# Perspectives on transdermal ultrasound mediated drug delivery

Nadine Barrie Smith

Department of Bioengineering, The Pennsylvania State University, PA, USA



**Abstract:** The use of needles for multiple injection of drugs, such as insulin for diabetes, can be painful. As a result, prescribed drug noncompliance can result in severe medical complications. Several noninvasive methods exist for transdermal drug delivery. These include chemical mediation using liposomes and chemical enhancers or physical mechanisms such as microneedles, iontophoresis, electroporation, and ultrasound. Ultrasound enhanced transdermal drug delivery offers advantages over traditional drug delivery methods which are often invasive and painful. A broad review of the transdermal ultrasound drug delivery literature has shown that this technology offers promising potential for noninvasive drug administration. From a clinical perspective, few drugs, proteins or peptides have been successfully administered transdermally because of the low skin permeability to these relatively large molecules, although much work is underway to resolve this problem. The proposed mechanism of ultrasound has been suggested to be the result of cavitation, which is discussed along with the bioeffects from therapeutic ultrasound. For low frequencies, potential transducers which can be used for drug delivery are discussed, along with cautions regarding ultrasound safety versus efficacy.

**Keywords:** ultrasound, drug delivery, cavitation, intensity, transdermal

## Introduction

Several methods exist for improving transdermal drug delivery such as chemical mediation using liposomes or chemical enhancers, and physical mechanisms such as iontophoresis, lasers, electroporation, microneedles and ultrasound (also called sonophoresis or phonophoresis) (Prausnitz 1997; Prausnitz 1999; Montorsi et al 2000; Wang et al 2005; Nanda et al 2006). Numerous studies of these methods have shown that ultrasound mediated transdermal drug delivery offers promising potential for noninvasive drug administration. However the broad literature on ultrasound drug delivery is not confined only to transdermal applications. A large body of work focuses specifically on delivery to internal organs, but does not cover tissues or gene delivery. Additionally for transdermal work, the reader is also directed to several well written articles for further reading and additional viewpoints on this topic (Mitragotri and Kost 2004; Pitt et al 2004; Brown et al 2006).

Passive drug delivery across the stratum corneum can be transported with molecules that have a weight less than 500 Da (Brown et al 2006). In general the stratum corneum, which varies in thickness (≈ 10–20 μm) depending on the body location, forms the barrier to drug diffusion. This low permeability is attributed to the outermost skin layer that consists of a compact and organized structure of cells named keratinocites surrounded by lipid bilayers. Ultrasound enhanced transdermal drug delivery offers advantages over traditional injection drug delivery methods which are invasive and painful. Currently few drugs, proteins or peptides have been successfully administered transdermally for clinical applications because of the low skin permeability to these relatively large molecules. However from a research viewpoint, the list of compounds

Correspondence: Nadine Barrie Smith
Department of Bioengineering, The Pennsylvania State University, 21 Hallowell Building, University Park, PA, USA 16802
Tel +1 814 865 8087
Fax +1 814 863 0490
Email nbs@engr.psu.edu

which have been shown to transdermally cross skin via ultrasound is ever increasing. One hypothesis indicates that once the drug has traversed the stratum corneum, the next layer is easier to cross and subsequently the drug can reach the capillary vessels to be absorbed (Mitragotri et al 1995b).

## Background on ultrasound delivery and biological effects

One of the earliest reports of the interaction between ultrasound and biological tissue can be traced back to the 1920s and the post-World War I experiments of Professor Paul Langévin (Graff 1981). Much of his work centered on the development of pulse-echo sonar for submarine detection, including the observation of bubble formation in the water and the killing of fish from the sound beam. Specific biological changes such as searing of skin, rupturing of red blood cells and lethal effects on mammals were observed by Wood and Loomis with 200–500 kHz high intensity ultrasound (Wood and Loomis 1927).

In contrast to ultrasound used for diagnostic imaging, therapeutic ultrasound can be described as a controlled sound wave intended for biological interaction for a curative benefit. Some of the first clinically significant application of this technology was developed by Francis and William Fry in the 1950s (Fry et al 1954; Fry 1954). Their work was applied to the development of ultrasound devices for noninvasive surgical treatment of neurological disorders including Parkinson disease. Results included both reversible and irreversible biological effects. Other early clinical applications at this same time include the treatment of arthritis using ultrasound with hydrocortisone to relieve pain (Fellinger and Schmid 1954).

