Published in final edited form as:
J Control Release. 2011 June 30; 152(3): 330–348. doi:10.1016/j.jconrel.2011.01.006.

Ultrasound-Mediated Transdermal Drug Delivery: Mechanisms, Scope, and Emerging Trends

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Abstract

The use of ultrasound for the delivery of drugs to, or through, the skin is commonly known as sonophoresis or phonophoresis. The use of therapeutic and high frequencies of ultrasound (≥ 0.7 MHz) for sonophoresis (HFS) dates back to as early as the 1950s, while low-frequency sonophoresis (LFS, 20 – 100 kHz) has only been investigated significantly during the past two decades. Although HFS and LFS are similar because they both utilize ultrasound to increase the skin penetration of permeants, the mechanisms associated with each physical enhancer are different. Specifically, the location of cavitation and the extent to which each process can increase skin permeability are quite dissimilar. Although the applications of both technologies are different, they each have strengths that could allow them to improve current methods of local, regional, and systemic drug delivery. In this review, we will discuss the mechanisms associated with both HFS and LFS, specifically concentrating on the key mechanistic differences between these two skin treatment methods. Background on the relevant physics associated with ultrasound transmitted through aqueous media will also be discussed, along with implications of these phenomena on sonophoresis. Finally, a thorough review of the literature is included, dating back to the first published reports of sonophoresis, including a discussion of emerging trends in the field.

Keywords

cavitation; drug delivery; phonophoresis; sonophoresis; ultrasound

1. Introduction

The use of ultrasound to deliver therapeutic compounds through the skin is generally referred to as sonophoresis (also known as phonophoresis)[1], and dates back to the 1950s. [2, 3] In these early studies, the most common applications involved the use of therapeutic or high-frequency sonophoresis (HFS, frequencies ≥ 0.7 MHz) for the local delivery of

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corticosteroids. HFS continued to be used for nearly four decades, with researchers investigating frequencies as high as 16 MHz.[4, 5] Typical skin penetration enhancements observed with HFS are between 1–10 fold.[4, 6–8] However, a crucial shift in the mechanistic understanding of sonophoresis occurred when the importance of acoustic cavitation was recognized.[5, 9–12] By exploiting the fact that cavitational effects exhibit an inverse relationship with ultrasound frequency,[13] Mitragotri *et al.* hypothesized that low-frequency sonophoresis (LFS), in the range 20 – 100 kHz, should be more effective than HFS in enhancing skin permeability.[7, 8] In these studies, it was shown that LFS at 20 kHz is up to three orders of magnitude more effective than HFS at 1 MHz. In the past decade, research has focused primarily on the use of LFS for transdermal drug delivery, due to the much greater enhancement ratios attained at these lower frequencies, while research with HFS has focused on topical or regional delivery. Readers who are interested in more in-depth background on the structure of the skin and its barrier properties, to facilitate reading of this review, are referred to recent reviews by Baroli, Cevc, and Polat *et al.*[14–16]

2. Background

2.1 Ultrasound Basics and their Implications in Sonophoresis

An ultrasound wave is a longitudinal compression wave with frequency above that of the audible range of human hearing (above 20 kHz). Sound waves propagate by causing local oscillatory motion of particles through the medium through which they are traveling. As the wave displaces particles at a given location, the local density and pressure of the medium increases or decreases depending on whether that location is in a rarefaction (low pressure) or compression (high pressure) cycle of the wave.[17] Many interesting phenomena occur in aqueous solution due to the resulting oscillation between low and high pressure, which will be discussed in Section 2.1.

Ultrasound waves are created by first generating an electric signal which is subsequently amplified before being sent to the ultrasound horn. Once the electric signal reaches the ultrasound horn, it is converted into a mechanical wave by piezoelectric crystals (which change their static dimensions in response to an electric field[18]) through the tip of the transducer, which is then transmitted to the desired medium. Two characteristics of ultrasound waves are most significant in sonophoresis: the amplitude and the frequency. The amplitude of the ultrasound wave is proportional to the displacement of the ultrasound horn during each half cycle. The frequency of the ultrasound wave corresponds to the number of times that the transducer tip is displaced per second of application time. Commonly used frequencies for sonophoresis are generally separated into two groups: (i) low-frequency sonophoresis (LFS), which includes frequencies in the range 20 – 100 kHz, and (ii) high-frequency sonophoresis (HFS), which includes frequencies in the range 0.7 – 16 MHz (the range of both therapeutic and high-frequency ultrasound), but most commonly 1 – 3 MHz. This distinction is made because of the different mechanisms of enhancement associated with LFS and HFS, as discussed in Section 3. The range of frequencies between ~100 kHz and 700 kHz, which is referred to as intermediate ultrasound, is not included in either (i) or (ii) above because this range of frequencies has not been thoroughly investigated in the context of transdermal drug delivery, and therefore, the primary enhancement mechanisms are not as well understood. The most likely reason that LFS and HFS have been utilized historically for transdermal delivery applications, while intermediate ultrasound has not, is because of the lack of commercially available ultrasound equipment in the range 100 – 700 kHz.

