INTRODUCTION

Sonophoresis is defined as the application of ultrasound to the skin resulting in enhanced transdermal transport of molecules. Low frequency sonophoresis or ultrasound is defined as sonophoresis or ultrasound at a frequency that is less than 2.5 MHz, more typically less than 1 MHz, more preferably in the range of 20 to 100 kHz. The transdermal delivery of biologics—as well as of conventional drugs—is growing in popularity because the technique offers numerous advantages. It reduces pain, bio hazardous waste, and risk of infection. Most importantly, needle-free drug delivery generally increases patient compliance. The present paper highlights the recent advancements in the field of sonophoresis, its mechanism and applications. Transdermal drug delivery (TDD) has several significant advantages compared to oral drug delivery, including elimination of pain and sustained drug release. However, the use of TDD is limited by low skin permeability due to the stratum corneum (SC), the outermost layer of the skin. Sonophoresis is a technique that temporarily increases skin permeability such that various medications can be delivered noninvasively. For the past several decades, various studies of sonophoresis in TDD have been performed focusing on parameter optimization, delivery mechanism, transport pathway, or delivery of several drug categories including hydrophilic and high molecular weight compounds. Based on these various studies, several possible mechanisms of sonophoresis have been suggested. For example, cavitation is believed to be the predominant mechanism responsible for drug delivery in sonophoresis. This review presents details of various studies on sonophoresis including the latest trends, delivery of various therapeutic drugs, sonophoresis pathways and mechanisms, and outlook of future studies.
Recently there has been an increased interest in using iontophoretic technique for the transdermal delivery of medications, both ionic and nonionic. This article is an overview of the history of iontophoresis and factors affecting iontophoretic drug transfer for the systemic effects and laws for development of Transdermal delivery system are discussed.

There are numerous methods of administering drugs to the body, both passive and active. Active methods include the use of penetration enhancers and assisted drug delivery. One of them is sonophoresis (phonophoresis). This term is used to describe the effects of ultrasound on the movement of drugs through intact living skin and into the soft tissues. Although the exact mechanism of sonophoresis is not known, drug absorption may involve a disruption of the stratum corneum lipids allowing the drug to pass through the skin. In the future, drug release systems aided by ultrasound may be able to provide slow release of vaccines. Researchers are currently exploring the applications in various areas like cutaneous vaccination, transdermal heparin delivery, transdermal glucose monitoring, delivery of acetyl cholinesterase inhibitors for the treatment of Alzheimer's disease, treatment of bone diseases and Peyronie's disease and dermal exposure assessment. The possibilities seem endless. Drug administration through skin patches, with the advent and development of ultrasound-mediated transdermal transport, may soon become the name of the game. Besides, taking into account the varied possible applications of sonophoretic transdermal drug transport in the fields of biotechnology and genetic engineering, we can envision a whole gamut of newer technologies and products in the foreseeable future.

The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from bypassing the first metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes and transit times can all be eliminated. In the development of new transdermal drug delivery devices the aim is to obtain controlled, predictable and reproducible release of drugs into the blood stream of the patient. The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of the skin, delivery of the drug is more reproducible leading to smaller inter and intrasubject variations, since the drug release from the device can be controlled accurately than the permeability of the skin.

The method of iontophoresis was described by Pivati in 1747. Galvani and Vota two well known scientists working in the 18th century combined the knowledge that the electricity can move different metal ions and the movement of the ions produce electricity. The method of
administering pharmacological agents by iontophoresis became popular at the beginning of 20th century due to the work of Leduc (1900) who introduced the term iontotherapy and formulated the laws for this process.

Iontophoresis is defined as the introduction, by means of a direct electrical current of ions of soluble salts into the tissue of the body for therapeutic purposes. It is a technique used to enhance the absorption of drugs across biological tissues such as the skin.