Thus it is appropriate to divide therapeutic ultrasound into two categories which use 'low' intensities and 'high' intensities ($>5$ W/cm$^2$) though this division is not precise (ter Haar 1999). High intensity focused ultrasound (HIFU) is an attractive means of noninvasive coagulation of deep tissues using external sources. Current clinical applications of ultrasound include transducer and array designs for the treatment of prostate cancer (Gelet et al 2004; Saleh and Smith 2004), liver tumors (Li et al 2004; Gignoux et al 2003), breast cancer (Jenne et al 2003; Wu et al 2004), bladder tumors (Wang et al 2003; Madersbacher and Marberger 2003) and uterine fibroids (Chan et al 2002; Tempany et al 2003). Low intensity ultrasound has been shown to mediate the transport of drugs across the skin and is clinically used in physical therapy to accelerate or stimulate a normal biological response through deep heating.

Many recent reviews have shown that ultrasound mediated transdermal drug delivery offers promising potential for noninvasive drug administration (Tachibana and Tachibana 2001; Pitt et al 2004; Mitragotri 2005). The working principle of sonophoresis, although not completely understood, has been suggested to be the result of cavitation (Mitragotri et al 1995b, 1997) although thermal effects can not be entirely discounted. Low frequency ultrasound is capable of generating microbubbles in the water and tissue. Because sound energy is transmitted in a fluid media, the large negative pressures cause violent collapse in bubbles, which results in the formation of water channels within the lipid bilayers. The resulting disorder created in the stratum corneum facilitates the crossing of a hydrophilic drug or molecule.

Table 1 sets out an overview of the transdermal ultrasound mediated drug delivery literature from the past several years with some commentary on notable contributions. Though not complete, the table lists the delivered compound or drug, its respective molecular weight (Daltons) and the experimental sample (animal) preparation including whether the experiment was performed under in vivo or in vitro conditions. Of major interest is the ability to reduce the research to clinical practice and therefore the reported ultrasound frequency and device is listed. For the table, ultrasound devices can be classified into different categories. The commercially made devices include sonicators (≈20 kHz), ultrasound heating devices intended for therapy ($>1$ MHz) and pre-fabricated transducers. Very few of the ultrasound devices listed are specifically designed for drug delivery and originally, like the sonicator, had a different intended purpose.

Many previous investigators using sonophoresis have found enhanced transdermal drug delivery over various frequency ranges using commercial sonicators or therapeutic devices. For example, a 14-fold increase of corticosterone transport has been shown using a 1 MHz therapeutic product used for the treatment of chronic and acute pain (Sonopuls® 463, Sugarland, TX) operating at 1.4 W/cm$^2$ for 24 hours (Johnson et al 1996). Significant transdermal transport of model drugs such as mannitol and inulin (plant starch) has been observed using a 20 kHz commercial sonicator (VCX400, Sonics and Materials, Newtown, CT) (Levy et al 1989). Previous work with high frequency ultrasound (≈1 MHz and at 1–3 W/cm$^2$) to enhance transdermal drug delivery has produced interesting results, which varied from drug to drug (Bommannan et al 1992a, 1992b; Mitragotri et al 1997). Pulsed ultrasound at 1 MHz has been used to increase transdermal absorption of indomethacin from an ointment in rats (Asano et al 1997). A combination of chemical enhancers and therapeutic ultrasound