Additional experimental variables that are important in sonophoresis include: i) the ultrasound duty cycle (ratio of the time that ultrasound is on), ii) the distance between the ultrasound horn and the skin (horn-to-skin distance), iii) treatment time, and iv) composition

of the ultrasound coupling medium (the medium between the ultrasound horn and the skin, which can be an aqueous solution or a gel-like formulation). Commonly used ultrasound duty cycles are 10% (e.g., 0.1s ON and 0.9 s OFF),[7, 8, 19–24] 50% (e.g., 5 s ON and 5 s OFF),[25–41] or continuous application.[20, 42–47] Ultrasound pulsing is common because it decreases thermal effects associated with ultrasound by allowing time for heat to dissipate from the coupling medium during treatment. Many different horn-to-skin distances have been utilized in sonophoretic research, ranging from placing the ultrasound horn in contact with the skin (zero tip displacement) to as far as 4.0 cm from the skin surface.[41, 42] The most common tip displacements reported for use with LFS range from 0.3 cm to 1.0 cm.[7, 8, 19–22, 24–29, 31–39, 44, 45, 47–55] With HFS, it is much more common to have smaller tip displacements, almost in contact with the skin, for reasons that will become clear when the enhancement mechanisms associated with HFS and LFS are discussed in Section 3. Treatment times can also vary greatly, from a few seconds,[56–59] to a few minutes,[25, 34, 39] or even to cases where steady-state is attained, which can take many hours to days.[21, 24, 60] Finally, formulation of the coupling medium is also a very important variable in sonophoresis. The viscosity, surface tension, density, acoustic impedance, and other bulk and interfacial properties of the coupling medium can all play significant roles in determining the extent of skin permeability enhancement observed as a result of the ultrasound treatment. Furthermore, the coupling medium can contain an active ingredient (e.g., a drug) or can include a chemical enhancer (co-enhancer), such as a surfactant. Because of the mechanisms associated with LFS and HFS (see Section 3), LFS coupling media are typically aqueous formulations, while HFS coupling media are typically gels. In both cases, the coupling solution has an acoustic impedance which is similar to that of the skin, such that there is no significant reflection of the ultrasound wave at the interface between the skin and the coupling medium. The mechanistic effects associated with the formulation used will be discussed further in Sections 3 and 4.

2.1.1 Acoustic Cavitation—Although all the mechanisms responsible for skin permeability enhancement by sonophoresis are not fully understood, it is generally accepted that the main contributor is acoustic cavitation, particularly in the case of LFS.[22, 43, 45, 61] The term cavitation can take multiple definitions depending on the source of the stress acting upon the system. Strictly speaking, cavitation is the process by which a liquid is pulled apart when it is acted upon by a force in excess of its tensile strength, causing the formation of voids in the system.[62] However, due to inhomogeneities in all real liquids, such as those induced by the presence of dissolved gases, microscopic gas bubbles, or other particulates, the theoretical tensile strength of a liquid is never observed in practice.[62] For this reason, cavitation in all systems is observed far below the theoretical limit, even in extremely purified liquids. This definition of cavitation is not well suited for systems involving acoustic pressure variations, as is the case with sonophoresis. Instead, acoustic cavitation can be loosely defined as the process by which any of the following occurs: i) small gas bubbles already present in a liquid pulsate or grow, ii) gas bubbles form in the bulk or on nuclei due to acoustic pressure variations, or iii) the occurrence of any other type of growth, splitting, or interaction of gas bubbles due to acoustic pressure oscillations in solution.[63]

Cavitation can be further divided into two types: stable and transient. Stable cavitation is defined as the pulsation of cavitation bubbles over many acoustic pressure cycles without collapse. Transient cavitation is defined as the rapid and uncontrolled growth of cavitation bubbles over several pressure cycles, eventually leading to their collapse into smaller bubbles or, if near a surface such as the skin, to the formation of a microjet.[64] A microjet results from the asymmetry in bubble collapse pressure near an interface. Depending on the properties of the interface, the bubble can either generate a jet towards the interface, away from the interface, or collapse in an alternate shape.[65] The collapse of a cavitation bubble

as a microjet directed towards the interface tends to occur near more rigid surfaces[65] and has been implicated in causing skin perturbation during LFS treatment.[25, 37, 43] The growth of gaseous bubbles in response to ultrasound occurs by a process called rectified diffusion, which is discussed in Section 2.1.2.

It is important to stress that the resonant radius of cavitation bubbles exhibits an inverse relationship with the applied ultrasound frequency.[13] Specifically, the linear resonant bubble radius is defined by the equation $r_{res} \cdot f = C$, where r_{res} and f are the resonant bubble radius and the applied ultrasound frequency, respectively, and C is a constant that depends on the properties of the solution in which cavitation is occuring.[13] Therefore, high-frequency ultrasound will generate bubble populations having smaller radii than low-frequency ultrasound. For example, the linear resonant bubble radius of air bubbles in water, which is assumed to be incompressible and inviscid, for ultrasound at 20 kHz is 150 μm, while at 3 MHz it is only 1 μm (see the equation above).[66, 67] The average size of cavitation bubbles in a given system will dictate where cavitation can occur in that system. For example, if the resonant bubble radius is larger than the dimensions of the skin voids available for cavitation to occur, it is unlikely that cavitation within the skin itself can play a significant role in skin permeability enhancement.[68] Therefore, cavitation within the skin is much more likely to occur with HFS, when the resonant bubble radius is on the order of microns or smaller, rather than with LFS. This will be discussed further in Section 3. Moreover, Ueda *et al.* have shown, through acoustic spectroscopy measurements, that the amount of transient cavitation generated in the coupling medium between the ultrasound horn and the skin membrane increases with decreasing ultrasound frequency, in the range 41 kHz – 445 kHz.[47] This suggests that not only cavitation bubble size, but also transient cavitation itself increases with decreasing ultrasound frequency, which has implications on the level of enhancement that can be achieved at lower ultrasound frequencies, relative to higher ultrasound frequencies (see discussion on mechanisms in Section 3).

