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4aBA7. "SonoBandage" a transdermal ultrasound drug delivery system for peripheral neuropathy

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Peripheral Neuropathy (PN) is a difficult disease to manage. Symptomatic treatment focuses primarily on pain relief, using NSAIDs, opioids, Tri-Cyclic Antidepressants, and selective serotonin norepinephrine reuptake inhibitors. There is potential for ultrasound transdermal drug delivery to improve the quality of care provided to patients with PN, since it is well-suited to peripheral nerves which are close to the skin. In addition, targeted delivery avoids many of the systemic consequences of taking a drug. We developed a wearable ultrasound drug delivery system called ?SonoBandage? that combines low-impedance miniaturization of ultrasound transducer, RF electronics and battery power supply, with a novel hydrogel coupling bandage loaded with salicylic acid NSAID. The design of the SonoBandage allows the device to be used over a range of ultrasound frequencies (0.1-3MHz), intensities (0.1-3W/cm2) and durations (0.25-4hrs) increasing system flexibility for drug delivery protocols. The SonoBandage with NSAID was evaluated on a bench-top model with freshly harvested porcine skin and synthetic biomimetic human skin membrane (Millipore Inc). Across the n=40 samples studied, salicylic acid drug flux was increased by 2-20x as compared to control samples ($p<0.01$) after 1-4 hours of ultrasound treatment. SonoBandage has potential to be used as a practical NSAID delivery platform for peripheral neuropathy.

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INTRODUCTION

Peripheral Neuropathy (PN) describes a broad variety of conditions where nerve conduction is disrupted. These disruptions are bilateral, and affect multiple large nerve bundles (Hughes, 2002). Sensory neurons, motor neurons, or a combination of sensory and motor neurons can be hindered (MacDonald *et al.*, 2000; Hughes, 2002; Tesfaye and Selvarajah, 2012). These problems manifest in the patient as numbness, atrophy, ataxia, pain, and autonomic nerve dysfunction. PN can be caused by an underlying medical condition, such as diabetes or alcoholism (Hughes, 2002; Pratt and Weimer, 2005; Tesfaye and Selvarajah, 2012). Chemotherapy agents can also cause PN, and the loss of nerve sensation can be the rate limiting factor in applying successive chemotherapy treatments (Pratt and Weimer, 2005).

Cases of PN can be generally classified as either myelin-linked or axonal (Poncelet, 1998). Myelin-linked neuropathies are a result of damage to the Schwann cells which line the axons, and produce myelin, a protein which assists the axon in rapid signal transmission. Axonal neuropathies are a result of damage to the neuron themselves, either from toxins, ischemia, or injury.

The various origins of PN make it a difficult disease to treat. PN caused by an underlying issue is best treated by resolving the condition giving rise to the neuropathy, but this is not always possible. Symptomatic treatment has focused primarily on pain relief, using NSAIDs, opioids, Tri-Cyclic Antidepressants (TCAs), and selective serotonin norepinephrine reuptake inhibitors (SSNRIs) (Backonja, 2002; Rosenstock *et al.*, 2004; Head, 2006; Wolf *et al.*, 2008; Obrosova, 2009). TCAs and SSNRIs primarily function in the central nervous system, rather than at the site of the injury (Dworkin *et al.*, 2007; Gillman, 2007). Opioid drugs have strong potential for addiction. NSAIDs are hard on the lining of the stomach and have systemic toxicities over the long term (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older, 2009).

There is a great potential for transdermal drug delivery to improve the quality of care provided to patients with PN. Transdermal drug delivery is well-suited to problems which arise in tissues close to the skin surface, like the peripheral nerves. In addition, localized delivery of the drug avoids many of the systemic consequences of taking a drug, which is of particular interest in chronic conditions that require extended dosing regimens.