**Table 1** A list of transdermally delivered drugs and compounds using ultrasound devices

| Compound | M.W | Preparation | Frequency | Device | Investigator |
|---|---|---|---|---|---|
| Aldosterone | 832 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |
| Benzene | 78 | in vitro human | 1–3 MHz | Therapeutic[5] | (Mitragotri et al 1995b) |
| Bicarbonate | 136 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 2000b) |
| Butanol | 74 | in vitro human | 1–3 MHz | Therapeutic[5] | (Mitragotri et al 1995b) |
| Butanol | 74 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |
| Caffeine | 194 | in vitro human | 1–3 MHz | Therapeutic[5] | (Mitragotri et al 1995b) |
| Caffeine | 194 | in vitro human | 20 kHz | +++ | (Boucaud et al 2001) |
| Caffeine | 194 | in vitro rat | 20 kHz | +++ | (Boucaud et al 2001) |
| Calcein | 623 | in vitro rat | 41, 158, 445 kHz | US transducer[13] | (Mutoh et al 2003) |
| Calcein | 623 | in vitro cell membrane | 20, 57, 76, 93 kHz | US transducer[17] | (Sundaram et al 2003) |
| Calcein | 623 | in vitro porcine | 20 kHz | US transducer[21] | (varez-Roman et al 2003) |
| Calcein | 623 | in vitro pig | 20 kHz | Sonicator[1] | (Kushner et al 2004) |
| Calcein | 623 | in vitro rat | 41 kHz | US transducer[9] | (Morimoto et al 2005) |
| Calcium | 40 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 2000b) |
| Corticosterone | 346 | in vitro human | 1 MHz | Therapeutic US[2] | (Johnson et al 1996) |
| Corticosterone | 346 | in vitro human | 1–3 MHz | Therapeutic US[5] | (Mitragotri et al 1995b) |
| Corticosterone | 346 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |
| Dexamethasone | 392 | in vitro human | 1 MHz | Therapeutic US[2] | (Johnson et al 1996) |
| Dexamethason | 392 | in vivo human | 1 MHz | US transducer[10] | (Darrow et al 1999) |
| Dextran++ | 2000 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 2000b) |
| Dextran | 70000 | in vitro pig | 58 kHz | US transducer[17] | (Tezel et al 2003) |
| Diclofenac | 296 | in vivo human | 1 MHz | Therapeutic | (Rosim et al 2005) |
| Diclofenac | 296 | in vivo rat | 1 MHz | Sonicator[12] | (Hsieh 2006) |
| Erythropoeitin | 48000 | in vitro human, | 20 kHz | Sonicator[1] | (Mitragotri et al 1995a) |
| Estradiol | 272 | in vitro human | 1 MHz | Therapeutic US[2] | (Johnson et al 1996) |
| Estradiol | 272 | in vitro human | 1–3 MHz | Therapeutic US[5] | (Mitragotri et al 1995b) |
| Estradiol | 272 | in vitro human | 20 kHz | Sonicator[1] | (Mitragotri et al 1996) |
| FD-4* | 4400 | in vitro rat | 41 kHz | US transducer[9] | (Morimoto et al 2005) |
| FD-40* | 38000 | in vitro rat | 41 kHz | US transducer[9] | (Morimoto et al 2005) |
| Fentanyl | 336 | in vitro human | 20 kHz | +++ | (Boucaud et al 2001) |
| Fentanyl | 336 | in vitro rat | 20 kHz | +++ | (Boucaud et al 2001) |
| FITC*** | 51000 | in vitro human | 20 kHz | Sonifier[19] | (Weimann and Wu 2002) |
| FITC*** | 2500 | in vitro human | 20 kHz | Sonifier[19] | (Weimann and Wu 2002) |
| Fluorescein | 389 | in vitro human | 20 kHz | Sonicator[14] | (Cancel et al 2004) |
| Fluorescein probes nile red | 535 | in vitro porcine | 20 kHz | US transducer[21] | (varez-Roman et al 2003) |
| Glucose | 182 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 2000b) |
| Glucose | 182 | in vitro human | 20 kHz | Sonicator[1] | (Kost et al 1996) |
| Glucose | 182 | in vitro porcine | 10 MHz | US transducer[20] | (Merino et al 2003) |
| Glucose | 182 | in vitro porcine | 20 kHz | Sonicator[21] | (Merino et al 2003) |
| Glucose | 182 | in vivo rat | 20 kHz | cymbal TDR | (Lee et al 2005) |
| Hyaluronan | 1000 | in vivo rabbit | 1 MHz | Therapeutic | (Park et al 2005) |
| Hydrocortisone | 362 | in vivo rat | 1 MHz | Therapeutic | (Koeke et al 2005) |
| Ibuprofen | 206 | in vivo human | 1 MHz | UStransducer[23] | (Kozanoglu et al 2003) |
| Insulin | 5807 | in vitro human, in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 1995a) |
| Insulin | 5807 | in vivo rat | 20 kHz | Sonicator[1] | (Boucaud et al 2000) |
| Insulin | 5807 | in vivo rat | 48 kHz | LAG-26[4] | (Tachibana and Tachibana 1991) |
| Insulin | 5807 | in vivo rabbit | 105 kHz | LAG-26[4] | (Tachibana 1992) |
| Insulin | 5807 | in vivo rabbit | 105 kHz | UStransducer[9] | (Tachibana 1992) |
| Insulin | 5807 | in vitro human | 20 kHz | Sonicator[6] | (Zhang et al 1996) |
| Insulin | 5807 | in vivo rat | 20 kHz | Sonicator[1] | (Boucaud et al 2002) |
| Insulin | 5807 | in vitro human | 20 kHz | cymbal TDR | (Smith et al 2003) |
| Insulin | 5807 | in vivo rat | 20 kHz | cymbal TDR | (Lee et al 2004a) |
| Insulin | 5807 | in vivo rabbit | 20 kHz | cymbal TDR | (Lee et al 2004b) |
| Inulin | 5000 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri and Kost 2000) |
| Inulin | 5000 | in vitro pig | 58 kHz | US transducer[17] | (Tezel et al 2003) |
| Ketoprofen | 254 | in vivo human | 1 MHz | Sonicator[22] | (Cagnie et al 2003) |
| Ketorolac-tromethamine | 376 | in vitro rat | 1 MHz | Sonicator[7] | (Tiwari et al 2004) |

(*Continued*)