2.1.2 Rectified Diffusion—Cavitation cannot be thought of as an isolated phenomenon, because it is strongly linked to many other processes that cause unique behaviors in acoustically cavitating systems. For example, the process of rectified diffusion causes oscillating cavitation bubbles to grow under an acoustic pressure field.[69, 70] It is this growth and the eventual collapse of cavitation bubbles that is believed to cause skin permeability enhancement during LFS.[43] During rectified diffusion, a bubble encountering a negative-pressure half-cycle of an acoustic field will grow due to the expansion of the gas inside the bubble. In addition, some of the liquid surrounding the bubble will diffuse through the boundary layer and vaporize, causing the amount of gas in the bubble to increase. In the subsequent positive-pressure half-cycle, the bubble will collapse to a size which is much smaller than that in its previous state. Depending on the temperature and the composition of the gas and liquid phases, some of the vapor will condense and join the liquid phase surrounding the bubble. This process favors bubble growth for two main reasons: (i) the “area” effect, and (ii) the “shell” effect.[71] The “area” effect simply occurs because the surface area of a bubble in the expanded state is much greater than in the collapsed state. Therefore, there is much greater area for diffusion into the bubble to occur in the expanded state than for diffusion out of the bubble to occur in the collapsed state. The “shell” effect occurs due to the existence of a diffusion boundary layer (see Figure 1), or shell, through which gas or vapor transfers between the gas phase of the bubble and the surrounding liquid phase. When the bubble is in an expanded state and the concentration of gas in the bubble is at its lowest point (Figure 1, right-hand side), the shell is thin and, therefore, there is a larger concentration gradient for diffusion into the bubble. Conversely, in the collapsed state, the boundary layer is thicker, because of the rapid collapse of the bubble, and therefore, the driving force for diffusion out of the bubble decreases. Opposing the forces of bubble growth is the Laplace pressure, caused by the

surface tension of the bubble. The Laplace pressure, ΔP_L, is given by: $\Delta P_L = 2\gamma/R$, where γ and R are the surface tension and radius of the gas bubble, respectively. If the radius of the gas bubble is exceedingly small, the Laplace pressure will be extremely large, causing the gas bubble to dissolve back into the bulk phase once the ultrasound is turned off.[72] In this respect, the duty cycle of the applied ultrasound can also play an important role. If the pulse rate is rapid, cavitation bubbles may not have sufficient time to grow, and therefore, when the ultrasound is in the OFF period of the duty cycle, bubbles may dissolve back into the solution,[73] and will be unable to contribute to skin permeability enhancement in subsequent cycles.

Rectified diffusion is most important to cavitation when the amount of liquid vaporized in the negative-pressure half-cycle is greater than the amount of vapor condensing in the positive-pressure half-cycle. In this case, there is net growth of the bubble through each consecutive pressure cycle of the acoustic wave. If this process proceeds quickly, with rapid bubble growth over a few cycles, the event is considered a transient cavitation bubble and the bubble will either collapse in the bulk or can generate a microjet near an interface.[64] The occurrence of transient cavitation depends on the ultrasound frequency, its amplitude, and the size of the cavitation bubble.[67] On the other hand, if this process proceeds slowly and an equilibrium is reached, a stable cavitation bubble will result and the bubble will continue to oscillate during many pressure cycles.[71, 74] The importance of transient and stable cavitation to ultrasound-induced skin permeability enhancement will be discussed further in Section 3.

2.1.3 Forces Acting on Acoustic Cavitation Bubbles—In addition to pulsating and growing in response to ultrasound, cavitation bubbles are also subject to radiation pressure and convective forces in an ultrasound field that can cause translational motion or interactions between bubbles. The first of these forces, the primary Bjerknes force, may play a role in LFS by causing translational bubble motion when buoyancy is not a factor (i.e. when the radius of the bubble is sufficiently small so that the upward buoyant force does not exceed the drag force and the gravitational force).[66] The primary Bjerknes force occurs as a result of the coupling of bubble oscillation with the applied acoustic pressure gradient. It causes bubbles that are smaller than the resonant bubble radius, at the applied frequency, to move up pressure gradients, or towards pressure antinodes, and bubbles that are larger than the resonant bubble radius to move down pressure gradients, or towards pressure nodes.[66] The effect of the primary Bjerknes force can be beneficial to LFS because, under typical operating conditions, the distance between the ultrasound transducer and the skin is less than one-fourth of the ultrasound wavelength, λ (in water at 20 kHz, λ = 7.5 cm), corresponding to the first pressure antinode ($\lambda/4$ ~1.9 cm). Therefore, any small bubble produced in the coupling medium between the ultrasound transducer and the skin will tend to move towards the surface of the skin as a result of this force. Even more significant than the primary Bjerknes force, however, is acoustic streaming, which is the convection-induced motion of cavitation bubbles due to the movement of the ultrasound horn itself.[62] Acoustic streaming causes the bulk fluid to move in the direction of the applied ultrasound field, which in the case of LFS is towards the skin surface. This causes smaller bubbles, which do no experience significant buoyancy, to also move towards the surface of the skin. Furthermore, this bulk fluid movement causes rigorous mixing of the coupling medium, which can have implications on enhancing mechanisms in areas of the skin where cavitation microjets do not occur (see Section 4.1).[24] This also implies that, at higher ultrasound intensities, when bubbles grow rapidly and larger bubbles are formed, bubbles will collect at the surface of the ultrasound transducer due to buoyancy, causing decreased process efficiency (which is observed in practice[41]).

