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Review Article

SONOPHORESIS: AN EMINENT ADVANCEMENT FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

Transdermal drug delivery is an alternative approach in comparison with conventional oral drug delivery systems. However, the stratum corneum, the outermost layer of the skin, 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. The generation of ultrasound and mechanism of sonophoresis with particular emphasis on the role of cavitation, convective transport, and mechanical effects also included. There are certain findings in the field of sonophoresis, namely transdermal drug delivery and transdermal monitoring. Ultrasound has been extensively used for medical diagnostics and to a certain extent in physiotherapy, ultrasonic surgery, and hyperthermia. The article also includes a brief discussion on the variation of sonophoretic enhancement from drug to drug, possible applications of sonophoresis in near future, and several commercially available sonophoretic systems.

Key words: Ultrasound; Sonophoresis; Transdermal; Stratum corneum; Hyperthermia.

1. Introduction

Transdermal therapeutic systems are those therapeutic systems that are self contained, discrete dosage forms which, when applied to the intact skin, deliver the drugs, through the skin, at a controlled rate to the systemic circulation and this delivery system offers an advantageous alternative to common delivery methods such as injections or oral delivery[1]. However, applications of transdermal delivery are limited by low skin permeability. Specifically, stratum corneum (SC), the outermost layer of the skin, provides an outstanding barrier against the external environment and is responsible for skin's barrier properties. SC is a relatively thin (10–15 μm) impermeable membrane that consists of flat, dead cells that are filled with keratin fibers (corneocytes) surrounded by lipid bilayers. The highly ordered structure of lipid bilayers confers upon the SC an impermeable character[2-7]. Different techniques, such as chemical enhancers, iontophoresis, electroporation, and ultrasound (sonophoresis) have been used to enhance transdermal drug transport[2, 4, and 8].

Sonophoresis is a phenomenon that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages by ultrasonic energy[9]. Sonophoresis is a localized, non-invasive, convenient and rapid method of delivering low molecular weight drugs and macromolecules into the skin[10]. Mechanistically, sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue[5]. Ultrasound at various frequencies in the range of 20 kHz–16 MHz with intensities of up to 3W/cm^2 has been used for sonophoresis[8, 11]. Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the later being the most important[12]. Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. Ultrasound mediated transdermal delivery of key compounds was first reported in 1954 by Fellinger and Schmid through successful treatment of digital polyarthritis using hydrocortisone ointment in combination with ultrasound[13].

Sonophoresis is the technique that is widely used in hospitals to deliver drugs through the skin. Thus, Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the the skin[14]. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis[15].

1.1 Advantages of using sonophoresis as a physical penetration enhancer

- Low risk of introducing infection as the skin remains intact.
- Allows strict control of transdermal penetration rates.
- Not immunologically sensitizing[16].
- Reduction of dosing frequency and patient compliance.
- Reduction of fluctuations in plasma levels of drugs[15, 17].

- Improved control of the concentrations of drugs with small therapeutic indices[14-15, 17].
- Permit both local and systemic effects[17].
- Less risk of systemic absorption than injection.
- Less anxiety provoking and painful than injection.
- Easy termination of drug delivery in case of toxicity, through termination of ultrasound[15-16].

1.2 Disadvantages of using sonophoresis as a physical penetration enhancer

- Stratum corneum must be intact for effective drug penetration.
- Can be time consuming to administer.
- Minor tingling, irritation and burning have been reported (controlled by adjustment of ultrasound) [16, 18].

2. Ultrasound

In 1877, Lord Rayleigh published the fundamental physics of sound vibrations, transmission and refraction in "The Theory of Sound", thereby providing a foundation for modern acoustics[19]. Ultrasound is a mechanical wave that traverses in the direction of propagation (i.e. longitudinal in nature) and causes vibrating disturbances in the media. Variation induces displacement on the particles at right angles to the direction of propagation which generates modulating pressure on the particles with symmetric zones of compressions and rarefactions, as shown in fig.1, sound can't exist in vacuum[20].

