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(54) **ULTRASONICALLY ENHANCED SUBSTANCE DELIVERY SYSTEM AND DEVICE**

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(57) **ABSTRACT**

A system for enhancing delivery of at least one substance situated substantially adjacent to a surface of a subject through the surface and into the subject. The device includes at least one ultrasound emitting device secured to the subject. The at least one ultrasonic emitting device emits at least one ultrasonic signal responsively to an input alternating between a square waveform and a sawtooth waveform so as to enhance movement of at least a portion of the substance into the subject.

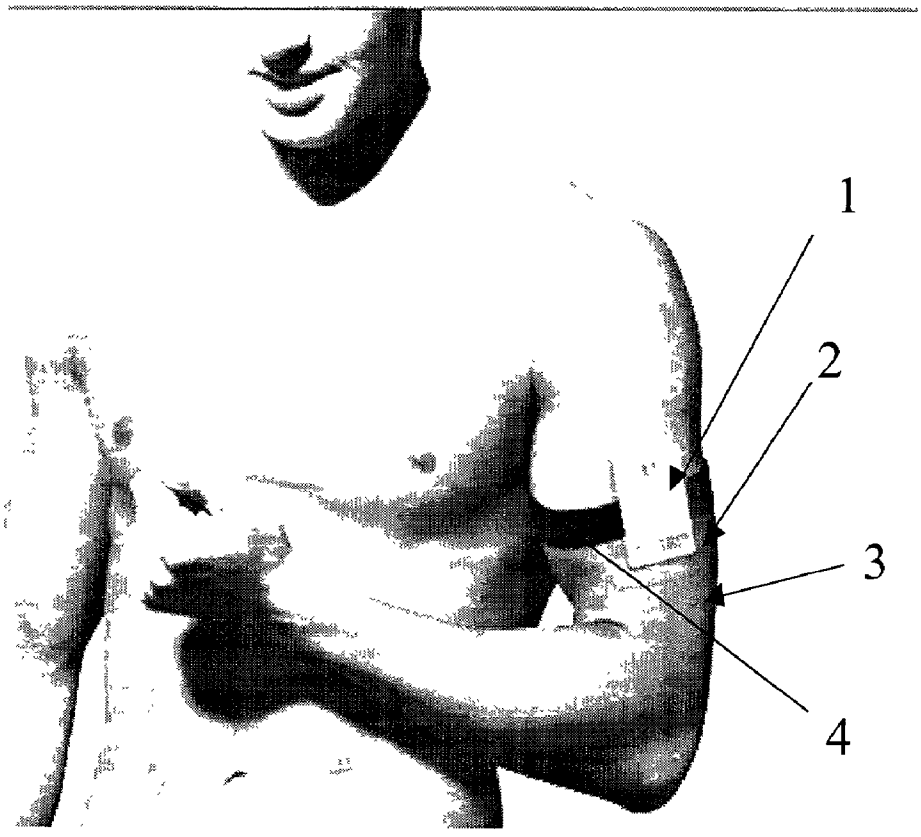


Fig. 1

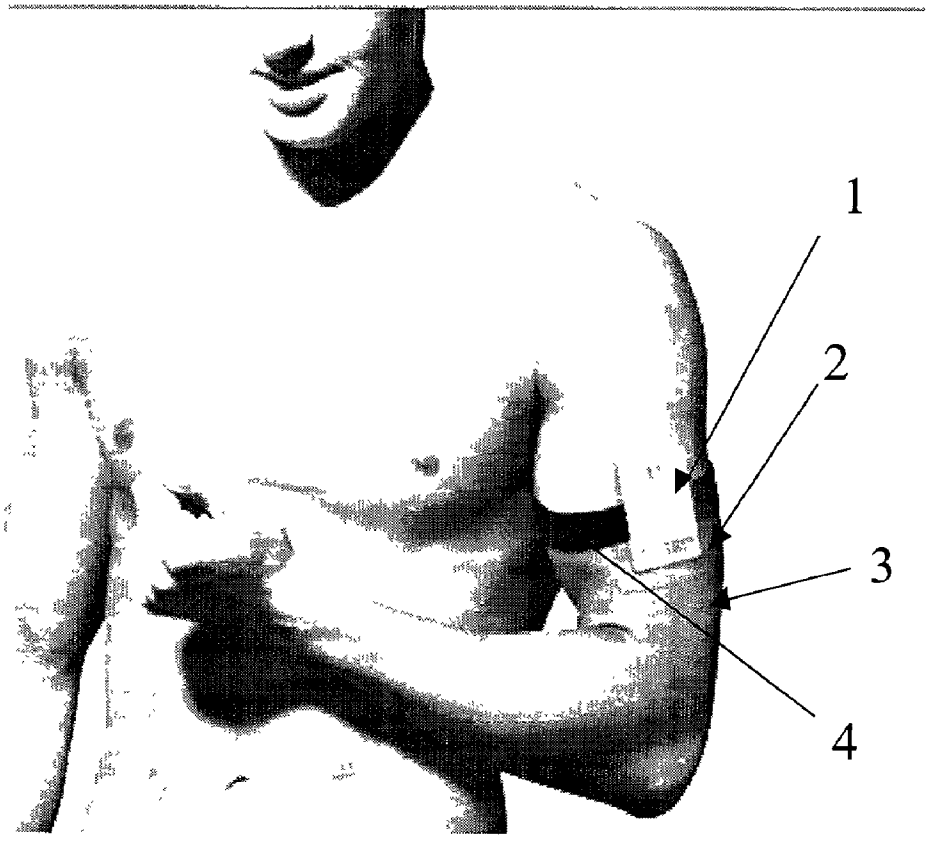


Fig. 2

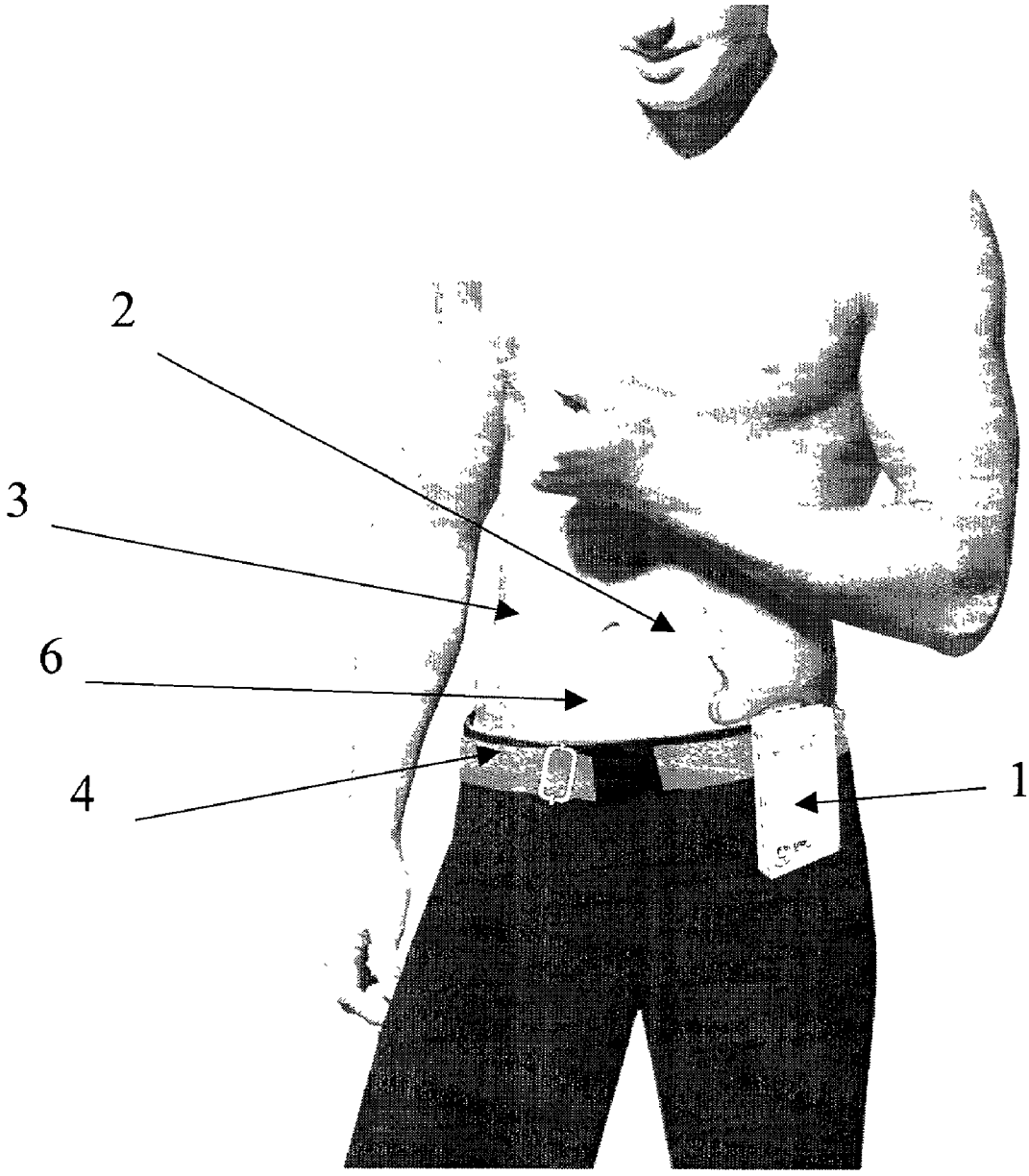


Fig. 3

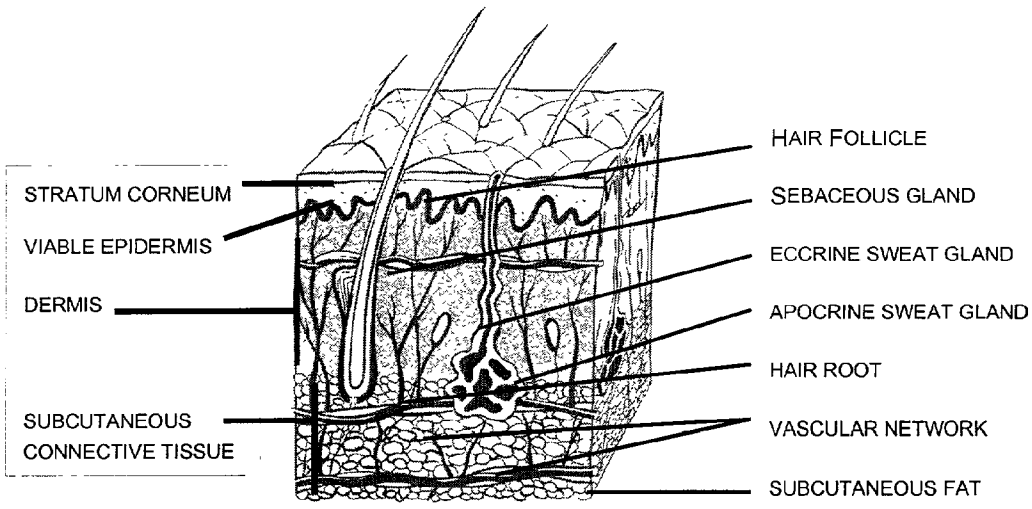

STRATUM CORNEUM
VIABLE EPIDERMIS
DERMIS
SUBCUTANEOUS CONNECTIVE TISSUE
HAIR FOLLICLE
SEBACEOUS GLAND
ECCRINE SWEAT GLAND
APOCRINE SWEAT GLAND
HAIR ROOT
VASCULAR NETWORK
SUBCUTANEOUS FAT