**Table 1** (*Continued*)

| Compound | M.W | Preparation | Frequency | Device | Investigator |
|---|---|---|---|---|---|
| Lanthanum droxide | 189 | in vivo guinea pigs | 2, 10, 16 MHz | Panametrics[3] | (Bommannan et al 1992a) |
| Lidocaine | 234 | in vitro human | 1 MHz | Therapeutic[2] | (Johnson et al 1996) |
| Linoleic acid | 280 | in vitro human | 1 MHz | Therapeutic[2] | (Johnson et al 1996) |
| Luteinizing hormone | 1311 | in vitro pig | 58 kHz | US transducer[17] | (Tezel et al 2003) |
| Mannitol | 183 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri and Kost 2000) |
| Mannitol | 183 | in vitro pig | 20 kHz | Sonicator[1] | (Mitragotri et al 2000c) |
| Mannitol | 183 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri and Kost 2000) |
| Mannitol | 183 | in vitro pig, in vitro human | 20 kHz | US transducer[1] | (Tang et al 2001) |
| Mannitol | 183 | in vitro pig, in vivo pig | 20 kHz | US transducer[1] | (Tang et al 2002) |
| Mannitol | 183 | in vitro pig | 20 kHz | Sonicator[1] | (Terahara et al 2002) |
| Mannitol | 182 | in vitro pig | 58 kHz | US transducer[17] | (Tezel et al 2003) |
| Mannitol | 183 | in vitro porcine | 10 MHz | US transducer[20] | (Merino et al 2003) |
| Mannitol | 183 | in vitro porcine | 20 kHz | Sonicator[21] | (Merino et al 2003) |
| Methylpredni-solone/ cyclosporine | 374 | in vivo human | 25 kHz | Sonicator[7] | (Santoianni et al 2004) |
| Oligonucleotides | [+++] | in vitro pig | 20 kHz | Sonicator[1] | (Tezel et al 2004) |
| Progesterone | 274 | in vitro human | 1–3 MHz | Therapeutic[5] | (Mitragotri et al 1995b) |
| Salicylic acid | 138 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |
| sodium lauryl sulfate | 288 | in vitro pig | 19.6, 36.9, 58.9, 76.6, 93.4 kHz | US transducer[17] | (Tezel et al 2001) |
| sodium lauryl sulfate | 288 | in vitro pig | 20 kHz | US transducer[11] | (Tezel and Mitragotri 2003) |
| sodium lauryl sulfate | 288 | in vitro porcine | 20 kHz | Sonicator[11] | (Paliwal et al 2006) |
| Sucrose | 342 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |
| Sucrose | 342 | in vitro human, pig | 20 kHz | US transducer[1] | (Tang et al 2001) |
| Testosterone | 288 | in vitro human | 1 MHz | Therapeutic[2] | (Johnson et al 1996) |
| Tetanus Toxoid (TTx vaccine) | 150000 | in vivo mice | 20 kHz | 600W Sonicator[11] | (Tezel et al 2005) |
| Triamcinolone- Acetonide | 434 | in vitro mice | 1, 3 MHz | US transducer[9] | (Yang et al 2006) |
| Urea | 60 | in vivo rat | 20 kHz | Sonicator[1] | (Mitragotri et al 2000a) |
| Vasopressin | 1056 | in vitro human | 20 kHz | Sonicator[6] | (Zhang et al 1996) |
| Water | 18 | in vitro human | 20 kHz | Sonicator[1] | (Johnson et al 1996) |

**Legend**
1. VCX 400, Sonics and Materials Inc., Newtown, CT
2. Sonopuls 463, Henley International
3. Precision Acoustic Devices and Panametrics
4. Leader Electronics Corp., Japan
5. Sonopuls 474, Henley International
6. W-385, Heat Systems Ultrasonics, Inc.
7. Brand not indicated
8. Cole Palmer Instrument Co, Chicago, IL
9. Transducer company not indicated
10. Omnisound 3000, Accelerated Care Plus-Physio Technology Inc., Topeka, KS.
11. Sonics and Materials, Newtown, CT
12. ITO Co, 1-23-15, Hakusan, Bunkyo-ku, Tokyu, Japan
13. Dai-ichi High Frequency, Tokyo, Japan
14. Model XL2020, Misonix Inc., Farmingdale, NY
15. Pro Seven 977 to 2000 model, Quark Productos Médicos, Brazil
16. Noblelife™ , Duplogen, Suwon, Korea
17. Piezo Systems, Cambridge, MA
18. Transducers made in-house
19. Model S-110, Branson Instruments Inc., Standford, CT
20. Sofranel, Zurich, Switzerland
21. VCX 400, Sonics and Materials Inc., Danbury, CT
22. Sonoplus 590, Enraf-Nonius BV, AV Delft, the Netherlands
23. Peterson®250 Ultrasound Equipment Petaş, Turkey

[+++]details not indicated.
*FITC-labeled dextrans.
***PBS solution was prepared using Milli-Q® water and a phosphate concentration of 0.01 M and NaCl concentration of 0.137 M.
[***]Fluorescein Isothiocyanate (FITC).
**Note:** Apologies are offered for any missing information.
**Abbreviations:** US, ultrasound; Therapeutic, commercially made ultrasound device for heating therapy; TDR, transducer.

