

● *Original Contribution*

ULTRASOUND-MEDIATED TRANSDERMAL *IN VIVO* TRANSPORT OF INSULIN WITH LOW-PROFILE CYMBAL ARRAYS

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Abstract—The purpose of this study was to demonstrate the feasibility of ultrasound (US)-mediated transdermal delivery of insulin *in vivo* using rats with a novel, low profile two-by-two US array based on the “cymbal” (due to its unique shape) transducer. As a practical device, the cymbal array ($f = 20$ kHz) was $37 \times 37 \times 7$ mm in size, and weighed less than 22 g. A total of 20 Sprague–Dawley rats (350 to 450 g) were divided into four groups, two controls and two US exposure, with five rats in each group. The rats were anesthetized and shaved; a water-tight standoff reservoir, which held the insulin or saline, was sealed against the rat’s abdomen and the US array. At the beginning of the experiment and every 30 min for 90 min, 0.3 mL of blood was collected from the jugular vein to determine the blood glucose level (mg/dL). For comparison between the rats, the change in the glucose level for each rat was normalized to a baseline (*i.e.*, 0 mg/dL). The first control group used insulin in the reservoir with no US and the second control group had saline in the reservoir with US operating at $I_{SPTP} = 100$ mW/cm² for 60 min. For the experiments, the third group employed insulin with US exposure for 60 min ($I_{SPTP} = 100$ mW/cm²), whereas the last group used insulin with US operating with a 20-min exposure ($I_{SPTP} = 100$ mW/cm²) to examine the effects of time on delivery. For the 60-min US exposure group, the glucose level was found to decrease from the baseline to -267.5 ± 61.9 mg/dL in 1 h. Moreover, to study the effects of US exposure time on insulin delivery, the 20-min group had essentially the same result as the 60-min exposure at a similar intensity, which indicates that the expose time does not need to be as long for delivery. (E-mail: nbs@engr.psu.edu) © 2003 World Federation for Ultrasound in Medicine & Biology.

Key Words: Ultrasound, Drug delivery, Transdermal, Insulin, *In vivo*.

INTRODUCTION

Past research has shown that ultrasound (US)-mediated transdermal drug delivery offers promising potential for noninvasive drug administration (Johnson et al. 1996; Mitragotri et al. 1995a; Mitragotri and Kost 2000; Zhang et al. 1996). Previously, researchers who have successfully used acoustic energy for drug delivery have used commercial sonicators or commercially constructed transducers. However, these large industrial devices are impractical for a feasible and transportable drug-delivery device.

Several methods exist for increasing transdermal drug delivery, such as chemical mediation using liposomes or chemical enhancers, and physical mechanisms such as iontophoresis, electroporation, and US (also

called sonophoresis or phonophoresis) (Machet and Boucaud 2002; Montorsi et al. 2000; Prausnitz 1999). Ultrasound-enhanced transdermal drug delivery offers advantages over traditional injection drug-delivery methods that are invasive and painful. Currently, few drugs, proteins or peptides have been successfully administered transdermally for clinical applications because of the low skin permeability to these relatively large molecules. This low permeability is attributed to the stratum corneum, the outermost skin layer that consists of a compact and organized structure of cells named keratinocytes surrounded by lipid bilayers. One hypothesis indicates that, after the drug has traversed the stratum corneum, the next layer is easier to cross and, subsequently, the drug can reach the capillary vessels to be absorbed (Mitragotri et al. 1995b).

Investigators have demonstrated the potential to deliver and control therapeutic doses of proteins, such as interferon gamma and erythropoietin, across *in vitro*

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human skin using US (Mitragotri et al. 1995a). Other researchers have investigated the *in vitro* penetration and the *in vivo* transport of flufenamic acid in skin with US (Hippius et al. 1998). In the flufenamic acid study, US exposure was from 5 to 30 min with intensities up to 1.5 W/cm^2 . US at 1 MHz has also been used to enhance the transdermal absorption of indomethacin, studied in rats using intensities from 0.25 to 1 W/cm^2 . The researchers reported no significant skin temperature rise and no notable damage to the skin; however, damage was noted as the intensity and the time of application of US increased beyond 1 W/cm^2 (Miyazaki et al. 1992).

