Novel Implantable Device to Negate Post-Amputation Pain

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U-18, Translating Discoveries into Effective Devices to Treat Pain

Motivation

Approximately 3.6 million Americans live with an amputated extremity, and the majority of these individuals are likely to suffer from chronic post-amputation pain. There is no consensus as to a recommended therapy for such pain, and many treatments do not provide sufficient pain control. Some studies have shown effective pain suppression from delivering an anesthetic agent directly to an injured nerve.

NovaFlux is currently developing a device that can be implanted to surround the injured nerves of an amputated limb to deliver loco-regional anesthetics over several months with no potential systemic toxicity.

In-vitro Drug Release

To assess the ability of our devices to release therapeutic amounts of drug substance (≥5 µg/mL) each day, test constructs were developed using just the hollow fibers and luer fittings, which could be attached to syringes for loading with drug formulation.

The test constructs (seen in Figure 3) were submerged in a vessel with phosphate buffered saline (PBS) to simulate nerve tissue. The vessel itself was placed into a shaker water bath at 37°C, 190 rpm. Eluate PBS is replaced at intervals and analyzed for drug release.

Results show supra-therapeutic release during a 70-day period for experimental constructs made with both polyamide-6 and polypropylene fibers, with 5 x 10 cm fibers each (see Figure 4 for graphical representations).

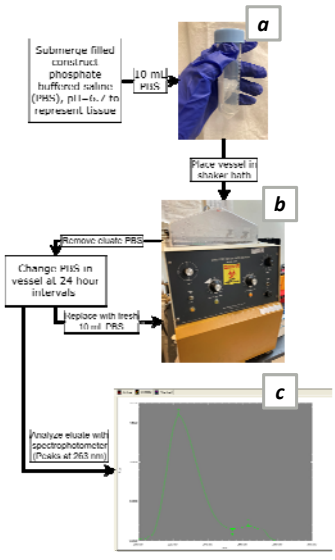
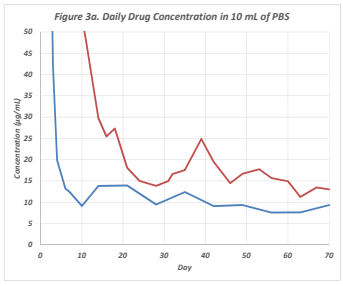


Figure 3. Pictured above is a graphical representation of our drug release experimental setup. The experiment starts when constructs (a) are loaded with drug formulation and submerged into a centrifuge tube along with 10 mL to represent the example nerve volume (10 mL). This centrifuge is placed in a shaker bath (b) with heat/speed settings set to mimic lymph circulation human body's. This PBS is collected and replaced at intervals of 24 hours, or multiples thereof if lidocaine release is evident but too low to read on a spectrophotometer. This culminates in testing the eluate PBS with a spectrophotometer (c). Solutions of known concentration were tested beforehand to create a linear calibration curve, and peaks were located at 263 nm.



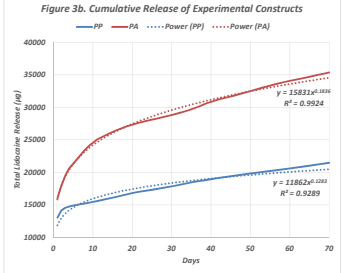
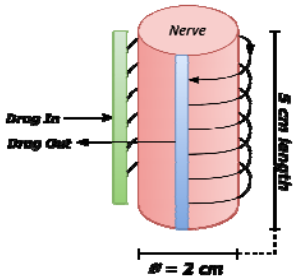


Figure 4. The plots pictured here show two ways to quantify drug release from test constructs. The daily drug concentration (a) indicates whether the daily release is considered therapeutic (≥5 µg/mL), while the cumulative release (b) provides a means of characterizing drug release from the fibers.

Figure 1. Example segment of nerve (based on sciatic nerve dimensions, amounting to approximately 10 mL of nerve tissue). Arrows and lines depict a proposed orientation of hollow fibers about the nerve, with arrows indicating the flow of the therapeutic formulation. Green and blue boxes represent proposed placement of the device headers, which allow fluid to be introduced to fibers from a system of tubing/subcutaneous port(s).



Hollow Fiber Fabric

Drug product is introduced to the tissues by means of a hollow-fiber fabric. These hollow fibers are similar to those used in hemodialysis, but woven into a flat fabric instead of potted as a bundle. The hollow fiber ends are to be potted into headers (Figure 1), which will be connected to subcutaneous ports. The resulting system is expected to allow easy external refilling for years to come.

Two types of biocompatible but non-resorbable polymers were considered as viable for use in the hollow fiber fabric, polypropylene and polyamide-6. The fabric, shown in Figure 2, is made with polyamide-6 membranes woven into a polyester structural fabric. The structural element is where the fabric's strength lies, and while the current iteration is not load-bearing, future versions may absolutely be developed to hold weight.

This fabric will be wrapped around the nerve to introduce drug product, whereupon it will diffuse radially inward into the tissues to provide treatment.

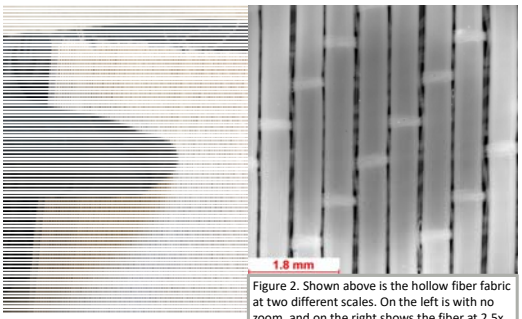


Figure 2. Shown above is the hollow fiber fabric at two different scales. On the left is with no zoom, and on the right shows the fiber at 2.5x magnification

Conclusions

In vitro drug release results have demonstrated the potential of our device to provide long term loco-regional therapy. This is made possible by the biocompatible hollow fibers, which have been successfully weaved into fabrics that can be used to make implantable devices. These devices have potential to be suitable for long term pain management.

Current efforts are geared toward continued optimization of the drug formulation, as well as moving towards animal studies.