(1 MHz, 1.4 W/cm$^2$, continuous wave (CW)) in transdermal drug transport has also been investigated with success (Johnson et al 1996).

A noteworthy difference between high (1–3 MHz) and low (≈20 kHz) frequency ultrasound appears to be that low frequency ultrasound enhances transdermal drug transport 1000 times more than high frequency ultrasound (Mitragotri et al 1996). The working hypothesis for the physical mechanism is that low-frequency ultrasound enhances transdermal transport through aqueous channels in the *stratum corneum* generated by cavitation induced bilayer disordering. However, the mechanism of the enhancement using ultrasound is far from being fully understood (Pitt et al 2004). Some researchers have concluded that at 168 kHz using CW ultrasound and at $1.9^* \times 10^5$ Pa, a new structural state was induced which generated defects in human stratum corneum specimens. They suggest that the dimensions of the defects (20 μm) were large enough to allow the transdermal passage of high molecular weight drug molecules, which normally elude the unenhanced transdermal drug delivery (Wu et al 1998).

Past research has demonstrated the possibility of delivering and controlling therapeutic doses of proteins such as interferon gamma and erythropoeitin across human skin using ultrasound (Mitragotri et al 1995a). Other researchers have investigated the in vitro penetration and the in vivo transport of flufenamic acid in skin with ultrasound (Hippius et al 1998). In the flufenamic acid study, ultrasound exposure was from 5–30 minutes with intensities up to 1.5 W/cm$^2$. Although there was a pronounced effect of ultrasound on the transmembrane absorption of the drug, there was also a rise in temperature up to 4.5 °C. Ultrasound at 1 MHz has also been used to enhance the transdermal absorption of indomethacin studied in rats using intensities from 0.25–1 W/cm$^2$. The researchers reported no significant skin temperature rise and no notable damage to the skin, although damage was noted as the intensity and the time of application of ultrasound increased beyond 1 W/cm$^2$ (Miyazaki et al 1992).

Other researchers have reported noticeable skin damage from ultrasound transdermal drug delivery experiments (Wu et al 1998). One group has examined the morphological changes induced in in vitro hairless mouse skin and human skin after ultrasound exposure to transdermal drug delivery systems. The skins were immersed in a commercial ultrasound water tank at 48 kHz and an intensity of 0.5 W/cm$^2$. Skins were compared to control skins under a scanning electron microscope. The researchers found that cells of the stratum corneum of the mouse skin surface were almost completely removed. Furthermore, on some of the the mouse samples, large craterlike pores with a diameter of 100 microns were formed sporadically. However in human skin, the surface exposed to ultrasound showed only slight removal of keratinocytes around the hair follicles. The researchers suggested that the removal of the stratum corneum and other alterations in hairless mouse and human skin may explain the enhancement of transdermal drug penetration (Yamashita et al 1997).

Convenient noninvasive methods for transdermal delivery of insulin or similar procedures for glucose sensing has particular public interest due to the increasing problem of diabetes. In the United State alone, approximately 16 million people suffer from diabetes mellitus. From a human and economic perspective, it is one of the most costly diseases (Congressionally Established Diabetes Research Working Group 1999; The Whitaker Foundation 2004). Management of diabetes often requires painful repetitive blood glucose tests and insulin injections up to three or four times each day. Between injections, blood sugar levels can fluctuate and remain out of balance until the next test or injection, increasing the risk of tissue or organ damage.

Specifically for insulin (Table 1), the amount of research for noninvasive insulin delivery is increasing every year. Over a frequency range of 20–105 kHz, enhanced transport in the presence of ultrasound has been shown in both in vitro and in vivo experiments. Many early experiments were performed using either an ultrasound sonicator, ultrasonic bath or commercial transducer. For example investigators have demonstrated effective in vivo transport of insulin at 48 kHz using an ultrasonic bath (Tachibana and Tachibana 1991) and at 105 kHz (Tachibana 1992) using a commercially obtained transducer. The major drawback so far in exploiting ultrasound for noninvasive drug delivery is the large size and poor mobility of the ultrasound device. Commercial sonicators are large, heavy, table-top devices specifically designed for lysis of cells, catalyzing reactions, creating emulsions or cleaning. A few commercial ultrasound devices do exist, specifically designed for ultrasound drug delivery, such as the SonoPrep® made by the Sontra Medical Corporation (Cambridge MA), which is a large ultrasound device that consists of a power control unit and a hand-held applicator.