Fig. 4A

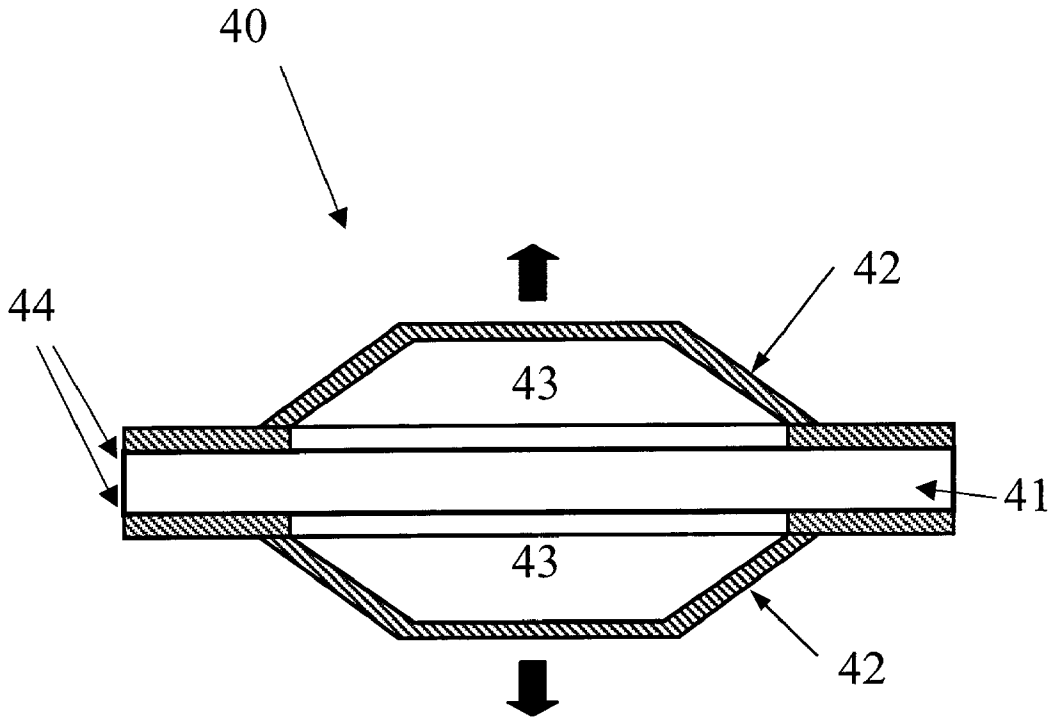


Fig. 4B

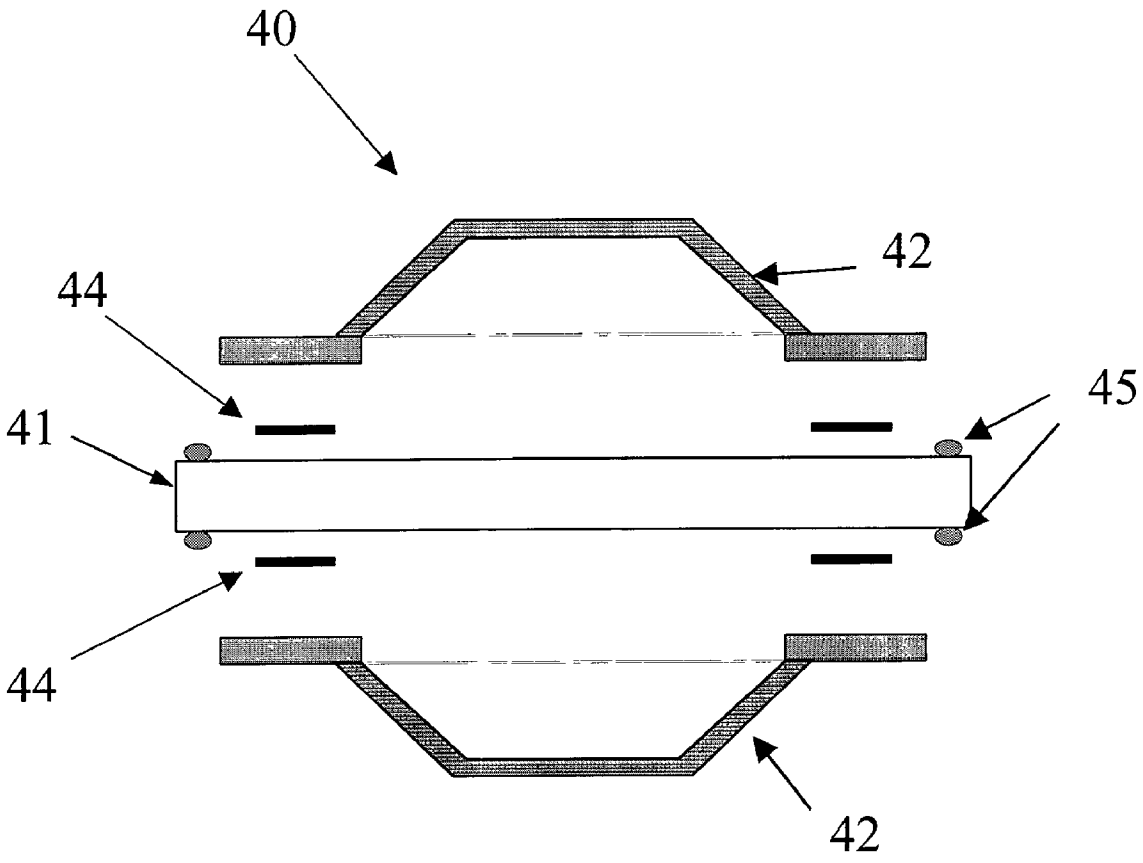


Fig. 4C

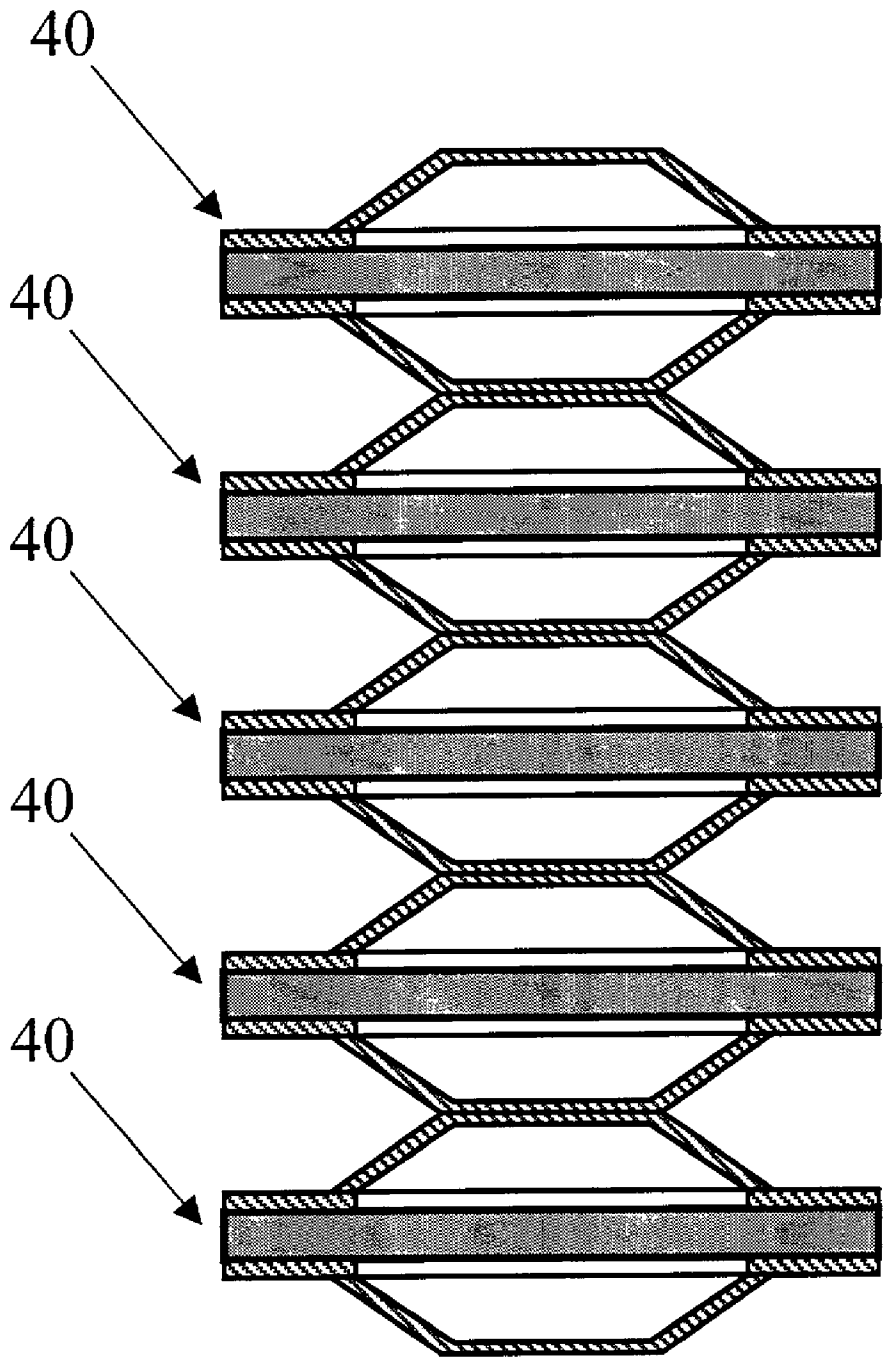


Fig. 5A

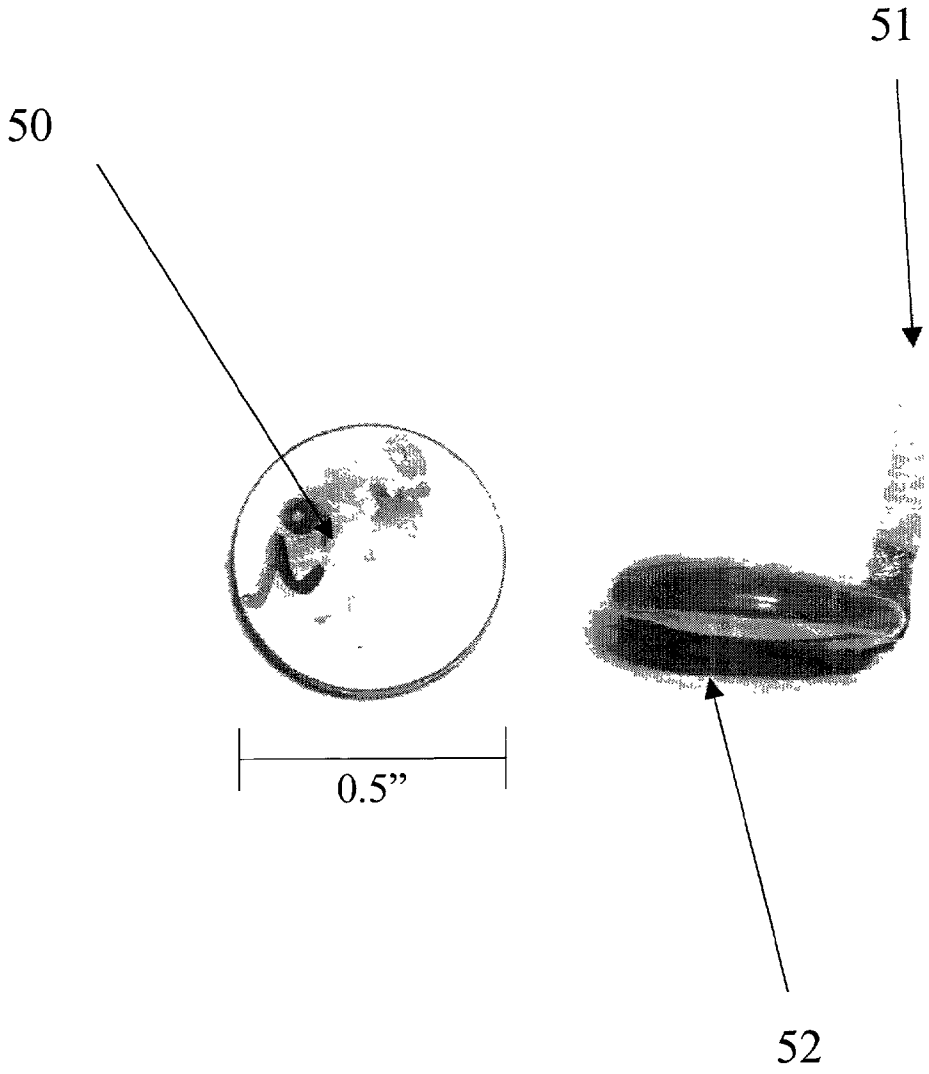


Fig. 5B