Sonophoresis is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages. Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. It is widely used in hospitals to deliver drugs through the skin. Pharmacists compound the drugs by mixing them with a coupling agent (gel, cream, ointment) that transfers ultrasonic energy from the ultrasound transducer to the skin. The ultrasound probably enhances drug transport by cavitation, microstreaming, and heating. Sonophoresis is also used in Physical Therapy. In addition to its effects in delivering compounds into the skin, sonophoresis is being investigated as a way of drawing compounds such as glucose out of the skin. During the AAPS National Biotechnology Conference in Boston, held June 19–21, a session entitled “Transdermal Delivery of Proteins,” explored some of the more popular technologies being used today. Among them are iontophoresis, sonophoresis (ultrasound), and microneedles. All of these approaches enhance transdermal drug delivery by increasing skin permeability and allowing the transmission of large molecules. Sonophoresis, or ultrasound, creates holes in the skin, and allows fluids to travel into or out of the body. “When sound is emitted at a particular frequency, the sound waves disrupt the lipid bilayers,” said Mitragotri. He pointed out that the ideal ultrasound frequency range for the transdermal delivery of biologics is 50-60 KHz. “The higher the frequency, the more dispersed the transmission,”
MECHANISM

There are numerous methods of administering drugs to the body, both passive and active. Active methods include the use of penetration enhancers and assisted drug delivery. One of them is sonophoresis (phonophoresis). This term is used to describe the effects of ultrasound on the movement of drugs through intact living skin and into the soft tissues. Although the exact mechanism of sonophoresis is not known, drug absorption may involve a disruption of the stratum corneum lipids allowing the drug to pass through the skin. In the future, drug release systems aided by ultrasound may be able to provide slow release of vaccines. Researchers are currently exploring the applications in various areas like cutaneous vaccination, transdermal heparin delivery, transdermal glucose monitoring, delivery of acetyl cholinesterase inhibitors for the treatment of Alzheimer's disease, treatment of bone diseases and Peyronie's disease and dermal exposure assessment. The possibilities seem endless. Drug administration through skin patches, with the advent and development of ultrasound-mediated transdermal transport, may soon become the name of the game.

Sonophoresis or ultrasound can be used to create holes in the skin for fluids to travel into or out of the skin. By emitting sound at a particular frequency, the sound waves disrupt the lipid-bilayer of the stratus corneum (outermost layer of skin which has the most barrier properties), creating more and larger microchannels in the skin. Drugs can be administered through these channels, but this project will primarily use this to draw up fluids.

The effects of ultrasound on extracting interstitial fluid (ISF) have been determined by various experiments on rats, cadavers, and human volunteers. Studies showed that low frequency ultrasound (~20 kHz) increased the permeability of the skin by many orders of magnitude better than high frequency ultrasound. Ultrasound treatment at 20 kHz with an intensity of 7 W/cm^2 for less than 1 minute increased skin permeability for up to 15 hours.
There is no pain or damage to the skin associated with this procedure, though it may slightly heat the tissue. However, further studies assessing the safety of ultrasound after repeated extractions are still required. A low strength vacuum need to be applied for approximately five minutes to extract an adequate amount of interstitial fluid for making glucose measurements. The ultrasound device can be battery powered and be about the size of a deck of cards. Studies showed that low frequency ultrasound can be used to deliver insulin (sonophoresis). Ultrasound enables efficient continuous transdermal monitoring - combined with other techniques, it can decrease the time for extracting ISF to less than 1 minute. The role played by each individual phenomenon associated with application of ultrasound to the skin and its relative importance in sonophoresis is elucidated below.

