AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

A review on Sonophoresis Mediated Transdermal drug delivery system

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ABSTRACT

Transdermal drug delivery offers an attractive alternative to the conventional drug delivery methods of oral administration and injection. However, the stratum corneum acts as a barrier that limits the penetration of substances through the skin. Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the skin. Ultrasound has been used extensively for medical diagnostics and to a certain extent in medical therapy (physiotherapy, ultrasonic surgery, and hyperthermia). The generation of ultrasound and mechanism of sonophoresis with particular emphasis on the role of cavitation (both inside and outside the skin), thermal effects, convective transport, and mechanical effects also included. There are certain findings in the field of sonophoresis, namely transdermal drug delivery and transdermal monitoring. The article also encompasses a discussion on the variation of sonophoretic enhancement from drug to drug, possible applications of sonophoresis in near future, some commercially available sonophoretic systems and future trends. Particular attention is paid to proposed enhancement mechanisms and future trends in the field of cutaneous vaccination and gene delivery.

Key words: Ultrasound, Sonophoresis, Transdermal, Stratum corneum, cavitation, thermal effects, convective transport, and mechanical effects, Hyperthermia.

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Received 16 March 2011, Accepted 1 May 2012

Please cite this article in press as: Modi SB *et al.*, A review on Sonophoresis Mediated Transdermal drug delivery system. American Journal of PharmTech Research 2012.

INTRODUCTION

Transdermal Drug Transport

The skin represents an extraordinary evolutionary feat. Not only does it physically encapsulate the organism and provide a multi-functional interface between it and its surroundings, but also it is perpetually engaged in the construction of a highly efficient homeostatic barrier. It provides impedance to TDT due to the stratum corneum (SC)—the skin's outermost dead layer (Figure 1). It comprises of densely packed disc-like keratinocytes that are abnucleate keratinised cells and are separated by multicellular lipid bilayers which function as cement (Figure 1). The keratinocytes are 50% (v/v) water-filled and the lamellar lipid region between two keratinocytes typically consists of 10 lipid bilayers (Figure. 1C). That confers an impermeable character to the SC due to multiple alterations of hydrophilic and lipophilic elements. [1,2]

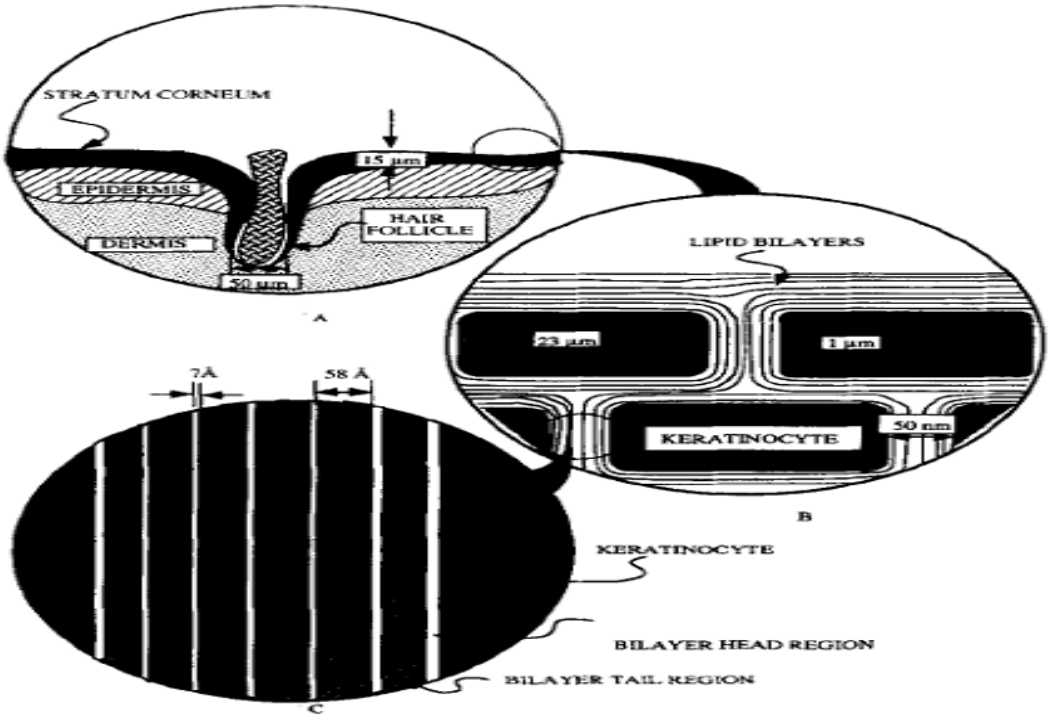


Figure 1: Schematic sketch of various transdermal transport pathways. Major pathway comprises the intercellular lipid bilayers. (A) Three principal layers of the skin. (B) Blown-up section of SC. (C) Details of intercellular lipid bilayers. [1]