A second force of interest in LFS is what is referred to as the secondary Bjerknes force. This force can cause the mutual attraction or repulsion of oscillating cavitation bubbles, and occurs as a result of the coupling of the sound field emitted by each oscillating bubble.[75, 76] However, the secondary Bjerknes force can also cause other, higher-order, phenomena such as acoustic streamers (the formation of stable pairs of bubbles that oscillate about an equilibrium distance from each other and move through an ultrasound field) and cavitation bubble clouds (localized collections of cavitation bubbles in an ultrasound field).[77–79] These phenomena may be significant in sonophoresis, particularly with respect to the recently recognized heterogeneous transport observed with LFS, as localized collections of cavitation bubbles may induce skin perturbation solely in discrete regions (see Section 4.1).[34, 37]

2.2 Modes of Skin Treatment with Sonophoresis

Ultrasound is applied to skin primarily in one of two ways: i) as a pretreatment of the skin prior to contact with a drug or permeant (which will hereafter be referred to as “pretreatment”), or ii) as a simultaneous application of ultrasound through a coupling medium containing the drug or permeant (which will hereafter be referred to as “simultaneous treatment”). Simultaneous treatment causes enhancement of drug transport in two ways: i) by structural changes to the skin that increase skin permeability, and ii) through convection-related mechanisms that occur only when ultrasound is applied.[80] Conversely, the pretreatment method only enhances skin permeability by mechanism (i), because the drug is applied only after ultrasound treatment is completed. The simultaneous protocol is still common in studies that utilize HFS.[81–85] With LFS, both types of skin treatments have been investigated in the past, although the most common type of current treatment is the pretreatment method, including in clinical use of the technology.[56–59] This is mainly because of three reasons. First, the action of ultrasound on drugs, or other active ingredients, can cause degradation of the molecules or other chemical reactions to occur. This can result in loss of activity or effectiveness of the therapeutic compound and may also cause undesired reactions that generate unknown species which could have deleterious biological effects.[86] Second, for clinical applications, simultaneous treatment requires that patients wear the ultrasound device for the duration of the treatment, while pretreatment has the advantage of requiring only that a patch be applied following a brief, ~10 second, ultrasound treatment.[80] Finally, the use of LFS for transdermal drug delivery has resulted in the ability to increase skin permeability to a greater extent than previously possibly with HFS,[7, 8] making it feasible for pretreatment of the skin to deliver therapeutic levels of drugs, without the need for the additional convection mechanism associated with the simultaneous treatment.

3 Mechanisms of Skin Permeability Enhancement in Sonophoresis

3.1 Non-Cavitational Mechanisms of Enhancement in Sonophoresis

In addition to cavitation, which will be discussed in Sections 3.2 – 3.4, there are several other mechanisms whose roles on skin permeability enhancement in sonophoresis have been investigated. These include: i) convection (acoustic streaming and resulting boundary-layer reduction),[8, 68] ii) thermal effects,[8, 20, 68, 87] iii) mechanical or radiation pressure effects,[6, 68] iv) lipid extraction,[23], and v) increase in the solution-membrane interfacial transfer rate,[88] among others.

3.1.1 Convection-Related Mechanisms—It is important to recognize that the mechanisms of enhancement depend on the skin treatment protocol used. For example, utilizing the simultaneous treatment protocol, enhancement of drug permeation by convection is quite feasible. However, using a pretreatment protocol, convection cannot play

any role in the enhancement of transport because the drug is not present in the coupling medium during the ultrasound treatment. Nevertheless, even with simultaneous treatment protocols, there have been conflicting claims about the role of convection in enhancing drug delivery. One likely explanation for this seeming incongruity is the skin model and skin thickness utilized. For example, using 20 kHz LFS (intensity of 1.6 W/cm^2) applied simultaneously with mannitol or sucrose, Tang *et al.* showed that convection only plays a significant role in transport across heat-stripped human skin (which contains solely the epidermis), while it was not significant in the case of the thicker split-thickness (0.7 mm) or full-thickness (≥1.4 mm) pig skin models.[21] Similarly, Mitragotri *et al.* showed that convection did not affect mannitol permeability in full-thickness pig skin (20 kHz, 7 W/cm^2).[19] In other words, the skin permeability to mannitol was the same regardless of whether mannitol was present in the LFS coupling medium or was applied post-treatment.

