New Approach of Transdermal Drug Delivery: Sonophoresis

Yan-yan MIAO, Zi-long WANG and Pei-yu ZHANG*
School of Physics and Electronics, Henan University, Kaifeng Henan 475004, China
*Corresponding author

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Abstract. The stratum corneum serves as a barrier that limits the penetration of substances to the skin. Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances through and into the skin. Various studies have been conducted on ultrasonic penetration in transdermal drug delivery, focusing on parameter optimization, delivery mechanism, transport pathways and delivery of multiple drugs. Cavitation effect is the main mechanism responsible for drug delivery. The studies on sonophoresis was discussed, including the latest trends, the delivery of drugs, the pathways and mechanisms of sonophoresis, and the outlook for future research.

Introduction

Effective therapeutic effects require not only proper drug selection but also an effective drug delivery system. Human skin is the largest surface area organ of the body's. Transdermal drug delivery, not the same as topical drug delivery to a specific area, refers to the transport of drugs through the skin into the circulatory system. Transdermal administration has many advantages over traditional oral and injectable administration methods: avoiding gastrointestinal digestive enzyme degradation and liver first-pass effects, painless et al. Moreover, drug can stably penetrate the skin to maintain a certain plasma concentration in the body[1].

Despite a great deal of research and development work in transdermal drug delivery systems, the low permeability of human skin remains a major obstacle to limit the effectiveness of transdermal delivery methods. The skin consists of the stratum corneum (SC), epidermis and dermis, and the skin is the body's primary defense system (Figure 1)[2]. Because of this hurdle, transdermal drugs that are useful are small molecules (<500Da). Since the transdermal amount of most drugs cannot achieve therapeutic effects, many chemical and physical methods are applied to reduce the barrier function of the stratum corneum and enhance the effect of transdermal drug delivery. Several physical methods used for skin penetration enhancement include cuticle exfoliation, microneedles, heating, iontophoresis, electroporation, and sonophoresis.

Figure 1. Cross-section of human skin (left) Barrier function of the stratum corneum (right).

Sonophoresis, also called ultrasonic transdermal therapy or ultrasound permeation, is defined as a method in which a drug enters the body circulation through the skin and enters the soft tissue during or after the influence of the ultrasonic disturbance to achieve a therapeutic effect. Ultrasound frequencies used in medicine can vary from 20 kHz to 16MHz. Low and mid-high frequency
ultrasonic frequencies (20-200 kHz and 0.2-1MHz, respectively) are mainly used for ultrasonic penetration because they have relatively high cavitation effects.

Ultrasound has been used in transdermal drug delivery technology for more than 50 years. Historically, ultrasonic permeation was first reported in the 1950s and was reported along with other therapeutic ultrasound applications, such as non-invasive neurological treatment. Ultrasound penetration method works in the frequency range of 20kHz-16MHz and the intensity is as high as 14 W/cm² (spatial average pulse intensity, $I_{SAP}$), to enhance skin permeability. High-frequency ultrasound (1-3MHz) was first studied for transdermal delivery, and high-frequency ultrasound is still used in treatment until now. The drug can penetrate the living skin into the soft tissue under the micro-oscillation of the ultrasonic wave, which obviously promotes the transdermal diffusion of water-soluble and fat-soluble drugs. In 1995, the Massachusetts Institute of Technology reported for the first time that the use of low-frequency ultrasound to successfully penetrate insulin into the skin [3], the study of low-frequency ultrasound (20-100 kHz) drug penetration has attracted widespread attention. At present, the research of low-frequency ultrasonic permeation technology is widely used to clinically increase the permeability of skin to various drugs and therapeutic compounds.

**Mechanism of Sonophoresis**

Although ultrasonic permeation is known to increase skin permeability, however, the mechanism of action of the ultrasonic permeation technology has been explored. At present, it is believed that ultrasonic waves may promote the permeability through thermal effects, mechanical effects, cavitation effects and radiation pressure effects. Among these effects, the cavitation effect is considered as the main mechanism of sonophoresis.

