Overview
For thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agents. (Prausnitz 2008) However, it was not until the twentieth century that the skin came to be used as a drug delivery route. In fact, Merriam Webster dates the word “transdermal” to 1944 (Merriam-Webster 2011) highlighting that it is a relatively recent concept in medical and pharmaceutical practice. While there are many advantages to transdermal drug delivery, there are also disadvantages and both must be considered. (Rios 2007) (Gordon 2005)

In 2008, Prausnitz and Langer published a paper in which they proposed three generations of transdermal drug delivery systems (TDDS): (Prausnitz 2008)

- 1st generation TDDS include traditional patches such as clonidine or estrogen
- 2nd generation TDDS include patches plus some type of enhancement to improve drug delivery
- 3rd generation TDDS use novel technologies to increase the scope of molecules that can be delivered through the skin

Objectives
- Review the anatomy of the skin, define what is meant by transdermal drug delivery, and examine the benefits and limitations of current transdermal drug delivery systems
- Define the three generations of transdermal drug delivery systems as proposed by Prausnitz and Langer
- Review the transdermal drug delivery systems currently approved by the FDA
- Review some novel transdermal delivery technologies that are in development or clinical trials

Anatomy of the skin
The skin is the largest organ in the body and, on average, accounts for about 6 lbs of our body weight. (Science Fact Finder 2006) Skin is approximately 1.5mm in thickness and has as its primary function to keep the body hydrated, or, in other words, to keep water inside the body. (Fukushima 2011) The skin also prevents foreign substances from entering the body from the environment.

Figure 1 represents a cross-sectional view of the skin. The major divisions of the skin, from bottom to top, are the hypodermis, the dermis, and the epidermis. The hypodermis is where fat is stored, as shown by the yellow ovals in the figure representing adipocytes. Larger blood and lymph vessels are also found here.
The dermis is where structures such as sweat glands, hair follicles, and the smaller blood vessels are located. Therefore, in order to have drug delivery via the skin, the drug must pass through the epidermis into the dermis where it can be absorbed by capillaries into the circulatory system.

Figure 2 shows a cross-sectional view of the epidermis. Of the five layers of the epidermis, the most important barrier layer is the outer layer, or stratum corneum (KOR-ne-um). The stratum corneum is made up of dead, keratinized cells called keratinocytes, or sometimes corneocytes. Although it represents the major barrier to drug absorption, the stratum corneum accounts for only about 0.1mm of the skin’s 1.5mm thickness.

The stratum corneum is often described as a “brick and mortar” structure (Figure 3) where the bricks represent the dead, keratinized cells and the mortar represents the lipid bilayers surrounding the cells. There are two possible ways that drug molecules can pass through this brick and mortar structure. One possibility is the transcellular route, or simply passing through both keratinocytes and lipids in what could be visualized as a straight path to the dermis. The other possibility is the intercellular route where the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis. Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes.

**Advantages and Disadvantages of Transdermal Drug Delivery**

First, there are biological advantages to delivering drugs through the skin (Rios 2007)(Gordon 2005):

- Transdermal delivery avoids the stomach environment where the drug can be degraded and rendered ineffective or where it can cause unpleasant gastrointestinal symptoms for the patient.
• Transdermal delivery avoids the first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects.

• Transdermal drug delivery provides steady plasma levels. When a patch is applied that lasts for 24 hours, or even 7 days, once steady state is reached the plasma levels remain constant because the rate of drug delivered from the patch is constant. When a drug is given four times a day, or even once a day, the drug levels rise after administration and then gradually fall until the next administration producing peaks and troughs throughout the course of therapy.

Other advantages to delivering drugs through the skin include the fact that:
• Transdermal drug delivery systems, especially simple patches, are easy to use and noninvasive and patients like noninvasive therapies.

• Because they are easy to use, patches can increase compliance and reduce medical costs. There are many studies that show a patient’s overall healthcare costs are reduced when pharmaceutical compliance is increased. In addition, there are specific studies that show that patient compliance increases and healthcare costs decrease when patches are prescribed.(Sclar, Utility of a transdermal delivery system for antihypertensive therapy: Part 1 1991)(Sclar, Utility of a transdermal delivery system for antihypertensive therapy: Part 2 1991)

• If a transdermal delivery system is used in place of a needle, then medical waste can also be decreased, again, decreasing healthcare costs.