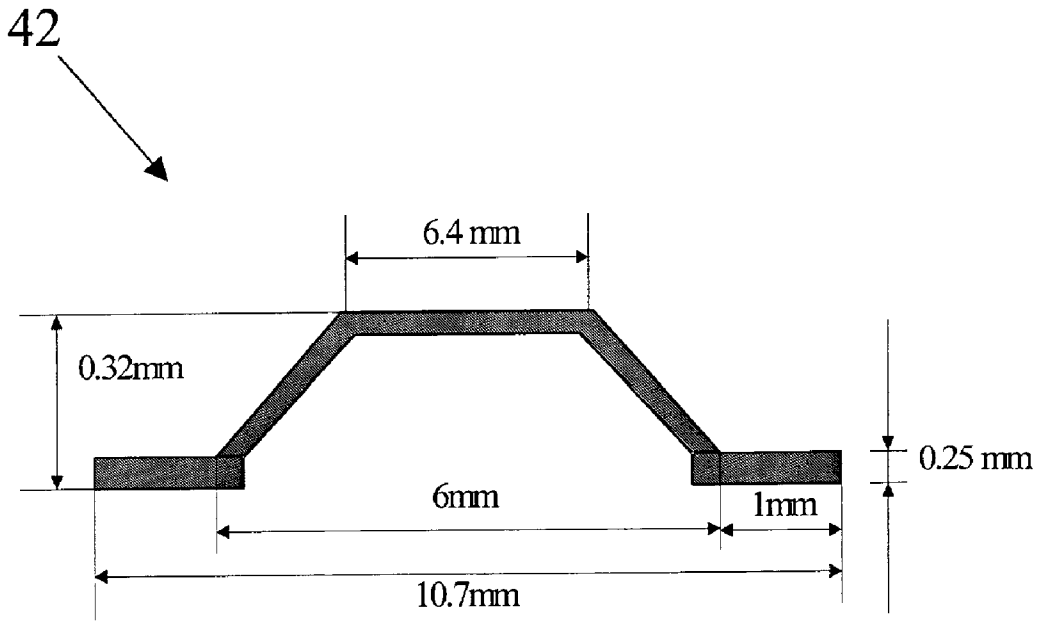


Fig. 6

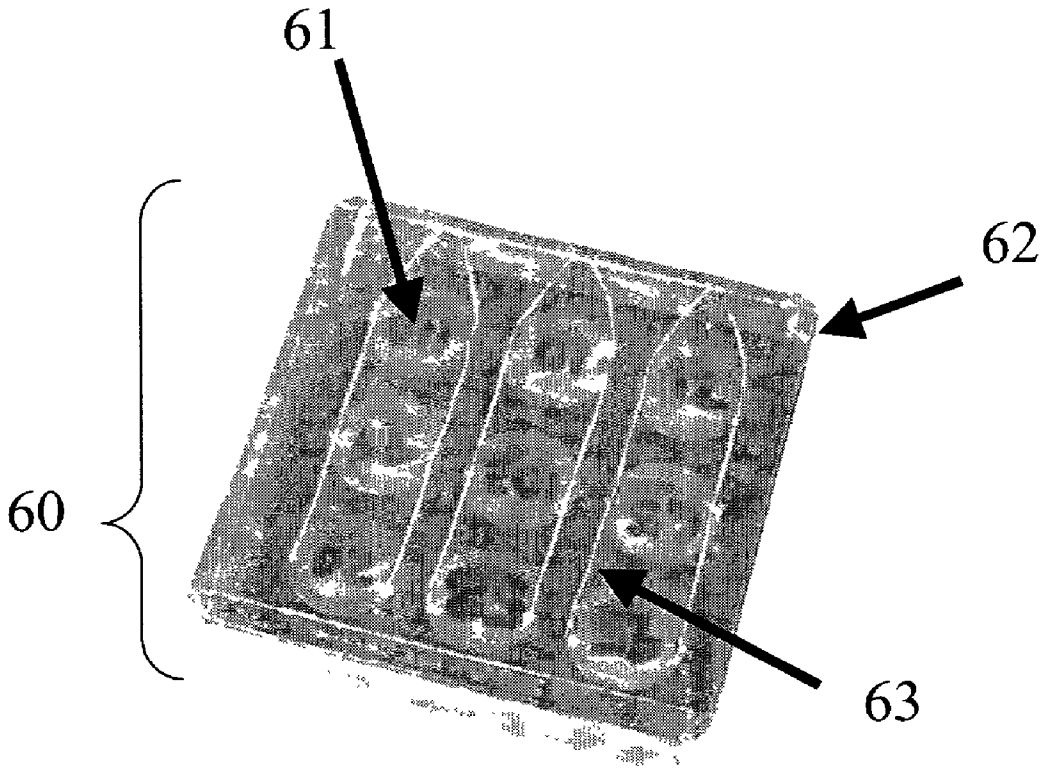


Fig. 7

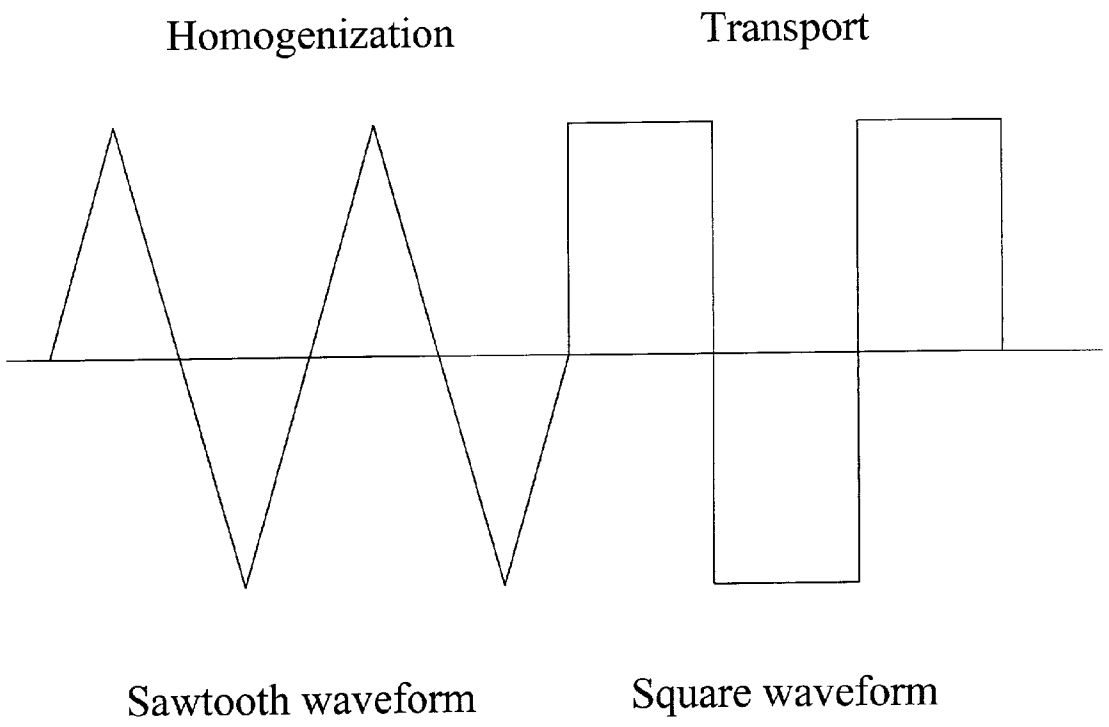
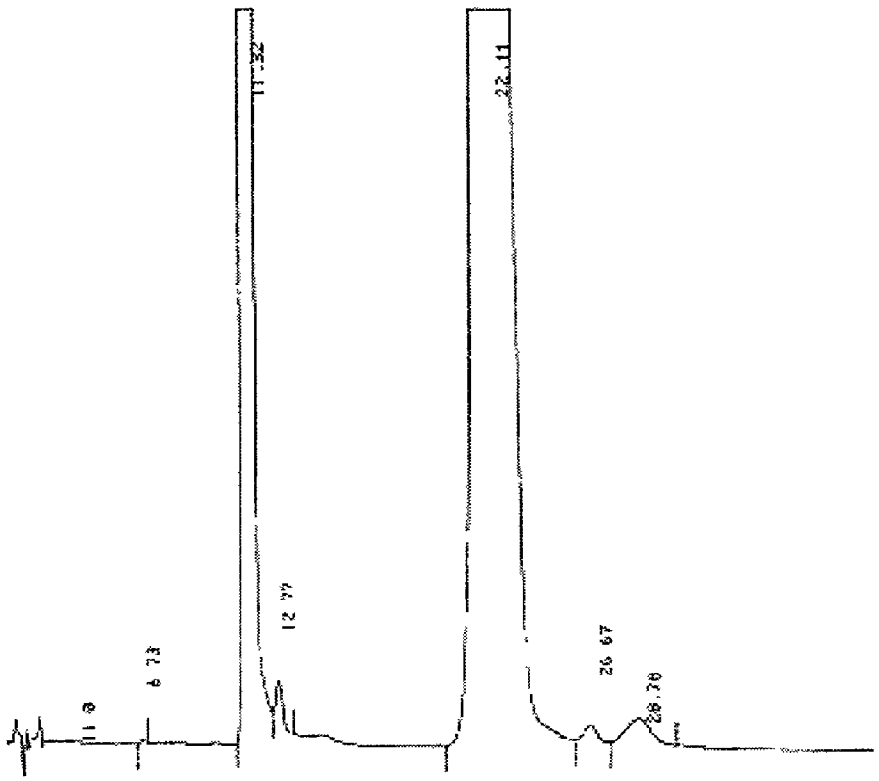
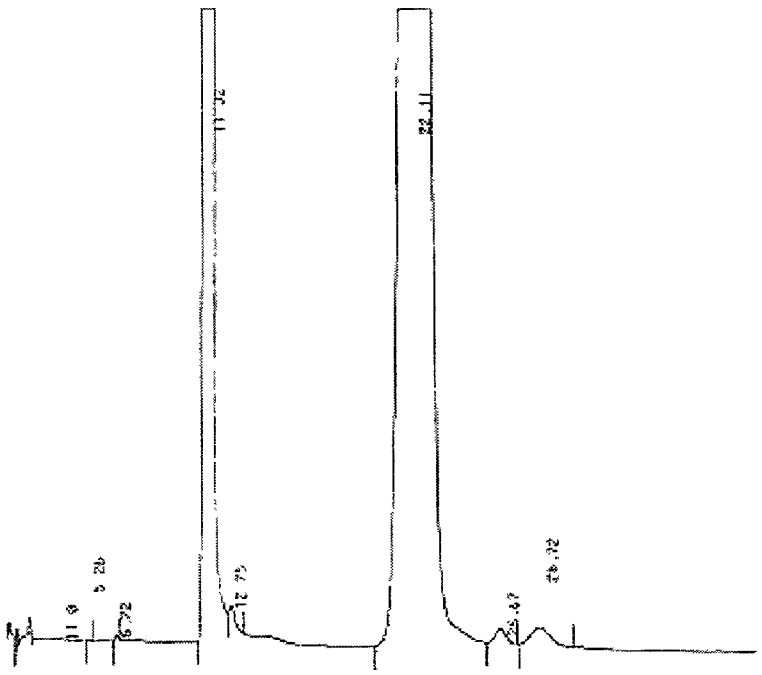