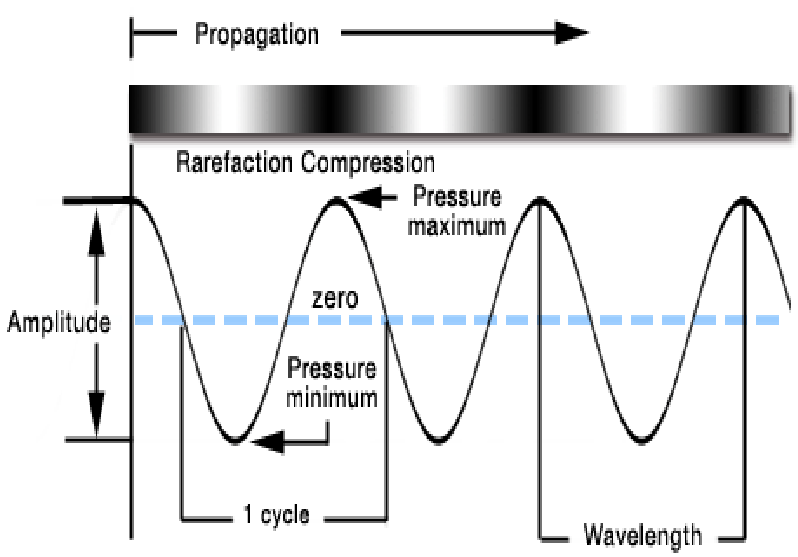

Fig.1: shows a schematic representation of wave propagation[21]

Sound waves travel through gases, liquids and solids by compressions and rarefactions. In liquids and gases, sound propagates as longitudinal waves, resulting in regions of high and low density because the molecules in the medium vibrate in the same direction as the wave. In solids transverse or shear waves are also present, where particle motion is perpendicular to the direction of wave propagation[19, 22], as shown in fig.2.

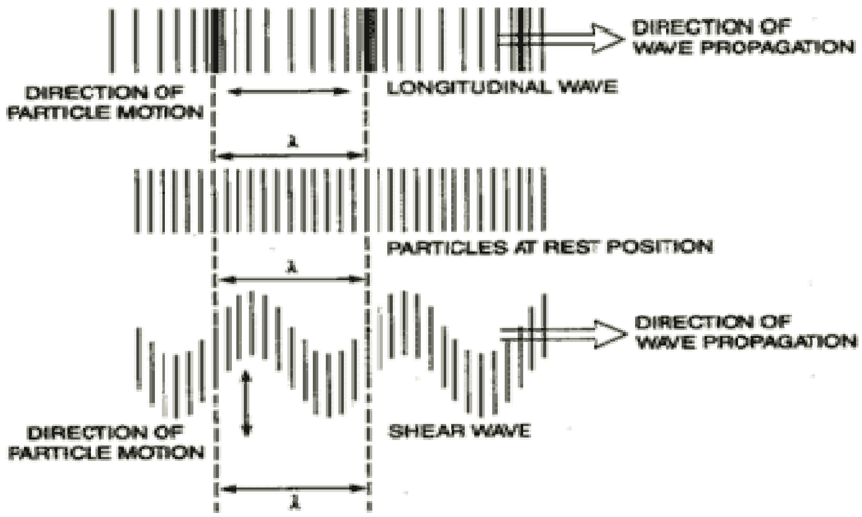

Fig.2. shows a schematic representation of both types of wave propagation[22]

The intensity is progressively lost when a sound wave passes through the body or is deviated from its initial direction, a phenomenon referred to as *attenuation*[16]. As the frequency increases the vibration amplitude falls, and attenuation increases. All the energy is dissipated over a short distance. Thus, the wavelength of US plays a significant role in drug delivery system[20].

The resistance of the medium to the propagation of sound wave is dependent on the acoustic impedance (*Z*), which is related to the mass density of the medium (ρ) and the speed of propagation (*C*), according to Equation 1:

$$Z = \rho \times C \text{ ………eq. 1}$$

The specific acoustic impedances for skin, bone and air are 1.6 × 106, 6.3 × 106 and 400.0 kg/ (m^2 s), respectively.

As ultrasound energy penetrates the body tissues, biological effects can be expected to occur if the tissues absorb the energy. The absorption coefficient (*a*) is used as a measure of the absorption in various tissues.