SONOPHORESIS

Sonophoresis is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages. Sonophoresis is a localized, non-invasive, convenient and rapid method of delivering low molecular weight drugs as well as macromolecules into the skin.[3] Mechanistically, sonophoresis is considered to enhance

drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue. [4] Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. 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, micro streaming, and heating. Sonophoresis is also used for drawing compounds such as glucose out of the skin. "Transdermal Delivery of Proteins," explored some of the more popular technologies being used today. Among them are iontophoresis, sonophoresis (ultrasound), and micro needles. 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,".[4,5]

Sonophoresis: A Historical Perspective

The first published report on sonophoresis dates back to 1950s. Fellinger and Schmidt reported successful treatment of polyarthritis of the hand's digital joints using hydrocortisone ointment with sonophoresis.[6] It was subsequently shown that hydrocortisone injection combined with ultrasound ''massage'' yielded better outcome compared to simple hydrocortisone injections for bursitis treatment. [7] Cameroy reported success using carbocaine sonophoresis for closed Colle's fractures.[8] In a series of publications Griffin et al. showed improved treatment of elbow epicondylitis, bicipital tendonitis, shoulder osteoarthritis, shoulder bursitis and knee osteoarthritis by combined application of hydropcortisone and ultrasound.[9-12] Improved dermal penetration using ultrasound was also reported for local anesthetics.[13-15] Studies demonstrated that ultrasound enhanced the percutaneous absorption of methyl and ethyl nicotinate.[16,17] by disordering the structured lipids in the stratum corneum. Similar conclusions were reached by Hofman and Moll who studied the percutaneous absorption of benzyl nicotinate.[18] While several investigators reported positive effect of ultrasound on drug permeation, lack of an effect of ultrasound on skin permeation was also reported in certain cases.[19] Levy et al. showed that 3–5 min of ultrasound exposure (1 MHz, 1.5 W/cm^2) increases transdermal permeation of mannitol and physostigmine across hairless rat skin in vivo by up to 15-fold.[20] Mitragotri et al. reported in vitro permeation enhancement of several low-molecular weight drugs under the same ultrasound conditions.[21] Bommannan et al. hypothesized that since the absorption coefficient of the skin varies directly with the ultrasound frequency, high frequency ultrasound energy would concentrate more in the

epidermis, thus leading to higher enhancements. In order to assess this hypothesis, they studied the effect of high-frequency ultrasound (2–16 MHz) on permeability of salicylic acid (dissolved in a gel) through hairless guinea pig skin in vivo.[17,22] They found that a 20 min application of ultrasound (0.2 W/cm^2) at a frequency of 2 MHz did not significantly enhance the amount of salicylic acid penetrating the skin. However, 10 MHz ultrasound under otherwise the same conditions resulted in a 4-fold increase and 16 MHz ultrasound resulted in about a 2.5-fold increase in transdermal salicylic acid transport.[17,18]

Advantages of using sonophoresis as a physical penetration enhancer

• Enhanced drug penetration (selected drugs) over passive transport.[23]

• Allows strict control of transdermal penetration rates.[23]

• Low risk of introducing infection as the skin remains intact.[23]

• Reduction of dosing frequency and patient compliance.[24,25]

• Improved control of the concentrations of drugs with small therapeutic indices.[24,25,26]

• Reduction of fluctuations in plasma levels of drugs.[24,25]

• Avoids hepatic first pass elimination and gastrointestinal irritation.[24,25]

• Substitutes oral administration when the route is unsuitable as in case of vomiting, diarrhea.[26]

• Permit both local and systemic effects and Less risk of systemic absorption than injection.[23,25]

• Easy termination of drug delivery in case of toxicity, through termination of ultrasound.[23,25]

Disadvantages of using sonophoresis as a physical penetration enhancer

• Stratum corneum must be intact for effective drug penetration.[23]

• Can be time consuming to administer.[23]

• Minor tingling, irritation and burning have been reported (controlled by adjustment of ultrasound).[23,27]

