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Ferroelectric transducer arrays for transdermal insulin delivery

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The goal of this research was the development of a portable therapeutic device for the treatment of diabetes. A 3×3 cymbal array has been successfully tested in noninvasive insulin delivery experiments. The cymbal is a composite flextensional transducer constructed from a poled PZT ceramic and shaped metal endcaps that amplify the transducer motions by two orders of magnitude. Nine cymbals are wired in parallel and potted in polyurethane to form the flat panel arrays. When driven near resonance (20 kHz), the array generated a low intensity acoustic beam of 100 mW/cm^2. Animal experiments on hyperglycemic rats and rabbits demonstrated the ultrasonic enhancement of transdermal insulin delivery.

1. Introduction

Flextensional transducers are mechanical amplifiers coupling the small longitudinal strains in piezoelectric drive elements to large flexural motions in a metal shell. By means of converting the high impedance of a stiff ceramic into a low acoustic impedance, the shell acts as a mechanical amplifier [1, 2]. The cymbal transducer is a miniature Class V flextensional transducer first developed at Penn State a decade ago [3–5]. Originally developed as a small actuator capable of generating moderate force and a sizable displacement, the cymbal was later utilized as an underwater acoustic projector [6]. The cymbal transducer consists of a piezoelectric ceramic disk poled in the thickness direction and sandwiched between two metal endcaps shaped similar to musical cymbals, hence the name cymbal transducer. By incorporating both flexural and rotational motions that convert the small radial displacements of the disk into large axial motions normal to the endcap surface, the endcaps act as mechanical amplifiers (Fig. 1). The simple manufacturing process of the cymbal is well-suited to inexpensive mass production and incorporation in a low-cost therapeutic device.

According to a recent epidemiological study, there are approximately 12 million diabetics in the United States [7]. Daily insulin injections are the usual treatment but a number of alternative therapies are under investigation.

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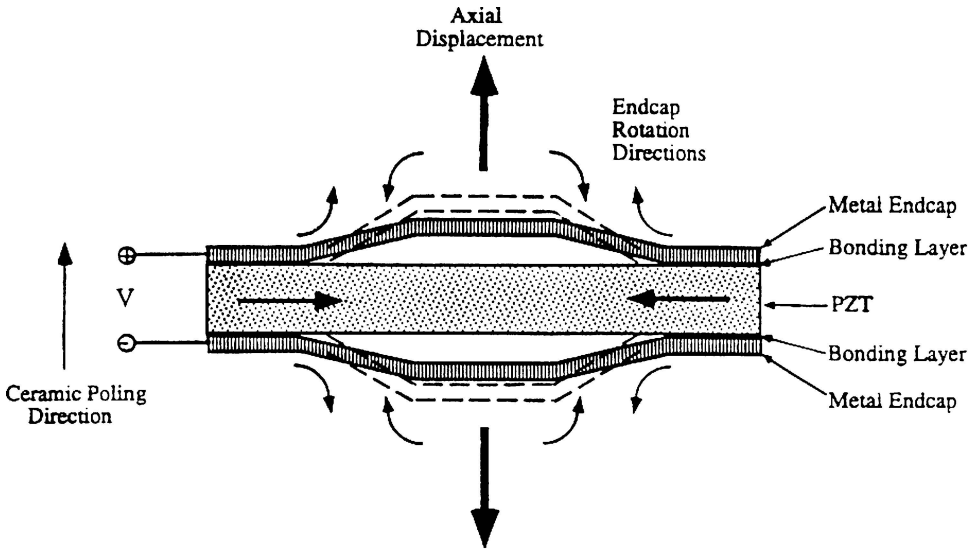

Figure 1 Cross-sectional view of a cymbal flextensional transducer where the hatched areas represent the metal endcaps, and the meshed area the poled PZT disk. Arrows incorporated into the schematic delineate the radial displacement of the disk and rotational motion of the endcaps, which both combine to produce the amplified axial displacement of the transducer [6].