No drug delivery system is without its disadvantages. Some of the challenges of transdermal drug delivery include:
• Only a narrow range of molecules can currently be delivered transdermally using available technologies. Only small, relatively lipophilic molecules can
pass through the lipid bilayer “mortar” of the stratum corneum using traditional patch technology. As drug treatments become more and more complex, drug molecules are becoming larger and more complex as well and new technologies will be needed to deliver these drugs through the skin (Prausnitz 2008).

Figure 4 is representative of the types of molecules that can currently be delivered through the skin. All of these molecules are organic in nature and are considered lipid soluble. Even though these molecules contain a few polar atoms such as oxygen and nitrogen, they are made primarily of carbon and hydrogen atoms that render them nonpolar. Nicotine is the smallest molecule represented with a molecular weight of only 162.24 g/mol. Although hormones or a molecule like fentanyl, with a molecular weight over 300 g/mol, are considered large organic molecules, they are still much smaller than even a small protein such as insulin.

- Currently, only small quantities of drug can be delivered through the stratum corneum. Therefore, drugs that are given transdermally must be relatively potent so that they can be effective at low doses.

- Patient trust issues can also be a barrier to effective transdermal drug therapy. The general public might have been willing to accept a 3-day scopolamine patch when it was introduced in 1979 but it was quite a challenge in 1984 to convince doctors and patients alike that a clonidine patch would control blood pressure for seven days continuously. In more recent years, there have been accidental overdose deaths from fentanyl patches (U.S. Food and Drug Administration 2007) and questions have been raised about the safety of transdermal contraception (Burkman 2007). As new transdermal technologies are introduced, there will certainly be
questions from patients and healthcare professionals about the safety and effectiveness of these new delivery systems.

1st Generation Transdermal Drug Delivery Systems
Currently, there are two types of simple patch design (Figure 5): (Scheindlin 2004)
The original patch design is a **liquid reservoir system** where the patch consists of a backing material that is both protective and adhesive, a liquid drug reservoir, a release membrane. Transderm Scop®, Catapress TTS®, Estraderm® and Androderm® use the liquid-reservoir design (Novartis Consumer Health, Inc. 2006) (Boehringer Ingelheim Pharmaceuticals, Inc 2010) (Novartis Pharmaceuticals Corporation 2005) (Watson Pharma, Inc 2010).

A more recent design is the **adhesive matrix system** where the adhesive and the drug are combined in the same layer leaving only three layers to the patch; the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin. Most currently available patches, except those previously mentioned, are the adhesive matrix design.

Table 1 is a list of current FDA-approved transdermal drug delivery systems. From 1984 to 2001, there was a new TDDS approved by the FDA about every 2-3 years. From 2003-2007, the rate of approval increased to one TDDS approximately every 7-9 months. In the years 2008 to 2010, only one TDDS was approved each year (Prausnitz 2008). Prausnitz and Langer, as well as others, would argue that transdermal drug delivery systems will not continue to be approved at a rapid pace again until new technologies can be developed that will allow for the enhanced delivery of organic molecules and, more importantly, the delivery of much larger molecules such as vaccines and insulin.

2nd Generation Transdermal Drug Delivery Systems
2nd Generation TDDS attempt to enhance the delivery of organic molecules through the stratum corneum by disrupting its barrier function and/or by providing some sort of driving force for the movement of molecules through the epidermis. (Dua 2009) This disruption should be reversible and avoid injury to the skin. However, it can be difficult to disrupt the barrier without causing damage or irritation,
especially when using chemical enhancers. In addition, these 2nd generation enhancement techniques are limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules. 2nd generation enhancement methods include chemical penetration enhancers, gentle heating, and iontophoresis.

