In Vitro Release of Doxorubicin from the GPX™ Embolic Device

Ryan G. O'Hara[1], Monika Sima[2], Russell J. Stewart[2], Joshua P. Jones[3]

1) Department of Radiology, University of Utah; Salt Lake City, Utah, USA
2) Department of Biomedical Engineering, University of Utah; Salt Lake City, Utah, USA
3) Fluidx Medical Technology; Salt Lake City, Utah, USA

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FLUIDX MEDICAL TECHNOLOGY

Introduction

Transarterial chemoembolization (TACE) is an important tool in the hands of interventional oncologists. However, TACE is limited to particle embolics or lipiodol slurries, with current liquid embolics unable to deliver chemotherapeutics. This study examined the feasibility of a doxorubicin (DOX) loaded version of the GPX Embolic Device (GPX-DOX). The study included an *in vitro* characterization of the loading, solidification, and drug release profile of GPX-DOX. The GPX Embolic Material is a novel liquid embolic that remains a low-viscosity fluid prior to exiting the catheter, where it then solidifies in response to physiological ionic strength (see Figure 1). The material follows vascular flow and is designed for deep distal penetration of distally-flowing vessels and complex vessel beds. Preclinical studies with the GPX Embolic Device (non-drug loaded) have demonstrated long-term occlusion without recanalization, and desirable handling characteristics. The GPX Embolic System (non-drug loaded) is currently in clinical testing and has shown promising early results in a variety of interventional oncology (IO) applications, including renal carcinomas, renal angiomyolipomas (AMLs) and portal veins. Two selected cases from this study are shown in Figure 2.

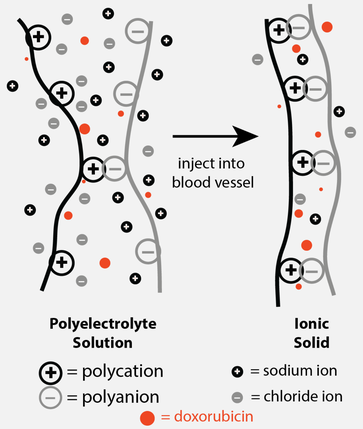
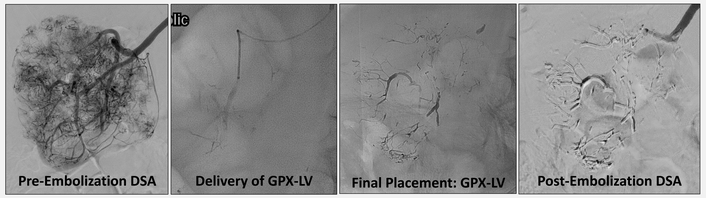


Fig 1: Mechanism of action. The GPX Embolic Material solidifies in response to physiological saline. Doxorubicin remains trapped in the material and is slowly released.

Renal Cell Carcinoma Embolization:



Renal AML Embolization:

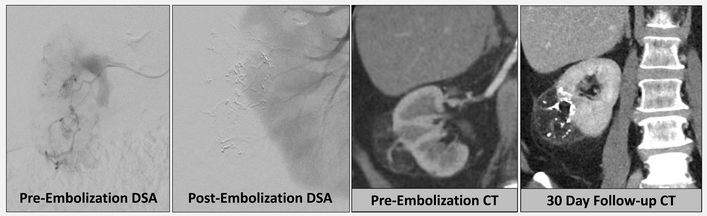


Fig 2: Examples of clinical cases with non-drug loaded GPX (GPX Embolic Device).

Results

- During drug loading, the red DOX powder readily dissolved in liquid GPX at concentrations up to 10 mg/mL.
- When delivered into physiological saline, GPX-DOX solidified into a microporous solid, with DOX appearing to concentrate within the pores (Fig. 3).
- Rheological frequency sweeps comparing the solidified GPX-DOX to standard GPX showed no adverse effect on mechanical properties (Fig 5).
- *In vitro* release studies showed a linear, zero-order release profile over the first 36 days, followed by continued release out to 100 days (Higuchi model)
- The release profile contained a minimal bolus release

Fig 3: GPX-DOX after *in situ* solidification.

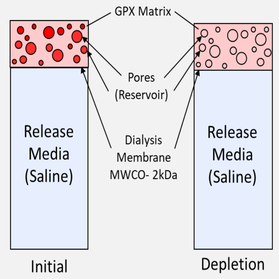


Fig 4: Schematic depicting drug elution assay from GPX-DOX using mini dialysis device.

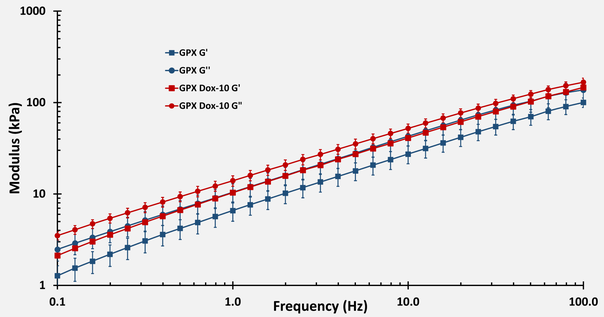


Fig 5: Frequency sweeps comparing the final solidified form of GPX-DOX to native GPX.

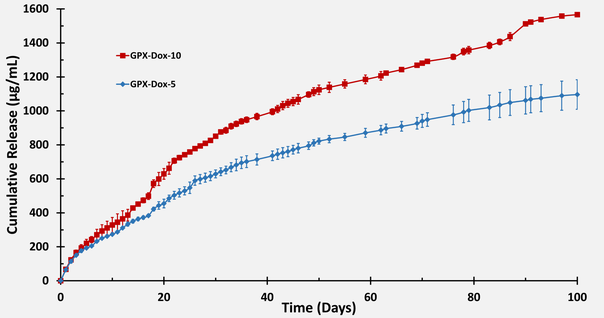


Fig 6: *In vitro* doxorubicin release from GPX-DOX formulations with DOX loading of 5 mg/mL and 10 mg/mL. Release is reported cumulatively as µg of DOX released per mL of embolic (GPX). A schematic depicting the experimental setup is shown in Fig. 4.

Materials & Methods

DOX was mixed directly into the liquid GPX Embolic Material at 5 and 10 mg/mL. For quantitative release studies, 50 µL of GPX-DOX was injected into a Float-A-Lyzer dialysis device (MWCO 2 kDa) and placed into a vial containing 1 mL of normal saline (see Fig. 4). The saline was replaced at each timepoint. DOX concentration in the release media was quantified by absorbance at 485 nm and used to calculate cumulative release. Frequency sweeps were performed on a strain-controlled rheometer at a fixed strain of 1%. Experiments were performed in triplicate.

Conclusions

Doxorubicin-loaded GPX provided a zero-order release profile for 5 weeks and sustained release out to 100 days. The long linear release profile is desirable in drug delivery, as a constant amount of drug is delivered regardless of the concentration within the carrier. These properties are unique in the field of liquid embolics and warrant further development and testing. Future studies will examine other chemotherapeutic agents and efficacy in animal models.