GENERATION OF ULTRASOUND

Ultrasound is a sound possessing frequencies above 20 kHz.[28,29] These waves are characterized by two main parameters frequencies and amplitude. Amplitude of ultrasound can be represented in the terms of peak wave pressure (in Pascal's) or in the terms of intensity (in the units W/cm2). Ultrasound can be applied either continuously or in a pulsed manner. Ultrasound is generated using a device referred to as a sonicator. It consists of an electrical signal generated which generates an electrical AC signal at the desired frequency and amplitude. This signal is applied across a piezo-electrical crystal (transducer) to generate ultrasound the thickness of the operating frequency. Sonicators operating at various frequencies in the range of 20 kHz to 3 MHz are

available commercially and can be used for sonophores. Duch sonicators operating at frequencies of 10 MHz and 16 MHz have been assembled by Bommannan et al.[30] For sonophoresis delivery, the desired drug is dissolved in a solvent and applied on the skin. Ultrasound is applied by contacting the transducer with the skin through a coupling medium to ensure a proper contact between the transducer and the skin. (fig. 2) This medium can be the same as the solvent used to dissolve the drug or it can be a commercially available ultrasound coupling gel (for e.g. Aquasonic, Polar, NJ) There are three distinct sets of ultrasound conditions based on frequency range and applications[31]:

- High-frequency or diagnostic ultrasound in clinical imaging (3–10 MHz).
- Medium-frequency or therapeutic ultrasound in physical therapy (0.7–3.0 MHz).
- Low-frequency or power ultrasound for lithotripsy, cataract emulsification, liposuction, cancer therapy, dental descaling and ultrasonic scalpels (18–100 kHz).