The use of ultrasound (US) to facilitate drug delivery has evolved over several decades (Bommannan *et al.*, 1992; Pitt *et al.*, 2004; Polat *et al.*, 2011). Perhaps the most extensively studied application is US to enhance transdermal drug delivery (Polat *et al.*, 2011). Exposure of skin to US over a wide range of frequencies increases the permeability of the stratum corneum, allowing transport across skin of therapeutic compounds that would otherwise be excluded and enhancing transport rates of others. Although thermal effects contribute, the key mechanisms of transport enhancement are acoustic cavitation, local convection, and acoustic streaming and micromixing (Johns, 2002; Tang *et al.*, 2002; Tezel *et al.*, 2002; Polat *et al.*, 2011). The effect of cavitation is perhaps the most dominant effect on enhanced transdermal delivery, where large pressure forces generated during the collapse of cavitation bubbles disrupt the adjacent stratum corneum, opening paths to underlying tissue and capillaries while the oscillation of bubbles causes local mixing. At lower pressure levels as well, ultrasound can generate acoustic streaming, which is a local convective motion of liquid due to oscillating bubbles. If the liquid contains a concentration gradient of a solute, acoustic streaming can enhance mass transfer of the solute without inducing a significant bulk motion of the liquid (Johns, 2002). Recently, high intensity focused ultrasound (HIFU) has been shown as an effective tool to target systemic drug treatments (Coussios *et al.*, 2007; Frenkel, 2008). Ultrasound mediated disruption of the blood brain barrier is being studied to help drugs escape the blood stream and enter the brain (Hynynen *et al.*, 2003; Hynynen, 2007; Hynynen and Clement, 2007; Meairs and Alonso, 2007; Yang *et al.*, 2008). US has also been shown to enhance the transport of molecules in agarose, muscle and brain tissue *in vitro* and *in vivo* (Lewis and Olbricht, 2007; Lewis *et al.*, 2007; Lewis *et al.*, 2009; Lewis Jr., 2010a; b; Lewis *et al.*, 2011; Lewis Jr. *et al.*, 2011).

One limitation that has prevented US-enhanced transdermal drug delivery is the size of the ultrasound delivery system and its efficiency. Current US delivery systems range in size from a shoebox to a cabinet and utilize a handheld ultrasound transducer applied to the skin with coupling therapeutic (Sanches *et al.*, 2011). In these devices, the efficiency of ultrasonic energy production and transfer into the patient is limited by AC/DC power conversion, electrical excitation generation, cable loss, and electrical-to-acoustic conversion at the transducer. On average, these losses reduce the total system efficiency to thirty percent (30%). Another limitation is the short treatment duration ultrasound drug delivery systems, typically only applied for under 30 minutes limiting the clinical efficacy of this treatment approach. Additionally, traditional ultrasound drug delivery systems are vulnerable to misapplication. The transmission of ultrasound from transducer into tissue is regulated by spatial variations in sound velocity, reflective surfaces, and boundaries inherent in the tissue. If the handheld transducer is not applied appropriately the delivery of ultrasound and therapeutic into the target will be substantially reduced. Traditional ultrasound transdermal drug delivery is messy, inconvenient, and standardized delivery is not readily available. Nevertheless, ultrasound mediated topical delivery is used globally in physical therapy clinics because of both the diathermic effect of ultrasound therapy and the improved penetration of surface therapeutics.

The technology investigated in this report, "The SonoBandage", is a long-duration, wearable ultrasound drug delivery system. It utilizes miniaturized ultralow impedance circuit architecture and transducer design to create a battery operated system that can be controlled by the end user. This system has previously been investigated for use in muscle spasms and chronic pain (Guarino *et al.*, 2011; Lewis Jr. *et al.*, 2012). This research takes the technology established in those earlier works, and investigates the ultrasonic parameters and treatment conditions that will give rise to optimal delivery of therapeutics. This challenge is two-fold. First, the ultrasound treatment must accelerate mass transfer across the skin barrier. That is the primary goal of ultrasonic drug delivery, using mechanical stimulation to speed transport. However, if the transport of therapeutic is accelerated through the soft tissue, the drug may be pushed out of the desired treatment area and into the circulatory system faster than it would be cleared natively. So the ideal ultrasound delivery system aids in mass transport across the skin, but provides minimal increase in delivery through soft tissue. Furthermore, the delivery platform must be able to provide sustained release kinetics over a desired treatment window i.e. 8 to 24 hrs with minimal manipulation by the end user.

