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Developing a Commercial Air Ultrasonic Ceramic Transducer to Transdermal Insulin Delivery

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ABSTRACT

The application of low-frequency ultrasound for transdermal delivery of insulin is of particular public interest due to the increasing problem of diabetes. The purpose of this research was to develop an air ultrasonic ceramic transducer for transdermal insulin delivery and evaluate the possibility of applying a new portable and low-cost device for transdermal insulin delivery. Twenty-four rats were divided into four groups with six rats in each group: one control group and three experimental groups. Control group (C) did not receive any ultrasound exposure or insulin (untreated group). The second group (T_1) was treated with subcutaneous insulin (Humulin® R, rDNA U-100, Eli Lilly and Co., Indianapolis, IN) injection (0.25 U/Kg). The third group (T_2) topically received insulin, and the fourth group (T_3) received insulin with ultrasound waves. All the rats were anesthetized by intraperitoneal injection of ketamin hydrochloride and xylazine hydrochloride. Blood samples were collected after anesthesia to obtain a baseline glucose level. Additional blood samples were taken every 15 min in the whole 90 min experiment. In order for comparison the changes in blood glucose levels" to " In order to compare the changes in blood glucose levels. The statistical multiple comparison (two-sided Tukey) test showed a significant difference between transdermal insulin delivery group (T_2) and subcutaneous insulin injection group (T_1) during 90 min experiment (P = 0.018). In addition, the difference between transdermal insulin delivery group (T2) and ultrasonic transdermal insulin delivery group (T3) was significant (P = 0.001). Results of this study demonstrated that the produced low-frequency ultrasound from this device enhanced the transdermal delivery of insulin across hairless rat skin.

Key words: *Insulin, rat, sonophoresis, transdermal drug delivery, ultrasonic transducer*

INTRODUCTION

Transdermal drug delivery has been studied as an alternative method for noninvasive drug administration. However, the superficial layer of the skin, stratum corneum (SC), limits this method because this layer is not sufficiently permeable to allow for the effective transfer of medication to the bloodstream.[1] Hence, it is necessary to enhance the transdermal delivery of drugs, especially with large high molecular weights, due to powerful skin barriers. To enhance the transport of drugs through the skin, several methods, including chemical enhancers, microneedles, iontophoresis, electroporation, and ultrasound have been studied as an alternative for needles.[2-6]

Among the noninvasive methods, low-frequency ultrasound (20–100 kHz) has demonstrated the enhancing transdermal delivery of drugs with large molecular weights like insulin because low-frequency ultrasound waves disturb the SC layers by cavitation.[7-11]

The ultrasound wave is longitudinal in nature. Longitudinal sound waves cause compression and expansion of the medium at the distance of half of the wavelength, which leads to pressure variations in the medium.[12]

Use of ultrasound for enhancing transdermal drug transport is named phonophoresis or sonophoresis.[9] Although considerable attention has been paid to the investigation of sonophoresis in the past years, its mechanisms have not been clearly understood, and it has been suggested to be the result of cavitation.[13,14]

Based on the experimental protocols, low-frequency sonophoresis can be classified into two categories of simultaneous and pretreatment sonophoresis. The first

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approach corresponds to a simultaneous application of drug and ultrasound to the skin while in the second method, a short application of ultrasound is used to permeabilize skin prior to drug delivery.[15]

Some published studies have shown that the frequency of ultrasound waves is a major determinant in phonophoresis. In this regard, some studies have reported that the use of low-frequency ultrasound is more effective than higher ultrasound in terms of enhancing transdermal transport.[9,16-18] Skin permeability increases as the frequency of ultrasound decreases and intensity and time length of ultrasound application increase.[19]

The prevalence of diabetes is increasing due to the aging of the population and improved diagnosis. Diabetics need to be monitored and receive insulin to keep their blood sugar normal; but, today, blood glucose monitoring is very inconvenient and painful.[20] Hence, diabetes is one of the most costly diseases and maintaining constant blood glucose level often requires painful, repetitive insulin injections as often as four times per day.[1]

Application of low-frequency ultrasound for transdermal delivery of insulin has received particular public interest due to the increasing problem of diabetes. Thus, the research for safe and convenient noninvasive insulin delivery is increasing every year. An increasing number of academic and industrial studies are focusing on transdermal devices with active mechanisms for skin permeation.[21] Recently, effects of simultaneous sonophoresis on transdermal insulin delivery in hyperglycemic rats and pigs have been investigated using a lightweight cymbal transducers array.[1,22,23] One of the many questions with simultaneous sonophoresis is providing a portable, cheaper, and less invasive device for transdermal insulin delivery. Therefore, the purpose of this research was to develop an air ultrasonic ceramic transducer for transdermal insulin delivery and evaluate the possibility of applying a new portable and low-cost device for transdermal insulin delivery.