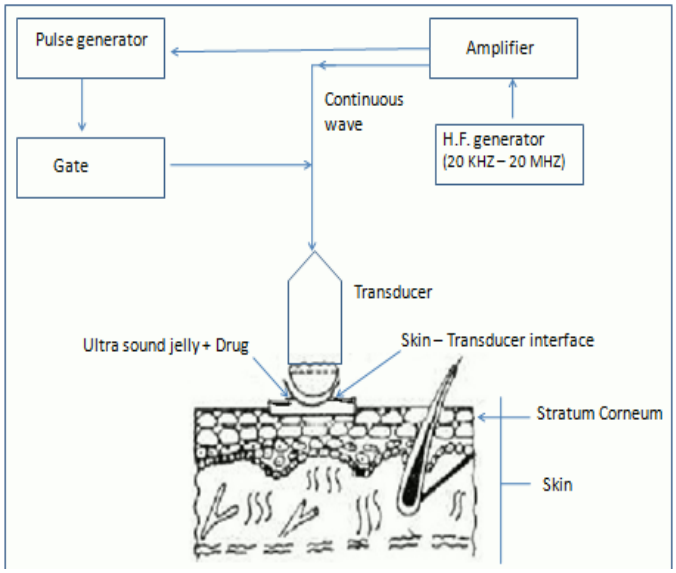


Figure 2: Electrical block diagram in ultrasonic generation system

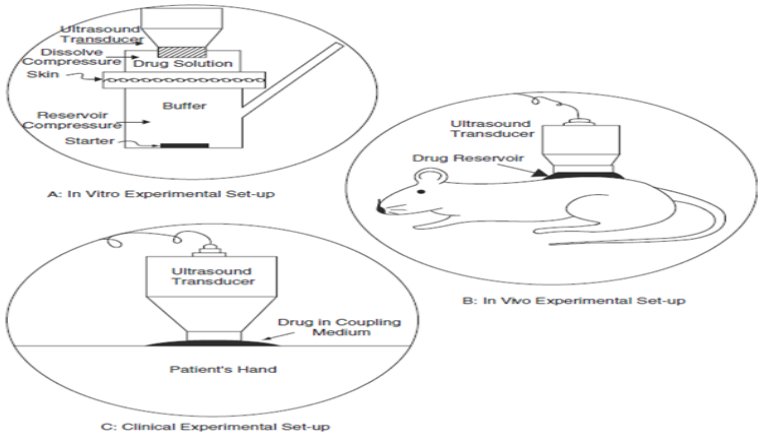


Figure 3: Experimental set up for sonophoresis delivery

Ultrasound–tissue interaction

The three major factors that govern sonophoretic drug delivery are the physicochemical properties of the drug formulation, the ultrasound parameters and the skin (Fig. 4).[32] Sonophoretic drug delivery is likely to be influenced by the structure and physiological changes in the skin, the vehicle used to deliver the drug, and the quantum of energy and the duration for which this energy is provided. Though the structure and physicochemical properties of the drug will influence the permeation rate. As the ultrasound energy interacts with the tissue it traverses, it will be encounter changes in density, pH and chemical constituents in the different layers.[33] These changes are not only mechanical effects but also relate to electrical conductivity, sonochemical changes and thermal effects. Since ultrasound is a form of energy, it will undoubtedly interact with the viable as well as dead layers of the skin. Histopathological studies are the best way to explore configurational changes in skin layers after ultrasound treatment. Sonophoretic enhancement has been observed and explained by several investigators over the years.[34-37] The complexity of the skin structure and the changes in tissue property vis a´ vis ultrasound inputs play important roles in transdermal drug delivery. Structural changes in the skin barrier layer are the result of various acoustic phenomena taking place at the skin–transducer junction, such as refraction, reflection, absorption and scattering. This leads to cause–effect phenomena like perturbation of bio membrane lipid–protein configurations, bubble formation, cavitation and even micro-streaming after long exposures at high intensities of ultrasound exposure.

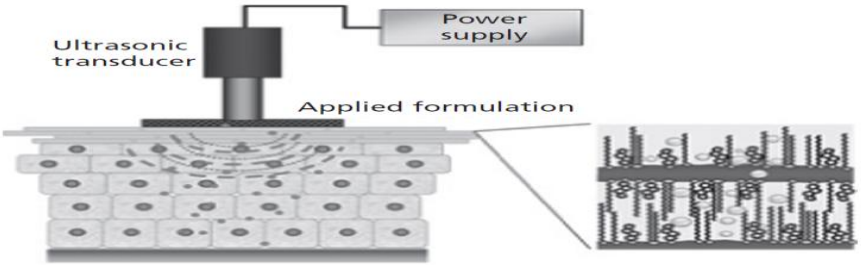


Figure 4: Sonophonetic drug delivery.

Drug is placed on the skin beneath the ultrasonic probe. Ultrasound pulses are passed through the probe, and it is hypothesised that drug molecules move into the skin by a combination of physical wave pressure and permeabilisation of intercellular bilayers.[32]

Biological Effects Of Ultrasound

Ultrasound over a wide frequency range has been used in medicine for the past century. For example, therapeutic ultrasound has been used for physical therapy; low frequency ultrasound

has been used in dentistry and high frequency ultrasound has been used for diagnostic purposes. The utility of ultrasound is continuously expanding and new clinical applications are constantly being developed, including the use of high-intensity focused ultrasound for tumour therapy,[38] lithotripsy,[39] ultrasound-assisted lipoplasty[40] and ultrasonic surgical instruments.[41,42] Ultrasound affects biological tissues via three main effects: thermal, cavitational and acoustic streaming.

Thermal Effects

Absorption of ultrasound increases temperature of the medium. Materials that possess higher ultrasound absorption coefficients, such as bone experience severe thermal effects compared with muscle tissue, which has a lower absorption coefficient.[31] The increase in the temperature of the medium upon ultrasound exposure at a given frequency varies directly with the ultrasound intensity and exposure time. The absorption coefficient of a medium increases directly with ultrasound frequency resulting in temperature increase. A recent study suggested the use of a new safety parameter, time to threshold (TT). TT indicates the time after which a threshold temperature rise is exceeded, and how long a piece of tissue can be safely exposed to ultrasound, provided the safe threshold is known.[43]

Cavitational Effects

Cavitation is the formation of gaseous cavities in a medium upon ultrasound exposure. The primary cause of cavitation is ultrasound-induced pressure variation in the medium. Cavitation involves either the rapid growth and collapse of a bubble (inertial cavitation), or the slow oscillatory motion of a bubble in an ultrasound field (stable cavitation).[44] The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity. Cavitation might be important when low-frequency ultrasound is used, gassy fluids are exposed or when small gas-filled spaces are exposed.

