

Feasibility of Ultrasound Assisted Drug Delivery via High Frequency Intense Therapy Ultrasound

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Abstract— Use of low frequency, low intensity ultrasound for transdermal drug delivery associated with cavitation is known [1]. We propose to establish feasibility of ultrasound assisted drug delivery using high frequency (2-10 MHz) intense therapy ultrasound with intensities up to 12 kW/cm² and acoustic pressure up to 30 MPa.

As the first approach, we have combined artificially created micropores (microchannels) 40-60 micrometers in diameter in membranes less than 1 mm thick with application of high frequency high intensity ultrasound (up to 2.1 kW). It was shown that high acoustic pressure (4.9-8 MPa) results in acoustic streaming with average velocities exceeding 480 mm/sec. and transfer of substantial amounts of up to 100 microliters/min. of high viscosity glycerin (612 Centipoise) and high molecular weight PEG (4,000 Da) via micropores.

In another approach high frequency high intensity bursts of ultrasound was applied to the superficial layers of ex-vivo samples of pig skin and in- vivo human skin to noninvasively overcome the skin barrier.

The study shows the possibility of driving high viscosity glycerin through porcine skin without thermal damage and 5% topical solution of lidocaine into the human skin via suggested mechanism of inertial cavitation and controlled temperature rise.

I. INTRODUCTION

Transdermal drug delivery despite its more than 50 year history has become an emerging modality lately, combining various energy methods (ultrasound, electroporation, micro-needle, laser and RF) [1, 2, 3, 4, 5, 6, 7]

High frequency (1-3 MHz) ultrasound diathermy and low frequency (20-100 kHz) sonophoresis at very low intensity range (from 50 mW/cm²- 3W/cm²) were widely researched with promising results but have not found broad acceptance to date. [1, 2]

We propose the feasibility of high frequency (2-10 MHz) and high intensity (2-12 kW/cm² or higher) to create nonlinear acoustic effects in first several millimeters of skin in short bursts up to 170 milliseconds to initiate acoustic streaming in micropores/microchannels and inertial cavitation for noninvasive skin barrier penetration in intact skin.

II. MICROPORES AND HIGH INTENSITY ULTRASOUND (ITU)

A. Materials

Spherically focused ultrasound transducers with high intensity gain (F-number \approx 1) were designed and constructed in the range of center frequency (high Q) from 2.1 MHz to 10.5 MHz. Transducers were tested, calibrated and electrically matched to high efficiency (70-94%) and maximum power.

Schlieren images of real time acoustic fields verified the focal positions and dimensions. (Fig. 1)

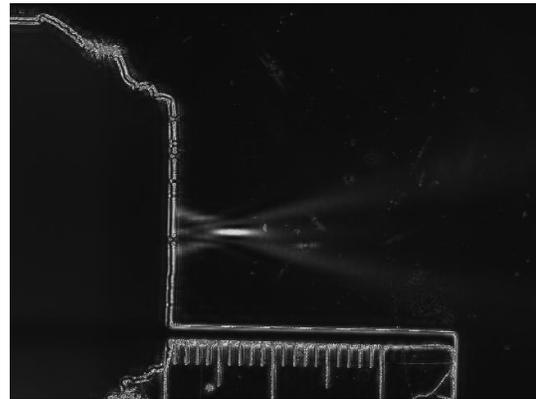


Figure 1-Schlieren image: 2.9 MHz, 5.5 mm focal distance

A custom broadband (1-10 MHz) RF power source was designed and fabricated, capable of 3 kW output bursts at low duty cycles.

Membranes of 0.8 mm thickness, perforated with micropores of 40-160 μ m diameter were mounted on small cylindrical containers. Membrane materials were silicone rubber and freshly excised pig skin in one set, and G10 and stainless steel in another. Soft tissue imitating materials were punctured with microneedles and hypodermic needle imitating hard materials, G10 and stainless steel were laser machined. Pore dimensions were verified by microscope measurements. (Fig. 2)

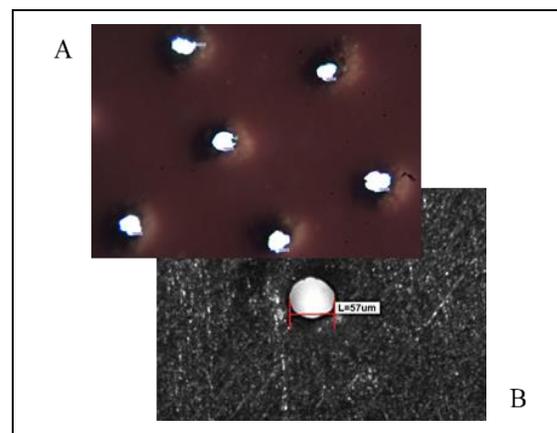


Figure 2-Perforated silicone rubber (A) and G10 (B) membranes

Color-coded high viscosity (up to 612 Centipoise, molecular weight 92 Da) glycerin as a model of biocompatible carrier and color-coded polyethylene glycol (PEG) solution with molecular weight of 4000 Da and viscosity of 323 Centipoise as a sample of longer molecules were utilized for the transfer through membranes.