1. Cavitation

Cavitation involves the generation and oscillation of gaseous bubbles in a liquid medium and their subsequent collapse when such a medium is exposed to a sound wave, which may be an ultrasound. It can generate violent micro streams, which increase the bioavailability of the drugs. Cavitation occurs due to the nucleation of small gaseous cavities during the negative pressure cycles of ultrasound, followed by the growth of these bubbles throughout subsequent pressure cycles. Whenever small gaseous nuclei already exist in a medium, cavitation takes place preferentially at those nuclei. This cavitation leads to the disordering of the lipid bilayers and formation of aqueous channels in the skin through which drugs can permeate. The minimum ultrasound intensity required for the onset of cavitation, referred to as cavitation threshold, increases rapidly with ultrasound frequency. The most commonly used ultrasound conditions for sonophoresis (frequency 1–3 MHz, intensity 0–2 W/cm²) are called the therapeutic ultrasound conditions. But as cavitation effects vary inversely with ultrasound frequency, it was found that any frequency lower than that corresponding to therapeutic ultrasound was more effective in enhancing TDT. This is a direct consequence of reduced acoustic cavitation (formation, growth, and collapse of gas bubbles) at high ultrasound frequencies. Application of ultrasound generates oscillating pressures in liquids and nucleates cavitation bubbles. At higher frequencies it becomes increasingly difficult to generate cavitation due to the fact that the time between the positive and negative acoustic pressures becomes too short, diminishing the ability of dissolved gas within the medium to diffuse into the cavitation nuclei. The number and size of cavitation bubbles is inversely correlated with application frequency. For example, application of ultrasound at 20 kHz induced transdermal transport enhancements of up to 1000 times higher.
than those induced by therapeutic ultrasound. Experiments on effect of ultrasound on the transdermal estradiol transport under a variety of conditions showed that cavitation might play an important role in the observed ultrasound-mediated transdermal transport enhancement. Cavitation may occur either inside the skin (in particular, inside the SC), outside the skin or in both the domains.[20]

2. Cavitation inside the Skin as a Possible Sonophoresis Mechanism

Cavitation occurs in a variety of mammalian tissues, including muscle, brain and liver, upon exposure to ultrasound in different conditions. This occurrence of cavitation in biological tissue is attributed to the existence of a large number of gas nuclei. These nuclei are gas pockets trapped in either intracellular or intercellular structures. It has been shown that cavitation inside the skin plays a dominant role in enhancing transdermal transport upon ultrasound exposure. Cavitation inside the SC can potentially take place in the keratinocytes or in the lipid regions or in both. Since the effects of ultrasound on transdermal transport depend strongly on the dissolved air content in the surrounding buffer and because most of the water in the SC is present in the keratinocytes, it can be said that cavitation inside cavitation the SC takes place in the keratinocytes (fig 4). Oscillations of the ultrasound-induced cavitation bubbles near the keratinocyte–lipid bilayer interfaces may, in turn, cause oscillations in the lipid bilayers, thereby causing structural disorder of the SC lipids. Shock waves generated by the collapse of cavitation bubbles at the interfaces may also contribute to the structure disordering effect. Because the diffusion of permeants through a disordered bilayer phase can be significantly faster than that through a normal bilayer, transdermal transport in the presence of ultrasound is higher than passive transport. This, in essence, is the mechanism of sonophoresis.

3. Cavitation outside the Skin as a Possible Sonophoresis Mechanism

Cavitation in the saline surrounding the skin does occur after ultrasound exposure. These cavitation bubbles can potentially play a role in the observed transdermal transport enhancement. Firstly, these bubbles cause skin erosion, following their violent collapse on the skin surface, due to generation of shock waves, thereby enhancing transdermal transport. Secondly, the oscillations and collapse of cavitation bubbles also cause generation of velocity jets at the skin–donor solution interface, referred to as microstreaming. These induce convective transport across the skin, thereby enhancing the overall transdermal transport.
Experimental findings suggest that cavitation outside the skin does not play that important a role in sonophoresis4,2

4. Thermal Effects
The increase in the skin temperature resulting from the absorbance of ultrasound energy may increase the skin permeability coefficient because of an increase in the permeant diffusion coefficient. A temperature increase of 10°C causes a twofold increase in the estradiol skin permeability. Because the typical skin temperature increase in case of therapeutic sonophoresis is ~7°C, it can be concluded that thermal effects are a non-significant phenomenon as they cannot explain the 13-fold increase in estradiol skin permeability.