Specifically for insulin, there has only been limited research, although positive results have been shown (Boucaud et al. 2002; Mitragotri et al. 1995a; Tachibana and Tachibana 1991; Tachibana 1992; Zhang et al. 1996). Over a frequency range of 20 to 105 kHz, enhanced transport in the presence of US has been shown in both *in vitro* and *in vivo* experiments. Yet, all of the experiments were performed using either an US sonicator, ultrasonic bath or commercial transducer. The major drawback so far in exploiting US for noninvasive drug delivery is the large size and poor mobility of the US device. Commercial sonicators are large, heavy table-top devices that are designed specifically to disrupt or destroy cells. For practical application of US-enhanced transdermal drug delivery, a smaller portable device is necessary.

Use of the low-profile, light-weight cymbal US array (a "cymbal" transducer consists of a piezoelectric disk sandwiched between two metal caps) has previously demonstrated transport enhancement of insulin across *in vitro* human skin (Smith et al. 2002). A two-by-two array made from four cymbal transducers was used to generate an I_{SPTP} of $173.7 \pm 1.2 \text{ mW/cm}^2$ and spectrophotometric absorption techniques were used for determining insulin transport across the *in vitro* skin. Compared to a passive transmission result of $4.1 \pm 0.5 \text{ U}$ of insulin over an exposure period of 1 h, the cymbal array facilitated over a sevenfold increase in the noninvasive transdermal transport of $45.9 \pm 12.9 \text{ U}$ of Humulin® R insulin. Using Humalog® insulin with the array, there was a fourfold increase in the US-facilitated transmission compared to the control. Based on the positive results from this *in vitro* human skin study, the purpose of this research was to study the feasibility of US-mediated transdermal delivery of insulin *in vivo* using hyperglycemic rats with the low-profile US array based on the cymbal transducer.

MATERIALS AND METHODS

Ultrasound array

Details regarding the design and construction of the cymbal transducer and the multielement array have been

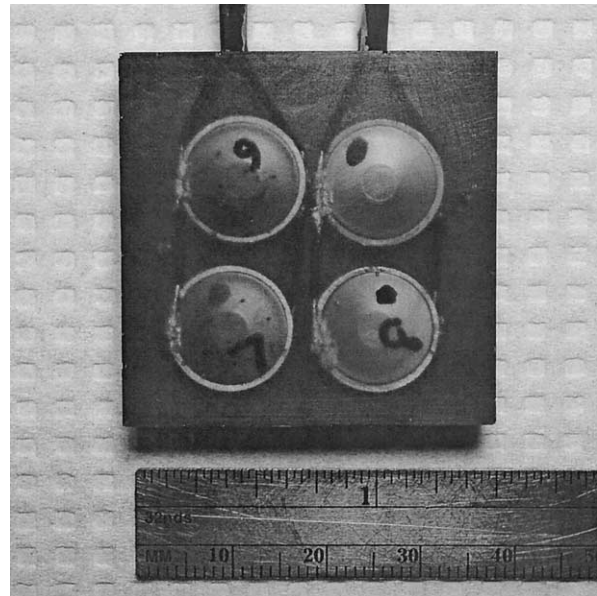


Fig. 1. For the cymbal array made up of four cymbal transducers, the cymbal elements were connected in parallel, encased in URALITE® polymer and arranged in a two-by-two elemental pattern. The dimensions of the array were $37 \times 37 \times 7 \text{ mm}$ and it weighed less than 22 g.