Other studies, however, have suggested that convection can be important using LFS. For example, Tachibana *et al.* showed that the analgesic effect of 2% lidocaine, simultaneously applied with 48 kHz ultrasound (0.17 W/cm^2), was greater than when applied with an aqueous formulation instead of with a gel.[89] These authors concluded that the most likely reason for this observation was that ultrasound-induced convective streaming processes (such as acoustic streaming, see Section 2.1.3) were enhancing the bioavailability of lidocaine at the skin surface in the less-viscous aqueous formulation. In addition to the studies using LFS, a number of HFS studies have investigated the effect of convective processes as potential mechanisms of therapeutic delivery. Using cellophane membranes as a model, Lenart *et al.* deduced that with 1 MHz HFS treatment (1.2–6.0 W/cm^2), the main mechanism of increased diffusion of electrolytes was due to the formation of acoustic microcurrents.[90] In addition, utilizing 1 MHz HFS (1.5–3.0 W/cm^2), Levy *et al.* concluded that a combination of convective mixing and cavitation were the main mechanisms of enhanced delivery of mannitol, inulin, and physostigmine.[11] Simonin also demonstrated, using a theoretical analysis, that convective reduction of the boundary layer above the skin by stirring of the donor compartment could decrease the overall resistance of the membrane by about 10%.[68] Convection has also been cited as a possible mechanism in other HFS studies,[91] while it has not been implicated in several others.[6, 12, 92, 93]

3.1.2 Thermal Effects—Thermal effects have been studied in great detail with respect to sonophoresis, because attenuation of an ultrasound wave leads to heating of the medium that the wave traverses. An increase in temperature can increase skin permeability by: i) increasing the kinetic energy and diffusivity of drug compounds, ii) dilating points of entry of the skin (e.g., hair follicles and sweat glands), iii) facilitating drug absorption, and iv) enhancing circulation of blood in the treated area (in *in vivo* experiments).[6, 68] Because thermal effects are directly proportional to the ultrasound intensity and duty cycle, reports have differed on the importance of heating as a mechanism of sonophoresis. Many studies have concluded that thermal effects do not play a role in HFS (1–16 MHz, 0.2–3.0 W/cm^2) enhanced transdermal transport, although the temperature in the donor solution was not observed to increase more than 1–2 °C in these studies.[5, 11, 92] Conversely, and not surprisingly, in studies that observed much larger temperature increases (in excess of 10 °C), thermal effects were found to play a role in increasing permeant transport, although a temperature increase alone could not explain the full enhancement observed with the HFS treatment (1 MHz, 1 W/cm^2).[91] Meidan *et al.* even concluded that heating is the main mechanism of action with HFS.[87] A study of sonophoresis, at an intermediate frequency of 150 kHz (2 W/cm^2), also concluded that thermal effects may be a significant mechanism of increased flux of hydrophilic permeants.[94] However, recent studies, especially those conducted with LFS at higher amplitudes, have paid more attention to controlling and minimizing thermal effects. This is because significant increases in temperature, and sustained exposure to high temperatures, can lead to many harmful side effects, such as

epidermal detachment, burns, and necrosis of the viable epidermis or underlying tissues.[20] Therefore, most current sonophoresis treatment protocols require periodic replacement of the coupling medium to minimize heating. Thermal effects have therefore been shown not to play a significant role in LFS studies.[22, 23, 45] For example, Polat *et al.* have shown that heating a solution to 37 °C does not increase the skin uptake of sodium lauryl sulfate (SLS) to a statistically significant extent, compared to controls at 25 °C, in 20 minutes of exposure (a typical duration for an *in vitro* LFS treatment, with replacement of the coupling medium every 2 minutes).[25] However, similar to observations with HFS, if the temperature is allowed to increase in the LFS experiments, and the increased temperature is maintained for an extended time, thermal effects will play a role. For example, Merino *et al.* demonstrated that during a 2-hour treatment using 20 kHz LFS (4.5–15.0 W/cm^2, 10% duty cycle), thermal effects could explain up to 25% of the observed mannitol transport, with the temperature increasing as much as 20 °C during the treatments.[40] These authors also stated that the remaining enhancement was likely due to cavitation (see Sections 3.2 – 3.4).

3.1.3 Other Proposed Mechanisms—Other mechanisms of enhancement have also been reported in the literature, albeit less often. One potential mechanism that has been considered is the direct force of the acoustic wave on the skin membrane or on the interface between the skin and the coupling medium.[90, 95] However, an investigation by Simonin has shown that this effect is exceedingly small and is therefore negligible relative to the overall skin permeability enhancement.[68] A unique study by Alvarez-Roman *et al.* showed that up to 30% of the stratum corneum lipids can be extracted into the coupling medium during LFS exposure (20 kHz, 15 W/cm^2).[23] These authors proposed that the decrease in skin lipids could explain previously observed phenomena such as: i) decreased skin electrical resistance, ii) increased water permeability, and iii) sustained permeability enhancement post-treatment. However, Alvarez-Roman *et al.* suggested that cavitation in the coupling medium is the most likely mechanism for the observed non-uniform enhancement across the skin surface, as well as a possible reason for the lipid extraction itself.[23] Therefore, lipid extraction due to LFS is likely a result of other enhancement mechanisms (e.g., cavitation), and not a direct mechanism of the LFS treatment. Finally, Julian and Zentner proposed that 20 kHz LFS (~13–46 W/cm^2) increased the diffusion of benzoic acid and hydrocortisone across model membranes (polydimethylsiloxane or cellulose) by decreasing the activation energy for diffusion, and thereby increasing the diffusion coefficients and partition coefficients between the solution and the membrane for these compounds.[88] However, no physical explanation was given as to how the ultrasound caused these changes, other than possible thermal effects. A subsequent theoretical analysis by Simonin to identify a microscopic physical interpretation as to why ultrasound decreases the interfacial energy barrier was unsuccessful.[68] Therefore, it is again possible that the proposed energy barrier reduction mechanism results simply from thermal effects (note the high amplitudes utilized in this study[88], which are reported above), instead of being a direct mechanism itself.