**Thermal Effects**

Ultrasound waves generate heat significantly when they propagate through the medium. The heat produces when the mechanical energy is converted into heat energy. It is obviously that the higher the absorption coefficient of the medium, the higher the temperature rise, and therefore the higher the thermal effect. For example, bone is an organ with a high ultrasonic absorption coefficient and muscle tissue has a low absorption coefficient. This is why using ultrasound on the brain is still a big challenge. There is a positive correlation between the degree of heat production and intensity. That is, the higher the intensity, the more the heat is generated. In addition, the movement of the probe and the different forms of the coupling agent affect the degree of heat production. The thermal effect is the main influencing factor of high-frequency ultrasound to increase the skin permeability [4]. After the cooling system is used in high-frequency ultrasound (1~3MHz), many molecules with molecular weights of 138~781KDa (azidethymine, digoxin, hydrocortisone, D-mannitol, estradiol, salicylic acid, etc.) did not show a significant increase in transdermal permeability, but thermal effects had little effect on low-frequency sonophoresis.

**Cavitation Effects**

The cavitation effect can be defined as the formation of bubbles in the vocal media. These bubbles are mainly formed due to pressure changes caused by ultrasonic waves in the medium, and cavitation occurs easily in the liquid medium. During the negative phase, the bubbles increase near their equilibrium radius; during the positive phase, the pressure increases, causing a decrease in the bubble radius (sometimes a dramatic decrease). Once the air bubbles implode, due to sonochemical reactions, collapse of the air bubbles leads to extreme conditions in its vicinity, producing temperatures above 5000K and pressures of about 3000bar [3]. Cavitation in liquid media exists in two forms, stable cavitation and temporary cavitation. Stable cavitation refers to those bubbles that vibrate several times near the equilibrium radius $R_r$. These bubbles occur during vibration with a series of second-order phenomena, including radiative forces and acoustic microjets. The latter can cause high velocity gradients and viscous stresses at the vibrating bubble surface, which is sufficient to produce a
biological effect on cells and biological macromolecules at the surface. The temporary cavitation has a very short time. During this process, the cavitation nucleus rapidly expands, and then suddenly shrinks, causing the collapse to implode, creating a shock wave that causes serious damage to cells and other organisms in the cavitation center. Cavitation may occur in cells and tissues. The intensity of cavitation can be determined by small pits. Scanning electron microscopy showed that ultrasound-irradiated living mouse skin had 100-150 μm lesions on the surface of the stratum corneum\textsuperscript{[5]}, consistent with the stable cavitation bubble size at 20 kHz.

Cavitation plays an important role in increasing the permeability of the skin. It can cause destruction of the stratum corneum lipid bilayer, alter the structure of the stratum corneum, increase the interstitial space of the stratum corneum, and form a water pathway between keratinocytes (water way). In turn, the skin permeability increases, and cavitation is the key mechanism for low-frequency sonophoresis. Using highly viscous coupling media to selectively suppress cavitation effects, it was found that the cavitation effect on the skin surface plays a key role in the increase of skin permeability.

Mechanical Effects

The mechanical effect is the most basic effect of ultrasound. Ultrasonic vibrations and sound pressure generated have a direct effect on cells and tissues. Mechanical effects can broaden the cell gap and have a role in increasing skin permeability. The agent penetrates through the skin in the form of a flow. Ultrasound drives the vibration of the skin tissue, promotes blood circulation and the transmission of drug molecules. It is also the basis of many ultrasound therapy. Simonin et al.\textsuperscript{[6]} demonstrated that the force generated by the sound waves is extremely small, and the effect of enhancing the skin permeability is negligible.

Other studies have also reported the other mechanisms of ultrasonic permeation, such as convection, attenuation, and lipid extraction. However, these mechanisms have been shown to be less important or attributable to the cavitation effects of ultrasound.

