Externally-triggered nanoparticle composite membranes for drug delivery

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Statement of Purpose: Sustained drug release technology has been applied to many medical fields. However, drug release kinetics from devices is usually monotonic over time. Drug delivery devices that can be externally and repeatedly switched on and off could be optimal for effective treatment of conditions such as diabetes, or for local pain relief or chemotherapy. Environmentally responsive materials have been used to develop triggerable devices toward this end, particularly those based on the thermoreversible polymer poly(N-isopropylacrylamide)(PNIPAm). Composite membranes containing PNIPAm-based nanoparticles and superparamagnetic ferrite nanoparticles have been demonstrated (Hoare T. Nano Lett. 2009; 9: 3651-3657). Drug flux across the membrane can be turned "on" by applying an external magnetic field, with continuous release rate and good reproducibility over multiple cycles. Here, we examine several membrane design parameters, such as thickness and PNIPAm nanoparticle concentration, and evaluate how they affect drug release characteristics.

Methods: We synthesized composite membranes containing ferrite and PNIPAm nanoparticles within an ethylcellulose matrix, where there PNIPAm forms an interconnected, disordered network within the matrix. Ferrite nanoparticles were synthesized from $FeCl_3$ and $FeCl_2$ precursors. Polymer nanoparticles were formed by copolymerization of PNIPAm with N-isopropylmethacrylamide and acrylamide. The nanoparticle components were mixed with ethylcellulose dissolved in ethanol, and the mixture was allowed to dry. We assayed membrane flux by compressing the membrane between two glass cell chambers, then releasing Na-fluorescein or model drug compounds from the donor cell into the receiving cell. Triggering was achieved either by applying an external oscillating magnetic field or by modulating the temperature of a water bath.

Results: Membranes containing 20 wt% magnetic nanoparticles were triggered with an external magnetic field. We also used thermal triggering to evaluate design parameters and their effect on membrane performance. For example, we compared membranes containing 12, 18, 25 or 32 wt% nanogel in both their "on" and "off" states. Across this concentration range, the membranes exhibited absolute drug release rates that differed by nearly two orders of magnitude, although all had on/off ratios of about 10, and could be triggered over several cycles with reproducible release rates. The thickness of the membrane is also a factor; membranes that are 250 µm vs. 100 µm thick exhibit release rates differing by about an order of magnitude. For all membrane formulations, we observed a linear release profile in both the on and off states (Figure 1). Finally, observed that these membranes are also effective for releasing larger molecules such as FITC-labeled dextran and bupivacaine.

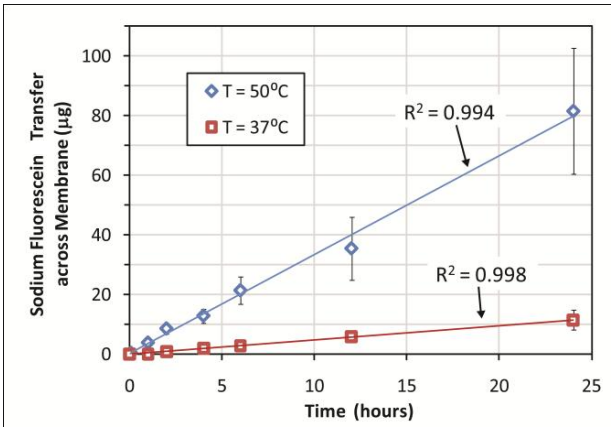

Figure 1. Release kinetics of sodium fluorescein from nanogel-filled magnetic membranes in the "off" (37°C) and "on" (50°C) states.

Conclusions: A composite nanogel-ferrofluid membrane has been developed that facilitates reproducibly triggerable, on-off switching of molecular flux upon the application of an oscillating magnetic field. Absolute drug flux from the membrane can be tuned by changing the nanogel concentration within the membrane, or changing the thickness of the membrane. The membrane facilitates constant release rates over multiple on-off cycles. The demonstrated capacity for engineering the membranes to tune the release kinetics for a wide variety of different drugs suggests the potential wide applicability of membrane-based devices in medicine.