3.2 The Role of Cavitation in HFS

In some of the first mechanistic investigations using HFS, Kost *et al.* and Levy *et. al.* hypothesized that cavitation could play a role in transdermal delivery with sonophoresis.[10, 11] It was then shown by microscopy-based histological examination that cavitation within the skin is a significant mechanism at 10 MHz and 16 MHz.[5] A following theoretical analysis suggested that, at frequencies above 1 MHz, cavitation within skin appendages (such as hair follicles) could explain observed skin permeability enhancements using HFS, although it was unlikely that cavitation within the stratum corneum lipid bilayers could occur.[68] However, the most significant experimental study into the mechanisms of HFS, at frequencies between 1–3 MHz, was conducted by Mitragotri *et al.*, and showed that

cavitation within the skin was the primary mechanism of skin permeability enhancement.[12] Moreover, the microscopy-based findings showed that cavitation occurs within cavities near the corneocytes of the stratum corneum, leading to the hypothesis that the direct interaction of the oscillating cavitation bubbles induces disordering of the stratum corneum lipid bilayers, causing the observed increase in skin permeability (see Figure 2).[12]

3.3 The Role of Cavitation in LFS

The role of cavitation as the primary mechanism of skin permeability enhancement during LFS was demonstrated by Tang *et al.* in a series of experiments involving the selective suppression of cavitation inside and outside the skin.[22] First, to show that cavitation outside the skin plays a more significant role than cavitation inside the skin, a highly viscous liquid, castor oil, was used in place of water in the coupling medium. This, in effect, completely suppressed cavitation in the coupling medium outside the skin, while not changing the conditions inside the skin significantly. It is important to note that the acoustic impedance of both water and castor oil are similar to that of skin, and therefore, the efficiency of energy transfer between the coupling medium and the skin is similar using either type of formulation. In the next series of experiments, a high-pressure diffusion cell was built, allowing for the suppression of cavitation in the entire system, both outside and inside the skin, by generating high static pressure. In both the castor oil and high-pressure studies, no significant change in skin permeability was observed compared to passive controls, and therefore, it was concluded that cavitation outside the skin was indeed the most important mechanism of skin permeability enhancement.[22] To elucidate whether transient or stable cavitation plays a more significant role in skin permeability enhancement by LFS, Tang *et al.* and Tezel *et al.* independently measured the pressure amplitudes of subharmonic emissions and broadband noise.[22, 45] Subharmonic emissions (i.e., $f/2$) are in part caused by the repeated oscillation of bubbles in an acoustic field and are associated with stable cavitation.[96] Broadband noise is associated with the rapid growth and collapse of bubbles and is therefore linked to transient cavitation. The findings of Tang *et al.* and Tezel *et al.* showed that there is no relationship between the sub-harmonic emission recordings and skin permeability enhancement. However, a strong correlation between skin permeability enhancement and broadband noise was observed.[22, 45] Therefore, it was concluded that transient cavitation is the most significant mechanism of skin permeability enhancement during LFS. It has also been shown that by enhancing cavitation activity outside the skin, by the use of porous resins as cavitation nuclei in the coupling medium, increased skin permeability can be attained. This further demonstrates the significance of cavitation outside the skin in causing skin permeability enhancement using LFS.[32]

The findings above, however, did not elucidate: (i) which types of transient cavitation events (microjets or shockwaves) lead to the observed enhancement of skin permeability, and (ii) the location of these transient cavitation events in the coupling medium: at the surface of the skin, close to the surface of the skin, or in the bulk. Tezel *et al.* were able to show that the critical distance of a bubble from the skin surface required to cause disruption to the surface is approximately one maximum bubble radius.[43] The maximum bubble radius is the largest radius to which the bubble expands to in the negative pressure half-cycle of the ultrasound field (which is a function of the operating ultrasound parameters). This corresponds to no more than about 150 μm at the operating frequency of 20 kHz.[43] However, a bubble which is only one diameter away from a solid surface is not likely to maintain symmetry during its oscillation.[97] Therefore, it is not likely that symmetric bubble oscillation resulting in shock waves plays a central role in the perturbation of the skin. This indicates that the most likely reason for skin permeability enhancement during LFS is microjet penetration into the skin surface, or microjet collapse near the skin surface, resulting in skin perturbation (see Figure 3).[25, 37, 43] Additional research by Ueda *et al.*

has revealed that transient cavitation in the vicinity of a membrane is only significant at frequencies in the LFS range. [47] Specifically, these authors demonstrated that 41 kHz LFS treatment caused the disruption of a rhodamine B layer adsorbed to a gelatin membrane in discrete regions, while cavitation in the vicinity of the membrane was not significant at 158 kHz and 445 kHz, because no disruption of the rhodamine B layer was observed.[47] Ueda *et al.* also demonstrated that transient cavitation generation increases with decreasing ultrasound frequency, which scales directly with the membrane permeability.[47] Furthermore, by conducting experiments at multiple frequencies in the range 20 kHz – 60 kHz, Polat *et al.* have recently shown that there is a strong correlation between skin pore radius and ultrasound frequency. This correlation scales similarly to the relationship between the resonant bubble radius and ultrasound frequency (see Section 2.1.1), suggesting that the direct action of cavitation bubbles collapsing onto the skin, likely as microjets (see Figure 3), accounts for the observed variation in skin pore radius with ultrasound frequency. [25] Other recent studies have also suggested that cavitation bubble collapses on the skin surface as microjets play a dominant role in skin permeability enhancement compared to other cavitation-related mechanisms, such as shock wave emission.[26] For example, Watanabe *et al.* have found that small pits can be observed on skin imaged with environmental scanning electron microscopy, which likely results from cavitation at the skin surface.[98]