Homogenization
Transport
Sawtooth waveform
Square waveform

Fig. 8A



HPLC scan of
Control Insulin

Fig. 8B



HPLC scan of Insulin Treated with Ultrasound for 8 continuous hours

Fig. 9

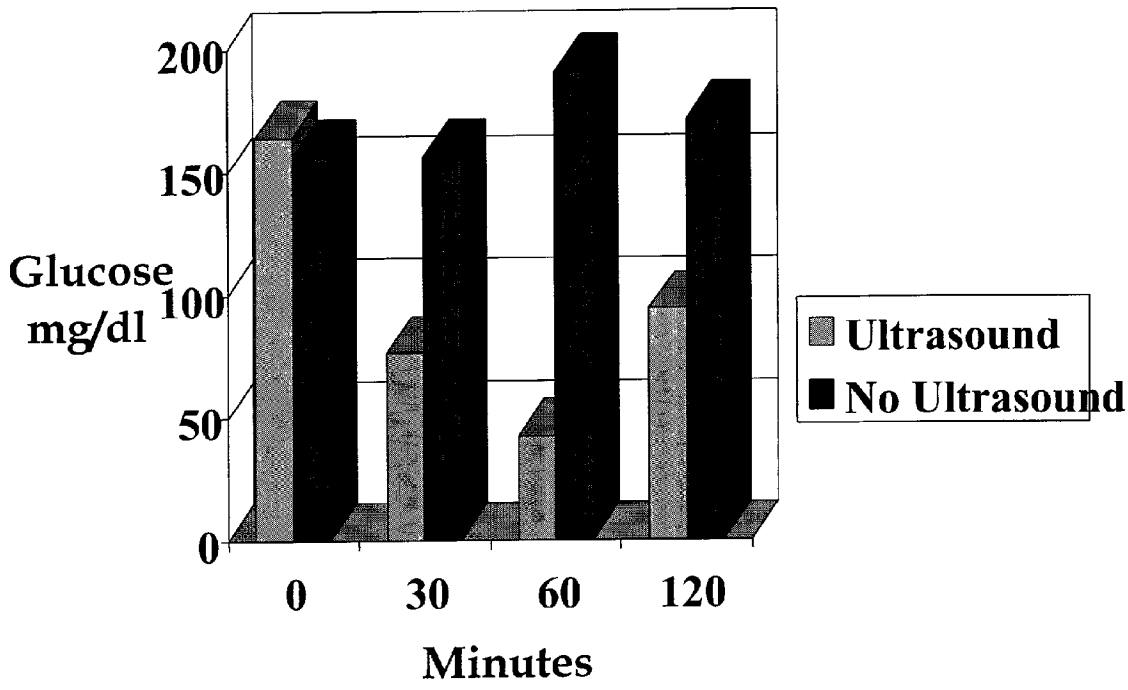
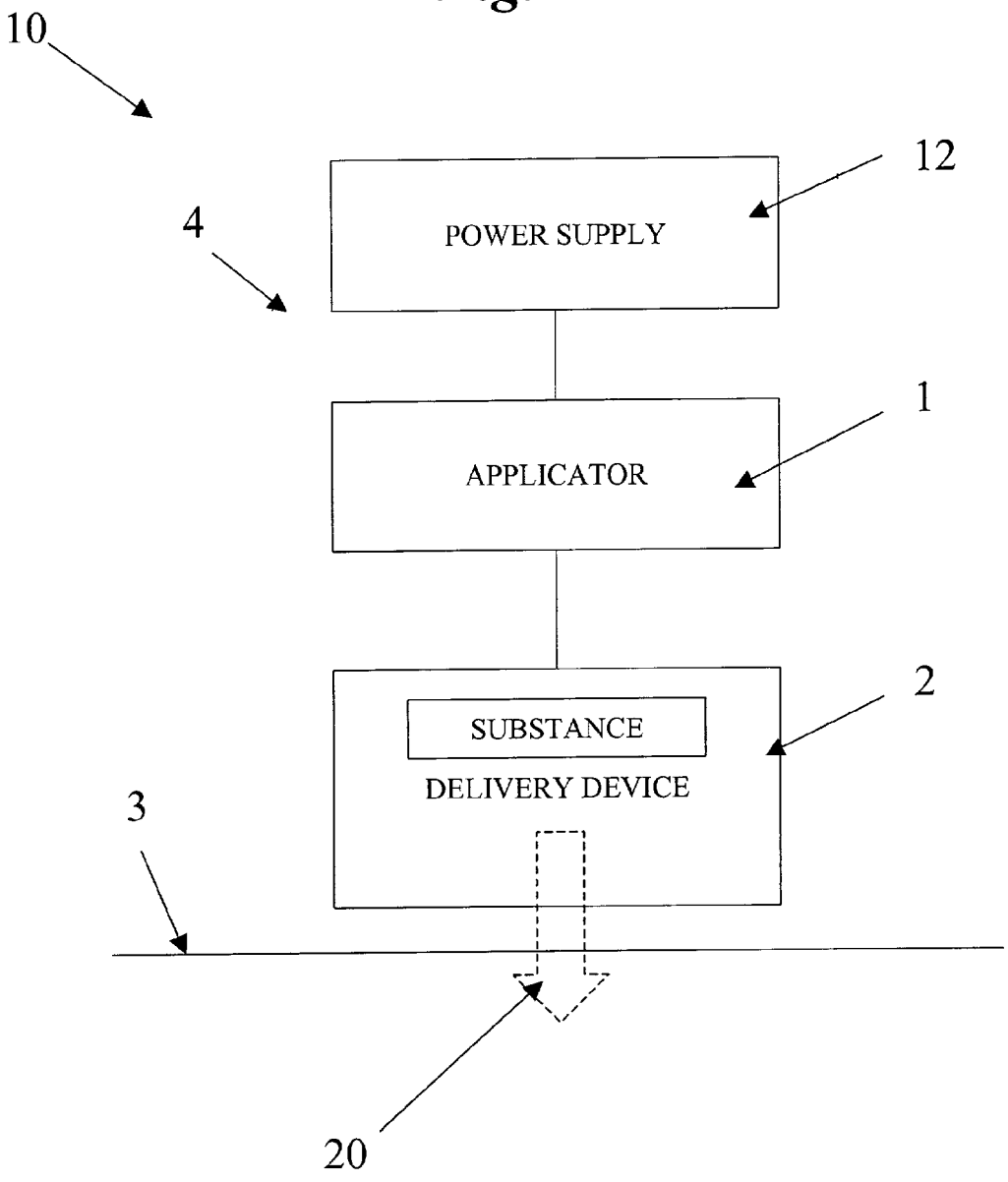

200
150
100
50
0
Glucose mg/dl
0
30
60
120
Minutes
Ultrasound
No Ultrasound

Fig. 10


10
12
4
POWER SUPPLY
1
APPLICATOR
2
SUBSTANCE
DELIVERY DEVICE
3
20

ULTRASONICALLY ENHANCED SUBSTANCE DELIVERY SYSTEM AND DEVICE

RELATED APPLICATIONS

[0001] This application claims priority of each of: U.S. Patent Application serial No. 60/300,343, filed Jun. 22, 2001 and entitled "ULTRASONIC TRANSDUCER APPARATUS AND METHOD OF USE SUITABLE FOR ULTRASONIC DRUG DELIVERY VIA A SYSTEM WHICH IS PORTABLE AND WEARABLE BY A SUBJECT"; U.S. Patent Application serial No. 60/300,292, filed Jun. 22, 2001 and entitled "TRANSDERMAL PATCH FOR USE IN ULTRASONIC DRUG DELIVERY APPLICATIONS"; and, U.S. Patent Application serial No. 60/227,359, filed Aug. 24, 2000, entitled "TRANSDERMAL DRUG DELIVERY SYSTEM UTILIZING A WEARABLE, PORTABLE SONIC APPLICATOR", the entire disclosures of which are each respectively hereby incorporated by reference herein as if being set forth in their respective entireties.

FIELD OF THE INVENTION

[0002] The present invention relates generally to substance delivery systems, and more particularly to portable, transdermal substance delivery systems.

BACKGROUND OF THE INVENTION

[0003] Transdermal substance delivery systems, such as drug delivery systems, may employ a medicated device or patch affixed to an exposed surface of a patient's skin. The patch allows a substance, such as a medicinal compound contained within the patch, to be absorbed into the skin layers and finally into the patient's blood stream. Transdermal drug delivery often avoids pain associated with drug injections and intravenous drug administration. Transdermal drug delivery may also be used to avoid gastrointestinal metabolism of administered drugs, reduce elimination of drugs by the liver, and for providing a sustained release of an administrated drug. Transdermal drug delivery may also enhance patient compliance with a drug regimen because of the relative ease of administration and the sustained release of the drug.

[0004] However, it is believed that several medicinal compounds are not suitable for conventional transdermal drug delivery, since they are absorbed through the skin with difficulty, due to the molecular size of the drug or other bioadhesive properties of the drug, for example. In these cases, when transdermal drug delivery is attempted, the drug may be found to merely pool on the outer surface of the skin and not permeate into the blood stream. Once such example is insulin, which has been found difficult to administer by means of conventional transdermal drug delivery.