5. Role of Convective Transport in Sonophoresis
Fluid velocities are generated in porous medium exposed to ultrasound due to interference of the incident and reflected ultrasound waves in the diffusion cell and oscillations of the cavitation bubbles. Fluid velocities generated in this way may affect transdermal transport by inducing convective transport of the permeant across the skin, especially through hair follicles and sweat ducts. Experimental findings suggest that convective transport does not play an important role in the observed transdermal enhancement.[4]

6. Role of Mechanical Stresses in Sonophoresis
Ultrasound is a longitudinal pressure wave inducing sinusoidal pressure variations in the skin, which, in turn, induce sinusoidal density variation. At frequencies greater than 1 MHz, the density variations occur so rapidly that a small gaseous nucleus cannot grow and cavitative effects cease. But other effects due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium, may continue to occur. Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayer permeability this increase is, however, non significant and hence mechanical effects do not play an important role in therapeutic sonophoresis. Thus cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport.
AN OVERVIEW OF IONTOPHORESIS

Iontophoresis is the method where the movements of ions across a membrane enhanced using an externally applied potential difference. When the membrane under consideration is skin, the method is called transdermal iontophoresis. The principle barrier to the transport of the molecules into an across the skin is stratum corneum (SC), this is the uppermost layer of the epidermis with a thickness of between 10-100 μm. The SC consists of several layers of corneocytes (a nucleate keratin filled cells) inlaid in a lipid matrix, a continuous medium through the SC, arranged mainly in bilayers. The intercellular lipids consist of approximately equal quantities of ceramides, cholesterol and free fatty acids.

Percutaneous absorption may take place simultaneously by any combination of the three main pathways that include; the intercellular (paracellular) pathway between the conneocytes along the lamellar lipids, the intracellular (transcellular) pathway through the cells or the appendageal (shunt) pathway via hair follicles, sweat ducts and secretary glands.

Ions prefer the routes of the least electrical resistance; in the SC this is believed to be via the pores. Some investigations indicate that these pores are sweat glands, others that transport occurs through both hair follicle and sweat glands.

The physicochemical properties of the molecules have an effect on the contribution of the follicular and non follicular routes of penetration. Hydrophilic molecules tend to localize in the hair follicles, whereas lipophilic molecules are mostly distributed in the lipid intercellular regions of the SC and the lipid membranes of the epidermal keratinocytes. Since passive transdermal permeation of the majority of the drugs needs enhancement to achieve clinically relevant plasma concentrations, both chemical and physical enhancement methods have been developed. Iontophoresis is one of the physical methods.
In iontophoresis, cationic or neutral therapeutic agents are placed under an anode or anionic therapeutic agents under a cathode. When a low voltage and low current density is applied, according to simple electrorepulsion, ions are repelled into and through the skin. Cationic drugs are driven into and through the skin by the anode (active electrode), which also extracts anion from the tissue underneath the skin into the anode. At the cathode (return electrode) anionic buffer ions are driven into the skin and cations from the tissues are extracted into the cathode. It is also possible to include an additional charged drug in the return electrode to be delivered simultaneously or to use a mixture of drugs in the active electrode to enhance the desired effect or to increase skin permeation, depending on which drugs/molecules are used.

**Transdermal iontophoretic system**

More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery. There are three major enhancing mechanisms for drug flux through the skin, of which iontophoresis (also known as electrorepulsion, or electromigration or the Nernst-Planck effect) is just one. The other mechanisms are electoroosmotic flow and current induced increase in skin permeation, also known as damage effect. Electroosmotic flow is a flux or bulk fluid induced by a voltage difference across a charged membrane; it is always in the same direction as the flow of counter ions. Since human skin is negatively charged under physiological conditions, the counter ions are cations and the electroosmotic flow is thus from anode to cathode. Therefore, the cathodic delivery of anions is hindered and the anodic delivery of cations is assisted by electrosmosis.

The improved movement of neutral molecules under iontophoresis is based on electrosmosis. Ions are influenced by all of the above mechanisms so that electrosmosis has a positive contribution to the transport of cations and a negative contribution to the transport of anions under normal physiological conditions. The impact of electrosmosis on ion transfer increases with the size of the ion. The contribution of electrosmosis can be so significant that the delivery of large anion from the anodic compartment can be more efficient than delivery from cathode, this is called wrong-way iontophoresis.

