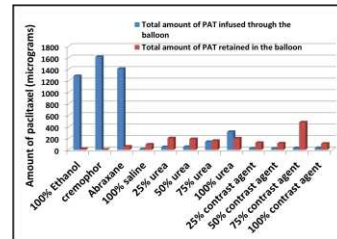


Fig 2: Total amount of PAT infused through the balloon.

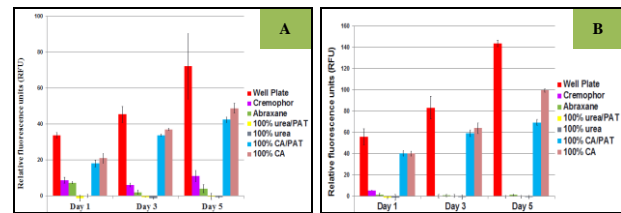


Fig 3. Effect of infused solutions on the growth of SMCs (A) and ECs (B).

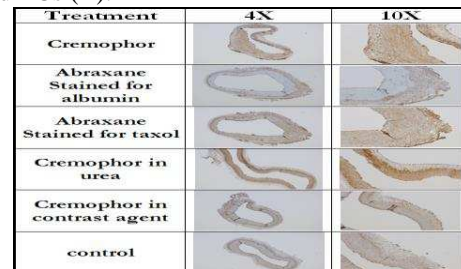


Fig 4. In vivo PAT tissue uptake for different excipients infused through the balloon.

A clinically relevant amount of PAT was released when cremophor and abraxane were used as excipients (Fig 2). Cremophor and abraxane based PAT effectively inhibited SMC growth (Fig 3A). However, these two solutions inhibited endothelial cell growth as well (Fig 3B). Urea by itself (without PAT) aggressively inhibited the growth of both SMCs and ECs (Fig 3). Contrast agent was inferior to all the other excipients for delivering PAT as well as inhibiting SMC growth. In vivo studies showed that urea, cremophor and abraxane showed better PAT uptake in the tissue than that of contrast agent (Fig 4).

**Conclusions:** This study demonstrated the use of infusion balloon catheters for local drug delivery.

**References:** (1) Circ Cardiovasc Intervent 2009;2:352-8.

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