For ultrasound consisting of longitudinal waves with perpendicular incidence on homogeneous tissues, Equation 2 applies:

$$I(x) = I_0 \times e^{-ax} \ldots\ldots\ldots\ldots eq.\ 2$$

Where $I(x)$ is the intensity at depth x, I_0 is the intensity at the surface and a is the absorption coefficient. To transfer ultrasound energy to the body it is necessary to use a contact medium because of the high impedance of air[23].

3. Mechanism of Generation of Ultrasonic Waves

Ultrasonic waves are generated by the phenomenon known as *piezoelectric effect*, in which the high frequency, alternating, electric current applies across a quartz or silicone dioxide crystal, or across certain polycrystalline materials such as lead- zirconate- titanate (PZT) and barium titanate. The crystal undergoes rhythmic deformation due to electric current, producing ultrasonic vibrations. In the process of ultrasonic wave generation, electric energy is converted into mechanical energy in the form of oscillations, which generates acoustic waves[3, 14, 16, 19, 23-25]. The electrical block diagram of the generation system is given in fig.3. Ultrasound can be applied either continuously or in a pulsed manner.

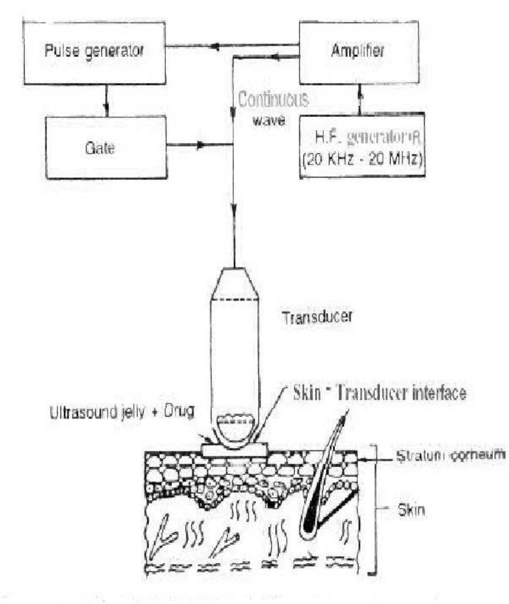

Fig.3: Electrical block diagram in the ultrasonic generation system[20].

4. VARIOUS TYPES OF MECHANISM FOR 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) [26]

➢ **Cavitation effects**

Cavitation is the formation of gaseous cavities in a medium ultrasound exposure. The primary cause for cavitation is ultrasound -induced pressure variation in the medium[16]. It is further of 2 types [6, 8, 13, 16]:

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. The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity[13, 16].

At higher frequencies it becomes 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 [3-4]. For example, application of ultrasound at 20 kHz induced transdermal transport enhancements of up to 1000 times higher than those induced by therapeutic ultrasound[27]. Fig.4 showing the mechanism of ultrasound induced cavitation.

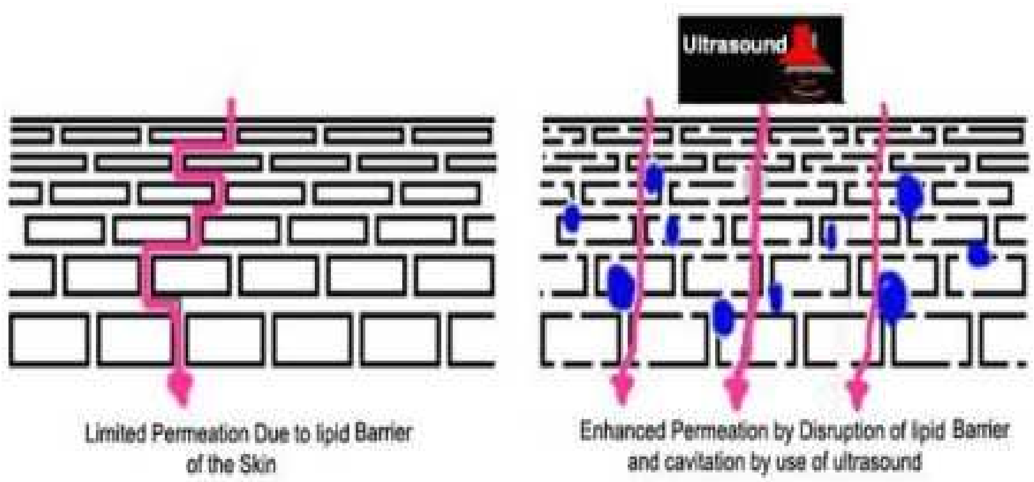

Fig.4: Enhanced transdermal permeation by cavitation upon application of ultrasound[14]