The electrorepulsion effect gives the largest enhancement to the flux of small lipophilic cations. When the concentration of the ionic drug is very high, so that the drug carries most of the current, electrosomotic flow has a very small effect on the drug flux.
Transdermal iontophoresis has been used for both local and systemic drug delivery. Applications include local delivery of anaesthetics (e.g. lidocaine) steroids and retinoids to treat acne scarring for the relief of palmar and plantar hyperhidrosis and the administration of pilocarpine in the diagnosis of cystic fibrosis. Other applications of transdermal iontophoresis include the administration of antiinflammatory drugs e.g. ketoprofen, in to subcutaneous tissues and joints. Iontophoretic delivery of several systemic drugs is still under investigation. These include the analgesic, fentanyl, a reversible cholinesterase inhibitor, tacrine III and several formulations of insulin The symmetrical nature of iontophoresis, where ions are driven both into and out of the body, has been utilized for extracting information from the body without the need for blood sampling.

**HISTORY OF TRANSDERMAL DELIVERY SYSTEM**

The first proposal for the use of electric current in the drug delivery dates from the mid 18\textsuperscript{th} century. Serious progress was made in the 19\textsuperscript{th} century notably by Benjamin Ward Richardson (1828-1896), Hermann Munk (1839-1912), William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (born 1868). Administration of metal ions as well as alkaloids was tried at that time. Until the early 20\textsuperscript{th} century, current medicated drug delivery was known as “cataphoresis”. Frankenhauser is said to have introduced the term “iontophoresis” before 1908. Recently researchers talk about “electrically-assisted transdermal drug delivery”. The technique was never widely adopted but always proved useful to some extent in solving particular drug delivery problems.

Twenty two years ago, the first transdermal drug delivery system was introduced in the US making a historic breakthrough, holding the promise that new compounds could be delivered in a safe, convenient way through this skin. And yet, during the last two decades, the
commercial success of transdermal delivery has been slow to develop. But, as a spate of newer products and technologies move towards the marketplace, transdermal drug delivery seems to have arrived.

America’s first commercially marketed transdermal patch used a passive mode of drug delivery that permitted the drug to diffuse through the avascular dermis to the deep dermis, allowing local action or penetration to the capillaries for a systemic effect. But these passive systems had limitations. This approach depended on the drug’s properties to facilitate transport through the skin by using a simple concentration gradient as a driving force. Also, few drugs were available with the right physicochemical properties to make good candidates for transport through the skin. Even with these limitations, passive transdermal patches are experienced ever-increasing acceptance today.

While passive transdermal technology grows in popularity, all the available transdermal delivery systems use passive technology. Passive technology has always depended on the physicochemical properties of the drug candidate, large molecule drugs, such as, proteins and peptides, could not be considered. But, advances in the research have led to a better understanding of the physiology of the skin and more familiarity with the drug transport characteristics.

FACTORS AFFECTING IONTOPHORESIS TRANSPORT
Many factors have been shown to affect the results of iontophoresis. These include the physicochemical properties of the compound (molecular size, charge, concentration), drug formulation (types of vehicle, buffer, pH, viscosity, presence of other ions), equipment used (available current range, constant vs. pulsed current, type of electrode), biological variations (skin site, regional blood flow, age, sex), skin temperature and duration of iontophoresis. The following factors have to be considered

Influence of pH
The pH is of importance for the iontophoretic delivery of drugs. The optimum is a compound that exists predominantly in an ionized form. When the pH decreased, the concentration of hydrogen ion increases and a vascular reaction (vasodilatation) is initiated because of C-fiber activation, thus it is important to keep the pH as close as possible to and, at least when working with vasodilators, at pH 5.5 and below. There is an increasing risk for vascular reaction due to the high concentration of hydrogen ions rather than the compound used. Since
hydronium ions are small they penetrate the skin more easily than larger drug ions. Laboratory findings vary on the effect of pH and drug behavior. According to the Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum IP, it is desired to have a relatively large proportion of the drug in the ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient.

