Engineering 2015, 1(3): 344–350
DOI 10.15302/J-ENG-2015077

Research
Medical Instrumentation—Article

Characterizing Thermal Augmentation of Convection-Enhanced Drug Delivery with the Fiberoptic Microneedle Device

R. Lyle Hood[1], Rudy T. Andriani[2], Tobias E. Ecker[2], John L. Robertson[3], Christopher G. Rylander[4*]

ABSTRACT Convection-enhanced delivery (CED) is a promising technique leveraging pressure-driven flow to increase penetration of infused drugs into interstitial spaces. We have developed a fiberoptic microneedle device for inducing local sub-lethal hyperthermia to further improve CED drug distribution volumes, and this study seeks to quantitatively characterize this approach in agarose tissue phantoms. Infusions of dye were conducted in 0.6% (w/w) agarose tissue phantoms with isothermal conditions at 15 °C, 20 °C, 25 °C, and 30 °C. Infusion metrics were quantified using a custom shadowgraphy setup and image-processing algorithm. These data were used to build an empirical predictive temporal model of distribution volume as a function of phantom temperature. A second set of proof-of-concept experiments was conducted to evaluate a novel fiberoptic device capable of generating local photothermal heating during fluid infusion. The isothermal infusions showed a positive correlation between temperature and distribution volume, with the volume at 30 °C showing a 7-fold increase at 100 min over the 15 °C isothermal case. Infusions during photothermal heating (1064 nm at 500 mW) showed a similar effect with a 3.5-fold increase at 4 h over the control (0 mW). These results and analyses serve to provide insight into and characterization of heat-mediated enhancement of volumetric dispersal.

KEYWORDS near-infrared laser, thermochemotherapy, agarose, photothermal heating, micro-catheter, malignant glioma

1 Background and objectives

Many novel approaches have been developed to circumvent the blood-brain barrier and deliver pharmaceuticals to intracerebral targets [1–5]. Convection-enhanced delivery (CED) is a promising technique that avoids this issue through using catheters to infuse drugs locally within intracerebral targets [6–8]. To accomplish this, one or more catheters are inserted through a burr-hole in the skull and advanced to a target site. Once placed, a gradual, continuous infusion is maintained to provide pressure-driven flow for the infusate of interest. CED approaches have been developed for treating neurodegenerative, epileptiform, and neoplastic maladies [7, 9–13]. Due to pressure limitations on feasible infusion rates, CED is frequently maintained at a slow rate for up to several days. Often compared to biodegradable polymer delivery systems, CED has been demonstrated to increase effective tissue penetration of infused drugs by over an order of magnitude relative to diffusion-based methods without causing cerebral edema [14, 15]. The method is particularly attractive for delivering larger molecules that cannot bypass the blood-brain barrier and have lower effective rates of diffusion, such as antibodies, chemotherapeutics, and immunotoxins [16–21]. Unfortunately, the PRECISE study, the first multi-center trial utilizing CED to treat malignant glioma, did not meet required minimum clinical outcomes. In a retrospective analysis by Sampson et al., this failure was attributed to CED not achieving sufficient dissemination of the chemotherapeutic immunotoxin throughout malignant volumes and the surrounding margins [22]. Despite these discouraging results, many groups still seek better strategies and solutions to leverage CED into a viable clinical tool.

Another strategy for enhancing the penetration of infused chemotherapeutic agents is thermochemotherapy, as heating of the drug solution has been shown to substantially increase the effective depth of treatment [23]. In addition, adjunctive hyperthermia has been demonstrated to significantly increase the cytotoxic capacity of many chemotherapeutic agents [24–26]. DeWitt et al. demonstrated that mild hyper-

[1] Department of Nanomedicine, Houston Methodist Research Institute, Houston, TX 77030, USA; [2] Department of Mechanical Engineering, Virginia Tech, Blacksburg, VA 24060, USA; [3] School of Biomedical Engineering, Virginia Tech, Blacksburg, VA 24060, USA; [4] Department of Mechanical Engineering, University of Texas, Austin, TX 78712, USA
* Correspondence author. E-mail: cgr@austin.utexas.edu
Received 1 August 2015; received in revised form 21 August 2015; accepted 4 September 2015

thermia could also increase the drug uptake into the cell, which was attributed to plasma membrane permeabilization [27]. This group has developed a technological solution enabling a combination of thermochemotherapy with intracranial CED via a novel fiberoptic catheter, the fiberoptic microneedle device (FMD), which enables co-delivery of fluid agents and laser energy. This design and its fabrication methods have been described previously [28], as have characterizations of its mechanical penetration, light-guidance, and fluid delivery [28–31]. This group previously demonstrated that photothermal heating at the point of infusion could increase volumetric dispersal of contrast agents delivered through CED within an *in vivo* rodent model [28].

This study sought to determine if the volumetric dispersal enhancement seen in rodent models was also observed in agarose phantoms and, if so, to begin characterizing the heat-mediated dispersal increase. Agarose tissue phantoms at a weight ratio of 0.6% are an accepted simulacrum of cerebral tissue [32, 33] and allow direct observation of infused volumes. Initial experiments mimicked our previous *in vivo* approaches through delivering contrast agents into agarose with concurrent photothermal heating. To better quantify thermal effects, additional experiments characterized infusions into agarose volumes heated at near-isothermal conditions via waterbath, removing the anisotropic photothermal heating element. These experiments utilized a simplified catheter prototype using a non-light-guiding silica capillary of identical dimensions to our co-delivery FMD design (365 μm in outer diameter (OD); 150 μm in inner diameter (ID)). Further analysis focused on characterizing the heat-mediated changes to dispersal of infused contrast agents.