### Currently Approved TDDS

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic (Brand) Names</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Scopolamine (Transderm Scop®)</td>
<td>Motion sickness</td>
</tr>
<tr>
<td>1984</td>
<td>Clonidine (Catapress TTS®)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>1986</td>
<td>Estradiol (Estraderm®)</td>
<td>Menopausal symptoms</td>
</tr>
<tr>
<td>1990</td>
<td>Fentanyl (Duragesic®)</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>1991</td>
<td>Nicotine (Nicoderm®, Habitrol®, Prostep®)</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>1993</td>
<td>Testosterone (Androderm®)</td>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td>1995</td>
<td>Lidocaine/epinephrine (Iontocaine®)</td>
<td>Local dermal analgesia</td>
</tr>
<tr>
<td>1998</td>
<td>Estradiol/norethindrone (Combipatch®)</td>
<td>Menopausal symptoms</td>
</tr>
<tr>
<td>1999</td>
<td>Lidocaine (Lidoderm®)</td>
<td>Post-herpetic neuralgia pain</td>
</tr>
<tr>
<td>2001</td>
<td>Ethinyl estradiol/norelgestromin (OrthoEvra®)</td>
<td>Contraception</td>
</tr>
<tr>
<td>2003</td>
<td>Estradiol/levonorgestrel (Climara Pro®)</td>
<td>Menopause</td>
</tr>
<tr>
<td>2003</td>
<td>Oxybutynin (Oxytrol®)</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>2004</td>
<td>Lidocaine/ultrasound (SonoPrep®)</td>
<td>Local dermal anesthesia</td>
</tr>
<tr>
<td>2005</td>
<td>Lidocaine/tetracaine (Synera®)</td>
<td>Local dermal analgesia</td>
</tr>
<tr>
<td>2006</td>
<td>Fentanyl/iontophoresis (Ionsys®)**</td>
<td>Acute postoperative pain</td>
</tr>
<tr>
<td>2006</td>
<td>Methylphenidate (Daytrana®)</td>
<td>ADHD</td>
</tr>
<tr>
<td>2006</td>
<td>Selegiline (Emsam®)</td>
<td>Depression</td>
</tr>
<tr>
<td>2007</td>
<td>Rotigotine (Neupro®)**</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>2007</td>
<td>Rivastigmine (Exelon®)</td>
<td>Dementia</td>
</tr>
<tr>
<td>2008</td>
<td>Granisetron (Sancuso®)</td>
<td>Chemo-induced emesis</td>
</tr>
<tr>
<td>2009</td>
<td>Oxybutynin (Gelnique®)</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>2010</td>
<td>Buprenorphine (Butrans®)</td>
<td>Chronic pain</td>
</tr>
</tbody>
</table>

Table 1--Italicized entries represent some TDDS other than a simple patch; **denotes products that were approved and later removed from the market
Chemical Penetration Enhancers

Figure 6 gives the structures of a few known chemical penetration enhancers.

DMSO is a polar, aprotic solvent that can disrupt the protein structure of the keratinocytes. Because it acts on the keratinocytes, DMSO will increase movement of drug molecules through the keratinocytes and enhance the transcellular route of delivery.

Small solvent molecules like ethanol and menthol will increase the solubility of drug molecules in the lipid bilayer and thereby enhance the intercellular route of drug movement.

Molecules whose structures mimic that of phospholipids, those with a small, polar head and a long, hydrocarbon tail, will insert into the lipid bilayer and increase the fluidity within that layer. If the bilayer is more fluid, it will be easier for drug molecules to move through it, also enhancing intercellular movement. Examples include glyceryl monooleate and lauryl lactate which are currently used in Androderm®, as well as Azone TS®, and the two NexACT® enhancers shown.

NexACT® enhancers are proprietary chemical compounds that are approved and being investigated in a number of therapies around the world (NexMed USA 2011). For example, NexACT enhancers are included in the following: a topical alprostadil cream (Vitaros®) approved in Canada to treat erectile dysfunction; an alprostadil-based cream (Femprox®) being investigated in the United States and China for female sexual dysfunction; and a terbinafine-based topical product (MycoVa®) that is being developed in Europe for onychomycosis.

Azone TS® and SEPA® are also compounds designed specifically as penetration enhancers. Azone TS is currently in Phase III clinical trials of a reformulated triamcinolone acetonide product (Durhalieve®)(Echo Therapeutics 2011). SEPA is currently in Phase II clinical trials of an econazole lacquer also used to treat
Onychomycosis (EcoNail®). In early trials of EcoNail®, the product was found to produce high econazole concentrations in the nail bed while clinical safety trials show no systemic detection of econazole (Access Pharmaceuticals, Inc 2011). SEPA® has also been investigated with alprostadil and sex hormones such as testosterone, estradiol and progesterone.