One alternative involves the use of ultrasound to enhance the painless transdermal delivery of insulin. Sonophoresis, as it is called, possesses many potential advantages, but the human skin is a stubborn obstacle to large molecules like insulin [8]. Low frequency ultrasound (20–100 kHz) is found to be about a thousand times more effective than high frequencies (1–3 MHz) [9]. Most of these sonophoresis experiments were carried out with immobile commercial sonicators, which are impractical for a small portable device. The low profile cymbal arrays described in this paper appear to satisfy this requirement. Earlier experiments using a 2×2 array demonstrated the transport of insulin across *in vitro* human skin and with live *in vivo* animal studies [10, 11].

This paper describes the design, fabrication, and testing of a 3×3 cymbal array for use in transdermal drug delivery. Due to an increase in spatial area of ultrasound output in the 3×3 array as compared to the 2×2 array, a comparison between the respective *in vivo* results of the two arrays will elucidate the effect of spatial area on insulin delivery and subsequent decrease in blood glucose levels.

2. Design and construction of a 3 × 3 array

U.S. Patents 5,729,077 and 6,232,702 describe the fabrication and performance of cymbal actuators and transducers [12, 13]. The cymbal transducers were 12.7 mm in diameter and 2.2 mm thick. Hard lead zironate-titanate (PZT 4, Piezokinetics, Bellefonte, PA) disks were used as the driving elements, and poled in the thickness direction. Circular titanium caps were punched from sheet metal 0.25 mm thick with a diameter of 12.7 mm and a cavity depth of 0.32 mm. Eccobond epoxy 0.02 mm thick was used to bond thecaps to the ceramic.

Individual cymbals resonate at 39±2 kHz in air and 20.5 kHz in water with an omni-directional beam pattern. The cymbals are wired into arrays to increase efficiency, source level, and transmitting voltage response (TVR). Nine cymbals were electrically wired in parallel and potted in polyurethane to lower the acoustic impedance and improve the coupling to human tissue. As shown in Fig. 2, the dimensions of the 3×3 array were 57×57×7 mm^3 and it weighed less than 35 g. Electrical leads were encased in heat-shrink tubing and assembled into a BNC connector. A water-tight square-shaped Plexiglass® standoff 2.25 mm thick was attached to the face of the array and provided a reservoir for insulin or for saline solution.

3. Ultrasound exposimetry

An electrical control system consisting of a radio-frequency (RF) waveform generator, digital oscilloscope, RF amplifier, and matching circuit was used to drive the 3×3 array. The voltage to the array was monitored in real-time using an oscilloscope probe. Conditions of the insulin delivery experiments required the waveform generator operating at 20 kHz, a pulse duration of 200 msec, and a pulse repetition period of 1 sec (20% duty cycle). The waveform generator output voltage and RF amplifier were set so that the maximum spatial peak-temporal peak acoustic intensity (I_{SPTP}) was 100 mW/cm^2 at an offset distance of 1 mm below the bottom surface of the array, simulating the thickness between the surface of the array and the skin.