- **Thermal effects**

Ultrasound does not pass through tissues with 100% efficiency. During its propagation, the ultrasound wave is partially scattered and absorbed by the tissue medium, resulting in attenuation of the emitted wave. The lost energy is converted into heat, while the remainder of the wave penetrates into and propagates through the medium[24].

- **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. Experimental findings suggest that convective transport does not play an important role in the observed transdermal enhancement[26].

- **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. Thus, cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport[16].

5. DEPENDENCE OF SONOPHORETIC SKIN PERMEABILISATION ON ULTRASOUND

- **Frequency:** Attenuation of an acoustic wave is inversely proportional to its frequency, and thus as the frequency increases, the ultrasound penetrates less deeply into the skin[28]. Low-frequency ultrasound (f~20 kHz) is significantly more potent in enhancing skin permeability compared to therapeutic ultrasound (f~1-3 MHz)[4].

- **Intensity:** The skin conductivity increases with increasing intensity, but upto a certain point, and then drops off. This is due to the increase in the total energy put into the system with increasing ultrasound intensity. The linearity between skin conductivity and ultrasound intensity may break down at higher intensities (I >15 W/cm^2) due to other effects such as 'acoustic decoupling' which is a phenomena where cavitation generated near the ultrasound source results in the formation of large number of gaseous cavities, thus reducing the amount of energy delivered to the system[29].

  The intensity $\boldsymbol{I}$ is directly dependent on the acoustic energy $\boldsymbol{E}$ emitted and the speed of sound $\boldsymbol{c}$ in the medium, according to Equation 3:

  $$\boldsymbol{I = c\,E} \quad \text{……..eq. 3}$$

  Energy $\boldsymbol{E}$ is itself dependent on the density of the propagation medium $\boldsymbol{r}$, on the total pressure $\boldsymbol{p}$ (equal to the sum of the atmospheric pressure and the pressure created by the ultrasound wave) and on the speed of sound $\boldsymbol{c}$, as Equation 4 shows:

  $$\boldsymbol{E = p^2/rc^2} \text{………… eq. 4}$$

  The employed intensities usually lie between 0.5 and 2 W/cm [28].

- **Mode:** Ultrasound can be applied in continuous or pulsed (sequential) mode. The rise in temperature is faster and more intense with the continuous mode. Hikima et al. (1998) have shown an increase of transdermal diffusion of prednisolone in vitro by 2-5 fold when increasing the exposure time from 10 to

60 min with 1 MHz ultrasound at intensity 4.3 W/cm² in continuous mode[30]. The pulsed mode is frequently used because it reduces the severity of side effects such as thermal effects. Boucaud et al. (2001) have shown the more effectiveness of pulsed mode in increasing transdermal penetration of fentanyl [31].

- **Threshold energy:** Skin conductivity enhancement is directly proportional to the incident ultrasound energy density. There exists a threshold ultrasound energy below which the effect of ultrasound on skin conductivity cannot be detected, and beyond the threshold value the conductivity increases with the energy density.

$$E = \textit{intensity} \times \textit{exposure time} \times \textit{duty cycle} \quad \text{……….eq. 5}$$

In other words, regardless of the intensity (higher than the cavitation threshold intensity), exposure time, and duty cycle used in experiments, the effect of ultrasound on skin permeability is similar if the total energy density delivered to the skin is maintained constant (eq.5). The threshold energy density for affect permeability is about 222 J /cm^2. The magnitude of the threshold depends on the skin itself and may vary between different skin models [29].