described elsewhere (Maione et al. 2002; Newnham and Dogan 1998; Tressler et al. 1998). Briefly, the cymbal transducer is a class V flexensional transducer capable of producing very low frequencies. The cymbal transducer has a compact, lightweight structure with an adjustable resonance frequency of between 1 and 100 kHz. In the cymbal transducer design, the caps on the lead zirconate-titanate (PZT) ceramic contained a shallow cavity beneath its inner surface. The fundamental mode of vibration is the flexing of the end caps caused by the radial motion of the ceramic. Therefore, the overall displacement of the device is a combination of the axial motion of the disk (d_{33}) plus the radial motion amplified by the end caps (d_{31}). Amplification factors can be as high as 40 times that of the ceramic by itself (Meyer et al. 2001). Specifically, the piezoelectric disc was made from PZT-4 (Piezokinetics, Inc., Bellefonte, PA), had a diameter of 12.7 mm, and was 1-mm thick. PZT-4 was chosen because this material has a high failure voltage threshold compared to ceramics with similar efficiency. Caps were made of 0.25-mm thick titanium and the thin glue layer between the caps and the ceramic disk was made of Eccobond® epoxy. For the array, four transducers were connected in parallel and encased in URALITE® polymer (FH 3550, H.B. Fuller, St. Paul, MN) to produce a transducer array arrangement. A two-by-two elemental pattern was used for the array and was in a $37 \times 37 \times 7 \text{ mm}$ block (Fig. 1).

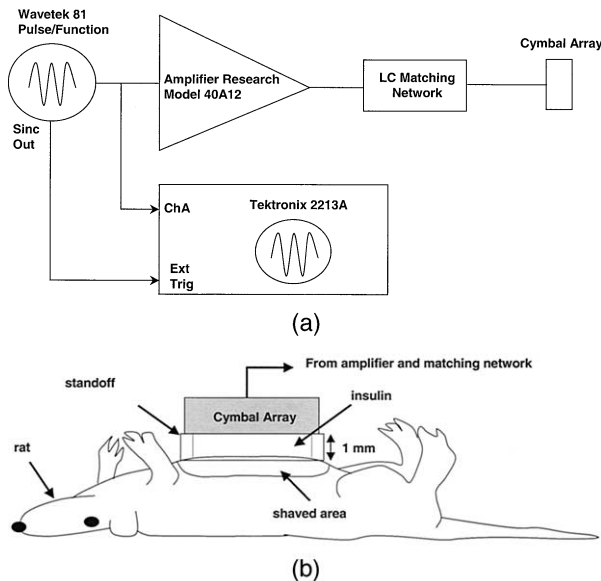


Fig. 2. (a) Experimental setup of the function generator and the amplifier used for driving the cymbal array. The pulsed signal ($f = 20$ kHz) from the signal generator was at 600 mVpp with a pulse duration of 200 ms and pulse repetition period of 1 s (*i.e.*, 20% duty cycle) and the amplifier gain was set to 50 dB. (b) Illustration of the experimental setup for the transdermal insulin transport. With the rat placed on its back, a 1-mm thick, water-tight standoff was arranged between the abdomen and the array. The reservoir inside the standoff was filled with either saline or insulin.

To drive the array (Fig. 2a), a radiofrequency (RF) signal was generated by a frequency pulse/function generator (model 393, Wavetek Inc., San Diego, CA) and amplified by an RF amplifier (model 40A12, Amplifier Research, Souderton, PA). The electrical impedance of the array was tuned to the output impedance of the amplifier by an external inductor-capacitor tuning network. Pulse period, duty cycle and exposure time of the RF signal from the frequency generator was monitored using an oscilloscope (Tektronix 2213A, Beaverton, OR). For the experiments, the signal generator operated at 20 kHz had a 600 mV (peak-to-peak) output with pulse duration of 200 ms and pulse-repetition period of 1 s (*i.e.*, 20% duty cycle); the amplifier gain was set to 50 dB. Pulsed US was used to avoid damaging heat build-up to either the array or animal skin.