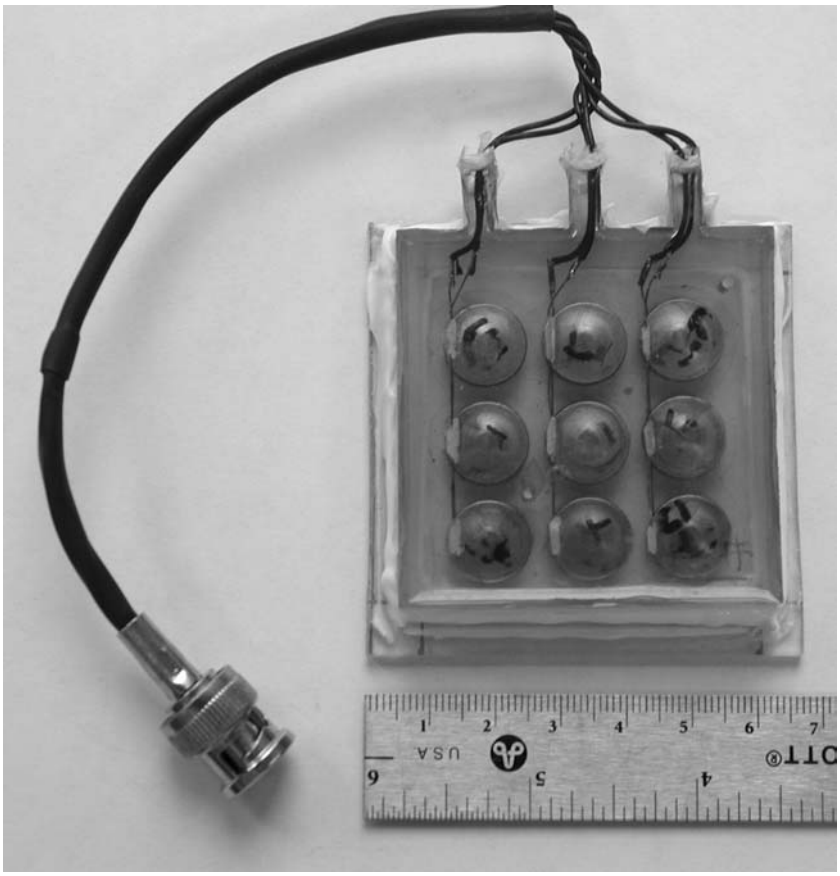

Figure 2 An assembled 3×3 cymbal array with BNC connector, heat shrink tubing, and Plexiglass ® standoff. Nine cymbal transducers are wired in parallel and potted in a polyurethane polymer. The overall dimensions of the low profile array are 57×57×7 mm^3 and weighing less than 35 g.

A calibrated, miniature omnidirectional reference hydrophone and a computer-controlled exposimetry system were used to make the intensity measurements. First, the hydrophone (Model TC4013, RESON, Inc., Goleta, CA) was stepped incrementally across the bottom surface of the array in 1 mm steps over a cross sectional area of $40\times40\ mm^2$. Two- and three-dimensional maps were generated to ensure that all cymbals were working individually and in conjunction, and that the I_{SPTP} output cone was centered over the face of the array. Second, by placing the hydrophone at an offset distance of 1 mm from the surface of the array over the central cymbal position and spanning the peak-to-peak input voltage from the waveform generator (at a constant input frequency of 20 kHz), a graph of maximum I_{SPTP} versus input voltage was obtained. By interpolating the results of these graphs, the input peak-to-peak voltage could be adjusted to produce the maximum I_{SPTP} output of 100 mW/cm^2 required for the animal experiments.

4. Animal experiments

The New Zealand White rabbits were anesthetized by procedures approved by the Institutional Animal Care and Use Committee (IACUC) at the Pennsylvania State University. A total of 17 rabbits (3.0–4.5 kg) were divided into three groups with five rabbits in "ultrasound only" control, five in "insulin only" control, and seven with "ultrasound & insulin". The rabbits were anesthetized with a combination of ketamine hydrochloride (40 mg/kg administered subcutaneously, Ketaject ®, Phoenix, St. Joseph, MO) and sodium xylazine (10 mg/kg administered subcutaneously, Xyla-ject®, Phoenix, St. Joseph, MO). In addition to anesthetizing the rabbits, the combination of ketamine and xylazine caused temporary but sustained (up to 12 hours) hyperglycemia in the test rabbits.

While anesthetized, the hair in the abdominal region of the rabbits was shaved with clippers and a depilatory cream was briefly applied to remove any remnant hair; the area was then thoroughly cleaned with water and alcohol. With the rabbit placed in the dorsal recumbent position, the 3×3 array with standoff was affixed to the exposed abdominal skin using double-sided industrial carpet tape (3M, St. Paul, MN) cut to the imprint shape of the standoff (Fig. 3).