6. VARIATION IN ENHANCEMENT OF SONOPHORESIS FOR VARIOUS DRUGS

The observed enhancement for a particular drug depends significantly on the physicochemical and pharmacokinetic properties of the permeant, and hence varies from drug to drug. Another factor of great importance in the selection of drugs is their biological half-life; the lower the half-life, the faster the rate at which steady state levels in blood are attained[26]. The sonophoretic enhancement of transdermal drug transport can be quantitatively predicted based on knowledge of two physiochemical properties of the drug: passive skin permeability, P^{P} and octanol–water partition coefficient, $K_{o/w,}$ using the following Equation 6:

$$e \sim \frac{K_{o/w}^{0.75}}{(4 \times 10^4)\, P^{P}} \quad \text{…………eq. 6}$$

Where '*e*' is the relative sonophoretic transdermal transport enhancement defined as: [(sonophoretic permeability / passive permeability) -1]. The drugs having a predicted *e* value smaller than 1 exhibit no sonophoretic enhancement (e.g., Lidocaine and salicylic acid) whereas all those having a predicted *e* value equal to or greater than 1 do exhibit sonophoretic enhancement (e.g., Hydrocortisone and indomethacin) [32]. The drugs passively diffusing through the skin at a slow rate are most enhanced by the application of ultrasound [26].

7. MARKETED PRODUCTS

- **Microlysis:** The Microlysis developed by Ekos is designed to deliver ultrasound and thrombolytic (clot-dissolving) drug directly into the area of a brain clot. The Microlysis device is a miniature catheter that is inserted into an artery in the brain until it reaches the clot. Drug is infused through the catheter to the tip, where a tiny ultrasound transmitter is located. The ultrasound and drug are designed to be administered simultaneously because it has been shown that ultrasound energy induces a temporary change in the structure of a clot that allows the drug to penetrate more efficiently into the inner reaches of the blockage[25].
- **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. ImaRx is now developing Sonolysis in which MRX-801 microbubbles and ultrasound waves are used to disperse the blood clots and restore blood flow[33].
- **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. The sound waves open small cavities in the skin by disorganizing the lipid bi-layer, creating tiny, reversible channels through which fluids can be extracted and delivered. The skin goes back to its normal state within 24 hours. 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 [10, 25]. Sontra Medical is also developing a vaccine against dengue fever [25].
- **Patch-Cap and U-strip:** 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[10, 25].

8. USES OF SONOPHORESIS

There are certain applications of sonophoresis technique in the transdermal drug delivery system as mentioned in table 1. And some are given as follows:

- Sonophoresis also used in treatment of glaucoma and corneal infection, to increase the permeability of drugs.
- Ultrasound can also be used for nail delivery of drugs [25].
- 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 [26].
- 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, skin rejuvenation, nerve stimulation, and improving the strength and elasticity of scar tissues [3, 25, 34-35].
- Sonophoresis is used in the treatment of damaged skin[3]. Process of cavitation takes place during the treatment but the cavities disappear after the treatment and histological examination has shown that the skin is normal after treatment.
- Hormone delivery [3, 25].
- Low-frequency ultrasonic gene delivery [3, 25, 35].
- Ultrasound is used for Calcific Tendinitis of the shoulder [3].

- The dolphin therapy and sonophoretic model[3]. 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 [36].
- In surgery it helps in incision (dissection), welding (connection), built-up (regeneration), and treatment of biological tissues [1, 14].
- Sonophoresis is also being used in drug enhancement in granulomas and tumors [1, 14, 34-35].
- In addition to its effect in delivering compounds into the skin, sonophoresis is being investigated as a way of extracting compounds such as glucose [14, 37].

Table -1: Research on uses of sonophoresis to administer different drugs through the Skin.