*Heat as a penetration enhancer*

Another form of penetration enhancement is the use of heat to increase the permeability of the skin. Unfortunately, the medical community was made aware that heat can increase the absorption of drugs through the skin in 2005 when the FDA began issuing warnings regarding the safe use of fentanyl patches after deaths had been attributed to wearing the patch while sleeping in heated water beds or using heating pads (U.S. Food and Drug Administration 2007). One safe use of heat as a penetration enhancer is the Controlled Heat-Assisted Drug Delivery, or CHADD, system. In a CHADD system, a mix of proprietary powders reacts with the air to generate heat that then warms the skin and increases the delivery of the drug. This heat device can be placed on top of an existing patch or other medication or it can be manufactured in combination with a drug of choice (MedGadget 2006).

The most well known of the CHADD systems is the lidocaine/tetracaine patch system which goes by the brand name Synera®. This system is made by ZARS Pharma and is advertised as the “precedural” treatment before a needle stick to reduce the pain of the procedure (ZARS Pharma 2011). The gentle heat is combined with a lidocaine/tetracaine mix that causes effective analgesia within 20 minutes. If a needle-stick procedure can wait 20 minutes, this can be a great way to make a needle stick easier for a child. Or, in the words of one medical blogger, “Happier babies, less traumatized anesthesiologists and ER docs, less snout [sic] and tears--can anyone ask for more?” (MedGadget 2006)

*Iontophoresis as a 2nd generation penetration enhancer*

Iontophoresis is the process of using small amounts of electrical current to move drugs across the skin and can also be used to enhance penetration of drug molecules through the stratum corneum (Prausnitz 2008).

In a Galvanic, or Voltaic, cell, the cathode is the electrode that attracts positively charged ions from the solution, thus the word “cation” to describe a positively charged ion such as Na+. Likewise, the anode is the electrode that
attracts negatively charged ions from the solution, thus the word “anion” to describe a negatively charged ion such as Cl⁻. If an anode attracts negatively charged particles, then it will repel positively charged ones.

In an iontophoretic system (Figure 7), the anode will repel positively charged drug molecules. Because most drugs are formulated as a salt, for instance fentanyl hydrochloride (Figure 8), the drug molecule becomes protonated and takes on a positive charge to the negative charge of the chloride anion. This means that the drug will be repelled away from the anode and through the stratum corneum toward the dermis.

One of the advantages of iontophoresis is that the rate of drug delivery is proportional to the electrical current (Prausnitz 2008). Since the amount of current in the system can be controlled, the rate of drug delivery can also be controlled and even varied. In a typical patch system, the rate of delivery is proportional to the size of the patch. This dose-to-size relationship can readily be seen in the size of fentanyl patches (Table 2). A 12 mcg/h patch has a surface area of 5.25 cm² while a 100 mcg/h patch has an area of 42 cm² or 3.5 times as large as the smallest size (Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009).

<table>
<thead>
<tr>
<th>Dose (mcg/h)</th>
<th>Area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5.25</td>
</tr>
<tr>
<td>25</td>
<td>10.5</td>
</tr>
<tr>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>75</td>
<td>31.5</td>
</tr>
<tr>
<td>100</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 2 (Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009)

Ionsys® is an iontophoretic fentanyl system that was approved by the FDA in 2006 (Mechcatie 2006). It was a small, pre-preprogrammed, needle-free, patient-controlled analgesia (PCA) unit that adhered to the patient’s skin like a patch. It was indicated for short-term, acute post-operative pain in hospitalized patients. The patient initiated a dose of fentanyl by double-clicking a red button on the iontophoretic unit. The system was capable of delivering up to six 40mcg doses/hour and up to 3.2mg of fentanyl in 24 hours. At the time of its approval, there were at least 7 comparative studies involving more than 3,400 patients ranging in ages from 18-90. Patients were described as thin to obese and included general, orthopedic, and gynecological surgery patients.
Iontophoretic fentanyl was found to have a similar side effect profile to intravenous (IV) PCA morphine with several advantages over the traditional IV PCA treatment (Viscusi 2004). Since there were no IV lines connected to the patient, this fentanyl TDDS did not interfere with the mobility of the patient. Because it was preprogrammed, there was less risk of medication error and less workload on nursing staff. Unfortunately, there were problems with the microprocessors in this device and the product was removed from the market in 2008 and has not returned (Macdonald 2008).