The reservoir created by the standoff was filled with saline solution for the ultrasound only control experiments and about 5 mL of insulin solution for the insulin only control and insulin combined with ultrasound experiments (Humilin®R, rDNA U-100, Eli Lilly and Co., Indianapo-

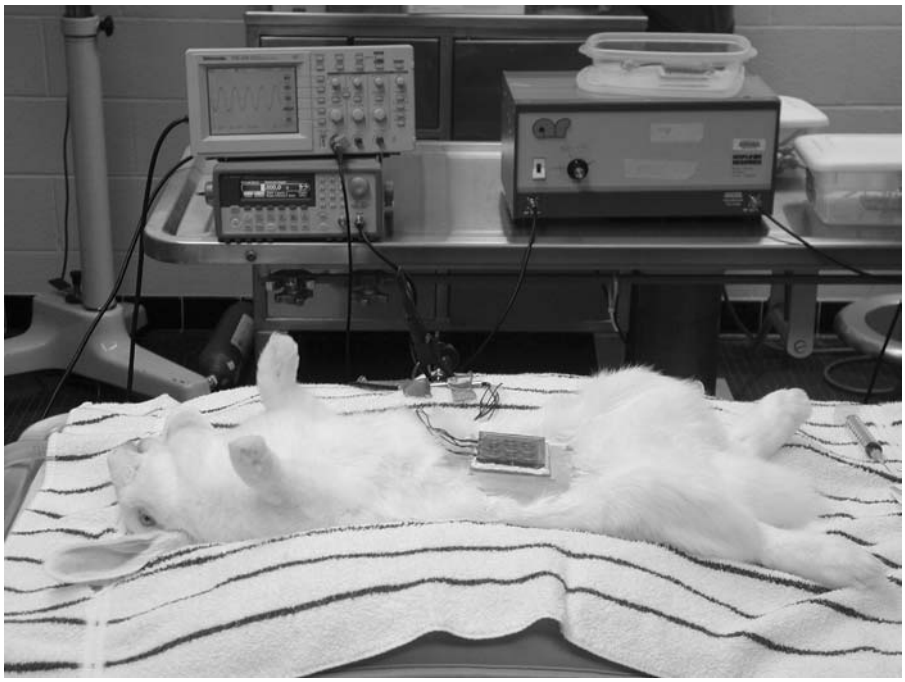

Figure 3 Experimental set-up of the rabbit, 3×3 cymbal array, and electronic drive system during the noninvasive transdermal insulin delivery experiments. With the rabbit anesthetized and lying in the dorsal recumbent position, the waveform generator provided a pulsed signal at 20 kHz, pulse duration of 200 msec, and a pulse repetition period of 1 sec (20% duty cycle). The input peak-to-peak voltage and amplifier gain were adjusted to supply an acoustic I_{SPTP} output of 100 mW/cm^2 through the 60 min exposure.

lis, IN). The fluids were added through small holes drilled through the top of the array. Care was taken to remove all bubbles from the solution within the reservoir. The insulin solution consisted of 10 mL insulin (100 U/mL) diluted with 10 mL saline to produce a total volume of 20 mL and a final insulin concentration of 50 U/mL. Previous research has shown that dilution of the insulin does not affect the transdermal delivery of insulin or subsequent decrement in blood glucose [11].

Prior to beginning the experiment, 0.03 mL of blood was collected from the ear vein of each rabbit for a baseline glucose comparison. The blood glucose level (mg/dL) was determined using an ACCU-CHEK™ Instant® (Roche Diagnostics Co., Indianapolis, IN) blood glucose monitor; multiple (3–6) blood glucose readings were recorded for the baseline value and every 15 min for 90 min after experiment initiation. The time elapsed between induction of anesthesia and the baseline glucose reading was about 30 min. In order to compare decrements in blood glucose between successive rabbit experiments, the blood glucose level was normalized to the baseline recording in each experiment.