Ultrasound exposimetry

For determining the intensity at a plane 1 mm from the transducer face, the ultrasonic intensities from the array were determined with a calibrated miniature (4-mm diameter) omnidirectional reference hydrophone (model TC4013, S/N: 5199093, RESON, Inc., Goleta, CA). The cymbal array was submerged in a water tank ($51 \times 54 \times$

122 cm) that was made almost anechoic by placing 1.27-cm thick rubber sound-absorbing material around its wall. A custom-made degasser, built in-house, reduced the dissolved oxygen content of the distilled water to 1 to 2 ppm to reduce cavitation effects. Pulse period, duty cycle and exposure time of the signal from the frequency generator and hydrophone were acquired using an Agilent 54622A 100-MHz digitizing oscilloscope (Agilent, Palo Alto, CA).

Precise, computer-controlled positioning of the hydrophone was performed by a Velmex Positioning System (Velmex Inc., East Bloomfield, NY). Pressure waves detected by the hydrophone were recorded by a digitizing oscilloscope. A computer-controlled exposimetry positioning system was used for automated scanning. The scanning step size for each device was 1 mm and the scanning area was 20×20 mm. Spatial peak-temporal peak intensity (I_{SPTP}) and spatial peak-pulse average intensity (I_{SPPA}) along with the peak compressional (P_c) and rarefactional (P_r) pressures, were determined over a plane 1 mm from the array face using the hydrophone, based on 3 to 5 scans of the array for a mean and SD of the results (AIUM 1998; IEEE 1990).

Animal experiments

The rats were anesthetized and euthanized by procedures approved by the Institutional Animal Care and Use Committee (IACUC) at the Pennsylvania State University. A total of 20 Sprague–Dawley rats (350 to 450 g) were divided into four groups with five rats in each group. Each animal was anesthetized with a combination of ketamine hydrochloride (60 mg/kg IM, Ketaject®, Phoenix, St. Joseph, MO) and sodium xylazine (10 mg/kg IM, Xyla-Ject®, Phoenix). The abdominal areas of the rats were shaved using an electric shaver, and a depilatory agent was applied to the skin to eliminate any remaining hair.

For both general anesthesia and hyperglycemia, xylazine was used to cause temporary, but sustained (up to 12 h), hyperglycemia in rats (Kawai *et al.* 1997; Pavlovic *et al.* 1996). With a rat placed in the dorsal decubitus position, a 1-mm thick, water-tight standoff was arranged between the abdomen and the array (Fig. 2b) and held in place using double-sided carpet tape (3 M, St. Paul, MN). The reservoir inside of the standoff was filled with saline, for the control experiment, or 4 mL of 50 Units/mL insulin (Humulin® R, rDNA U-100, Eli Lilly and Co., Indianapolis, IN) through holes in the back of the array. Care was taken to remove all bubbles from the solution in the reservoir between the abdomen and the array.

Before beginning the experiment, 0.3 mL of blood was collected from the jugular vein of each rat for a baseline glucose analysis. The glucose level (mg/dL) in

the rat blood was determined using ACCU-CHEK™ blood glucose monitoring system (Roche Diagnostics Co., Indianapolis, IN) and multiple samples (3 to 6 each time) were taken from each rat every 30 min for 90 min. The time from the initial injection of the ketamine-xylazine until the baseline glucose measurement was no greater than 25 min. For comparison between the rats, the change in the blood glucose level was normalized to a baseline with respect to each animal's initial blood glucose recording at 0 min.

For each rat, the entire experiment lasted a total of 90 min. The first control group ($n = 5$) used insulin in the reservoir with no US and the second control group ($n = 5$) was a negative control and had saline in the reservoir with US operating at $I_{SPTP} = 100 \text{ mW/cm}^2$ for 60 min ($P_c = 37.9 \text{ kPa}$, $P_r = 38.6 \text{ kPa}$). For the experiments, the third group ($n = 5$) employed insulin with US exposure for 60 min ($I_{SPTP} = 100 \text{ mW/cm}^2$), whereas the last group ($n = 5$) used insulin with US operating with a 20-min exposure to examine the effects of time ($I_{SPTP} = 100 \text{ mW/cm}^2$). For all four groups, the standoff reservoir with the insulin or saline was removed at 60 min, although glucose determination continued until 90 min from the start. At the end of the experiments, the rats were euthanized under anesthesia.