[0005] Further, some critically needed medications are presently administered either by injection or oral dosage forms. In particular, chemotherapeutic agents are often administered in increased dosages because of their need to survive degradation in the gastrointestinal tract, for example. Also, many critical treatments for AIDS require a cocktail of drugs taken orally in solid dosage forms, several times a day, to be effective. These medications are not believed suitable for conventional transdermal drug delivery use because of the extensive dosing requirement, and the inability of the drug molecule to remain stable in a transdermal form, for example. Moreover, the unsuitability for conventional transdermal to skin transfer of the drug leads to low bioabsorbance of the drug across the skin layers.

[0006] Generally, conventional transdermal drug delivery methods have been found suitable only for low molecular weight medications such as nitroglycerin (for alleviating angina), nicotine (for smoking cessation regimens), and estradiol (for estrogen replacement in post-menopausal women). Larger molecular medications such as insulin (a polypeptide for the treatment of diabetes), erythropoietin (used to treat severe anemia) and gamma-interferon (used to boost the immune system's cancer fighting ability) are all compounds not normally effective when used with conventional transdermal drug delivery methods, for example.

[0007] Other methods of increasing the permeability of skin to drugs have been described, such as iontophoresis. Iontophoresis involves the application of an external electric field and topical delivery of an ionized form of drug or unionized drug carried with the water flux associated with ion transport (electro-osmosis). While permeation enhancement with iontophoresis has been effective, control of drug delivery and irreversible skin damage are problems that may be associated with the technique.

[0008] Ultrasound has also been suggested to enhance permeability of the skin and synthetic membranes to drugs and other molecules. Ultrasound has been generally defined as mechanical pressure waves with frequencies above about 20 kHz. Ultrasound signals can be generated by vibrating a piezoelectric crystal or other electromechanical element, such as through passing an alternating current through the material. The use of ultrasound to increase the permeability of the skin to drug molecules has been termed sonophoresis or phonophoresis.

[0009] However, while the use of ultrasound for drug delivery has been generally suggested, results have been largely disappointing in that enhancement of permeability has been relatively low. Further, it is believed that there is no consensus on the efficacy of ultrasound for increasing drug flux across the skin. While some studies report the success of sonophoresis, others have obtained negative results.

[0010] Many conventional ultrasonic transdermal delivery systems envision a typical ultrasonic wand or sonicator as an ultrasonic applicator, not taking into account the power utilization of the transducer and the size of the device.

[0011] Since ultrasound is rapidly attenuated in air, a coupling agent, preferably one having a low realizable absorption coefficient that is non-staining, non-irritating, and slow drying, may be needed to efficiently transfer the ultrasonic energy from the ultrasound transducer into the skin. When a chemical enhancer fluid or anti-irritant, or both, are employed, they may function as the coupling agent. For example, glycerin used as an anti-irritant may also function as a coupling agent. If needed, additional components may be added to the enhancer fluid to increase the efficiency of ultrasonic transduction.

[0012] In general, ultrasound exposure times for permeation through human skin have conventionally been 10 minutes to 24 hours. The depth of penetration of ultrasonic energy into living soft tissue is inversely proportional to the frequency, thus high frequencies have been suggested to

improve drug penetration through the skin by concentrating the effect in the outermost skin layer, the stratum corneum.

[0013] Although it has been acknowledged that enhancing permeability of the skin may make it possible to transport molecules into the body for therapeutic purposes, portable programmable devices and methods have not been disclosed.

[0014] In view of the foregoing problems and/or deficiencies, the development of a transducer device for safely enhancing the permeability of the skin for noninvasive drug delivery in a more rapid time frame would be a significant advancement in the art.

SUMMARY OF THE PRESENT INVENTION

[0015] A system for enhancing delivery of at least one substance situated substantially adjacent to a surface of a subject through the surface and into the subject, the device including: at least one ultrasound emitting device secured to the subject; wherein, the at least one ultrasonic emitting device emits at least one ultrasonic signal responsively to an input alternating between a square waveform and a sawtooth waveform so as to enhance movement of at least a portion of the substance into the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The present invention will be more readily understood in connection with the non-limiting, attached figures, wherein:

[0017] **FIG. 1** is an artist's depiction of an ultrasonic drug delivery apparatus, worn by a patient upon the arm.

[0018] **FIG. 2** is an artist's depiction of an ultrasonic drug delivery apparatus, worn by a patient upon the abdomen.

[0019] **FIG. 3** is an illustration of the structure of human skin.

[0020] **FIG. 4A** illustrates a cross section view of an embodiment of the transducer element of the present invention, said transducer element being a "cymbal" type transducer design.

[0021] **FIG. 4B** illustrates the fabrication steps to produce a "cymbal" type transducer element .

[0022] **FIG. 4C** illustrates a cross section view of transducer element a stacked "cymbal" type transducer designed to provide higher ultrasonic efficiency, intensity and power output.

[0023] **FIG. 5A** illustrates dimensional characteristics of an embodiment of the present invention, including use of a polymer potting used as a resonance compatible coupling agent coating over the surface of the transducer element.

[0024] **FIG. 5B** illustrates the small dimensions obtained in the fabrication of a "cymbal" type transducer element.

[0025] **FIG. 6**. Illustrates an array of transducers used to enhance sonic efficiency and to provide multiple delivery sites to the skin.

[0026] **FIG. 7**. depicts the use of an alternating waveform suitable for driving one or more ultrasonic transducers, which alternates from sawtooth to square wave.

[0027] **FIG. 8A** shows a scan using a HPLC of insulin, Humilin Regular, supplied by Eli Lilly Co., where no ultrasound was applied.

[0028] **FIG. 8B** shows a scan using a HPLC of insulin, Humilin Regular, supplied by Eli Lilly Co., after the sample was treated with low frequency and low intensity ultrasound continuously over a eight hour period.

[0029] **FIG. 9** shows the results of glucose analysis in the blood of subject rats, where the transducer array was used in a test for the transdermal delivery of insulin.

[0030] **FIG. 10** illustrates a block diagram of a system according to an aspect of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0031] It is to be understood that the figures and descriptions of the present invention have been simplified to illustrate elements that are relevant for a clear understanding of the present invention, while eliminating, for purposes of clarity, many other elements found in conventional ultrasonic substance delivery systems. Those of ordinary skill in the art will recognize that other elements are desirable and/or required in order to implement the present invention. However, because such elements are well known in the art, and because they do not facilitate a better understanding of the present invention, a discussion of such elements is not provided herein.

[0032] Reference is hereby made to commonly assigned and copending U.S. patent application Ser. No. _____, entitled "ULTRASONICALLY ENHANCED SUBSTANCE DELIVERY METHOD", filed on even date herewith, the entire disclosure of which is hereby incorporated by reference herein.

[0033] According to an aspect of the present invention, at least one ultrasonic transducer device may be provided for enhancing transdermal substance delivery by the use of ultrasound, especially of larger pharmaceutically active compounds for example. The terms "drug" or "pharmaceutically active compound" as used herein should be understood to be used in a non-limiting manner and for purposes of explanation only, as the present invention is suitable for delivering many substances including drugs and pharmaceutically active compounds not only transdermally, but transmucosally as well for example. The transducer device may be small in size, battery powered, highly efficient and able to generate an ultrasonic transmission suitable for effecting the transmission of a pharmaceutical compound from a transdermal patch. The ultrasonic transducer device may be placed directly in contact with a transdermal delivery device or patch for the purpose of both enhancing and controlling the delivery of medications contained within the patch into and through the skin layer of a target patient. The transducer device may be placed directly within a drug-containing patch or worn over the patch, and held in place by adhesive strips or body affixing straps, for example. The transdermal patch may contain a particular medication or cocktail of medications for treatment of disease or relief of pain.

[0034] According to an aspect of the invention, the transducer device is suitable for applying ultrasound to a transdermal patch for controlling transdermal and/or transmu-

cosal flux rates of drugs and other molecules into the body and the bloodstream. A Class V flextensional cymbal transducer and transducer array may be used to deliver low frequency ultrasound in a portable device at high efficiency for transdermal drug delivery and therapeutic applications.

[0035] According to an aspect of the present invention, transport of drug molecules may be accomplished using pathways associated with hair follicles and skin pores. A method for non-invasive delivery of biologically active molecules through the skin and mucosal membranes using ultrasound may be accomplished.

[0036] According to an aspect of the invention, several areas of the skin, i.e. transport sites, may be treated simultaneously or sequentially using multiple transducers configured into one or more transducer arrays, for example. Various ultrasound frequencies, intensities, amplitudes and/or phase modulations may be used to control the magnitude of the transdermal flux to achieve a therapeutic or nutritional level. According to an aspect of the invention, the programmability and flux control may allow for optimized therapeutic delivery for an individual patient (examples may include patients that are at different stages of the disease, elderly patients, young, juvenile, or according to gender). The optimization may be substance specific, for example. The molecular structure of each biologically active molecule is different and responds differently to ultrasound. Control of the frequency, intensity, concentration, timing of delivery, drug regimen can optimize delivery of each drug type.

[0037] According to an aspect of the invention, the transducer or array of transducers can be built into the patch or slid into the patch, for example. According to an aspect of the invention, the transducer device can be used for insulin delivery.

[0038] According to an aspect of the invention, phase modulation, alternating waveforms and/or frequency modulation can be used to enhance ultrasonic transdermal substance transport and increase a rate of substance delivery to a subject, e.g. human, other mammal, animal or any other object of which substance delivery through a surface thereof may be ultrasonically enhanced. The ultrasound may be combined with iontophoresis, electroporation, depilatories, and/or chemical enhancers such as surfactants to facilitate transdermal permeation.

[0039] According to an aspect of the present invention, acoustical energy delivered by a portable, self-powered, programmable ultrasonic transducer placed over a substance containing patch causes the substance to be transferred across the surface, e.g. skin, barrier.

[0040] According to an aspect of the present invention, a portable programmable ultrasonic device, which may be worn by a patient over a transdermal drug delivery patch may be provided for the purpose of enhancing the penetration of substances such as medicinal compounds or drugs contained within the transdermal patch, through the skin into the patient's blood stream. Further, the portable ultrasonic applicator may be programmed to apply acoustical energy at different times and thereby cause the delivery of a varying quantity of the medicinal compound over time. The portable ultrasonic applicator may be programmed to deliver a medicinal compound to the patient continuously (sustained release) and/or intermittently (pulsed release), whichever may be deemed more appropriate to a drug maintenance and treatment regimen for a particular patient.

[0041] According to an aspect of the present invention a device, which may be worn by the patient, is programmed to deliver an ultrasonic signal through a transdermal patch according to a timing circuit. Transducers used may be sufficiently small and compact to allow for convenient portability and wearability. The transducers may be powered by a battery, which may also be portable and worn by the patient.

[0042] According to an aspect of the present invention, some parameters of applied ultrasound that can be changed to improve or control penetration include frequency, intensity, and time of exposure. Any or all three of these parameters may be modulated simultaneously in a complex fashion to increase the effect or efficiency of the ultrasound as it relates to enhancing the transdermal molecular flux rate either into or out of the human body.