MATERIALS AND METHODS

Design of the SonoBandage

The SonoBandage is a high efficiency ultrasound generation system with closely coupled electronics, transducer and lithium-polymer rechargeable battery. The devices are based on ultralow impedance design (Lewis and Olbricht, 2009; Lewis Jr., 2011; Lewis Jr. and Olbricht, 2011; Lewis Jr., 2012) that allowed us to streamline circuit architecture, optimize electro-acoustic signal conduction, and produce a low-profile encapsulated system. SonoBandage systems were designed to operate from 100 kHz to 3 MHz, and work in conjunction with a disposable ultrasound coupling and drug-loaded hydrogel. The front of the 3 MHz device shown in Figure 1 is a lead-zirconate-titanate (PZT-8), silver-plated piezocrystal composite. The back is an electronic protoboard with a circuit housed in an epoxy-resin. Wire leads from the device are connected to either a lithium-polymer battery or a 2-10 V power supply that regulates ultrasound output intensity. The SonoBandage prototype (Figure 1B) has the same circuit and crystal as in Figure 1A, but it is housed in a biocompatible ring with a 5 degree diverging lens made from Rexolite®. The housing and lens protect the electronics and piezocrystal from deterioration, which accounts for its bright color. The wire leads can be attached to a power supply or to the coin battery shown in Figure 1C. Figure 1D shows a side view of the device.

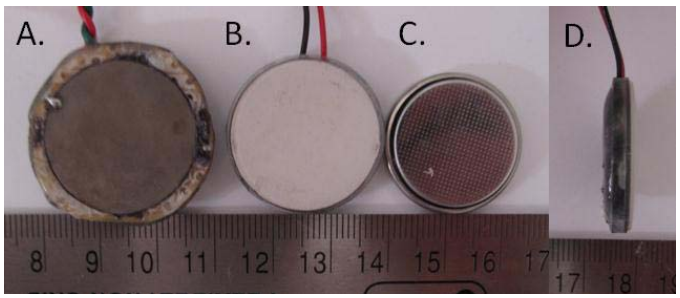

FIGURE 1. *A) SonoBandage prototype operating at 3 MHZ. B) The device with a biocompatible lens and housing. C) Coin battery capable of powering the device at 0.7W. D) Side view of the device in 2B.*

Preparation of the SonoBandage

To evaluate the SonoBandage in these studies, a Poly (Ethylene oxide) (PEO) hydrogel disk approximately 31.75 mm in diameter and 2 mm in height was immersed in a 2 g/L solution of salicylic acid (Sigma-Aldrich, Milwaukee, WI) for a period of 3 hours. Due to the short diffusion length to the center of the gel (1 mm) and the low molecular weight of salicylic acid (138 Da), this time was sufficient for the gel to reach equilibrium saturation.

Testing Mass Transport with the SonoBandage

To evaluate the mass transport and release kinetics of NSAIDs out of the SonoBandage and into tissue, a novel experimental design utilizing engineered materials to mimic tissue and skin was developed. To mimic the tissue, disks of 5.5% PEO hydrogel approximately 31.75 mm in diameter and 2 mm in height were stacked vertically, confined by a polyurethane ring. The disks were wet prior to stacking, and stacked smoothly to ensure there were no air bubbles and there was good contact between the disks. These disks are less dense than tissue, but this was chosen to expand the range of distances which the salicylic acid would diffuse, and allow for a better visualization of the transport profile.

To mimic human skin, the Strat-M Membrane (EMD Millipore, Billerica, MA) was employed. The Strat-M Membrane was designed for use in Franz cell experiments, and has been validated for use as a human skin analog in the case of acetyl-salicylic acid. A 47 mm diameter Strat-M Membrane was placed on top of the hydrogel stack tissue analog, with the side that is supposed to face the acceptor chamber in Franz cell experiments against the top disk.

The hydrogel which had been prepared with salicylic acid was placed on top of the membrane, on the side designated for the donor chamber in a Franz cell experiment. Then the SonoBandage device was placed against the back of the hydrogel. The experimental configuration was varied to include the skin mimic, and both active and inactive devices were used (Figure 2)

LITUS Device Parameters of Operation

The SonoBandage was tested in both a high frequency and a low frequency mode of operation. The low frequency mode tested was 175 kHz, and the high frequency mode was 3 MHz. The 175 kHz exposure was provided at both a 10% duty cycle and a 50% duty cycle, which corresponded to electrical power of 0.8 W and 4 W, respectively from a 4.9 cm^2 transducer face. The 3 MHz treatment was operated in continuous wave mode, with a power output of 0.7 W from a 4.9 cm^2 transducer face. In addition, to measure the effect of different treatment durations, the experiments were conducted for one hour and four hours of operation.