Acoustic Streaming Effects

Acoustic streaming is the development of unidirectional flow currents in fluid that are the result of the presence of sound waves. The primary cause of acoustic streaming is ultrasound reflections and other distortions that occur during wave propagation.[45] Oscillations of cavitation bubbles might also contribute to acoustic streaming. The shear stresses developed by streaming velocities might affect the neighboring tissue structures. Acoustic streaming might be important when the medium has an acoustic impedance that is different from that of its surroundings, the fluid in the biological medium is free to move or when continuous wave application is used. Nightingale et al used acoustic streaming to help distinguish cystic from solid presence or absence of acoustic streaming as an indicator of whether a lesion was cystic or solid.[46] Shi et al.

used acoustic streaming detection as a tool for distinguishing between liquid blood and clots or soft tissue in haematoma diagnosis.[47]

MECHANISMS OF SONOPHORESIS

Although considerable attention has been given to the investigation of sonophoresis in the past years, its mechanisms were not clearly understood, reflecting the fact that several phenomena may occur in the skin upon ultrasound exposure. These include:

• Cavitation (generation and oscillation of gas bubbles).

• Thermal effects (temperature increase).

• Induction of convective transport.

• Mechanical effects (occurrence of stresses due to pressure variation induced by ultrasound).[48]

Cavitation effects

Cavitation is the formation of gaseous cavities in a medium. The primary cause of cavitation is ultrasound - induced pressure variation in the medium.[23] It is of 2 types: [23,49-51]

1. **Inertial cavitation:** The rapid growth and collapse of a bubble.
2. **Stable cavitation:** The slow oscillatory motion of a bubble in an ultrasound field.

Collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue. Ultrasound can generate violent microstreams, which increase the bioavailability of the drugs. Tissues contain air pockets that are trapped in the fibrous structures that act as nuclei for cavitation upon ultrasound exposure. The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity.[23,51,52,53] 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.[54,55] 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,[23] fig.5 shows the mechanism of ultrasound induced cavitation.

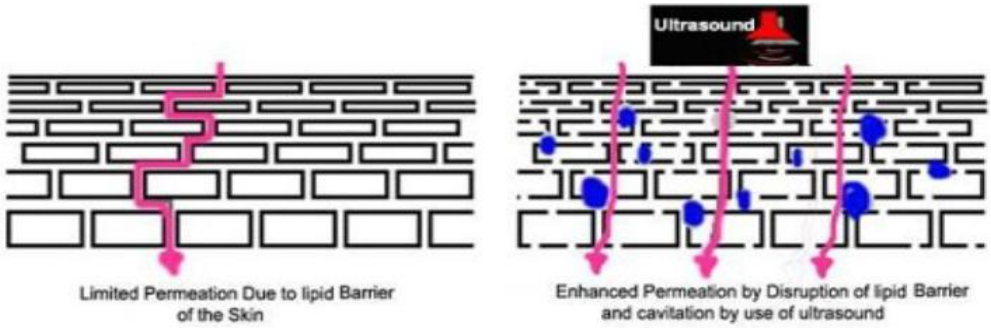


Figure 5:Enhanced transdermal permeation by cavitation upon application of ultrasound[26]

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.[53] Cavitation inside the SC can potentially take place in the keratinocytes or in the lipid regions or in both. Since the effects of ultra sound on transdermal transport depends 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. 6). 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.[4]

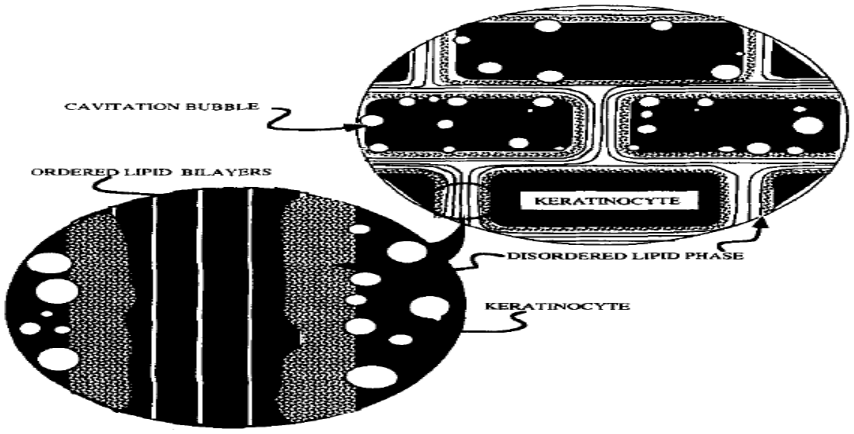


Figure 6: Schematic sketch of cavitation occurring in the keratino-cytes.

Cavitation occurs preferentially at the interface between the keratinocytes and the lipid bilayers.fig is reproduced from ref.[4]

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 micro streaming. 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 sonophoresis.[4,22]

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. Convective Transport

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. Mechanical effects

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 cavitational 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.