[0043] According to an aspect of the present invention, a microprocessor coupled with an EEPROM, a timer unit, and a waveform generator may be used to provide for programmability and time-dependent operation of the transdermal drug delivery system. As is well understood in the pertinent arts, this is often termed a "control unit". Of course, alternative devices for effecting analogous controls for implementing the present invention may be provided. Programmability may include the ability to control a quantity of drug delivered, the time interval and duration of drug delivery, and the frequency and intensity of the applied control waveforms to the transducer. Both programmable and manual operation may be utilized. The waveform generator may be programmed to provide a sine, a square or a sawtooth waveform used to control the transducer. Of course, other waveforms may also be utilized. The frequency of the controlled waveforms may be from about 20 k Hz to about 100 k Hz. The waveforms may be sequentially interleaved to provide different waveforms for different durations and/or different amplitudes. Multiple waveforms may also be generated simultaneously.

[0044] A method of superpositioning or summing of waveforms may also be provided to combine, for example, square and sawtooth waveform at the transducer inputs. Waveform control outputs may be applied to a plurality of transducers simultaneously or may be divided and time phased so as to permit sequential operation of different transducer elements. The timing generator and EEPROM may serve to store drug specific delivery scenarios in memory. For example, a basal timing sequence and a bolus timing sequence may be programmed, stored, and then retrieved and executed; thereby controlling the transducer or transducer array in a specific drug delivery operation.

[0045] A pulsed or continuous mode of operation may also be selected. In addition, an electric signal, which may be directed through the skin of the subject at any time during the drug delivery sequence, may also be provided. The electric signal may be programmed to be anywhere in the range of 1 to 20 Volts, for example. The electronic control unit may be battery operated for portability and ease of use.

[0046] According to an aspect of the present invention, multiple transducers configured in an array may be used so as to change the area of the skin used for drug absorption, i.e. the transport sites.

[0047] According to an aspect of the present invention, transdermal delivery of pharmaceutical agents using ultrasonic stimuli may be improved using variable frequencies and intensities in order to deliver therapeutic quantities of drugs to patients. Variables such as fat content and mass of a particular patient's tissue, through which the drug will be delivered, may vary the frequency and intensity requirements used to obtain an effective dosing regimen.

[0048] According to an aspect of the present invention, encapsulation of substances and/or various compounds to be delivered may increase the permeability thereof and allow for slow time release of medication, for example. According to an aspect of the present invention, excipients may be used to improve transport through the stratum corneum and absorption into the blood stream. Several substances, such as drugs, may be applied using this method for local application of medication.

[0049] Referring now to **FIGS. 1 and 10** there is shown a wearable, non-invasive, ultrasonic-transdermal drug delivery system **10** including an ultrasonic applicator **1** shown placed directly over a transdermal delivery device or patch **2**. The applicator **1** and/or patch **2** may be attached to an exterior of a patient's skin **3** by means of adhesive and/or a strap **4**, which holds the ultrasonic applicator **1** and patch **2** in place. Power for the ultrasonic applicator **1** is provided by power cells **12**, for example which may be rechargeable, and may be located within the strap **4** itself, for example. Alternatively the power supply may be contained within the ultrasonic applicator device **1** itself or provided by any conventional external source.

[0050] **FIG. 1** illustrates applicator **1**, patch **2** and band **4** on the arm of the patient. It should be recognized however that a system according to the present invention may be placed over the patient's chest (as in the case of nitroglycerin drug delivery for example) abdomen (abdomen **6** as seen in **FIG. 2**), or any other suitable part of the patient's body as determined by the medical personnel administrating the drug treatment regimen. Other body placements include, but are not limited to, the neck, back and legs, for example. **FIG. 2** shows ultrasonic applicator **1** affixed directly over the transdermal patch **2** and held onto bare skin **3** of a patient, wherein the transducers **4** are placed directly in contact with the transdermal patch **2**, in this instance affixed to the patients abdomen **3**.

[0051] **FIG. 3** illustrates the structure of human skin. Essentially there are three pathways through the skin into the bloodstream: 1) breaching the Stratum Corneum; 2) passing a pharmaceutical agent through pores in the skin; and, 3) passing a pharmaceutical agent through the skin by following the hair follicle to the hair root, and from there into the vascular network located at the base of the hair root.

[0052] According to an aspect of the present invention, transdermal drug delivery may be provided by utilizing drug pathways associated with the pore and the hair follicle system on the patient's skin. More particularly, according to an aspect of the present invention, the ultrasonic frequency, intensity level and/or waveform dynamics of delivered ultrasound are adjusted to exploit drug delivery through the hair follicle pathway primarily and through the pores in the skins surface secondarily, but not directly through the stratum corneum, as it is believed the amount of energy needed for piercing the stratum corneum may be excessive and potentially damaging to fatty tissue.

[0053] According to an aspect of the present invention, through the use of alternating waveforms, the amount of energy transmitted to the surface of the skin may be minimized while also providing a pressure wave effect upon the skin, enhancing drug delivery through the hair follicle and pore system. Referring to **FIG. 7**, according to an aspect of the invention, an ultrasonic waveform dependent upon a sawtooth to square wave alternation is utilized. The amplitude of and intensity of such wave shaping aids in both the homogenization of a drug contained within the transderrnal patch and miniaturizing a beadlet size of the active pharmaceutical substance within the patch, and in drug transport through the skin. The short, peaked portion of the ultrasonic waveform resulting from a sawtooth shaped input helps with drug homogenization, without imparting destructive frequencies and cavitation to the drug substance. Upon conversion to the square waveform, the ultrasonic transmission acts to massage and open the fatty tissue surrounding the hair follicle and pores. Drugs permeating from the transdermal patch are preferably in monomer form and/or reduced in droplet size, below approximately 50 Angstroms, making them more suitable in dimension to pass through the skin. The square waveform may help to "push" the drug through the pores and alongside the hair follicles, where the drug makes its way to the hair root, and directly into the bloodstream at the vascular network.

[0054] According to an aspect of the present invention, the frequency and intensity of that portion of the ultrasonic signal resulting from the square waveform portion and impinging a transport site may be about 20 kHz at about 125 mW/sq. cm to about 225 mW/sq. cm, while the frequency and intensity of the portion of the ultrasonic signal resulting from the sawtooth waveform portion is about 20 kHz at about 125 mW/sq. cm to about 225 mW/sq. cm. Further, each waveform can be provided for about 100 milliseconds, before transitioning to the other, for example.

[0055] Referring again to **FIG. 10**, to achieve ultrasound promoted transdermal delivery 20 of substances such as drugs, transdermal patch **2** may be designed to work in conjunction with ultrasonic applicator **1**. Reference is hereby made to commonly assigned and copending U.S. patent application Ser. No. _____, entitled "SUBSTANCE DELIVERY SYSTEM", filed on even date herewith, the entire disclosure of which is hereby incorporated by reference herein. In summary, this application describes a patch suitable for use in combination with the present invention, and the reader is advised to study this application for a more detailed analysis there-regarding. In particular, the contact between the applicator and the patch preferably promotes efficient acoustic energy transmission. The selection of the materials and adhesives is important to maintain the intensity and power output of the ultrasonic transmission from the transducers through the transdermal patch. It is believed that insulin, one of many active pharmaceutical substances being suitable for enhanced drug delivery via the present invention, has a large molecule size, and forms hexamers generally over about 50 Angstroms, making it difficult to permeate through the pores of the skin. Further, insulin molecules tend to agglomerate when stored and as a result zinc. Insulin stored within the patch may therefore tend to agglomerate into even larger drug clump sizes, further reducing skin transport potential.

[0056] To help alleviate this problem and to keep the drug at a size sufficiently small enough for skin transport, the ultrasonic signal may be altered, from time to time, using a sawtooth to a square waveform stimuli. It should be understood however that other varying waveforms having alternating average imparted powers for example can of course be utilized. Nonetheless, for purposes of illustration **FIG. 7** shows an alternating waveform, wherein a sawtooth waveform (of relatively low average power) is used to drive one or more transducers to homogenize a drug within a patch, leading to increased skin transport as the ultrasonic waveform stimuli switches to a square wave shape (of relatively high average power). As will be readily understood by those possessing an ordinary level of skill in the pertinent arts, the sawtooth waveform portion leads to a short period of high energy, with a short duration of pressure amplitude, leading to a vibration effect with the targeted pharmaceutical substance. This vibration is with a low heat potential and may have the effect of mixing or homogenizing the drug within the patch. Thus, smaller beadlet sizes may be made possible by the sawtooth waveform portion.

[0057] Conventional transdermal substance delivery pathways through the stratum corneum may enable initial quantities of a drug to permeate through the skin, but as longer periods of ultrasound are applied to the same location on the skin the delivery rate may drop off or be reduced to zero. This may imply that ultrasound applied to same site at the skin's surface should not be continued for lengthy periods of time. It is believed that one or more attempts in the previous art to breach the stratum corneum failed over time because cavitation eventually over-heated the fatty tissue contained within the epidermis, resulting in a changed density of the fatty composites within this skin layer. An increase in such density may retard further drug permeation through the skin.

[0058] **FIG. 4A** illustrates the design of a cymbal type of ultrasonic transducer **40** which can be utilized according to an aspect of the present invention. Cymbal transducer **40** includes piezoelectric disc **41**, such as PZT4 available from Piezokinetics Corp., Bellefonte, Pa., connected to two metal caps **42**, which may be composed of titanium foil for example. **FIG. 4A** illustrates that there is a hollow air space **43** between the piezoelectric disc **41** and the end caps **42**. The end caps **42** are connected to the piezoelectric disc **41** by a non-electrically conductive adhesive **44** to form a bonded layered construction to the transducer **40**. Cymbal transducers offers a thin, compact structure well suited for a portable ultrasonic drug delivery apparatus. Additionally such a transducer offers sufficient efficiency for the conversion of electric power to acoustically radiated power. Such a transducer design also provides potential to be battery powered, and is small and lightweight.

[0059] **FIG. 4C** illustrates a stacked cymbal type of ultrasonic transducer **40** which can be utilized according to an aspect of the present invention. In a stacked transducer construction greater intensity of ultrasonic signals can be utilized. U.S. Pat. No. 5,729,077, issued Mar. 17, 1998, entitled "METAL-ELECTROACTIVE CERAMIC COMPOSITE TRANSDUCER" (Newnham et al.), the entire disclosure of which is incorporated by reference herein, discloses the use of stacked transducers, essentially transducers fitted atop each other, to increase ultrasonic intensities while maintaining a given frequency level. A stacked transducer construction may be used to increase intensity while improving the power utilization of the transducer system.

[0060] **FIG. 5A** illustrates the sizing of the transducers which may be used, and which can be about 0.5" inches in diameter. The use of such a relatively small size transducer enables the transducers to fit within the dimensions of a transdermal patch, for example. In addition the small size enables a lower weight potential for the transducers, again aiding in the portability of the invention. The transducer element **50** is a cymbal type construction attached to a power cable **51**. The transducer element **50** is coated in a polymer housing **52**, composed of a polyurethane material suitable for castings, coatings, and/or adhesives, such as a Uralite resin for example, which is used to avoid short circuits between the two metallic caps **42** (See, **FIG. 4A**) and provides acoustic coupling for the sonic transmission.

[0061] **FIG. 5B** illustrates possible dimensions using a "cymbal" type transducer element. The cymbal type transducer design offers several advantages to the present invention, including, but not limited to: compact structure, with small surface area; high acoustic pressure and high acoustic intensity at low resonance frequency; high efficiency, making the system require less driving power; the use of low resonance frequency to avoid a high cavitation threshold, i.e., the intensity required to generate air bubbles within the stratum corneum of the patient's skin tissue. The cavitation threshold is inversely proportional to the frequency applied so the choice of a low resonance frequency of the transducer permits a lower acoustical pressure applied to the surface of the skin and transdermal drug delivery is effected.