3.4 Difference in the Mechanisms of LFS and HFS

It is essential to recognize that different mechanisms are responsible for skin permeability enhancement in LFS and HFS. A common erroneous practice in the sonophoresis literature is to rationalize observations made using LFS by invoking enhancement mechanisms which are only applicable using HFS. In particular, a serious mistake involves identifying the actual location of cavitation during the ultrasound treatment (compare Figures 2 and 3). In HFS, as stated earlier in Section 2.1.1, the linear resonant bubble radius is on the order of less than 1 μm, which is comparable to the thickness of the lipid bilayers of the stratum corneum. This suggests that it is possible for cavitation to occur within skin appendages (hair follicle shafts, sweat glands, etc.)[68] or in lacunar cavities within the skin itself.[12] Indeed, there have been numerous studies reporting that cavitation within the skin is an important factor in skin permeability enhancement using HFS, at frequencies ranging from 1– 16 MHz. [5, 10–12] In fact, it was believed that cavitation outside the skin would decrease the efficiency of the HFS treatment by decreasing energy transfer between the ultrasound horn and the skin treatment site.[4] Therefore, for these applications, it was suggested that suppressing cavitation in the coupling medium would be advantageous for overall skin permeability enhancement, which could be achieved by utilizing non-aqueous media, such as mineral oil, in the coupling solution. Unfortunately, when the switch from HFS to LFS was made,[7] it was still believed that cavitation within the skin would continue to play a dominant role. This has led to many erroneous citations and claims in the literature that transient cavitation within the skin is significant in LFS enhancement of skin permeability (e.g., [42, 49, 99, 100]). However, since that time, it has been shown conclusively through cavitation suppression experiments, chemical and acoustic dosimetry methods, and theoretical analysis, that cavitation in the coupling medium near the skin surface is, in fact, the primary mechanism of skin permeability enhancement in LFS.[22, 25, 26, 43, 45] Therefore, careful attention should be paid when designing experiments and explaining observed trends, depending on the frequency of ultrasound utilized. For example, when utilizing LFS, cavitation above the skin has been shown to be the primary mechanism of enhancement, and therefore, the utilization of experimental protocols that suppress this mechanism, such as degassing of the coupling medium, placing the ultrasound horn in contact with the skin, or using a coupling medium with a high viscosity, is not recommended, unless suppression of cavitation above the skin is actually desired.

4. Phenomena Observed in Sonophoresis-Mediated Transdermal Drug Delivery

4.1 Localized Transport Regions

An important discovery in the area of skin permeability enhancement by LFS was the identification of heterogeneity in the enhancement of skin perturbation. Tang *et al.*[31] and Tezel *et al.*[54] observed independently that LFS operating at 20 kHz, with a colored permeant present in the coupling medium, produced highly-stained regions of LFS-treated skin. These regions of hypothesized high permeability were given the name localized transport regions (LTRs). Kushner *et al.* verified that these regions are indeed regions of increased permeability by using a unique masking method on LFS-treated skin.[34] Experiments using solely LFS (20 kHz, 15 W/cm^2) showed that only a single LTR formed during sonication of skin samples, directly below the ultrasound transducer.[23] However, further investigation into the phenomenon of LTR formation showed that when 1% w/v SLS was added to the LFS coupling medium (frequencies of 19.6 – 58.9 kHz), LTRs formed in stochastic patterns across the surface of the skin, ranging in coverage from 5 – 25% of the skin surface area (see Figure 4).[33, 34, 45, 54] In addition, Kushner *et al.* showed that the LTRs are not only highly perturbed (5000-fold decrease in skin resistivity), but that the non-LTRs are also permeabilized relative to untreated skin (170-fold decrease in skin resistivity) when SLS is present during the skin treatment.[34] This is a significant finding because it shows that two levels of skin electrical resistivity enhancement are present. In comparison, in the case of LFS alone, only the LTRs were shown to be perturbed to a significant extent, with minimal change to the skin in the non-LTRs.[23] The frequency dependence of the skin permeability enhancement in the presence of SLS was studied by Tezel *et al.* at 20 kHz and 1.08 W/cm^2, and the following trends were observed: (i) as the ultrasound frequency increases, the threshold ultrasound intensity for the observation of skin conductivity enhancement increases, (ii) at lower ultrasound frequencies, localized transport plays a more significant role, with LTRs observed on the surface of the skin, and (iii) at higher ultrasound frequencies, transport occurs more homogenously across the surface of the skin.[54] In another study utilizing multiple ultrasound frequencies (41 kHz, 158 kHz, and 445 kHz), Ueda *et al.* were able to show that disruption of the surface of gelatin membranes occurred only at 41 kHz, in discrete spots.[47] This suggests that localized transport is only significant when treating skin in the LFS range. Furthermore, in a recent study, Polat *et al.* showed that the pore size within LTRs in skin treated with LFS/SLS is frequency dependent, while in non-LTRs no frequency dependence was observed.[25] Because the size of cavitation bubbles is also frequency dependent[13], the authors concluded that cavitation-induced microjet collapse at the skin surface is the most likely mechanism of LTR formation and of skin permeability enhancement within LTRs. Conversely, within non-LTRs, due to the frequency independence in the observed pore size, the action of SLS on the skin was concluded to be the main mechanism of non-LTR enhancement, with increased uptake of SLS into the non-LTRs taking place via a convection-related mechanism, such as boundary-layer reduction by acoustic streaming (see Section 2.1.3).[25] It is noteworthy that there have been no reports of LTR formation with HFS, which is expected because it is known that localized transport is more significant only at lower ultrasound frequencies (interested readers are referred to Refs. [37, 54] for a more detailed discussion of LTRs).