Compound	**Formul-ation**	**Experimental conditions**	**Membrane used**	**Results**	**Refere nce**
Aldosterone (either ^3H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm², 100msec pulses applied every sec	Human cadaver skin *In vitro*	1400-fold increased in concentration of drug in skin	5
Arnica montana	Gel	1 MHz, 0.5 W/cm², P	Rat skeletal muscle	The massage with arnica gel proved to be an effective anti-inflammatory on acute muscle lesion in topic use, also show the ineffectiveness of Arnica Montana sonophoresis	38
Butanol (either ^3H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm², 100msec pulses applied every sec	Human cadaver skin *In vitro*	29-fold increased in concentration of drug in skin	5
Caffeine	Solution in pH 7.4 phosphate buffer	40 KHz, 0.44 W/cm², C	Hairless mouse skin *In vitro*	4-fold increased in concentration of drug in skin	39
Caffeine	Drug diluted in saline	20 KHz, 2.5 W/cm², P	Human and hairless rat skin	Transdermal transport of drug was enhanced by both	31

	solution	20 KHz, 2.5 W/cm²,	*In vitro*	continuous and pulsed mode	
Calcein & D_2O	Calcein dissolved in PBS	41-445 KHz, 60-240 mW/cm², 30 min	Excised hairless rat skin *In vitro*	The calcein flux was increased by 22.3-, 6.3-, and 3.8-fold at frequencies of 41, 158, and 445 KHz respectively	40
Corticosterone (either ^3H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm², 100msec pulses applied every sec	Human cadaver skin *In vitro*	80-fold increased in concentration of drug in skin	5
Cyclosporin A	Suspension	20 KHz, 0.8 W/cm², P	Rat skin *In vitro*	7-fold increased in concentration of drug in skin	41
Digoxin	Tritiated Digoxin	3.3 MHz, 1-3 W/cm², C	Human and hairless mice skin *In vitro*	Treatment at 3 W/cm^2 significantly increased absorption of digoxin across mouse skin but no enhancement across human skin	42
Doxorubicin	Micellar-encapsulated doxorubicin	20,476 KHz, 1 W/cm², 15 min treatment	Rats *In vivo*	Application of ultrasound in combination with drug therapy was effective in reducing tumor growth rate, irrespective of which frequency was employed	43
EMLA	Cream	1 MHz, 1 W/cm², 10 min treatment	Human volunteers	10, 30, 60-min EMLA application and sonophoresis aided EMLA application were statistically better than control. The sonophoresis aided EMLA application was not satisfactory as compared to the 60 min application of EMLA cream	44
Estradiol	Solution	20 KHz,	Human	3-fold increased in	5

(either ^3H or ^{14}C labelled)	of the radiolabelled permeant in PBS	125mW/cm², 100msec pulses applied every sec	cadaver skin *In vitro*	concentration of drug in skin	
Fentanyl	Solution in PBS	20 KHz, 2.5 W/cm², P 20 KHz, 2.5 W/cm², C	Human and hairless rat skin *In vitro*	Pulsed mode was found to be more effective in increasing penetration of fentanyl	31
Heparin	Solution of Heparin	20 KHz, 7 W/cm², P	Pig skin *In vitro*	21-fold increased in concentration of drug in skin	45
Hyaluronan	Solution	1 MHz, 0.4 W/cm², 10 min treatment	Rabbit *In vivo*	Synovial fluid analysis revealed increased absorption and fluorescence microscopy showed deeper penetration of both HA1000 and HA3000, more so with the latter	46
Ibuprofen	Cream	1 MHz, 1 W/cm², C	Human (Target knee joint) *In vivo*	Ibuprofen phonophoresis found to be effective and generally well tolerated after 10 therapy sessions but it was not superior to conventional ultrasound in patients with knee osteoarthritis	47
Indomethacine	Ointment	1 MHz, 0.25,0.5,0.75, 1 W/cm², C	Rats *In vivo*	0.75 W/cm^2 appeared to be the most effective intensity in improving the transdermal absorption of indomethacin, while the 10 min ultrasound treatment was the most effective	48
Insulin	Insulin reservoir	20 KHz, 100 mW/cm², 20 or 60 min	Rats *In vivo*	For the 60 min exposure group, the glucose level was found to decrease from the baseline to	49