B. Methods

Containers with membranes were filled with glycerin and PEG and immersed in optically transparent water tank. High intensity up to 2.1 kW/cm² was applied to the membranes inside the containers, resulted streaming flows were photographed at 120 frames/second and velocities were measured for a variety of ultrasonic parameters. (Fig. 3)

Liquid transfer volumes delivered through membranes were estimated for a variety of acoustic parameters. Thermocouples immersed at and near membranes monitored the average temperature change for the ultrasonic treatment periods and for the change of acoustic parameters.

III. NONINVASIVE LIQUID TRANSFER VIA HIGH INTENSITY ULTRASOUND (ITU)

A. Materials

High intensity spherically focused transducers as described above (part II, A) at 2.9 MHz, 7.5 MHz and 10.0 MHz were used for experiments.

Freshly excised pig skin was used for ex vivo samples at 2.9 MHz. Human volunteers forearm skin was subjected to a series of short bursts of 7.5 MHz and 10MHz ultrasound.

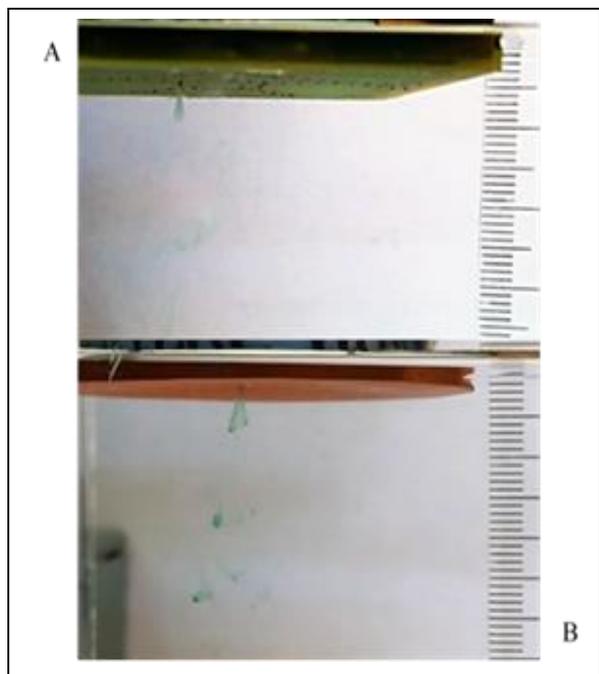


Figure 3-Acoustic streaming flow: A: G10, 50 μm microchannels, B: Silicone rubber membrane, 100 μm micropores

In the case of pig skin samples, we utilized color-coded glycerin of high viscosity (612 Centipoise) as a transfer liquid. For human in vivo experiments we applied a topical solution of 5% lidocaine with negligible acoustic attenuation of < 1dB/cm /MHz to the surface of the skin.

Passive cavitation detectors were designed and fabricated with very broadband receive (>100%) and frequency of 2MHz and 10MHz.

Active cavitation detection was measured by a high frequency imaging system Spark (Arden Sound Inc.) with a broadband 17 MHz imaging transducer array.

B. Methods

Freshly excised pig skin samples were covered with thin layer of color-coded glycerin at the surface of the skin. 2.9 MHz short bursts (up to 170 msec) of high intensity ultrasound up to 7kW/cm² were applied to the skin surface in series of exposures. Samples were kept at ambient temperature (20-21° C) and temperature of the samples during the exposures monitored by thermocouples inserted into the subcutaneous tissue of the samples.

Subsequently the samples were sliced along the axial direction of the ultrasound beam propagation, gross pathology examined under magnification and photographed.

Human experiments were performed with lines of the short bursts of 7.5 MHz and 10 MHz high intensity (up to 15 kW/cm²) applied to the 5% topical solution of lidocaine on the surface of the skin and compared with regular acoustic gel coupling utilized for the exposure on adjacent areas of the skin. Pain scores on a 10-point scale were assessed. Surface of the skin was photographed for both “lidocaine” and “no lidocaine” exposures for the assessment of erythema and “welts” in the adjacent area. (Fig. 7)

Presence of inertial cavitation broadband signals during ultrasonic exposures was measured by passive cavitation detectors described in (III, A) above, amplitude and lengths of cavitation signals measured and recorded. (Fig. 4)