Influencing Factors of Sonophoresis

Sonophoresis can be divided into low-frequency sonophoresis (LFS, 20~100 kHz), high-frequency sonophoresis (HFS, 0.7~1.6MHz) and dual-frequency sonophoresis. The influencing factors of sonophoresis mainly include ultrasonic frequency, ultrasonic intensity, temperature and etc.

Ultrasonic Frequency

According to a large number of experiments, the permeation effect of low-frequency ultrasound (20~60 kHz) is much higher than that of high-frequency ultrasound. With the increase of ultrasonic frequency, the phase of acoustic wave expansion becomes shorter and the cavitation nucleus will not have enough time to grow to a cavitation bubble that can produce an effect. Even if cavitation bubbles are formed, the compression phase time of the acoustic wave is short and the cavitation bubble may not have collapse enough, and the cavitation effect becomes weaker.

Ultrasonic Intensity

In a certain range, ultrasonic permeation through the skin is closely related to ultrasonic intensity. High ultrasonic intensity will enhance the cavitation effect and thus enhance the effect of promoting osmosis. However, using high-intensity ultrasound may cause damage to the skin.

Temperature

Within a certain range, the increase of temperature can promote the accelerated flow of blood to diffuse the drug and facilitate the generation of cavitation bubbles. However, when the temperature is higher than a certain value, the temperature rise will increase the vapor pressure of the solution, reducing the cavitation nucleus in the liquid, and the cavitation strength decreases when the bubble collapses. The molecular weight and polarity of the drug also directly affect its permeability.
Compared with hydrophilic or low-molecular-weight substances, low-frequency ultrasound-induced
fat-soluble or higher molecular weight drugs have a relatively small penetration promoting effect.
In addition, because different people have different skin types, different thicknesses of the stratum
cornueum, and even differences in the thickness of the stratum cornueum that act on the site of the same
person to promote permeation, will lead to difference inn the effect of ultrasonic permeation.

**Emerging Trends of Sonophoresis**

LFS is not limited by its molecular size because proteins, vaccines and even nanoparticles have been
shown to be delivered by LFS. Therefore, emerging trends in LFS include the provision of therapeutic
drugs for systemic, regional or local conditions. Percutaneous administration of vaccines is known as
an immunoadjuvant by targeting surviving epidermal Langerhans cells. moreover, it has been
demonstrated that LFS can be used to deliver high molecular weight vaccines, such as tetanus toxoid,
and can provide the same protection as intramuscular injection. Therefore, it is not surprising that
LFS transdermal patches are an area of growing research interest. Transdermal patches have the
advantage of increased safety, reducing needle misuse, abuse, or risk of reuse, especially in
low-income regions and countries where these types of problems may exist.

Another area of interest is the use of LFS for the transdermal delivery of drug carriers that can be
used to target or systemically deliver agents. With further research in this area, drug delivery vehicles
can be designed for skin administration that can be treated by LFS, such as for use in transdermal
inoculate.

Recently, high-frequency sonophoresis using UCAs has been used to enhance TDD, and it has been
demonstrated that the presence of air bubbles caused by UCAs having a resonance frequency can
increase skin permeability by actively inducing cavitation without damage on the skin.
Ultrasound can enhance percutaneous transport by inducing structural changes in the skin and by
inducing dynamic transport. Various other methods of transdermal enhancement techniques,
including chemical penetration enhancers, iontophoresis, and electroporation, may synergize with
ultrasound to enhance drug delivery.

To develop this technology into home healthcare, it is necessary to develop a portable and
easy-to-use ultrasonic permeation instrument. Although ultrasound penetration enhancement systems
have been developed for laboratory use, clinically approved systems are rarely found in clinics.
Ultrasound penetration is expected to be a useful tool for the diagnosis and treatment of diseases such as diabetes.

**Summary**

The effect of ultrasonic wave to promote the transdermal delivery of drugs has been verified through
the study of the mechanism of ultrasonic permeation and penetration pathways, as well as the drugs
that can be used for ultrasonic percolation. The cavitation effect is the main mechanism of
sonophoresis, and the sonophoresis promotes the diffusion of drug across the skin through tortuous
pathways.

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