For each rabbit, the entire experiment lasted a total of 90 min. The first control group ($n = 5$) was exposed to insulin solution in the reservoir but no ultrasound (designated "insulin only") to study the effects of passive diffusion. The second control group ($n = 5$) involved the application of ultrasound (100 mW/cm^2 for 60 min) with saline in the reservoir (designated "ultrasound only") to study the effects of ultrasound alone. The final group ($n = 7$) combined the application of ultrasound (100 mW/cm^2 for 60 min) with insulin solution in the reservoir (designated "insulin & ultrasound"). For all three groups, the reservoir with saline or insulin and the array were removed after 60 min exposure, although the blood glucose continued to be monitored at 15 min intervals for an additional 30 min.

5. Results

An initial exposimetry of the 3×3 ultrasound array indicated the integrity of the array design and assembly. As shown in Fig. 4, the initial I_{SPTP} acoustic intensity output resembles a relatively smooth, centered cone. Each 3×3 array was constructed with the cymbal having the lowest fundamental resonance peak positioned in the center location. This minimized detrimental acoustic interactions resulting in a more controlled, rounded peak, rather than an exaggerated spike. Once the array integrity was verified, a more rounded 100 mW/cm^2 I_{SPTP} output was achieved through the addition of a RF matching circuit, Plexiglass® standoff, and interpolation of input peak-to-peak voltage graphs.

The anesthetic combination of ketamine and xylazine induced a hyperglycemic state in all rabbits by increasing their normal blood glucose levels of 100–130 mg/dL to 197.6 ± 26.9 mg/dL immediately before the start of the transdermal insulin delivery experiments. This was the initial blood glucose reading at 0 min and was thus

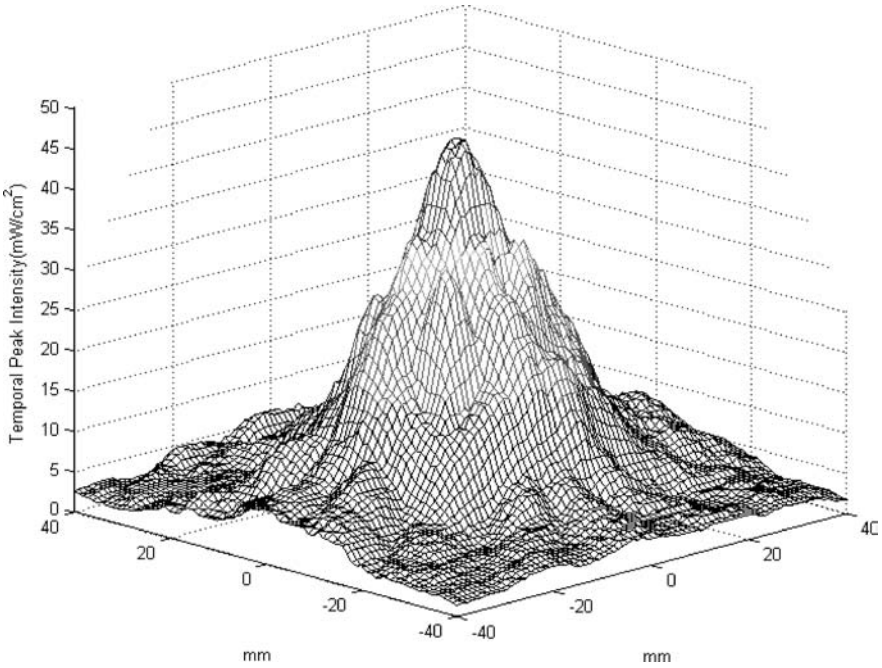

Figure 4 Exposimetry integrity test results of a correctly fabricated 3×3 cymbal array: 3D I_{SPTP} contour plot with reference bar. This initial exposimetry measurement was performed without the enhancement of the RF matching circuit or Plexiglass ® standoff, and was used to validate that the transducers were working in concert to produce a smooth and centered I_{SPTP} output cone.