Visualizing the Transport of Salicylic Acid

Following the mass-transport experiment, the hydrogel disks that had been stacked as the tissue analog were separated carefully using a tweezers. The tweezers was rinsed to prevent transfer. Each disk was immersed in 25 mL 0.1% Iron (III) Chloride for a period of 90 seconds. The Fe^{3+} ion reacted with phenols to create a brightly colored violet complex. Developed disk stacks showed areas of deep purple

where salicylic acid had penetrated. These stacks were imaged. The area and intensity of the purple color was quantified using ImageJ. To control for variability in pictures or camera position, each experiment was normalized. The intensity of the purple color in each disk was divided by the intensity in the source disk, creating a relative intensity scale from 0 to 1. Additionally, the area stained purple on each disk was measured, and the overall disk area, 8 cm^2, was used to convert from a pixel area to a stained area. Additionally, the volume stained could be estimated by multiplying the area stained on each disk by 2 mm, the thickness of the disks. To estimate the total amount of salicylic acid that had transfered into each disk, the area (cm^2) which was stained was multiplied by the relative intensity of the stain. The total salicylic acid delivery into the tissue analog was the sum of the salicylic acid over all of the disks.

$$I_{relative} = \frac{I_{disk} - I_{background}}{I_{source} - I_{background}} \quad (1)$$

$$A_{purple} = A_{disk}(cm^2) * \frac{Pixels_{purple}}{Pixels_{disk}} \quad (2)$$

$$\dot{m} = I_{relative} * A_{purple} \quad (3)$$

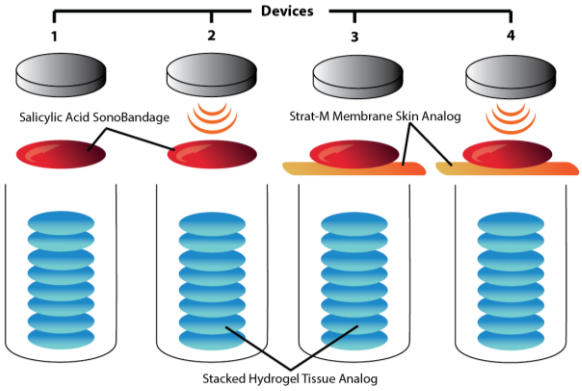

FIGURE 2. *Schematic representing the configuration of the four different experimental configurations performed. Each configuration was performed using 3 different ultrasound settings, and for both 1 hour and 4 hour treatment durations.*

RESULTS

Ultrasonic Treatment Enhances Transport through Skin Analog

Salicylic acid delivery through a skin and soft tissue analog was measured with and without ultrasound exposure. Both low and high frequency ultrasound enhanced transport of salicylic acid through the membrane. The optimum transmission of salicylic acid through the skin analog and into the hydrogel occurred with a high duty cycle, low frequency input (Figure 3, Table 1). For a one hour treatment, the 50% duty cycle, 175 kHz treatment mediated relative transmission of 0.6±0.1 (arbitrary units). The control experiment, without ultrasound, demonstrated minimal transdermal transport of salicylic acid, 0.02±0.01. This 25-fold improvement in transmission through the skin membrane caused by ultrasound treatment represents a significant increase ($p=0.0002$). This pattern continued with a longer dose interval. For a four hour treatment, the 50% duty cycle, 175 kHz treatment provided a relative transmission of 3±1, while the control experiment demonstrated transmission of 0.8±0.3. This was a 3.5-fold improvement relative to the control experiment ($p=0.0282$). Ultrasound treatment provided a significant increase in both the speed and the total quantity of delivery of salicylic acid through the skin analog.

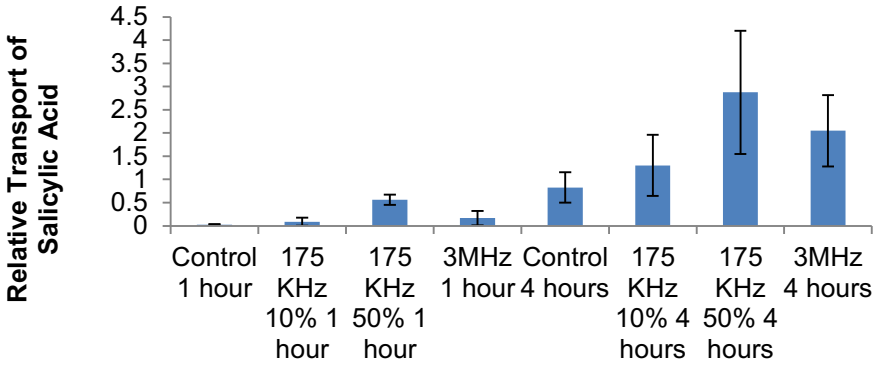

FIGURE 3. *The relative transmission of salicylic acid through the Strat-M Membrane under conditions of no ultrasound treatment and ultrasound treatment. The error bars show the standard deviation of the data across three experiments.*