As opposed to the intricate microprocessor systems used in Ionsys®, there are also simpler systems being developed. One such system is a simple circuit that would deliver a fixed amount of drug until the battery runs out. There is less control over the delivery in this system but the total amount of drug delivered is consistent. This type of system has been studied with granisetron for nausea and vomiting of chemotherapy (Prausnitz 2008).

Another simple system involves administration of a single-dose of 5% acyclovir cream to treat herpes labialis, or cold sores (PR Newswire 2006). In clinical trials, this one-time dose showed a 1.5-day reduction in healing time, which makes this treatment comparable to currently available treatments. However, penciclovir (Denavir®) must be applied every 2 hours while awake for 4 days and n-docosanol (Abreva®) must be applied 5 times daily until the lesion is healed. This iontophoretic acyclovir has been given the brand name SOLOVIR®. If successful, it would be marketed as a handheld, reusable device with prefilled drug cartridges.

Vyteris makes an iontophoretic delivery system that has been given the name Smart Patch® because the system can be programmed to deliver drug through the skin in a variety of ways. (Vyteris, Inc. 2010). The Smart Patch® can mimic a single IV injection, a rapid onset drug followed by sustained release, a pulsed delivery, or a bolus dose followed by maintenance.

The Smart Patch® is also referred to as the “active” patch to contrast the active, iontophoretic delivery of drugs from this system with the passive diffusion found in a 1st generation patch. Vyteris is investigating the use of its Smart Patch® with zolmitriptan for migraine and NSAIDS for chronic pain.

Figure 9--Smart Patch Delivery Profile (Vyteris 2010)
Iontophoresis begins to bridge the gap between 2nd and 3rd generation TDDS because it can be used to enhance the delivery of small, organic molecules (Viscusi 2004) as well as larger, biological molecules (Badkar 2007).

3rd Generation Transdermal Drug Delivery Systems
3rd generation TDDS aim to severely disrupt the stratum corneum to allow large molecules to pass into the circulation. While iontophoresis can be used to deliver small molecules such as fentanyl, it can also be used to deliver much larger molecules as well.

Iontophoresis as a 3rd generation penetration enhancer
One such molecule, also being tested with the Smart Patch® iontophoretic technology, is human gonadotropin-releasing hormone (GnRH) for infertility (Koenig 2009)(Vyteris, Inc. 2010). As can be seen from Figure 10, GnRH is not a small, organic compound but a somewhat larger oligopeptide. Phase II clinical trials for the delivery of GnRH were completed in January of 2010 and included 350 women, from 35 sites, ranging in age from 18-38 who wished to become pregnant. A pulsatile delivery of 10mg GnRH every 90 minutes was used to mimic the body’s own hormone release pattern. The patch was changed every 12 hours for 21 days. In August of 2010, Vytera reported that the pulsatile delivery of GnRH achieved ovulation rates similar to those achieved with other standards of therapy.

Thermal ablation as a penetration enhancer
Thermal ablation is another example of a 3rd generation technique that seeks to severely disrupt the stratum corneum. Thermal ablation heats the skin to 100s of degrees for very short periods of time (micro- to milli-seconds) and forms painless, reversible microchannels in the stratum corneum without damaging the underlying tissue (Prausnitz 2008).

The Prelude SkinPrep System®, developed by Echo Therapeutics, is one such TDDS system (Echo Therapeutics 2011). The Prelude SkinPrep System® is easy to use, low cost, handheld, and painless. The system also contains a feedback control system used to achieve optimum permeability without damaging underlying tissue. Echo plans to deliver low and high molecular weight drugs with this system and expects the system to be available by the 3rd quarter of 2011 (Pharmacy Choice 2011).
Altea Therapeutics also has a thermal ablation product known as the PassPort® (Cress 2007) (Altea Therapeutics 2010). This device will deliver up to 10mg of protein and over one hundred milligrams of hydrophilic drug, making this one of the first TDDS that will deliver significant quantities of a hydrophilic drug.