COMMERCIALLY AVAILABLE SONOPHORETIC SYSTEMS

- **PatchCap and Ustrip:**

In June 2005, Dermisonics obtained the patent for the ultrasonic Patch-Cap and a flexible patch for transdermal delivery of drugs via ultrasound. The U-Strip is a drug delivery system

incorporating a transdermal patch in combination with microelectronics and ultrasonic technology. It has been designed to facilitate the needle-free delivery of drugs with large molecular structures, such as Insulin into the bloodstream.[3,56]

- **Sonoderm Technology:**

The sonoderm is a device based on the generation of low frequency ultrasounds waves acting on a vibratory and thermal way, this technology is called ultrasonotherapy. Many drugs, particularly large molecules such as insulin, are not absorbed by the oral route and have to be injected frequently, in these cases the sonoderm technology, ultrasound assisted transdermal drug transport, is useful. ImaRx has developed novel ultrasound enhanced transdermal drug delivery systems.[3,57] ImaRx is now developing Sonolysis in which MRX-801 microbubbles and ultrasound waves are used to disperse the blood clots and restore blood flow.[3,45,56]

- **SonoPrep:**

Sontra Medical Corporation is the pioneer of SonoPrep, a non-invasive and painless ultrasonic skin permeation technology. The medical device, uses an ultrasonic method to make skin temporarily more permeable. The small, battery powered device applies a low-frequency, ultrasonic energy to the skin for 15 seconds. Sontra is investigating the delivery of several large proteins and peptides by incorporating the use of the SonoPrep device in combination with transdermal patches to deliver the drug transdermally.[3,56] Sontra Medical is also developing a vaccine against dengue fever.[56]

- **Microlysis:**

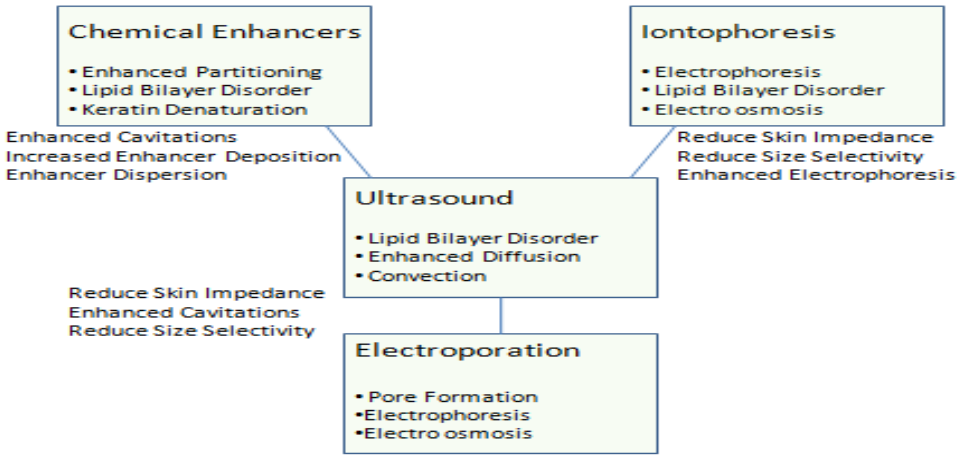
The Microlysis developed by Ekos is designed to deliver ultrasound and thrombolytic (clot-dissolving) drug directly into the area of a brain clot. Ekos developed the EkoSonic Endovascular System (EkoSonic ES) with rapid pulse modulation for the dissolution of vascular blood clots. This is the only endovascular system that can deliver microsonic energy and thrombolytic drugs simultaneously, providing a safer, faster and more complete way to remove clots by accelerating dissolution. The EkoSonic ES recently received approval by the US Food and Drug Administration.[3,56]

SYNERGETIC EFFECT WITH OTHER ENHANCERS

While low-frequency ultrasound has been shown to enhance transdermal drug transport, its combinations with other enhancers have been shown to be more effective compared to ultrasound alone. Low-frequency ultrasound has been shown to synergistically enhance skin permeability with chemical enhancers and iontophoresis.