**Current strength**

There is a linear relation between the observed fluxes of a 1-cm², the current is limited to 1 mA due to patient comfort considerations. This current should not be applied for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non-specific vascular reactions (vasodilatation) increases. At a current of 0.4-0.5 mA/cm² such a vascular reaction is initiated after a few seconds of iontophoresis with deionised or tap water. This latter effect is probably due to current density being high enough a small area to stimulate the sensory nerve endings, causing reactions such as the release of substance P from C-fiber terminals.

**Current density**

Current density is the quantity of current delivered per unit surface area. The following criteria should be considered in selecting proper current densities for IP. The current should be sufficiently high to provide a desired drug delivery rate. It should not produce harmful effects to the skin. There should be a quantitative relationship between the applied current. The drug should be electrochemically stable.

**Ionic competition**

In a solution of sodium chloride, there is an equal quantity of negative (Cl⁻) and positive (Na⁺) ions. Migration of a sodium ion requires that an ion of the opposite charge is in close vicinity. The latter ion of opposite charge is referred as a counter-ion. An ion of equal charge but of different type is referred as a co-ion. When using iontophoresis, it is important to know that pH adjustment is performed by adding buffering agents. The use of buffering agents as co-ions, which are usually smaller and more mobile than the ion to be delivered results in a reduction of the number of drug ions to be delivered through the tissue barrier by the applied current. In our example, this means that when a positively charged drug is diluted in saline, the sodium ions will compete with the amount of drug ions to be delivered. Ideally, the use of
a buffer system should be avoided in iontophoresis, but if this is not possible, alternative buffers, consisting of ions with low mobility or conductivity are preferred.

**Drug concentration**

Depending on the drug used, the steady-state flux (ion movement) has been shown to increase with increasing concentration of the solute in the donor compartment, i.e. in the delivery electrode. Increased uptake by the skin during and after IP with an increase in drug concentration has been reported. A limiting factor to be considered is the strength of the current used. At higher drug concentration, probably because of the saturation of the boundary layer relative to the donor bulk solution (Phillips *et al.* 1989).

**Molecular size**

It has been shown that the permeability coefficients in positively charged, negatively charged and uncharged solutes across human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases. However, there are certain solutes with a relatively high molecular size (e.g. insulin, vasopressin and several growth hormones), which have also been to penetrate the skin barrier into the systemic circulation.

**Connective or electro-osmotic transport**

When performing iontophoresis with a specific current, the flow of ions across the membrane induces a flow of solvent called electro-osmosis. Compared to the ion transport, the electro-osmotic contribution is small. The penetration of uncharged substances (e.g. bovine serum albumin) has been shown to be facilitated by the volume flow effect induced by an applied potential difference across the membrane. Iontophoresis has also been observed to enhance the penetration of a number of dipolar ions (zwitter ionic substances like phenylalanine). Most of these substances have been shown to be delivered in significantly higher amounts by
anodic delivery than by cathodic delivery. In general, iontophoresis is more effective for charged compounds, especially monovalent ions.

**Current-continuous vs. pulsed mode**

Application of a continuous current over a long period of time can modulate iontophoresis delivery. Continuous DC current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery in proportion to the length of current application. This polarization can be overcome by using pulsed DC, a direct current that is delivered periodically. During the ‘off time’ the skin becomes depolarization using pulsed DC can, however, decrease the efficiency of pulsed transport if the frequency is too high. Enhanced iontophoretic transport has been reported for peptides and proteins by using pulsed DC compared to convenient DC. Most of the drug ions used for diagnostic purposes in combination with iontophoresis and LDPM are small in size. As a result, the time needed for an effect is relatively short (5-20 s) compared to when iontophoresis is used for therapeutic purposes (20-40 min).

**Physical factors**

Iontophoresis reduces intra and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments in vivo iontophoretic give support for clinical findings that there are small differences in the flux rate following transdermal iontophoresis between males and females, as well as between hairy and hairless skin. The status of the vascular bed is also important; for instance, a pre-constricted vascular bed decreases the flux through the skin while a dilated vascular bed increases the yield of the drug through the skin.