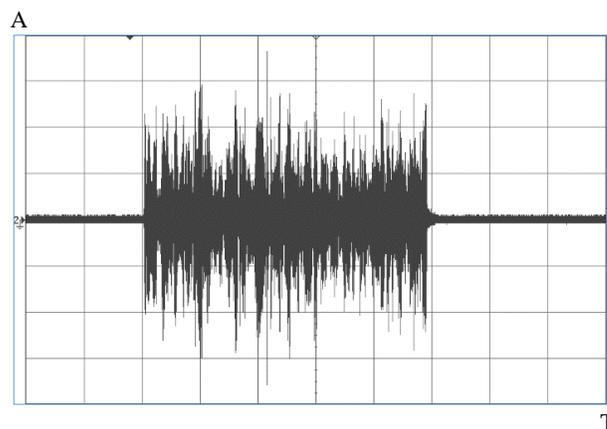


Figure 4- 2 MHz passive cavitation detector output signal, A : 0.5v/div, T: 200 microsecond/div.

IV. RESULTS

A. Micropores and High Intensity Ultrasound

Micropores created by microneedles in soft materials imitating upper portions of human skin appeared to have no flow of both glycerin and PEG transfer materials without application of ultrasound, in the ranges of 40 to 110 μm diameter.

Hard materials imitating the inner portions of hypodermic needle, G10 and stainless steel, had micropores range of 40-60 μm in diameter created by laser machining with no visible flow through the membrane without application of ultrasound.

Varying frequency of the applied intensity, length of the ultrasonic burst and viscosity of the transfer materials the flow velocity of the very short bursts 1-20 msec and longer bursts up to 120 msec yielded variety of the average streaming velocities up to 480 mm/sec. [Table I]. Acoustic attenuation of the transfer liquids was measured and taken into account for intensity calculations.

| Membrane | Micropore Diameter, μm | Liquid | Viscosity, Centipoise | Frequency MHz | Intensity, W/cm^2 | Burst, msec | Average Streaming Velocity, mm/s |
|----------------|-----------------------------------|---------------|-----------------------|---------------|-----------------------------------|-------------|----------------------------------|
| 0.8mm silicone | 160 | 100% glycerin | 612 | 3.3 | 808 | 120 | 45 |
| 0.8mm silicone | 100 | 100% glycerin | 612 | 5 | 1446 | 120 | 50 |
| pigskin | 100-110 | 100% glycerin | 612 | 3.3 | 808 | 120 | 50 |
| PCB, 0.8mm | 40-50 | 100% glycerin | 612 | 6.9 | 2084 | 73 | 24 |
| PCB, 0.8mm | 40-50 | 75% glycerin | 21 | 2.15 | 1838 | 1 | 80 |
| PCB, 0.8mm | 40-50 | 75% glycerin | 21 | 2.15 | 1838 | 2.5 | 210 |
| PCB, 0.8mm | 40-50 | 75% glycerin | 21 | 2.15 | 1838 | 5 | 270 |
| PCB, 0.8mm | 40-50 | 75% glycerin | 21 | 2.15 | 1838 | 14 | 300 |
| PCB, 0.8mm | 40-50 | 75% glycerin | 21 | 2.15 | 1838 | 23 | 330 |
| PCB, 0.8mm | 40-50 | 50% glycerin | 4.2 | 2.15 | 1864 | 14 | 480 |
| PCB, 0.8mm | 40-50 | 50% PEG | 322 | 2.15 | 1434 | 19 | 100 |

Table 1- Streaming flow average velocity summary (stainless steel membrane not shown)

Transfer of the materials volumes normalized to one micropore was estimated of up to 100 microliters/min. at the burst repetition frequency of 2.5 Hz.

There was no appreciable temperature increase at or near membranes during the exposures at burst lengths up to 120 msec and 2.5 Hz PRF summarized in Table I.

B. Noninvasive material transfer via high intensity ultrasound

Photographed and measured gross pathology samples of freshly excised pig skin showed the diffusion of color-coded glycerin carrier through the skin and up to approximately 1.5 mm depth in the sample, compared with no traces of the transfer liquid in the cross sections adjacent to the exposure sites. (Fig. 5)

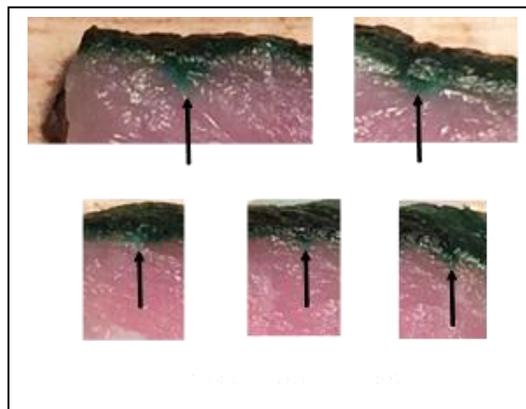


Figure 5- Gross pathology cross-sections of pig skin: penetration of color-coded (green) glycerin at acoustic beam propagation axis up to 1.5 mm

No statistically significant changes in the temperature during the exposure bursts up to 170 msec occurred and no thermal damage was visible in the gross pathology observations.