The PassPort® system has been shown effective in transdermally delivering small, organic molecules such as hydromorphone, morphine, and fentanyl. As expected, the patch size for the PassPort® fentanyl delivery system is smaller than the size of a traditional fentanyl patch. In studies by Altea, the thermal ablation patch has a surface area of only 1cm² compared to a marketed fentanyl patch with an area of 5cm². And, as can be seem from the graph in Figure 11, the thermal ablation patch achieves higher serum concentrations than the larger, traditional patch (Altea Therapeutics 2010).

Perhaps, more interesting than novel ways to deliver small molecules such as fentanyl are novel ways to deliver larger macromolecules such as insulin. Iontophoresis is being investigated as one of these novel delivery technologies. As opposed to oral dosage forms or patch applications, diabetics must endure needle sticks multiple times a day and there has been no significant advance in the delivery of insulin since its introduction in the 1920s. The PassPort® system has also been shown to be effective in transdermally delivering insulin. Phase I clinical trials show that the PassPort® system was able to deliver a therapeutically significant amount of insulin through the skin (Figure 11). Clinical studies are also underway using the PassPort® system to deliver macromolecules such as interferon-alpha, parathyroid hormone, and hepatitis B surface protein antigen. Preclinical trials are investigating the delivery of vaccines and erythropoietin (Altea Therapeutics 2010).

One way to create these thermal ablation microchannels in the skin is by using radio frequency (RF) waves (Galit 2008). These waves cause ions in the surrounding cells to vibrate, the vibrations cause heat, the heat causes evaporation, and the evaporation of water from the cells causes ablation. TransPharma has created the ViaDor® System which uses RF energy to cause thermal ablation of the stratum
corneum (TransPharma Medical Ltd. 2008). In partnership with Eli Lilly, this TDDS is in clinical trials with a GLP-1 agonist to treat type II diabetes, calcitonin for musculoskeletal disorders, and teriparatide to treat osteoporosis. The hand-held ViaDor® System is used to cause ablation, the device is removed, and the patch is folded over the newly formed microchannels. An animated demonstration of this product can be view at http://www.transpharma-medical.com/ViaDor_system.html.

*Ultrasound as a penetration enhancer*

Still is another 3rd generation technology that can be used to increase delivery of drugs across the skin is the use of ultrasound waves (Prausnitz 2008). Physical therapists and athletic trainers have used ultrasound for many years to deliver small molecular weight molecules such as dexamethasone, ketoprofen, or lidocaine to their patients. Using ultrasound to deliver drugs across the skin is also referred to as phonophoresis or sonophoresis. This is the same type of ultrasound technology that is used in lithotripsy to break up kidney stones and gallstones.

There are two possible mechanisms of action when ultrasound is used as a TDDS. First, the application of sound waves to the skin causes increased fluidity in the lipid bilayer and can increase the permeability of the skin using the transcellular pathway (Prausnitz 2008). This would allow for increased delivery of small molecules, such as lidocaine, but would not have much effect on larger molecules such as proteins or vaccines.

The other mechanism of action takes advantage of cavitation, or the formation of small gas bubbles, that results from ultrasound treatment (Hua 2002)(Maione 2002). When these bubbles aggregate and burst on the surface of the stratum corneum, small holes, or pores, are formed in the stratum corneum that would allow for the transport of larger molecules. Some of the drugs that have been studied using cavitational ultrasound to enhance delivery include insulin, heparin, and tetanus toxoid vaccine.

An early application of this technology was the SonoPrep® Skin Permeation device made by Sontra (MedGadget 2004) (Cress 2007). This device was given marketing clearance by the FDA in 2004 and was used to deliver lidocaine as a pretreatment for needle-stick procedures. The device could pretreat the skin in as little as 15 seconds and would decrease the time to lidocaine effectiveness from one hour down to 5 minutes.