2 Materials and methods

2.1 Fiberoptic microneedle device designs

To determine if agarose exhibited a heat-mediated increase in volumetric disposal, an experiment was conducted with a two-fiber FMD design. FMD catheters were created through bonding fused silica capillary tubing (150 μm/365 μm ID/OD, Polymicro Technologies, Phoenix, AZ, USA) along the length of a multimode fiberoptic (100 μm/110 μm/125 μm core/cladding/buffer, numerical aperture (NA) = 0.22, Polymicro Technologies, Phoenix, AZ, USA). A nested syringe-needle system was necessary to allow fluid coupling into the capillary without running the fiberoptic through the fluid line. One end of the capillary was epoxied into the tip of a 22G dispensing needle, while the infusing length extended ~ 10 cm beyond the needle. This setup enabled fluid coupling via the dispensing needle's Luer-Lock. The capillary and 22G needles were threaded alongside the fiberoptic into a secondary 18G needle that acted as a housing. The endfaces of the fiberoptic and capillary co-terminated 2.5 cm from the tip of the 18G housing. Following immobilization of the glass fibers, the housing was filled with epoxy to promote lateral stability. This assembly is depicted in Figure 1.

A simplified FMD prototype was employed for isothermal agarose infusions with the goal of simplifying the heating profile to better characterize the heat-mediated transport. These

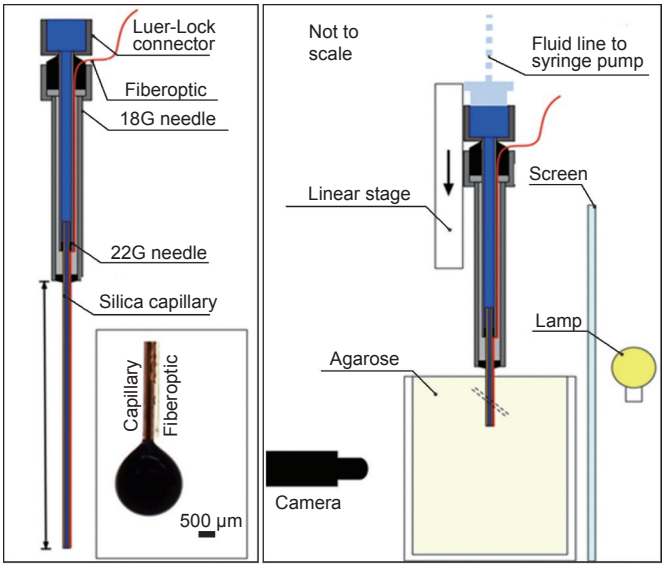

Figure 1. (a) Depiction of FMD design; (b) experimental setup.

FMDs were fabricated through adhering fused silica capillary tubing within a 1 in (1 in = 2.54 cm), 22G, stainless-steel dispensing needle (McMaster-Carr, Atlanta, GA, USA). The capillary tubing was cut to 3.75 cm in length and adhered within the dispensing needle so that the capillary extended 2.5 cm from the blunt end of the dispensing needle. This assembly is shown in Figure 2. The Luer-Lock fluid couple at the proximal end of the dispensing needle allowed attachment to the fluid system.

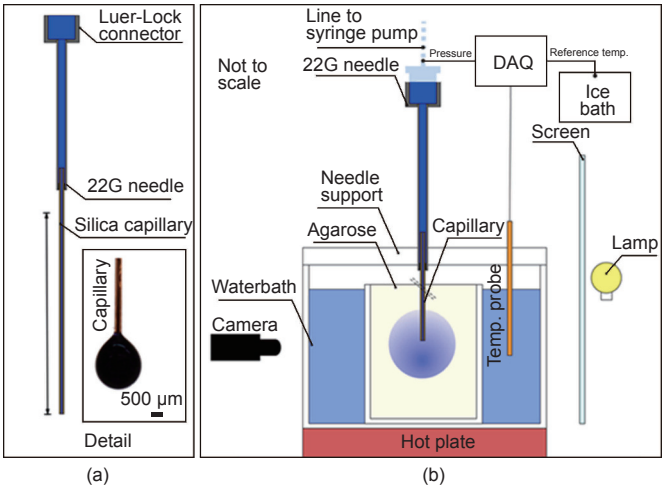

Figure 2. (a) The FMD assembly made from a 22G needle and a length of silica capillary, with an inset showing the tip; (b) a diagram of the experimental setup: The diagram is simplified to a single needle, although actual experiments were done with three needles in parallel (into the page from this perspective) delivering simultaneously. DAQ stands for data acquisition unit.

2.2 Co-delivery into agarose

The proof-of-concept co-delivery infusions with the two-fiber FMDs were conducted within rectangular, polystyrene molds (1.7 cm × 8.1 cm × 3.9 cm) open at the top. An agarose (certified molecular biology grade, Bio-Rad Laboratories, Hercules, CA, USA) solution was mixed at 0.6% (w/w) with de-ionized water, boiled, and decanted into the molds after a brief cool-