MATERIALS AND METHODS

Physical Characteristics of Ultrasound

Ultrasound was produced by a transducer composed of a piezoelectric crystal which converts electric energy into mechanical energy in the form of oscillations which generate acoustic waves. These waves are partially reflected by the medium in which they are propagated, the other part penetrates and propagates into the medium. During its propagation, a wave is partially scattered and absorbed by the medium, resulting in attenuation of the emitted wave; the lost energy is converted into heat.

The ultrasonic transducers are made of high-power piezoceramic (PZT) such as lead zirconate titanate-4 (PZT-4). Most of the medical imaging transducers have a backing layer which provides the damping required to produce short pulses while the air-backed transducers are used in ultrasound therapy applications.[24]

An appropriate ultrasonic transducer should be small enough to allow a portable device for transdermal drug release to be positioned on the skin. Based on the results from other investigators, the maximum temperature rise allowed for delivery without damage to the skin is not higher than 1–2°C at the intensities of approximately 200 mW/cm^2.[25,26]

Air Ultrasonic Ceramic Transducer

Ultrasound was produced by an air ultrasonic ceramic transducer (SQ-40-T-10B) composed of a piezoceramic disc which converts electric energy into mechanical energy in the form of oscillations which generate ultrasonic waves. This phenomenon is known as the piezoelectric effect and is used in most modern ultrasound devices.

The ultrasonic transducer probe is shown in Figure 1. The diameter of each ultrasonic transmitter was 9.8 mm. The resonant frequency of this ultrasonic transmitter was 40 ± 1.0 kHz and their transmitting sensitivity was 110 dB.[27] Figure 1 also shows an array air ultrasonic ceramic transducer applied in this study. The array included three ultrasonic transmitters connected in parallel. It was driven by a signal generated by an oscillator and amplified by a push-pull amplifier. Since the intensity of ultrasound waves decreased with distance from the source, the ultrasonic transducer perpendicular to the rat skin surface was used.

Animal Experiments

All the animal procedures were performed in accordance with the protocols approved by Ethical Committee of Urmia University of Medical Sciences in the use of lab

Figure 1: Shape of SQ-40T transducer (left) and an array of air ultrasonic ceramic transducer (right)

animals (approval number 56–06). The male Albino Wistar rats (270–420 g) were obtained from the affiliated experimental animal center. Twenty-four rats were divided into four groups with six rats in each group: One control group and three experimental groups. Control group (C) did not receive any ultrasound exposure or insulin (untreated group). The second group (T_1) was treated with subcutaneous insulin (Humulin® R, rDNA U-100, Eli Lilly and Co., Indianapolis, IN) injection (0.25 U/Kg). The third group (T_2) received topically insulin, and the fourth group (T_3) received insulin with ultrasound waves. The dose of insulin selected for the injection group (0.25 U/kg) was based on the published insulin doses used in the previous study.[1] All the rats were anesthetized by the intraperitoneal injection of ketamin hydrochloride (60 mg/kg) and xylazine hydrochloride (10 mg/kg). Xylazine was used for general anesthesia and inducing a temporary, but sustained (up to 12 h), hyperglycemia in the rats.[28,29]

For the ultrasonic transdermal insulin delivery, the abdominal area of the rats was shaved with a width of two inches and a depilatory agent was applied to the abdominal skin to eliminate any remaining hair.

With the rat in the dorsal decubitus position [Figure 2], a 1 mm thick, water-tight standoff was attached between the skin and the transducer array. The reservoir within the standoff was filled with 1.0 ml insulin (Humulin® R, rDNA U-100, Eli Lilly and Co., Indianapolis, IN) for the third and fourth experimental groups. Care was taken to remove all the bubbles from the solution in the reservoir to prevent the disruption of ultrasound transmission.

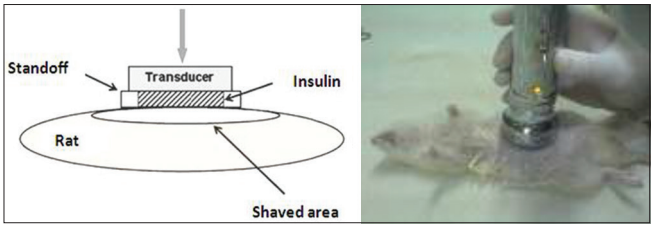

Figure 2: Illustration of the experiment with a 1 mm thick water tight standoff arranged between the abdomen area and the transducer; the reservoir within the standoff was filled with insulin (left). A photograph of the rat placed in a dorsal decubitus position with the transducer array attached (right)

The ultrasound waves with 40 kHz frequency were applied for 60 min in pulse mode to avoid any undesirable damage to the skin as a result of the produced heat. The blood samples were collected from the tail vein of the animals once before anesthesia to confirm the uniformity of the glucose levels in all the animals. They were also collected after anesthesia to obtain a baseline glucose level. Additional blood samples were taken from the tail vein every 15 min in the whole 90 min experiment. The glucose level (mg/dl) in the blood was determined using ACCU-CHEKTM blood glucose monitoring system (Roche Diagnostics Co., Indianapolis, IN, USA). Each sample was tested for three times to confirm the accuracy of the reading.