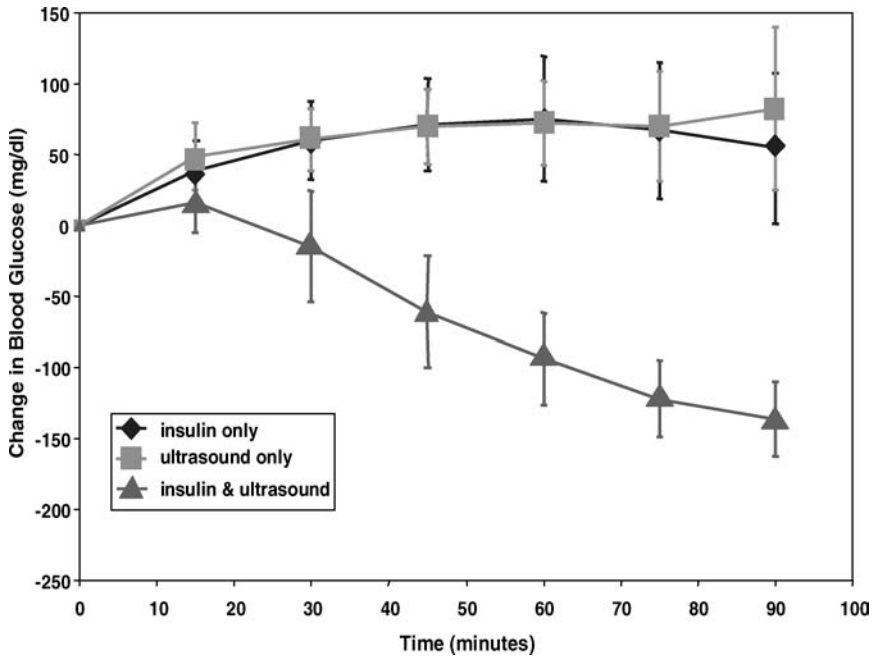

Figure 5 Graph of the change in blood glucose over the 90 min transdermal insulin delivery experiment duration, comparing both controls ("insulin only" and "ultrasound only") to the "insulin & ultrasound" results generated by the 3×3 array. The two controls showed an increase in the normalized blood glucose level to ∼70 mg/dL after 60 min. The collaboration of insulin with ultrasound resulted in the normalized blood glucose level decreasing to −94.1 ± 32.3 mg/dL after 60 min exposure and to 136.1 ± 26.1 mg/dL at 90 min.

considered the baseline value. For comparison between rabbits in the three groups, the change in the blood glucose level was normalized to the baseline value. The normalized blood glucose levels for the three rabbit groups in the experiments are graphed in Fig. 5 as a mean and standard deviation (mean ± SD) for each group at each particular time interval. The results illustrate the change in blood glucose levels during the 90 min (15 min increments) experiment. For the "ultrasound only" control group, the blood glucose increased to 69.7 ± 26.8 mg/dL

after 45 min and maintained approximately at that level until 90 min, where it increased to 82.5 ± 57.7 mg/dL. For the "insulin only" control group, the blood glucose continually increased to 75.2 ± 44.0 mg/dL after 60 min and then decreased to 54.6 ± 52.8 mg/dL at 90 min. For the "insulin & ultrasound" group, the blood glucose decreased to −94.1 ± 32.3 mg/dL after 60 min exposure, at which time the insulin and array were removed, and continued to decrease to −136.1 ± 26.1 mg/dL at 90 min. Results from the "ultrasound & insulin" rabbit group indicate that the ultrasound enhanced the delivery of insulin. The initial hyperglycemic blood glucose levels for the rabbits in this group returned to the normal blood glucose range via the ultrasonic enhancement of transdermal insulin delivery. A careful examination of the rabbit skin was performed after ultrasound exposure to detect any visible lesions on the skin surface. Visual examination of the ultrasound exposed skin did not reveal any palpable damage or significant change in the skin.

A statistical analysis between the blood glucose decrements achieved utilizing the earlier 2×2 array and 3×3 array calculated that there exists no significant statistical difference [14].