During the exposures the inertial cavitation measurements were performed utilizing passive cavitation detection. The resultant broadband cavitation transmission was recorded at the focal site consistent with a possible inertial cavitation mechanism of liquid transfer inside the soft tissue. (Fig. 6)

Human skin in vivo testing was done on several volunteers. 21 sequential exposures at center frequency of 10 MHz focused at 1.5 mm under skin surface were performed with average power of 10 W and burst duration of 100 msec each forming a treatment line. Treatment lines on adjacent areas of the skin shown in Figure 7 demonstrated clear absence of the inflammatory “welt” with 5% lidocaine applied to the skin compared to regular acoustic coupling gel treatment sites with only slight transient erythema. Pain levels for the treatment lines were down approximately 2 points on a 10-point scale (4-5 points down to 2-3 points) for lidocaine coupled exposures compared to acoustic coupling gel exposures.

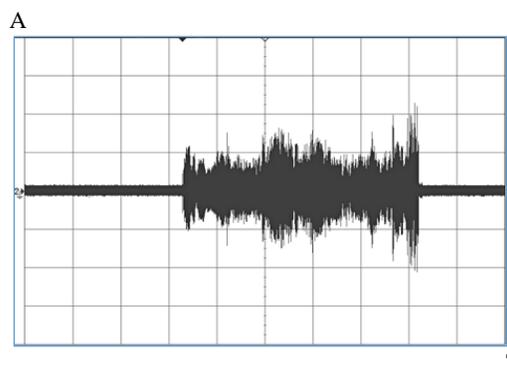


Figure 6- 10 MHz coaxial passive cavitation detector output signal, A: 0.5/div, T: 2 msec/div

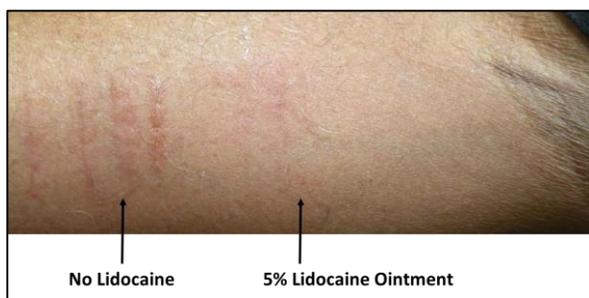


Figure 7- Human forearm skin adjacent treatment sites with and without 5% topical lidocaine coupling, 10 MHz Treatment lines; 10w; 100 ms bursts; 21 bursts per line at 1.5 mm spacing

Cavitation detection results showed persistent inertial cavitation transmission at each exposure with a typical broadband spectrum. (Fig. 6)

V. DISCUSSION AND CONCLUSIONS

Both ultrasound aided drug delivery (UADD) approaches described here are aimed at increased diffusion of the drugs through the skin barrier via minimally invasive (artificial micropores/microchannels) and noninvasive methods of high frequency high intensity ultrasound use. Transfer of substantial volumes of liquid carrier represented by biocompatible high viscosity glycerin through micropores/microchannels was done without appreciable thermal effects in the tissue. Higher molecular weight compounds represented by PEG in this case did have slightly lower transfer rate [Table 1].

Noninvasive qualitative results in skin using suggested inertial cavitation mechanism of diffusion had no appreciable thermal effects in ex vivo pig skin and clearly demonstrated controlled thermal effects in human live skin. Anti-inflammatory properties of lidocaine are known [8] and reduction of pain could be tell-tale signs of the topical anesthetic working as deep as 1.5 mm into the skin. 7.5 MHz exposures at 3mm focal distance produced no effects similar to 10 MHz which could be explained by lower intensity ($< 1\text{ kW/cm}^2$) at the epidermis and deeper focal distance (3mm). While this work is showing non-optimized and somewhat arbitrarily chosen set of acoustic parameters the new approaches to the skin barrier penetration may be useful especially broadening the transfer liquid vehicles and optimizing time and efficiency of the process itself. Controlled temperature elevation conformally applied to the delivery sites should only increase the diffusion of the drugs delivered with or without ablative effects of high intensity ultrasound. [9]

In conclusion, it appears to be feasible to combine micropores/microchannel based delivery of drugs with the application of high frequency/ high intensity ultrasound. High intensity/ high frequency bursts delivered noninvasively may help the penetration of drugs through the skin barrier possibly via inertial cavitation mechanism of action.

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