Statistical analysis was performed using Microsoft Excel® (Microsoft Corp, Redmond, WA) and the data were pooled for each group and analyzed as its mean and SD. An ANOVA was used to analyze the statistical significance of the differences among the means of groups. The p value was used to determine if the between-group differences were significantly greater than chance.

RESULTS

Results for *in vivo* US-mediated insulin transport rates for the four groups are plotted in Fig. 3. These results illustrate the changes in the blood glucose levels over 90 min for the four experimental groups. Immediately after anesthesia using ketamine-xylazine, the average glucose level of the 20 rats was $419.1 \pm 31.4 \text{ mg/dL}$, which is consistent with glucose levels in rats made diabetic using streptozotocin. Generally, for rats, the normal blood glucose level without xylazine is $\approx 100 \text{ mg/dL}$. For comparison between the rates and groups, the change in the blood glucose level was normalized to a baseline.

Data were graphed as it mean and SD of each group. For the first (insulin, no US) and second (saline, US) control group, the glucose level varied no greater than 40 mg/dL from the baseline over the 90-min period. For the 60-min US-exposure group (insulin with US), the glucose level decreased to $-175.2 \pm 63.2 \text{ mg/dL}$ at 30 min

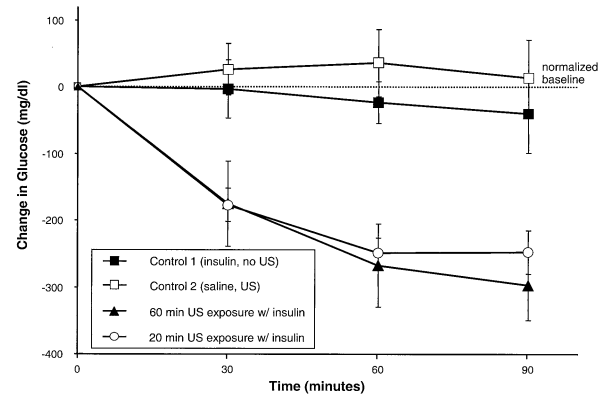


Fig. 3. Over a period of 90 min, the blood glucose level of the rats decreased from the insulin with US exposure ($I_{SPTP} = 100 \text{ mW/cm}^2$) using the cymbal array. Both control experiments (insulin, no US or saline and US) varied no greater than 40 mg/dL over the 90 min from the baseline. With 60 min of US exposure, the glucose level decreased to -267.5 mg/dL and the 20-min of US exposure had roughly the same effect.

and $-267.5 \pm 61.9 \text{ mg/dL}$ at 60 min. After the US was disabled at 60 min and the standoff removed, the glucose level continued to decrease to $-296.7 \pm 52.8 \text{ mg/dL}$ at 90 min. To determine if the same results could be obtained in less time, the last group used insulin, but with a 20-min US exposure. Similar to the 60-min results with the third group, the 20-min exposure group indicated a decrease in the blood glucose of $-177.1 \pm 25.1 \text{ mg/dL}$ at 30 min and $-249.3 \pm 22.3 \text{ mg/dL}$ at 60 min, which indicates that the US does not need to operate as long to obtain the same results as the 60-min exposure.

To determine the statistical significance between the results in Fig. 3 of the four groups at 60 min, an ANOVA was used to analyze these data. Table 1 lists the p values between group comparisons used to determine if the

Table 1. An ANOVA was used to analyze the statistical significance between the four groups (*i.e.*, control 1, control 2, 60 min and 20 min of US exposure) using the 60 min results in Fig. 3

	Control 1	Control 2	60 min	20 min
Control 1	X	–	–	–
Control 2	0.08	X	–	–
60 min	0.0002*	0.00003*	X	–
20 min	0.001*	0.0002*	0.15	X

Control 1 = insulin, no US; control 2 = saline and US; 60 min = 60 min US exposure with insulin; 20 min = 20 min US exposure with insulin; X = ANOVA not performed for identical groups; – = transpose of compared groups listed in table; * p value exceeds the 0.01 level of significance.