6. Conclusions

An exposimetry system was employed to quantify the spatial and temporal acoustic intensity (I_{SPTP} [mW/cm^2]) and was used to validate the performance of the 3×3 cymbal arrays utilized in the insulin delivery experiments: the I_{SPTP} output was centered with a smooth three-dimensional cone in all the 3×3 cymbal arrays.

Enhanced transdermal insulin delivery via ultrasound was demonstrated using the 3×3 cymbal arrays. Following an approved IACUC protocol, five New Zealand White rabbits were utilized in rotation and were anesthetized using a combination of ketamine and xylazine, which also induced a hyperglycemic state in the rabbits (blood glucose levels increased from 100–135 mg/dL to 197.6 ± 26.9 mg/dL at the start of the experiments). A total of 17 rabbit experiments were conducted, and were divided into three categories: ultrasound only control ("ultrasound only"); insulin only control ("insulin only"); and, the combination of insulin with ultrasound ("insulin & ultrasound"). The two controls, determined to be not significantly different ($p > 0.5$), showed an increase in the normalized blood glucose level to ∼70 mg/dL after 60 min. Conversely, by applying ultrasound with an insulin solution contained within the reservoir, the normalized blood glucose level decreased to −94.1 ± 32.3 mg/dL after 60 min exposure and to 136.1 ± 26.1 mg/dL at 90 minutes. The decrement in blood glucose due to the 3×3 array was determined to be not significantly different ($p > 0.5$) to the decrement in blood glucose level for the 2×2 array under similar experimental conditions [14]. Therefore, the increase in spatial area of ultrasound output appears to have a negligible effect on insulin delivery. This result is beneficial in that a small, portable insulin delivery device can potentially deliver the same amount of insulin and cause a similar decrease in blood glucose levels as a large, immobile device. The transdermal delivery of insulin may only be dependent upon the ultrasound dosage. Feasibility studies that independently vary the ultrasound dosage - quantified by exposure time, acoustic intensity, or ultrasonic frequency — may elucidate a direct relationship.

Transdermal insulin delivery experiments on pigs are now being performed as a prelude to therapeutic use on human beings. A greater correlation between ultrasound dosage and transdermal insulin delivery is a notable objective. The transdermal delivery of other drugs such as steroids and antibiotics are also worthy goals for future work.

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References

1. K. D. ROLT, *J. Acoust. Soc. Am.* **87**(3) (1990) 1340.
2. W. J. TOULIS, Us Patent 3,277,433 (1966).
3. Y. K. SUGAWARA, S. YOSHIKAWA, Q. C. XU and R. E. NEWNHAM, *J. Amer. Ceramic Soc.* **75** (1992) 996.
4. J. F. TRESSLER, Q. C. XU, S.YOSHIKAWA, K. UCHINO and R. E. NEWHAM, *Ferroelectrics* **156** (1994) 67.
5. A. DOGAN, K. UCHINO and R. E. NEWHAM, *IEEE UFFC* **44** (1997) 597.
6. J. F. TRESSLER and R. E. NEWHAM , *J. Acoust. Soc. Am.* **105(2)** (1999) 591.
7. American Diabetes Association, *Diabetes Care* **26**(Supp. 1) (2003) s121.
8. S. MITRAGOTRI, *J. Pharm. Sci.* **84** (1995) 697.
9. *Idem., Pharm. Res.* **13** (1996) 411.
10. N. B. SMITH, S. LEE, E. MAIONCE, R. B. ROY, S. MCELLIGOTT and K. K. SHUNG, *Ultrasound Med. Biol.* **29** (2003) 311.
11. N. B. SMITH, S. LEE and K. K. SHUNG, *ibid.* **29** (2003) 1205.
12. R.E. NEWNHAM and A. DOGAN, US Patent 5,729,077 (1995).
13. R.E. NEWNHAM and J. ZHANG, US Patent 6,232,702 (1999).
14. S. LEE, "Ultrasound-Mediated Transdermal Insulin Delivery and Glucose Measurement Using the Cymbal Array," Ph.D. Thesis, Penn State University (2004).