Ultrasound and Chemicals

Mitragotri et al. performed an evaluation of the synergistic effect of low-frequency ultrasound (20 kHz) with SLS.[58] Application of SLS alone as well that of ultrasound alone both increased skin permeability. Application of SLS alone for 90 min induced about 3-fold increase in mannitol permeability, while application of ultrasound alone for 90 min induced about 8-fold enhancement. However, when combined, application of ultrasound from 1% SLS solution induced about 200-fold increase in skin permeability to mannitol. Ultrasound also reduced the threshold ultrasound energy required to induce a detectable change in skin permeability. Specifically, in the absence of surfactants, the threshold ultrasound energy for producing a detectable change in skin impedance was about 141 J/cm^2. Addition of 1% SLS to the solution decreased the threshold to about 18 J/cm^2.[59]



Ultrasound and Iontophoresis

Synergy between low-frequency ultrasound and iontophoresis is expected since they enhance transdermal transport through different mechanisms. Indeed, this combination has been found to enhance transdermal transport better than each of them alone. Specifically, Le et al. performed an investigation of the synergistic effect of ultrasound and iontophoresis on transdermal transport using a model drug, heparin.[59] Ultrasound was applied only once to each skin piece (along with 1% solution of dodecyl pyridinium chloride) for about 10 min prior to application of iontophoresis. The enhancement of heparin flux due to ultrasound + iontophoresis treatment was about 56-fold. This enhancement was higher than the sum of those obtained during ultrasound alone (3-fold) and iontophoresis alone (15-fold). Thus, the effect of ultrasound and iontophoresis on transdermal heparin transport was truly synergistic.

FUTURE TRENDS

Vaccination

In recent years, the potential for exploiting the skin for purposes of vaccination has received a great deal of attention.[60-64] Transcutaneous immunization provides access to the immune system of the skin, which is dominated by densely distributed and potent antigen presenting cells (Langerhans cells). Langerhans cells have been shown to play essential roles in the induction of Tcell- mediated immune reactions against a wide variety of antigens.[64,66] In order for this technique to be practical, the vaccine, which is generally a large molecule or complex, has to penetrate the stratum corneum barrier. Normally, skin is not permeable under these conditions. Glenn et al. found that applying cholera toxin to the surface of the skin stimulates an immune response to vaccine compounds such as diphtheria or tetanus toxoids.[67]

Gene Therapy

Another future application for ultrasound as a topical enhancer, which seems to show promise, lies in the field of topical gene therapy.[68,69] Gene therapy is a technique for correcting defective genes that are responsible for disease development, most commonly by replacing an 'abnormal' disease-causing gene with the 'normal' gene. A carrier molecule (vector) is usually used to deliver the therapeutic gene to the target cell. The identification of genes responsible for almost 100 diseases affecting the skin has raised the option of using cutaneous gene therapy as a therapeutic method.[70] The most obvious candidate diseases for cutaneous gene therapy are the severe forms of particular genodermatoses (monogenic skin disorders), such as epidermolysis bullosa and ichthyosis. Other applications might be healing of cutaneous wounds such as severe burns and skin wounds of diabetic origin.[71]

BEYOND TOMORROW

Sonophoretically enhanced TDT promises to radically change the way in which we inject drugs in the near future. The efficacy of low-frequency ultrasound in enhancing the transdermal transport of high-molecular weight proteins like insulin, as well as of low molecular weight drugs makes it a potential non-invasive substitute for injections. For example in the delivery of heparin and low-molecular-weight heparin, both of which are the most commonly used anticoagulant for treatment of venous thromboembolism, or in the delivery of anesthetics or drugs like ibuprofen.[72,73] With further research, patients may soon possess small pocketsize sonicators used to 'inject' drugs whenever required. Furthermore, these devices could be coupled with sensors that can monitor drug concentrations in the blood to formulate a self controlled drug delivery method that can potentially eliminate patient compliance.[74,75] A possible model for the pocket size sonicator could be consisting of a protective covering enclosing a battery driven

electronic ultrasound emitter that is strapped on the wrist.[76,77] The patient compliance can be monitored by labeling the drug with, say, fluorophore and incorporating detection mechanisms for receiving and recording the signals generated. This method may, particularly, be a boon for haemophiliacs. Patients suffering from this condition require frequent intravenal injections of the various clotting factors to reduce the severity of their ailment and to boost their recovery from injuries. Ultrasound mediated TDT via skin patches provides a sustained delivery of the drug over a Period of about 7 days, it eliminates the danger posed by the administration of, say, cancer chemotherapeutic agents. These toxic agents can cause even death when given at dosages that are needed to be effective. (Chemical sound energy for the treatment of cancer is a new field termed as 'Sonodynamic Therapy').[78] Today there are more than 125 million diabetics worldwide. Diabetics need to monitor and inject insulin to keep their blood sugar normal but blood glucose monitoring today is very inconvenient and painful. With the introduction of sonicated TDT, we could provide the diabetics a steady supply of insulin and the associated sensors could easily carry out frequent self-monitoring of glucose levels reducing the inconvenience associated with conventional methods of finger lancing.[72,76,79,80] Researchers are currently exploring the applications of low-frequency sonophoresis in various areas like vaccination, transdermal heparin delivery and glucose monitoring, and 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.[80]