[0062] For a more thorough discussion regarding cymbal transducers in general, the reader is referred to the following U.S. Pat. No. 4,999,819, issued Mar. 12, 1991, entitled "TRANSFORMED STRESS DIRECTION ACOUSTIC TRANSDUCER" (Newnham, et al), U.S. pat. No. 5,276,657, issued Jan. 4, 1994, entitled "METAL-ELECTROACTIVE CERAMIC COMPOSITE ACTUATORS" (Newnham, et al) and the aforementioned U.S. Pat. No. 5,729,077 (Newnham, et al), the entire disclosures of which are hereby respectively incorporated by reference as if being set forth in their respective entireties herein.

[0063] **FIG. 6** shows an array **60** including more than one-cymbal element **61** arranged in a pattern (or array) onto a substructure or encased within a polymer housing **62**. The array can take any suitable form, such as a 2×2 array or a 3×3 array, for example. The cymbal elements **61** may be connected in parallel by a series of electrical connections **63**. The array **60** may be sealed in polymer potting material **62**, again composed of Uralite for example. Such an array enables a portable, battery powered, ultrasonic transmission with sufficient power to effect drug delivery via a transdermal patch.

[0064] According to an aspect of the present invention, the sonic applicator **1**, as shown in **FIG. 6**, can transmit ultrasonic signals through multiple transducers, that is at multiple transport sites. The activation of one or more elements of the transducer array may be sequenced from transducer element to transducer element, optionally using different waveforms, frequency, amplitudes, and duty cycles between each transducer element, for example. It is believed that this serves to advantageously relieve the skin transport sites from con-

tinual ultrasonic stress and provide increased variability in ultrasonic skin transport energy manipulation. The transducers can act in tandem, transmitting together.

[0065] The transducer array as shown in **FIG. 6** provides for spreading out drug pathway sites along the skin surface by providing ultrasonic transmission from the multiple transducer elements **61** of the array acting upon the skin. The transducer elements **61** may be activated simultaneously or sequentially to transmit ultrasound through a patch and through differing multiple sites on the skin surface, for example. Additionally, the frequency, intensity and/or waveform of an applied signal may be altered at each transducer element **61** within the array **60**. This variation may result in increased efficiency, enhanced power utilization and lengthening the life span of the battery of the portable system, for example. Additionally, alternating transducer elements **61** may help keep a drug homogenized within a pocket of the transdermal patch and help ensure that the skin is not overexposed to an excessive frequency of ultrasound.

[0066] An array of two or more transducers, of the cymbal type for example, may help to push drugs through multiple skin transport sites. The transducer array may further reduce skin damage and improve an efficiency and transmitted acoustical intensity. By alternating the transducer activation sequence for example, it is possible to mitigate skin exertion and to assure greater longevity for the skin transport sites.

[0067] The application of ultrasound according to the present invention can be coupled with iontophoresis, the application of electric currents applied to the skin, in various forms of substance, or drug, delivery. Ultrasound can be applied together with iontophoresis or as a pre-treatment to the application of iontophoresis, for example. Iontophoresis and/or electroporation in combination with the method and apparatus of the present invention may be used to enhance molecular transport through the skin. According to an aspect of the present invention, chemical substances, such as chemical enhancers, may be used to enhance substance transport as well.

[0068] The present invention may be used to enhance delivery of a wide variety of substances, such as medications or medicaments, nutritional supplements or any other suitable substance to a subject, such as a human patient. As described in greater detail herein below, a medication for example may be delivered transdermally, transcutaneously, intralumenally, and within solid tissue sites, where in all cases absorption of the medication or a pharmacologically active portion thereof into the underlying or surrounding tissue is phonophoretically enhanced by the application of ultrasonic or sonic energy. The substance, or medicament for example, may take any conventional form, including liquids, gels, porous reservoirs, inserts, or the like, and the medication or pharmacologically active portion thereof may be intended to treat or alleviate an existing condition or prophylactically prevent or inhibit another condition of the patient. The effect of the medication may be local, such as providing for anti-tumor treatment, or may be systemic. Suitable medicaments include broad classes of compounds normally delivered through the skin and other body surfaces or into solid tissues, for example.

[0069] In general, such medications may include or incorporate anti-invectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimatics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta-blockers, and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. By the method of the present invention, both ionized and nonionized drugs may be delivered, as can drugs of either high or low molecular weight.

[0070] Proteinaceous and polypeptide drugs represent a class of drugs being suitable for use in conjunction with the presently disclosed invention. As will be evident to those possessing an ordinary skill in the pertinent arts, such drugs cannot generally be administered orally in that they are often destroyed in the gastrointestinal tract or metabolized in the liver, for example. Further, due to the high molecular weight of most polypeptide drugs, conventional transdermal delivery systems are not generally effective.

[0071] Common examples of pharmaceutical or nutritional compounds which may be used with the present invention, and may be contained within a transdermal patch for example, include, but are not limited to: Acetaminophen, Antibiotics, Aspirin, Corticosterone, Erythromycin, Estradiol, Ibuprofen, Insulin, Nitroglycerin, Nicotine, Steroids such as Progesterones, Estrogens, Vitamins.

[0072] Other substances, such as pharmaceutical or nutritional compounds, for nutraceutical, medicinal or pharmaceutical use may also be utilized. It may also be desirable to use the method and apparatus of the invention in conjunction with substances, such as drugs, to which the permeability of the skin is relatively low, or which may give rise to a long lag-time. Application of ultrasound as described herein is believed to significantly reduce the lag-time involved with the transdermal administration of most drugs.

[0073] Applicants have noted that many drugs may be immersed within an excipient binder fluid, such as saline or an acetate composition, to make them injectable. Insulin is often placed in acetate mixes for example. By altering the excipient solution transdermal transport and the homogenization effect within a patch pocket may be hastened and enhanced in conjunction with the application of ultrasound. Excipient solutions high in metallic or salt content, for example, may enhance the interaction between the drug and ultrasound. It is believed that the effect of ultrasound at high intensity, or at low intensity but generating cavitation, can have a damaging effect upon many drug substances, such as insulin, whereupon a protein may become altered or damaged by excessive ultrasonic or cavitation frequencies and intensities. Using an appropriate excipient carrier solution, selected consistently with conventional techniques for example, a substance, such as an active drug, may mitigate damage to the substance such that it remains biofunctional after skin transport.

[0074] The following non-limiting examples are provided for purposes of providing a clear understanding of particular embodiments of the present invention.

[0075] According to an aspect of the present invention, the Cymbal Transducers can be constructed as follows: the piezoelectric ceramic material can take the form of a PZT4 disc 0.5 inch diameter, 1 mm thickness (PKI402) SD 0.500 -0.000-0.040 - 402. This is available from Piezo Kinetics Inc., Mill Road and Pine St., PO Box 756, Bellefontte Pa. 16823, for example. Titanium caps can be formed of Alfa Aesar, Titanium Foil, 0.25 mm thick, metal basis 5%, Item #10385, available from Alfa Aesar, A Johnson Matthey Company 30 Bond Street, Ward Hill, Mass. 01835-8099, USA. A bonding layer material can take the form of Eccobond 45LV+catalyst 15LV, available from Emerson & Cuming, 46 Manning Road, Billerica, Mass. 01821. Low temperature soldering material suitable for use in connection with the Cymbal transducers include Indalloy Solder #IE, 0.30" diameter×3 ft long, which is available from The Indium Corporation of America 1676 Lincoln Ave., Utica, N.Y. 13502. Wires can be formed from stranded wire, Gauge/AWG: 30, Catalog number (Digikey):

[0076] A3047B-100-ND, Note: Maximum Temperature: 80 C., Conductor Strand: 7/38, Voltage Range: 300V, Number of Conductors: 1, available from Alpha Wire Corporation. A polymer housing can be formed of Uralite FH 3550 part A/B, available from the HB Fuller Company. Ethyl Alcohol used is preferably about 200 proof, and fine scale sand paper can be utilized.

[0077] Referring to **FIG. 4**B, the titanium foil may be dye cut titanium foils into several disks using a circular saw having 10.7 mm diameter, for example. One side of the disks results with edges as is conventionally understood, these edges may be removed with sand paper (fine scale). An alcohol bath can then be used to remove dust generated by sanding the disks. The disks may then be placed into a high pressure (12000 torr) shaping tool (polished side up). This step may be performed using a custom-made punch dye in order to shape the disks into the dimensions reported in **FIG. 2**, for example. Resulting rough edges can again be sanded, and the sanded disk again immersed in alcohol to remove dust. The disk may be wiped to remove alcohol and dust from disk.

[0078] The thickness of the cap may be measured using a conventional techniques. Caps having matching or substantially matching thicknesses may be matched together. This step may be accurate, because slight differences between the two caps may generate spurious resonance into the cymbal.

[0079] The piezo disk ceramic (piezo disks) may be cleaned with alcohol. Epoxy bond may then be screen printed onto both sides of the piezo disk ceramic using a process similar to T-shirt screen-printing for example. A ring of epoxy may be generated to glue the caps with the disks. This ring may be accurate and regular in order to avoid spurious resonances.

[0080] The cymbals may then be placed on ceramic disks, and the composite structure placed into a press. This press may just keep the cymbal made in place, a tool where several cymbals are kept in place, for example. The pressed, compound structures may then be heated to approximately 70° C. for four (4) hours utilizing an oven, for example. The wires may then be soldered (**45**) using a maximum temperature of about 270° C. at the electrical contact points, 4 points per piece, for example.

[0081] A transducer produced by the above procedure may be termed to be of a standard construction. To form a stacked construction transducer, two or more transducers **40** may be placed directly atop one another as shown in **FIG. 4**C and fitted together. To form an array, the transducers may be generally connected in parallel, electrically within the polymer or epoxy bonding material as shown in **FIG. 6**, in either single element form or in a stacked construction format, for example.

[0082] A series of physical tests were conducted using the single element cymbal transducer fabricated according to the steps outlined above, using standard analysis procedures common to the ultrasonic and transducer industry. The single element transducer is a highly efficient system producing an ultrasonic transmission within two ranges:

RANGE - A	
TRANSDUCER TYPE	Single element "Cymbal" design
FREQUENCY	20 k Hz
INTENSITY: LOWEST SETTING	125 mW/sq. cm.
DESIGN	Standard Construction

[0083]

RANGE - B	
TRANSDUCER TYPE	Single element "Cymbal" design
FREQUENCY	20 k Hz
INTENSITY: LOWEST SETTING	225 mW/sq. cm.
DESIGN	Stacked Construction

[0084] Referring again to **FIG. 6, a** series of physical tests were conducted using an array of cymbal transducer elements fabricated according to the steps outlined above, using standard analysis procedures common to the ultrasonic and transducer industry. The single element transducer is a highly efficient system producing ultrasonic transmission within two ranges:

RANGE - A	
TRANSDUCER TYPE	Single element "Cymbal" design
FREQUENCY	20 k Hz
INTENSITY: LOWEST SETTING	125 mW/sq. cm.
DESIGN	Standard Construction using nine elements

[0085]

RANGE - B	
TRANSDUCER TYPE	Single element "Cymbal" design
FREQUENCY	20 k Hz
INTENSITY: LOWEST SETTING	225 mW/sq. cm.
DESIGN	Stacked Construction using nine elements

[0086] Arrays with different orientation of cymbals and with combinations of standard and stacked arrays may be used to increase efficiencies and to improve the effective delivery of drugs.