Although diabetics have an aversion to injecting insulin they probably hate the more frequent finger-stick for blood glucose samples even more. A number of different techniques for monitoring blood glucose using non-invasive or minimally invasive methods are under investigation including near-infrared spectroscopy, implantable glucose sensors, reverse sonophoresis, reverse iontophoresis and

interstitial fluid sampling devices (Kost 2002). The latter three techniques extract glucose transdermally and measure glucose in interstitial fluid. Dermal interstitial fluid glucose concentration is highly correlated with the plasma glucose concentration and capillary blood glucose concentration. Thus transdermal extraction of interstitial fluid offers a noninvasive method of obtaining a sample for blood glucose measurements (Cantrell et al 2000; Kost 2002). Previous results has demonstrated positive results in the use of ultrasound to facilitate the noninvasive extraction of interstitial skin fluids (ISF) for blood glucose monitoring through an electrolytic reaction with glucose sensitive enzymes (Kost et al 2000).

## Mechanism of ultrasound

Although ultrasound is known to increase transdermal protein delivery (Tachibana 1992; Mitragotri et al 1995a) the mechanisms of this enhanced transport have not been fully characterized (Pitt et al 2004). Bioeffects from ultrasound include the thermal or mechanical (cavitation) mechanism (AIUM 2000). One effect of cavitating ultrasound is its ability to increase permeability of the outer skin layer (stratum corneum), which is thought to be a primary barrier to protein diffusion. Cavitation represents the rapid expansion and collapse of gaseous bubbles in response to an alternating pressure field. Cavitation types can be broken into two non-exclusive categories (Flynn 1982). The first is stable cavitation where the cavity oscillates about its equilibrium radius in response to relatively low acoustic pressures. The second is transient cavitation (also known as inertial cavitation) whereby the equilibrium size varies greatly in response to very few acoustic cycles. During transient cavitation, the rapid, violent collapse of bubbles is associated with high acoustic pressures and temperatures of the order of 1000–2000 K (Apfel 1981, 1986). Transient cavities are generated in response to high acoustic pressures and/or lower frequencies. The violent hydrodynamic forces (Figure 1) due to a collapsing bubble can cause severe damage within biological media. Indeed free radicals can be produced by this violent phenomena (Edmonds and Sancier 1983; Mason and Lorimer 1988).

There exists several definitions for the threshold for transient cavitation in terms of such physical parameters as acoustic pressure, frequency or bubble radius. For diagnostic ultrasound, one (of many) definitions of the cavitation onset is the peak rarefractional pressure divided by the square root of the frequency (Apfel and Holland 1991). From previous research, the measured cavitation pressure amplitude in dog thigh muscle in vivo was found to depend linearly on frequency with a slope of 5.3 MPa/MHz (Hynynen 1990). Compared to the kilohertz range, ultrasound in the megahertz range also produces cavitation although much higher pressures are required to exceed the cavitation threshold. Beyond the threshold, cavitation has been shown to disrupt cells and damage tissue (Dalecki et al 1996; Miller et al 1996). Mechanical bioeffects in tissues with gas bodies include lung hemorrhage in mice, rats, monkeys and pigs (AIUM 2000). Cavitation has also been shown with diagnostic ultrasound levels (Apfel 1986; Roy et al 1990) which has motivated the introduction of the mechanical index to identify a threshold pressure for the onset of inertial cavitation (AIUM-NEMA 1996). Even in the absence of well-defined gas bodies, there exist non-thermal bioeffects due to ultrasound, which are known to occur in the absence of excessive heating or evidence of cavitation bubbles. In this situation, the mechanism is in the form of radiation force or torque or acoustic streaming (Beyer 1997).

The dynamics of acoustic cavitation in liquid alone differ considerably to cavitation at liquid-solid interfaces. Ultimately acoustic bubble dynamics are quite complex and beyond this overview (Apfel 1981; Leighton 1994; Hamilton and Blackstock 1998). Determining the threshold and energy from a cavitation event is difficult under the best conditions. Researchers in ultrasound try to follow three experimental rules with respect to cavitation: understand the liquid including impurities, understand the sound field, and know when something happens (Apfel 1981). The first rule refers to the cavitation threshold while the second rule relates to accurate measurements of the acoustic field. The third relates to observable cavitation events or secondary related information. Rule two deals with a commentary regarding information which could have been included in Table 1 but was intentionally omitted. Though many of the papers listed in Table 1 report an ultrasound intensity, the drawback is that much of the literature gives a value but does not specify details of the exposimetry such as spatial (average, peak) or temporal (average, peak) values. To report the determination of an acoustic field, it is essential to supply enough information, such as calibrated hydrophones, dissolved gas concentration, anechoic conditions, etc., so that intensity experiments can be repeated by others. Therefore accurate and precise evaluation of acoustic fields should follow exposimetry and dosimetry procedures previously recognized in the ultrasound literature (Schafer et al 1990; Lewin and Ziskin 1992; AIUM-NEMA 1996; Lewin et al 2003). Without such information, comparing the intensity of enhanced transport between many of the