![Figure 12--Cymbal Transducer Array (Park 2007)](image-url)
One historic disadvantage of ultrasound treatment was the large size of the device needed to deliver the sound waves (Maione 2002). Park and colleagues have recently reported the use of a small, lightweight array of cymbal transducers (Figure 12) to deliver insulin transdermally (Park 2007). Pigs were chosen for this study since their size, 100 to 140 lbs, more closely represented the size of a human than smaller laboratory animals. The delivery device consisted of a 3x3 array of cymbal transducers that measured about 2.5x2.5 inches. The device was attached to the pig’s skin with a reservoir of insulin between the skin and the device. The control group received only a reservoir of insulin but no ultrasound array. The data collected in this study show that the blood glucose level of the control group continued to rise throughout the 90-minute experiment while the blood glucose level of the TDDS group fell during the same study period. The authors conclude that the use of this cymbal transducer array shows promise in safely lowering blood glucose to normal, human values.

**Microneedles as a penetration enhancer**

Reports about microneedles can be found in both the scientific literature as well as the popular media (Sanders 2010) (University of Kentucky 2008). Microneedles are designed to penetrate the stratum corneum and deliver drug without reaching the nerves in the underlying tissues. Microneedles can be 200-750 microns in length (Cleary 2010) and are fabricated in groups called arrays that can contain 150-650 microneedles/cm². Some of the materials that have been used to make microneedles include silicon, metal, sugar, and plastics. Microneedles can be hollow and deliver drug through the pores of the needles or they can be coated with active ingredients that deliver the drug as the microneedles dissolve in the skin (Peterson 2006). Solid microneedle arrays can even be effective in delivering drug simply by creating temporary holes in the stratum corneum that remain in effect long enough for an applied drug solution to enter the dermis (Martanto 2004).

![Figure 13](from left to right) Dissolving microneedle array (Fukushima 2011); Solid microneedle array with hypodermic needle for comparison (Martanto 2004); Hollow microneedle array (Nordquist 2007)

The data in Table 3 was compiled from a search of the term “microneedles” on clinicaltrials.gov. As can be seen from the table, there are several microneedle projects in various stages of clinical trials. In addition, it is clear that the delivery of insulin and vaccines is a very high priority in microneedle research.
One available microneedle product seen in Table 3 is the NanoPass MicronJet® (NanoPass 2011). The MicronJet® is a single-use array of MicroPyramids that can be used to deliver intradermal doses of liquid medications such as vaccines and insulin. The MicronJet fits a standard syringe, thus replacing the hypodermic needle, and has received approval for marketing from the FDA.

Why give vaccines using microneedles? Microneedles have been proven to be pain-free and they deliver the vaccine intradermally which has been shown to improve vaccine response rates, especially in the elderly, while using lower doses of the vaccine (Kenney 2004) (P. e. Van Damme 2009). Intanza® is a seasonal flu vaccine that has been approved in Europe since 2009. Van Damme and colleagues compared Intanza® vaccine to the traditional IM injection plus an adjuvant in elderly patients (P. e. Van Damme 2010). While a slightly higher incidence of site reaction was seen with the microneedle product, these reactions were mild and short-lived. It was also found that microneedle delivery had similar tolerability and immunogenicity to the traditional IM vaccine plus adjuvant.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Updated</th>
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<tr>
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<td>Pilot</td>
<td>NanoPass Tech.</td>
<td>11/07</td>
</tr>
<tr>
<td>Low-dose Fluarix®</td>
<td>Seasonal flu</td>
<td>Pilot</td>
<td>NanoPass Tech.</td>
<td>11/07</td>
</tr>
<tr>
<td>Safety/PK/PD of insulin w/MicronJet®</td>
<td>Diabetes</td>
<td>Pilot</td>
<td>NanoPass Tech.</td>
<td>4/08</td>
</tr>
<tr>
<td>Insulin delivery w/microneedles</td>
<td>Type I diabetes</td>
<td>Phase II/III</td>
<td>Emory Univ</td>
<td>2/09</td>
</tr>
<tr>
<td>Pandemrix® w/micro-needles</td>
<td>H1N1 flu</td>
<td>Safety/efficacy</td>
<td>Hadassah Medical Org.</td>
<td>12/09</td>
</tr>
<tr>
<td>PK/PD of intradermal insulin</td>
<td>Type 1 diabetes</td>
<td>Phase I/II</td>
<td>Becton,Dickinson Co.</td>
<td>3/10</td>
</tr>
<tr>
<td>Microarray delivery of lidocaine</td>
<td>Topical anesthesia</td>
<td>Phase II/III</td>
<td>Univ. of OK</td>
<td>6/10</td>
</tr>
<tr>
<td>Low-dose vaccine w/MicronJet 600®</td>
<td>H1N1 flu</td>
<td>Safety/efficacy</td>
<td>Univ. of Hong Kong</td>
<td>7/10</td>
</tr>
<tr>
<td>Tolerability of Microstructure TDDS</td>
<td>Drug delivery</td>
<td>Phase I</td>
<td>Northwestern Univ &amp; 3M</td>
<td>12/10</td>
</tr>
</tbody>
</table>