In order for comparing the changes in blood glucose levels, the data were corrected by subtracting the baseline glucose for each rat from each blood glucose level at any time. Statistical analysis was performed using SPSS software (ver. 16), by SPSS Inc. (IBM corporation, Armonk, USA). for Windows. One-way ANOVA statistical test was used to confirm the uniformity of the weight in all the rats and blood glucose levels before anesthesia. In addition, the statistical multiple comparisons (Dunnett and Tukey) tests were used to compare the difference between the glucose levels in the studied groups after anesthesia. The significance level was selected as 0.05 for all the statistical tests. The blood glucose versus time data were pooled for each group and analyzed as its mean and standard deviation (SD).

RESULTS

The goal of this study was to determine if an air ultrasonic ceramic transducer could be used for *in vivo* transdermal insulin delivery in rats. Visual examination of the rats' skins at the end of ultrasonic exposimetry did not show any damage or significant change to the skin. Table 1 shows the changes of blood glucose levels with time in different groups.

One-way ANOVA test between four studied groups showed no significant difference between the weight of the rats ($P = 0.167$) and blood glucose concentration before anesthesia ($P = 0.366$). The blood glucose concentration before anesthesia between the studied groups was within the range of 100–121 mg/dl. Following the administration of xylazine, the initial blood glucose levels increased to 195 ± 11 mg/dl (mean ± SD) after anesthesia, which was called the baseline

Table 1: Changes of blood glucose levels with time in different groups

Groups	Mean±SD of blood glucose levels (mg/dl)							
		After anesthesia						
	Before anesthesia	0 min	15 min	30 min	45 min	60 min	75 min	90 min
C group	109.94±7.52	183.21±13.21	242.67±17.95	253.66±21.42	280.33±19.13	285.33±22.03	286.33±18.12	287.26±16.43
T_1 group	121.02±9.05	209.32±17.61	184.54±17.93	125.76±20.55	94.85±17.78	83.55±15.32	73.44±16.26	66.46±23.01
T_2 group	114.23±8.68	199.76±16.28	178±16.77	175.54±16.07	172.46±19.83	182.46±19.03	178.56±16.40	171.13±11.18
T_3 group	111.34±6.84	188.20±18.06	183.18±23.61	170.88±21.46	136.63±19.68	117.22±17.21	101.63±19.10	89.37±21.04

SD – Standard deviation

glucose level. The parametric multiple comparisons statistical test (Dunnett) showed no significant difference between the mean glucose levels in the treatment groups compared to the control group immediately after anesthesia ($P > 0.05$).

The blood glucose levels of all the rats were graphed and recorded as mean ± SD of each group every 15 min in the whole 90 min experiment [Figure 3]. For comparison between the rats, change in the blood glucose level was normalized to a baseline glucose level for each rat. For the control group (ketamin and xylazine), the glucose level increased to 92 ± 16 mg/dl compared to the initial baseline over the 90 min experiment. For the subcutaneous injection of 0.25 U/kg insulin, the blood glucose decreased to 129 ± 23 mg/dl after 90 min. In the transdermal insulin delivery group (insulin without ultrasound), the blood glucose decreased to 24 ± 11 mg/dl at the end of 90 min. In the ultrasound exposure groups (insulin with ultrasound), the blood glucose decreased to 106 ± 21 mg/dl at the end of 90 min.

Results of the statistical multiple comparison (Tukey) test showed a significant difference between transdermal insulin delivery group (T_2) and subcutaneous insulin injection group (T_1) during the 90 min experiment ($P = 0.018$). In addition, comparison of the ultrasonic transdermal insulin delivery group (T_3) and the subcutaneous insulin injection group (T_1) demonstrated no significant difference ($P = 0.621$), while the difference between transdermal insulin delivery group (T2) and ultrasonic transdermal insulin delivery group (T3) was significant ($P = 0.001$).