		treatment		-267.5 ± 61.9 mg/dL in 1 h. Moreover, the 20 min group had essentially the same result as the 60 min exposure at a similar intensity, which indicates that the expose time does not need to be as long for delivery	
Ketorolac Tromethamine	Gel	1 MHz, $1W/cm^2$, P	Rats *In vivo*	The drug showed significant anti-hyperalgesic and anti-inflammatory effects	50
Lanthanum hydroxide	Suspension	10 and 16 MHz, 0.2 W/cm^2, 5 or 20 min	Hairless guinea pigs *In vivo*	The 5 min exposure of skin to the ultrasound induced rapid facilitation of LH transport via an intercellular route	51
Lidocaine Hydrochloride	Gel	0.5 MHz, $2W/cm^2$, C	Healthy volunteers	Surface anaesthesia sonophoresis group showed a significantly higher pain threshold than other groups	52
Mannitol	^3H-mannitol in PBS solution	20 KHz, 2.39-33.46 W/cm^2, P 40 kHz, 0.40-43.3 W/cm^2, P	Pig skin *In vitro*	The intensity at which enhancement is maximum occurs at about 14 W/cm^2 for 20 KHz and about 17 W/cm^2 for 40 KHz. The skin conductivity enhancement was found to be inversely proportional to the distance of horn from skin	8
Morphine	Solution in pH 7.4 phosphate buffer	40 KHz, 0.44 W/cm^2, C	Hairless mouse skin *In vitro*	10-fold increased in concentration of drug in skin	39
Oligonucleotides	Radiolabelled solution of drug in PBS	20 KHz, 2.4 W/cm^2, P	Full thickness pig skin *In vitro*	Successful delivery of antisense oligonucleotides	53
Salicylic	Solution	20 KHz,	Hairless rat	Application of low-	5

acid (either ^3H or ^{14}C labelled)		125mW/cm², 100msec pulses applied every sec	skin *In vivo* Human cadaver skin *In vitro*	frequency ultrasound enhances transdermal salicylic acid transport in vivo by at least 300-fold, an enhancement comparable to the 400-fold enhancement measured in vitro across human cadaver skin	
Salicylic acid	Gel	2,10,16 MHz, 0.2 W/cm², 20 min treatment	Hairless guinea pigs *In vivo*	Sonophoresis for 20 min at 2 MHz caused no significantly increase, but at 10 and 16 MHz significantly elevated drug transport by 4 and 2.5-fold respectively	54
Sucrose (either ^3H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm², 100msec pulses applied every sec	Human cadaver skin *In vitro*	5000-fold increased in concentration of drug in skin	5
Testosterone	Solid Lipid Micro-particles	1 MHz, 0.5 W/cm², C 20 KHz, 2.5, 3.25, 5 W/cm², P	Rat abdomen skin *In vitro*	Low-frequency ultrasound resulted in higher transdermal permeation than high-frequency	55
Triamcinolone Acetonide	Gel	1,3 MHz, 1,2.5 W/cm², C and P	Mouse skin *In vitro*	The highest permeation was observed at an ultrasound conditions of 1 MHz, 2.5 W/cm^2 and in continuous mode	56
Water (either ^3H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm², 100msec pulses applied every sec	Human cadaver skin *In vitro*	113 -fold increased in concentration of drug in skin	5

9. EXPLORING CHARACTERISATION TOOLS

- **Vaccination:** In recent years, the potential for exploiting the skin for purposes of vaccination has received a great deal of attention. 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 activation of T cell- mediated immune reactions against a wide variety of antigens. 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[3, 23].
- **Gene Therapy:** Another future application for ultrasound as a topical enhancer, which seems to show promise, lies in the field of topical gene therapy. 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. 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, healing of cutaneous wounds such as severe burns and skin wounds of diabetic origin. Topical gene therapy acquires the penetration of a large complex to or through the skin. Ultrasound pretreatment of the skin will increase its permeability and permit the delivery of the carrying vector [3, 23].

Conclusion

From the study done by the article, it may be concluded that ultrasound can markedly increase percutaneous absorption. Understanding of the mechanisms by which biological effects are produced is still insufficiently understood, and more recent research on this is indicated if the therapeutic potential of ultrasound is to be fully realised. 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.

Several experiments performed by several investigations 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 high molecular weight drugs. 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. Future research is also required for the better implementation of the ultrasonic technique as it is an eminent technology.

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