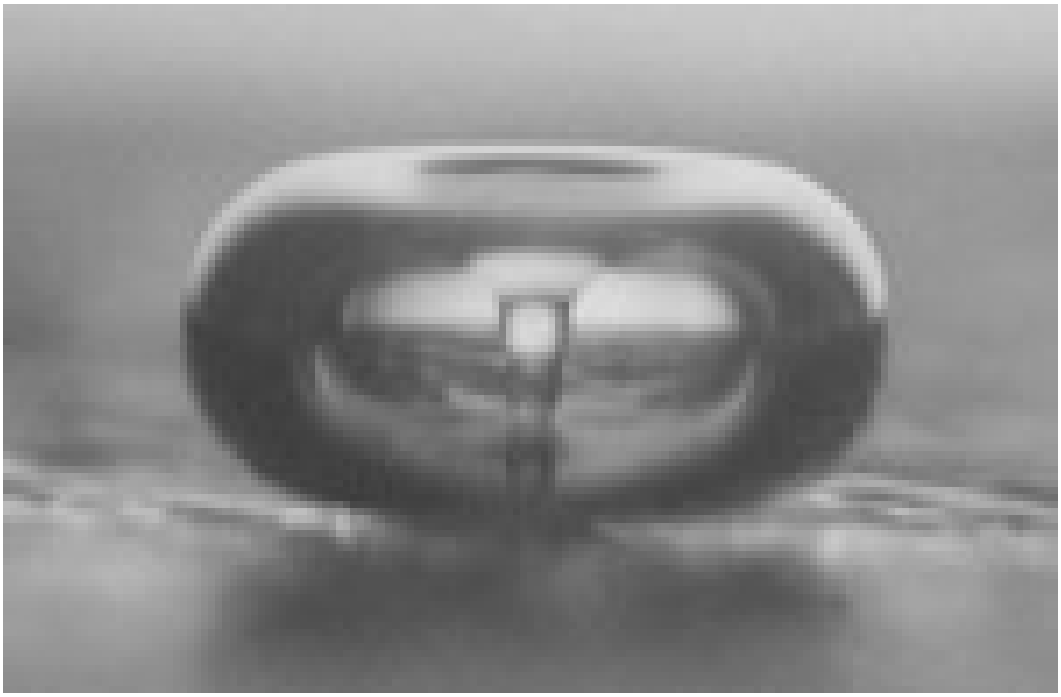

**Figure 1** With transient cavitation the bubble dynamics have two basics stages comprising the initial formations of the cavity followed by the growth and asymmetric violent collapse. The photo shows the jet produced by the collapse of a cavitation bubble at a liquid-solid interface. [Photo courtesy of Dr. Lawrence Crum at the University of Washington.]

drug delivery publications, or determining potential bioeffects, is impossible.

## Future of transdermal drug delivery

Use of transdermal drug delivery techniques has the most practical clinical application for medications which need to be injected multiple times either daily or weekly. Though infrequent, other injectable drug avoidance situations could include the use of needles on infants, children and pets or under harsh conditions (battlefield or first responder) where needles are not feasible. As seen in Table 1, many previous researchers who have successfully used acoustic energy for drug delivery have used commercial sonicators or off-the-shelf transducers. These large industrial devices are impractical for a feasible and transportable drug delivery device. Much of the previous ultrasound transdermal dry delivery research has focused on low frequencies primarily because commercial sonicators were designed to operate only at one frequency. To bring this research to clinical practice will require more investigation into the optimal frequency and intensity of each particular drug. As with diagnostic ultrasound imaging, drug delivery using ultrasound requires a delicate balance between safety and efficacy and requires careful scientific study.

Other recent reviews on drug delivery state similar views to those expressed here, for example, "small-sized low-frequency transducers need to be developed so that patients can wear them" (Pitt et al 2004). Although there are several possible low frequency transducer designs that can be used in a drug delivery application, such as the low frequency flextensional resonators (Stansfield 1990), tonpilz transducers (Wilson 1988), or "thickness"-type resonators (Shung et al 1992), the "cymbal" transducer design is a good choice for a portable device. This Class V flextensional transducer has a thickness of less than 2 mm, weighs less than 3 g, resonates between 1 and 100 kHz depending on geometry, and has a large scale manufacturing cost of less than $5.00/unit (Newnham et al 1991, 1994; Dogan et al 1997; Newnham, 1998; Tressler et al 1998). With the low profile cymbal design, high frequency radial motions of the ceramic translates into low frequency displacement motions through the cap covered cavity. If the diameter of the ceramic is increased (ie, a larger single element), then the frequency of the transducer decreases towards a lower range. If the diameter increased, the capsule depth of the flextensional design also needs to increase thereby increasing the thickness and slightly increasing the profile. Cymbals can be arranged into multi-element array designs (Figure 2) since this can increase the effective aperture of ultrasound area with respect to skin area. Some research indicates that the delivery dose increases with ultrasound exposure area (Smith et al 2003).