DISCUSION

In this study, the feasibility of using a practical device for transdermal insulin delivery was examined by the application of an array of air ultrasonic ceramic transducers. Figure 3 shows the actual blood glucose level concentrations (mg/dl) over the 90 min recording period in the 15-min steps. Control group (C) showed increased glucose level from minimum at zero time to maximum at 90 min point. Rapid linear increase was noticed during the first 15 min with an almost linear increase until the end of the 45 min experiment; afterwards, the blood glucose level remained almost constant until the end of the 90 min experiment. Treatment groups, on the other hand, showed a gradual increase to reach peak values at the 15 min time points with sharp linear reductions afterward for both groups T_1 and T_3. However, group T_2 had a different behavior. Treatment group T_3 showed a close behavior to group T_1 with elevated blood glucose level during the first 15 min after the start of the intervention period, gradually decreased to reach a lower than baseline level at the 30 min time point, and continued to decrease afterward.

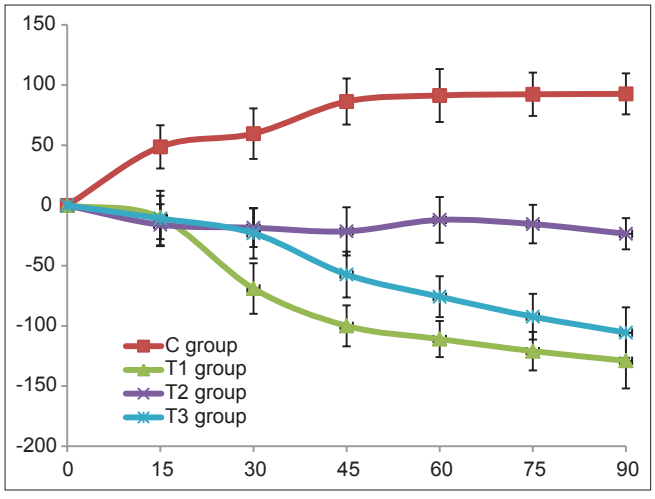

Figure 3: Change of blood glucose levels during the experiment period

Many previous investigations of sonophoresis have found that ultrasound enhances transdermal drug delivery over various frequency ranges. The number of studies on noninvasive insulin delivery is increasing every year.[30] Insulin, similar to many other large molecule drugs, is not absorbed by the oral route and has to be injected frequently; in this case, the administration of ultrasound to a transdermal insulin delivery can be useful. Enhanced delivery in the presence of ultrasound (20–105 kHz) has been shown in both *in vitro* and *in vivo* experiments.[29] The first time ultrasonic vibration was used to deliver insulin through the skin of the hairless mice partially immersed in an aqueous solution of insulin by Tachibana *et al*.[31] They reported that the application of low-frequency ultrasound (48 kHz) enhances the transdermal transport of insulin across the hairless mice skin *in vivo*. Mitragotri *et al*.[9] showed the transdermal delivery of insulin across the skin using commercial sonicators operating at 20 kHz. In addition, the studies conducted by Park *et al*. demonstrated that the transdermal permeation of insulin molecules in rat and pig models can be enhanced by low-frequency ultrasound (20 kHz) produced by the cymbal array transducers.[1,23]

Use of ultrasound in therapeutics and drug delivery has gained importance in recent years, which is evident by the increased number of filed patents and newly launched commercial devices.[32] The major problem in transdermal insulin delivery via sonophoresis is in terms of providing a practical device which is portable, smaller, and lighter. Weight of the ultrasonic probe from a commercial sonicator for demonstrating drug delivery can be approximately 1 kg. Although the cymbal array weighs can be very low, the miniaturization of portable power has been under research recently.[23,33,34] Osama *et al*.[3] demonstrated that ultrasound piston PZT transducers could facilitate insulin delivery across the skin of rabbits regardless of the driving frequency in the tested range from 100 to 1000 kHz.

According to the estimation of World Health Organization, more than 346 million people worldwide have diabetes. This number may be doubled by 2030 without intervention.[35] Hence, effective interventions are needed in this context. Based on the

previous studies, many possible mechanisms of sonophoresis have been suggested. It is believed that cavitation is the most important mechanism in drug delivery via sonophoresis.[36] Nowadays, researchers try to find new methods for controlling hyperglycemia in diabetes. Using transdermal insulin delivery enables the administration of insulin by the skin rather than injection. This approach might allow for the self-regulation of pain by patients. The goal of this study was to determine if an air ultrasonic ceramic transducer device could be used for *in vivo* transdermal insulin delivery in rats. The results demonstrated that the produced low-frequency ultrasound from this device enhanced the transdermal delivery of insulin across hairless rat skin. Therefore, the results indicated that it was capable of reducing a diabetic glucose level to a normal range by increasing the permeability of the SC and enabling pain control by the animal. In conclusion, the present results provided an encouraging preclinical outcome for the portable and low-cost device to be used for ultrasound enhanced *in vivo* insulin transport. However, further studies are necessary to evaluate different ultrasonic frequencies, develop a clinically approved device, and apply this method in humans.

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