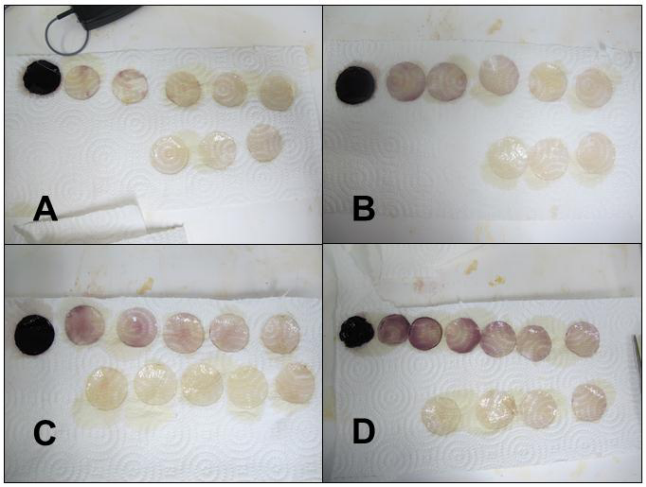

FIGURE 4. *Typical mass-transfer test results with the skin and tissue analogs. The top left disk in each picture is the drug loaded hydrogel of the SonoBandage . Salicylic acid is chelated by Fe^{3+} to produce the purple color. (A) No Ultrasound Treatment for 1 hour. (B) 175 kHz, 50% duty cycle ultrasound treatment for 1 hour. (C) No ultrasound treatment for 4 hours. (D) 175 kHz, 50% duty cycle ultrasound treatment for 4 hours.*

TABLE 1. *Mass-trasfer experiment results with a skin barrier present.*

Ultrasound Treatment Parameters	Relative Transmission of Salicylic Acid
No US, 1 hour	0.02±0.01
175 kHz, 10%, 1 hour	0.09±0.09
175 kHz, 50%, 1 hour	0.6±0.1
3 MHz, 100%, 1 hour	0.2±0.2
No US, 4 hours	0.8±0.3

175 kHz, 10%, 4 hours	1.3±0.7
175 kHz, 50%, 4 hours	3±1
3 MHz, 100%, 4 hours	2.0±0.8

Ultrasonic Treatment Provides Incremental Increase or No Increase in Transport Through Soft Tissue

For experiments conducted on the soft tissue analog, without the skin analog present, ultrasound treatment mediated a small increase in the transmission of salicylic acid. Interestingly, in contrast with the experimentation run with the skin analog, the duty cycle did not correlate with the transmission of salicylic acid through the soft tissue, with the 10% duty cycle mediating similar or higher transmission as the 50% duty cycle. In terms of the distribution of the salicylic acid, it was generally observed that disks had been treated with ultrasound maintained a more uniform color throughout, indicating that the treatment was reducing spatial heterogeneity in the drug delivery (Figure 6).

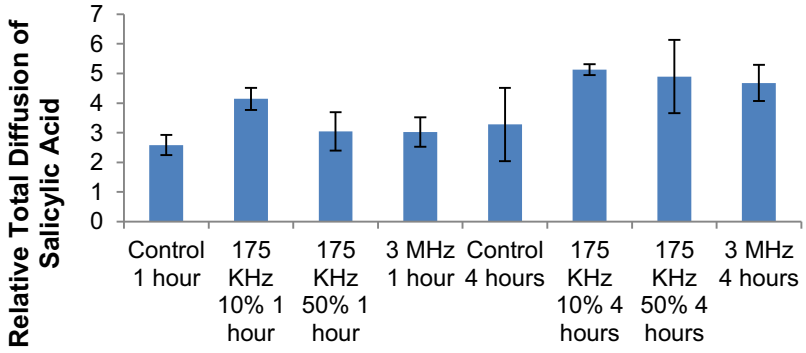

FIGURE 5. The relative transmission of salicylic acid through the hydrogel tissue analog under conditions of no ultrasound treatment and ultrasound treatment. The error bars show the standard deviation of the data across three experiments.