[0087] Alternating frequency outputs from the transducer array may be obtained. In tests, an array using nine-single elements in a standard construction and in a stacked construction produced frequency outputs, which could be varied from about 20 kHz to about 100 kHz. Ultrasonic transmissions were found to be most uniform at the lower frequency range, i.e. about 25 kHz as compared to 40, 60 or 80 kHz. Ultrasonic transmissions were found irregular at these higher frequencies. In all cases, the transducers could be made to emit responsively to a purely sinusoidal waveform or be converted to a combination waveform including sawtooth and square waves as illustrated in **FIG. 7**. In these tests the ultrasonic driver circuit, e.g. the frequency generator, was set to propagate 100 milliseconds of sawtooth waveform followed immediately by 100 milliseconds of square waveform, before re-cycling back to sawtooth waveform.

[0088] The transducers, whether configured in a single element or as a array, in either a standard or stacked construction, operate using low power. The portable nature of the final drug delivery device, as depicted in **FIGS. 1 and 2** for example, is achieved by the present system, which is worn by the patient. Accordingly, a portable power source, such as a rechargeable battery, can be used to drive the ultrasonic system. As a result, according to an aspect of the invention: 1) low power is used to drive the transducer, from standard commercially available battery sources for example; and, 2) long duration power, providing at least one full day of continuous power is provided.

[0089] Tests were conducted using a nine element standard cymbal design array set to operate at 20 k Hz frequency and at varying intensity levels, powered by a standard "A" or "C" type battery. A useful power life of 25 hours was obtained at a intensity level of 200 mW/sq. cm., with continued constant usage to the transducer array. Of course, other suitable power sources can be used, such as "9 Volt" type batteries, for example.

[0090] Thus, transducers used may be effectively battery powered so as to drive the ultrasonic signal, and have an efficiency of the power utilization such that a low battery drain rate is exhibited, thereby extending the life of the power source. Accordingly a portable or wearable ultrasonic drug delivery system employing ultrasonic drug delivery is possible utilizing conventional battery sources coupled with the transducers which may be used according to the present invention.

[0091] The effect of the ultrasonic signal discussed in connection with the present invention upon an active pharmaceutical substance was tested. High intensity and high frequency ultrasound may be capable of inducing a cavitation effect within a drug, leading to an increase in temperature and a degradation of the drug molecule. Insulin (Humulin Regular-supplied by the Eli Lilly Company) was subjected to ultrasound emitted from a stacked array of the transducers as described above, set to operate at a 20 k Hz frequency and at 125 mW/sq. cm intensity level, for one, eight and eleven continuous hours of exposure. The insulin was placed in a plastic pouch within a hydrophone tank containing water and stirred during ultrasonic exposure. A control sample, which was untreated, but allowed to sit in the pouch and tank for one, eight and eleven hours, was also made. Samples were sent for independent analysis. All samples showed no change in the insulin from the untreated insulin.

[0092] **FIG. 8A** shows the HPLC scan of the control sample, showing no degradation of either the insulin or the excipient solution of the Humulin Regular sample. **FIG. 8B** shows the HPLC scan of the ultrasonically treated eight hour sample, showing that there also was no degradation of either the insulin or the excipient solution of the ultrasonically treated Humulin Regular sample, even after eight hours of continuous exposure.

[0093] Accordingly, there appears to be no damage caused to the insulin molecule as a result of exposure to ultrasonic transmissions associated with the present invention (e.g. low frequency, low intensity and alternating waveform, for example).

[0094] A four-element transducer was fabricated using four standard cymbal element transducers in one array system (Array #1) and four stacked cymbal element transducers in another system(Array #2). Array #1, the standard array, was set to operate at 20 k Hz frequency and at 125 mW/sq. cm intensity level. Array #2, the stacked array, was set to operate at 20 k Hz frequency and at 225 mW/sq. cm intensity level.

[0095] The transducer arrays were fitted with a reservoir at a bottom end, into which Humulin Regular Insulin (supplied by Eli Lilly Company) was inserted. A total of 100 cc of insulin was added, providing 100 units of insulin for the each test.

[0096] Ten test rats were assembled and anesthetized. The belly of the rats were shaved to produce a skin area as close in configuration as would be present in a human situation. The transducer arrays were placed directly onto the rat skin surface and adhered to the skin by means of adhesive. Two groups of test rates were assembled. The first group (Group-1) were subjected to ultrasonic transmission while the second group (Group-2) received no ultrasound. In the second group (Group-2), the transducers arrays were loaded with insulin and the insulin was allowed to pool onto the surface of the rat skin, but there was no active ultrasonic transmission.

[0097] Next a frequency generator was employed to propagate a pulsed ultrasonic transmission, which used 100 millisecond pulses, with a pulse rate of one pulse per second, and a duty cycle of 10%, for one hour.

[0098] Both Group-1 and Group-2 animals were tested for 120 minutes. Blood samples were taken from the animals according to standard investigative procedure every 30 minutes for the first hour and every hour after and analyzed for glucose levels and the presence of insulin. The Group-1 animals were exposed to ultrasound for 60 minutes, after which the ultrasound was terminated for the balance of the test period. Glucose levels in both groups were observed over the 120 minute period.

[0099] **FIG. 9** illustrates the results of these tests, with an average of the data compiled across the number of tests conducted. Specifically this data relates the average Glucose level of the Group-1 animals treated with ultrasound and the

Group-2 animals, which were untreated, but where the insulin was placed in a blank array (containing no transducers) and placed upon the skin surface. At minute 0, before the ultrasound was activated, both groups had similar starting glucose levels. At minute 30 and minute 60 the Group-1 animals showed a significant reduction in glucose levels while the Group-2 animals showed no lowering in glucose level. At minute 60, the ultrasound was terminated and the animals monitored for another 60 minute period. The Group-2 animals showed no decrease in glucose levels, as the insulin was not absorbed through the skin. The Group-1 animals, which had a lowering of their glucose levels during active ultrasound transmission, indicating that the ultrasound enabled the permeation of the insulin through the skin, were observed to have a rise in their glucose levels upon termination of the ultrasound.

[0100] At minute-120 the Group-2 animals showed no decrease while the Group-1 animals showed their glucose levels to be rising to the previous pre-ultrasound levels. This test showed that the insulin was only permeated through the skin via the ultrasound emitted from the transducer arrays, and only with the presence of active ultrasound. The tests also confirmed that insulin, placed on the skin or delivered via a transdermal patch did not permeate through the skin on its own. These tests also confirm the validity of the transducer designs described herein as an effective means for delivering ultrasonically enhanced transdermal drug delivery.

[0101] These tests also showed that insulin delivered transdermally by the portable transducers can effectively decrease glucose levels. This result showed that the insulin is not only absorbed through the stratum corneum but it is also absorbed into the blood stream in an effective form and can cause its metabolic effect of lowering glucose.

[0102] Examination of the skin features of the tested rats showed no damage to the skin surface, no discoloration or abnormal fractures after the application of ultrasound emitted from the transducers.

[0103] The device of this invention provides certain drug delivery functions, including but not limited to: non-invasive drug delivery through the use of ultrasound applied transdermally to a patient's skin surface; penetration/absorption enhancement through the skin so that medicines contained within a transdermal patch become more readily absorbed through the skin layers into a patient's blood stream; homogenization and droplet size reduction of pharmaceutical agents contained within a transdermal patch, to make the resulting ultrasonically treated drug more readily absorbable through a patient's skin layers.

[0104] The method and apparatus of the present invention may be especially well suited for difficult to administer drugs such as insulin and various hormone medicines; the device may go with the patient, to be wearable by the patient, and use rechargeable batteries to provide treatment mobility.

[0105] Some elements of this invention also worthy of noting include, but are not limited to: (a) The ability to provide a portable and wearable ultrasonic drug delivery device which goes with the patient. (b) The use of drug delivery pathway which includes hair follicle and skin pore delivery as opposed to breaching the stratum corneum. The drug contained within the drug pocket of the transdermal patch may ultimately penetrate into the patient's blood stream, aided by the sonic transmission through the skin pores or hair follicles and into the muscular of the patient. This pathway approach may reduce the chance of damaging the skin and enables the use of lower ultrasonic frequencies and intensities. (c) The use of a transducer array, which enables ultrasonic skin transport at more than one site on the skin, which may provide a greater chance of effective skin transport and avoid overtaxing just one delivery site. The use of multiple transducers may offer varied treatment effects to facilitate maximum skin transport of the target active pharmaceutical agent, by providing tandem drug transport across multiple transducer elements, by enabling sequencing of the transducer elements in the array, whereupon the transducers may act at different frequencies and intensity levels of ultrasound. (d) Using an array of transducers in a portable, wearable ultrasonic drug delivery device, especially utilizing cymbal type transducers, may provide higher power utilization efficiencies and helps to avoid the damaging effects of excessive cavitation upon the skin. Using an array may help enable long duration battery supplies providing sufficient power to enable the apparatus to function for several days between recharge or replacement cycles. The use of a rechargeable battery supply, with batteries contained with the strap of the device for example, may afford total mobility for the patient and a reliable power supply for the device over several months of recycled use, for example. (e) Applicants further note that the use of transmission in both the sonic and ultrasonic ranges may be combined to achieve optimal transport through the skin or mucosal membranes. (f) To deliver the proper dose of a drug across the skin, in minutes as opposed to the hours noted in the previous art. (g) The use of low frequency ultrasound, from about 20 k Hz-about 100 kHz, with an alternating waveform (from sawtooth to square wave for example), with cymbal type transducers, may enable battery powered ultrasonic transmission. Further, a transducer array may help to avoid over exerting a single skin transport site and providing versatility in ultrasonic frequency and intensity ranges per transducer element.

[0106] Having described the invention in the above detail, those skilled in the art will recognize that there are a number of variations to the design and functionality for the device, but such variations of the design and functionality are intended to fall within the present disclosure. Further, although the invention has been disclosed with a certain degree of particularity, it is understood that the present disclosure of the preferred forms has been made by way of example, and that numerous changes in the details of construction and combination and arrangement of parts and steps may be made without departing from the spirit and scope of the invention as hereinafter claimed.

What is claimed is:

1. A device for enhancing delivery of at least one substance situated substantially adjacent to a surface of subject through said surface and into said subject, said device comprising:

at least one ultrasound emitting device secured to said subject;

wherein, said at least one ultrasonic emitting device emits at least one ultrasonic signal dependent upon an alter-

nating input so as to enhance movement of at least a portion of said substance into said subject.

2. A system for enhancing delivery of at least one substance situated substantially adjacent to a surface of a subject through said surface and into said subject, said device comprising:

at least one ultrasound emitting device secured to said subject;

wherein, said at least one ultrasonic emitting device emits at least one ultrasonic signal responsively to an input alternating between a square waveform and a sawtooth waveform so as to enhance movement of at least a portion of said substance into said subject.

* * * * *