The p values of the comparison between groups were used to determine if the between-group differences were significantly greater than chance.

between-group differences were statistically significant. Six different comparisons were made between the four different groups, but comparison were not made between identical groups. The *p* value result for the comparison of the two control groups was 0.08, which indicated that there was no statistical difference between these groups. Comparison of the two control groups (control 1 and 2) with the US-exposed groups (60 and 20 min.) indicates that the results were statistically significant at a *p* value of 0.01 or better. Additionally, a comparison of the results with 20 and 60 min of US exposure indicated that there was no statistically significant difference between them (*p* = 0.15).

A gross examination of the rat skin was performed after exposure to detect visible lesions on the skin surface. Visual examination of the post-US exposed skin did not indicate any noticeable damage or significant change to the skin.

DISCUSSION

The goal of this research was to determine if an US device based on the low profile, light-weight cymbal transducer device could be used for ultrasonic transdermal insulin transport *in vivo*. Sonicators have been shown to transdermally deliver insulin across *in vitro* and *in vivo* skin using intensities as low as 12.5 mW/cm² (Mitragotri *et al.* 1995a). Based on the *I*_{SPTP} results, the cymbal array produced intensities that have previously been shown to transdermally deliver insulin across skin using a sonicator. Although a commercial sonicator has been an excellent device for demonstrating drug delivery, the ultrasonic probe or converter from commercial sonicators can weigh almost a kilogram or more; the cymbal array weighs less than 22 g.

For these experiments, xylazine was used to cause hyperglycemia in the rats (Pavlovic *et al.* 1996; Kawai *et al.* 1997). Immediately after anesthesia using ketamine-xylazine, the average glucose level of the 20 rats was 419.1 ± 31.4 mg/dL, which is consistent with glucose levels in streptozotocin rats compared to the normal blood glucose level of ≈ 100 mg/dL (Harkness and Wagner 1995; Hillyer and Quesenberry 1997). The purpose of using hyperglycemic rats for insulin delivery was to demonstrate the feasibility of reducing a high glucose level (above 200 mg/dL) to a normal glucose level (below 100), albeit for a rat model. The “gold standard” for diagnosing diabetes in humans is an elevated blood sugar level of 140 mg/dL after fasting. People without diabetes have fasting sugar levels that generally run between 70 to 110 mg/dL. When fasting, glucose of 110 to 126 mg/dL is classified as impaired fasting glucose, 140 to 200 mg/dL is impaired glucose tolerance and greater than 200 mg/dL is considered to be diabetic.

The US-mediated insulin transport *in vivo* experiment results indicated that both control experiments had very little effect on the blood glucose level of the rats (Fig. 3). In the first control experiment (insulin, no US), the glucose level remained near the normalized baseline level over 90 min, but decreased below the initial level because of the passive permeability of the skin to insulin. The result of the second control experiment (saline and US) indicated that US did not alter the glucose level of the rats by itself. Results of the ANOVA analysis indicated there was no statistical difference between the two control groups (Table 1). The insulin with 60 min of US exposure results indicate that the glucose level decreased near the normal blood glucose level of rats (*i.e.*, ≈ 110 mg/dL) in 90 min. Between-group differences were determined to be statistically significant at a *p* value of 0.01 or better for both control groups (control 1 and 2) compared with the US-exposed groups (60 and 20 min). Moreover, the results of the 20-min US exposure indicates that the exposure time does not need to be as long as 60 min for the same reduction in blood glucose (*p* = 0.15).

Given the number of other drugs that have been shown to be deliverable using US (*e.g.*, erythropoietin, interferon gamma), the novel development of a totally portable, battery-operated device can potentially be applied to other drugs that require repeated injections (Mitragotri *et al.* 1995a) or a drug delivery method for infants, where it is hard to establish and maintain catheters. In conclusion, results herein demonstrate a promising outcome for the low-profile cymbal array to be used for US-enhanced *in vivo* insulin transport.

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