**Drug salt form**

It has been reported that different salt forms have different specific conductivities and that conductivity experiments in vitro will provide information concerning the general suitability of a drug for IP. The salt form of drugs must be considered along with the pH of the solution for determining the amount of drug in the ionized state.

**Patient anatomical factors**

Patient anatomical factors that influence the depth of penetration that is variable from patient to patient include skin thickness at the site of the application, presence of subcutaneous adipose tissue and the size of other structures, including skeletal muscle. Additionally, the
presence and severity of inflammation can influence drug penetration due to the increased temperature (which may increase and may serve to transport the drug throughout the body.

**Type of matrix containing the drug, gel vs. solutions**
The migration of the drug under the influence of the electrical current will be different as the matrices are different. This can be related to differences in viscosities, material electrical charge and porosities.

**Stability of the drug during the IP process**
The drug undergoing IP must be stable in the solution environment up to the time of Ip and also during the iontophoresis process. Oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will complete with the drug ion and reduce the overall trans membrane rate of the drug.

**Laws for the development of transdermal drug system**
Transdermal drug delivery systems follow the general law of developing and evolving according to an “S-Curve” profile (the plot of a major index of the system performance versus time). All transdermal systems consist of four essential parts, an energy source, a sub-system that transmits system energy to those locations where it is required for performance, the part (or parts) that actually accomplish the main function of the system, and, a control system that monitors and controls system functioning. These four essential parts need to be complete in order for the system to function at a high level. A most important aspect of the further development of transdermal drug delivery systems will be breakthroughs in how effectively energy is transmitted throughout the system. There are six measures of ideality of transdermal drug delivery systems. These can be used as predictive gauges to indicate where a particular transdermal delivery system is on its S-curve and the next developmental design step. Transdermal drug delivery systems of the future will minimize human involvement, and will even include additional features and functions previously requiring human actions. There will always be a specific sub-system that represents the largest opportunity for system development. This opportunity can be identified by through the use of technical innovation algorithm (TIA). Transdermal drug delivery systems developed by traditional approaches will become far more complex in their construction (this is not true for TIA-developed systems, which stress system and elegance). An important developmental direction that transdermal drug delivery systems will take is the path of increasing flexibility, controllability,
directability and adjustability. Major breakthroughs in transdermal drug system designs will occur because of the introduction of new, modified energy sources (detailed information about this law may not be provided because of its highly proprietary nature). There is a law that defines the relationship between transdermal drug delivery systems and other existing and new systems. Next generation transdermal drug delivery systems will show improved degrees of coordination among certain system parts, and intentional dis-coordination among other system parts. The purpose of this coordination or dis-coordination by design is to achieve significant breakthroughs in o

APPLICATIONS
Besides, taking into account the varied possible applications of sonophoretic transdermal drug transport in the fields of biotechnology and genetic engineering, we can envision a whole gamut of newer technologies and products in the foreseeable future. An ultrasonic transducer that operates in flexure mode provides a highly efficient and compact sonophoresis device. Such a device is particularly useful for efficiently enhancing permeation of a substance through a membrane, such as dermal and mucosal membranes for purposes of transdermal/transmucosal drug delivery and/or body fluid monitoring. Many conventional sonophoresis devices have been developed and they are categorized into basic types, namely the disk-type and the horn-type. The literature review has shown that these devices have three major drawbacks: low efficiency, “dead” drug solution, and high electrical power consumption. Transdermal drug delivery offers an attractive alternative to injections and oral medications. However, applications of transdermal drug delivery are limited to only a few drugs as a result of low skin permeability. Application of low-frequency ultrasound enhances skin permeability, a phenomenon referred to as low-frequency sonophoresis. In this method, a short application of ultrasound is used to permeabilize skin for a prolonged period of time. During this period, ultrasonically permeabilized skin may be utilized for drug delivery. In addition, a sample of interstitial fluid or its components may be extracted through permeabilized skin for diagnostic applications.

REFERENCES