Table 3--Clinical Trial Data Search from April 2011

Intanza® seasonal flu vaccine is currently in clinical trials in the US sponsored by Sanofi-Pasteur. These microneedles will even be investigated for patient self-administration in the near future (Dalhousie University 2010).

In addition to vaccine delivery, there is also much research devoted to using microneedles to painlessly deliver insulin though the skin. Gupta and colleagues conducted a small, proof-of-concept study delivering insulin via hollow microneedles to two adult subjects with type I diabetes, one female and one male...
Both subjects had similar HbA1c levels, comparable weights, BMI, mean insulin usage/day and insulin to carbohydrate ratio. When microneedles were used to deliver insulin, microneedle trials resulted in higher plasma levels of insulin than with catheter delivery. As expected from the plasma insulin levels, microneedles also resulted in lower postprandial plasma glucose levels than the catheter delivery. The study authors believe that, if combined with current microneedle technologies to sample blood glucose levels intradernally (Wang 2005), a complete blood glucose monitoring and treatment system could be developed in one unit.

Zosano Pharma has developed what they call ZP Patch Technology® (Zosana Pharma 2011). ZP Patch Technology® uses a delivery device to insert an array of drug-coated microneedles into the skin. This system has efficacy and safety comparable to approved injectables, needs only a few minutes of patch wear for drug delivery, and does not require refrigeration for medication stability. Zosano Pharma reports that over 20,000 ZP Patch® systems have been used in Phase I-II clinical trials, that 30 drugs have been tested in pre-clinical trials, and that 450 patients have been tested with 5 peptides and one vaccine.

One current study uses the ZP Patch® for the delivery of parathyroid hormone, or teriparatide. Current PTH therapy requires a daily injection, the injection pen must be refrigerated, and the pen must be discarded after 28 days of use even if medication remains in the pen. ZP PTH® patch (Figure 14) is applied for a few minutes once daily, requires no refrigeration, and has a shelf-life of two years. When compared to conventional therapy (teriparatide injection, [Forteo®]), ZP-PTH® has a more rapid onset, a higher $C_{max}$, and a shorter half-life. Microneedle delivery of PTH has been shown to be more effective than placebo and equally effective as conventional therapy at increasing lumbar spine strength. In addition, microneedle delivery of PTH has been shown to be more effective than both placebo and conventional therapy at increasing total hip bone mineral density (Daddona 2011). Zosano is ready to begin phase III clinical trials of this product.

Conclusions
An April 2011 search of the word “transdermal” at clinicaltrials.gov returned 456 entries (U.S National Institutes of Health 2011). The focus of these trials is both novel products and novel delivery routes of existing products. The scope of some of
these transdermal clinical trials include:

- An insulin patch
- Sufentanil patch for chronic cancer pain
- Varenicline patch for smoking cessation and a high-dose nicotine patch for fast metabolizers
- Estrogen and testosterone patches for post-menopausal women
- Selegiline patch for depression in the elderly and cocaine addiction
- Clonidine transdermal for the treatment of delerium in trauma patients
- Dexamethasone iontophoretic delivery for the treatment of tennis elbow
- An iontophoretic sumatriptan patch for migraine treatment, and
- Transdermal glyceryl trinitrate for acute stroke therapy, to name a few.

Despite some disadvantages, transdermal drug delivery offers many advantages capable of improving patient health and quality of life. 1\textsuperscript{st} and 2\textsuperscript{nd} generation TDDS offer these advantages but are limited in the scope of molecules that can be delivered through the skin. Exciting technologies exist that have the potential to transform TDDS in the near future and offer even more clinical advantages to the patient.

**Bibliography**


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