TABLE 2. *Transport experiment results with no skin membrane above tissue analog.*

Ultrasound Treatment Parameters	Relative Transmission of Salicylic Acid
No US, 1 hour	2.6±0.3
175 kHz, 10%, 1 hour	4.1±0.4
175 kHz, 50%, 1 hour	3.0±0.6
3 MHz, 100%, 1 hour	3.0±0.5
No US, 4 hours	3±1
175 kHz, 10%, 4 hours	5.1±0.2
175 kHz, 50%, 4 hours	5±1
3 MHz, 100%, 4 hours	4.7±0.6

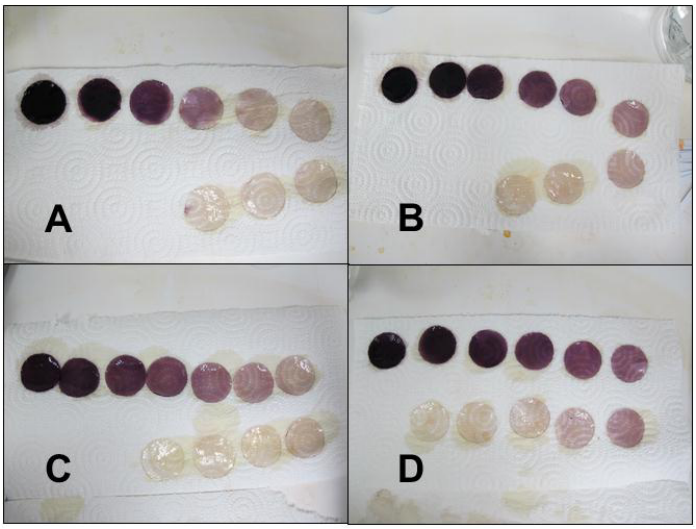

FIGURE 6. Typical mass-transfer test results with the tissue analog. The top left disk in each picture is the SonoBandage. Salicylic acid is chelated by Fe^{3+} to produce the purple color. (A) No Ultrasound Treatment for 1 hour. (B) 175 kHz, 50% duty cycle ultrasound treatment for 1 hour. (C) No ultrasound treatment for 4 hours. (D) 175 kHz, 50% duty cycle ultrasound treatment for 4 hours.

DISCUSSION

Low frequency ultrasound treatment is well-suited to mediate localized transdermal drug delivery because it simultaneously boosts mass-transfer of a drug molecule through the skin barrier, but can be controlled to not significantly boost the mass-transfer rate through soft tissue. This study visualized the transfer of salicylic acid into a soft tissue analog using a novel methodology for cleanly sectioned and developed horizontal slices. There were clear, significant differences in the transfer across a skin analog membrane when ultrasound was applied. Additionally, in the soft tissue, ultrasound treatment appeared to reduce spatial heterogeneity in the delivered drug dose, which would help prevent any localized areas of toxic concentration from developing during the treatment.

This study represents a clean experiment determining the kinetics of transdermal drug delivery using ultrasound to assist in transfer across the skin barrier. The results indicate that NSAIDs have their transfer through the skin membrane accelerated with ultrasound treatment. Coupled with ultrasound treatment's other indications for pain therapy, and this combined treatment regimen seems very promising.

Between these studies and studies demonstrating safety of transdermal NSAID delivery in animals (Yuan *et al.*, 2009), the groundwork for clinical research involving the delivery of NSAIDs to treat peripheral nerve pain appears complete. The next logical step for this work is to take the results of these works, estimate dose transfer levels, and titrate the dose in the SonoBandage to ensure the greatest area of effective treatment concentrations. With a precise dose calibrated, it would be possible to begin clinical trials, using ultrasound as an enhancer.

In conclusion, these experiments demonstrate that ultrasound treatment at low frequencies acts to assist in the transfer of NSAID molecules through a skin analog. The high frequency treatment protocol outlined in this study did not have a significant impact on transport through the skin membrane, but a higher intensity signal may have an impact. With further study, it should be possible to develop the SonoBandage and its associated ultrasound protocol to deliver NSAIDs transdermally in a manner that will allow for pain treatment along with a reduction of systemic side effects and overall drug dose.

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