Recovery Of The Skin Barrier Properties After Sonophoresis

Numerous reports exits to suggest that application of therapeutic ultrasound (1-3 MHz, 0-2W/cm2) does not induce any irreversible change in the skin permeability to drugs in vivo. Quantitative measurement of estradiol transport across human skin (in vitro) have also shown that application of therapeutic ultrasound (1 MHz, 2W/cm2) does not induce any statistically significant irreversible change in skin barrier properties. Similar studies have also been performed using very low frequency ultrasound (20 kHz, 125mW/cm2, 100ms pulse applied every second) to assess whether application of low frequency ultrasound result in any permanent loss of the barrier properties of skin measured in terms of water permeability. It has been found that in the case of a 1 h long ultrasound exposure, the skin permeability to water measured within 2h postexposure was comparable to the passive skin permeability 2 h post-exposure was about 6times higher than the passive permeability to water. However, this value contained to decrease, and was within a factor of 2 of the passive skin water permeability 12 h post-exposure. Studies have also been performed to assess whether application of higher frequency ultrasound induces

any irreversible damage to the barrier properties of the skin measured in terms of trans-epidermal water loss (TEWL) across hairless mice skin exposed to high frequency ultrasound (16 MHz). No significant difference in TEWL values of the skin exposed to ultrasound and that not exposed to ultrasound was found.

APPLICATIONS OF SONOPHORESIS

There are certain applications of sonophoresis technique in the transdermal drug delivery system are given as follows:

- Ultrasound helps in treatment of wide varieties of sports injuries such as tennis elbow, tendon problems, repairing damaged ligaments, muscle spasms, stiff joints, fractured bones and cartilage. Also used in healing of wounds, damaged skin, skin rejuvenation, nerve stimulation, and improving the strength and elasticity of scar tissues.[53,56,81,82]
- Ultrasound with Topical Anesthesia rapidly decreases pain of intravenous cannulation.
- Low-frequency ultrasonic gene delivery.[52,56,82]
- The dolphin therapy arouses a great interest in the whole world, since it causes analgesic effects, removal of depression, and improvement of learning abilities of the children suffering from autism.[83]
- Sonophoresis is also being used in drug enhancement in granulomas and tumors.[26,81,82]
- sonophoresis is being investigated as a way of extracting compounds such as glucose.[26]
- In the treatment of sick fish by University of Maryland's Center of Marine Biotechnology. The current method uses intraperitoneal injections which are costly and highly labour intensive. In this experiment, ultrasound was applied to water containing fish and compound of interest. The ultrasound waves increases the permeability of compound into the tissues of the skin and gills. This method is highly cost and labour effective.[48]
- Sonophoresis also used in treatment of glaucoma, corneal infection and nail delivery, to increase the permeability of drugs.[56]

CONCLUSION

Application of ultrasound enhances transdermal drug transport, a phenomenon referred to as sonophoresis. Proper choice of ultrasound parameters including ultrasound energy dose, frequency, intensity, pulse length, and distance of transducer from the skin is critical for efficient sonophoresis. The numerous attempts made over the last 50 years can be classified into three categories; therapeutic frequency high frequency and low frequency ultrasound; the first

represents the most commonly used ultrasound condition for sonophoresis although recently attention has been more focused on low and high frequency condition. Mechanism experiments performed by several investigation suggest that cavitation disorganizes the lipid bilayers of the skin through which enhanced transport of drugs may occur. Various studies have indicated that application of ultrasound under conditions used for sonophoresis does not cause any permanent damage to the skin or underlying at definite conclusion more work is required before arriving at definite conclusion regarding the safety of ultrasound exposure. Low-frequency sonophoresis has been shown to increase skin permeability to a variety of low- as well as highmolecular weight drugs including insulin and low molecular weight heparin. Ultrasound mediated enhancement of transdermal transport is mediated by inertial cavitation. Collapse of cavitation bubbles near the stratum cornuem is hypothesized to disrupt its structure due to cavitation-generated shock waves or microjets. Ultrasound also works synergistically with several other enhancers including chemicals and iontophoresis.

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