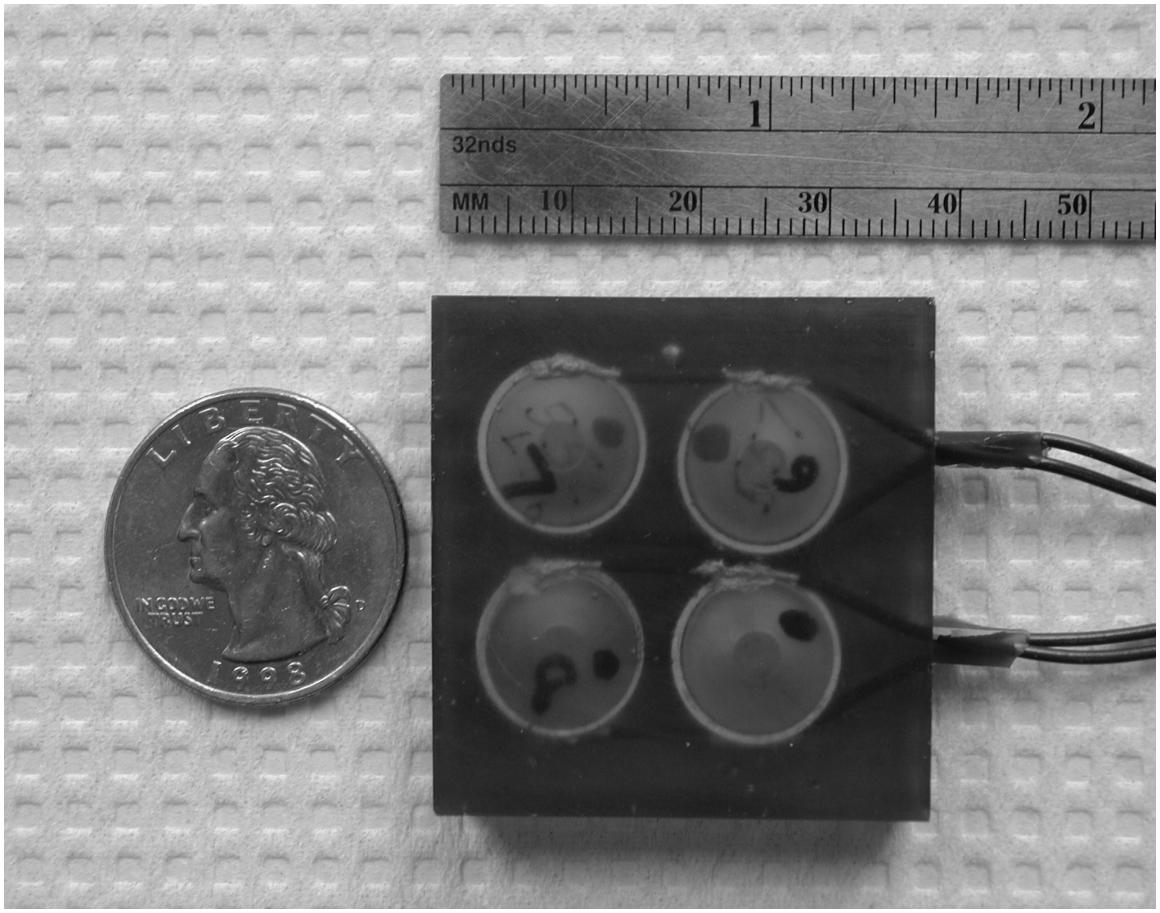


**Figure 2** The future of practical noninvasive drug delivery may be in the use of novel transducers or ceramics for producing ultrasound. One example is the cymbal transducer made of piezoelectric material PZT-4 operated at a frequency of 20 kHz. The light-weight, low-profile array was constructed using cymbal transducers which were connected in parallel, and encased in URALITE® polymer. The dimensions of the array were $37 \times 37 \times 2$ mm$^3$ and is comparable in size to a US quarter; it weighed less than 22 g.

Interestingly the cymbal design originates from underwater research for naval applications and current research is underway to incorporate existing battery technology in the miniaturization of portable power for both insulin delivery and glucose sensing (Lee et al 2004, 2005).

In general the future for noninvasive drug delivery is encouraging. Exploiting transdermal ultrasound drug delivery beyond the feasibility stage will require the cooperation of medical doctors and engineers so that the technology aids the construction of a clinical device. As with diagnostic ultrasound, the bioeffects and safety of each device needs to be carefully monitored, because it will not matter how much of any drug can be transported if the skin is burned, damaged or the procedure is painful.

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