4.2 Synergism of Sonophoresis and Chemical Enhancers

One of the most significant phenomena observed with sonophoresis is that its combination with chemical enhancers, such as surfactants, results in synergism in the enhancement of transdermal transport. Chemical enhancers alone are known to permeabilize skin by solubilizing or extracting skin lipids and by denaturing corneocytes.[101] However, their effect on skin permeability can be even more dramatic when combined with ultrasound. One

of the first rigorous studies on the synergism between chemical enhancers and ultrasound was conducted by Johnson *et al.*, who showed that different combinations of chemical enhancers in the presence of HFS causes an increase in the permeability and flux of lipophilic permeants across *in vitro* human cadaver skin.[102] Their major finding was that for the model permeant corticosterone, a combination of ethanol and linoleic acid, in equal proportions, enhanced the skin permeability by a factor of 8.7 and the flux by a factor of 903. However the same formulation, when combined with HFS (1 MHz, 1.4 W/cm^2), enhanced the skin permeability by a factor of 14.4 and the flux by a factor of greater than 13,000.[102] The authors explained that the observed enhancement induced by HFS/linoleic acid was caused by either an increase in the fluidity of the lipoidal domain in the stratum corneum or by the formation of a separate bulk oil phase in the skin. Another study by Meidan *et al.* demonstrated the synergism between 1.1–3.3 MHz HFS and the chemical penetration enhancer laurocapram (Azone) in delivering hydrocortisone across *in vitro* rat skin.[103] Their mechanistic findings suggested that the synergism between the two enhancers was due to accelerated laurocapram diffusion into the skin due to ultrasonic thermal effects. Furthermore, Liu *et al.* showed that the combined treatment of rat skin using LFS (20 kHz) with laurocapram or SLS exhibited synergistic topical delivery of cyclosporin A.[104] Specifically, the combination of LFS and chemical enhancers caused an increase in cyclosporin A skin concentration of over an order of magnitude compared to controls. Additional studies demonstrating synergism between chemical enhancers and ultrasound include: i) HFS (1 MHz) and d-limonene in ethanol on the percutaneous absorption of ketorolac tromethamine through *in vitro* rat skin,[105] ii) HFS (1 – 1.1 MHz) and thiazone or glycerol (among several others) to increase skin optical clearing,[106–110] iii) HFS (0.8 MHz) and laurocapram, oleic acid, or 2-propanediol on the delivery of sinomenine hydrochloride through rat skin,[111] iv) HFS (0.8 MHz) and ethanol-containing aqueous gel formulations (hydroxypropyl methylcelullose) on the delivery of ibuprofen through *in vitro* and *in vivo* rabbit skin,[84] v) ultrasound (150 kHz) and 7 different enhancers (menthol being the most thoroughly investigated) on the delivery of aminopyrene, vi) LFS (20 kHz) and capsaicin or nonivamide on the transdermal flux of indomethacin across nude mouse skin[112], vii) LFS (20 kHz) and 14 different chemical enhancers (the best of which was 5% citral in 1:1 ethanol:PBS) on the transdermal permeation of tizanidine hydrochloride across mouse skin,[113], and viii) LFS (20 kHz) and liposomes/SLS to deliver antigens through *in vitro* and *in vivo* rat skin,[114] among others.

4.2.1 Synergism of LFS and Surfactants—The synergism between LFS and surfactants has been shown to be quite significant. For example, Mitragotri *et al.* showed that by adding a common anionic surfactant, SLS, to the LFS coupling medium (20 kHz), skin permeability to mannitol increased 200-fold over 90 minutes of treatment, while for LFS and SLS treatments alone, only 3-fold and 8-fold enhancements were observed, respectively.[19] Furthermore, these authors showed that the energy density threshold required to observe any skin permeability enhancement decreased by nearly an order of magnitude from 141 J/cm^2 to 18 J/cm^2, with the inclusion of SLS in the LFS coupling medium. In addition, Mitragotri *et al.* demonstrated that skin permeability enhancement is linearly proportional to SLS concentration, in the range 0 – 1 wt% SLS, and is also proportional to the LFS intensity and exposure time, but independent of duty cycle.[19] In a following study, Tezel *et al.* studied the synergism between LFS (20 kHz) and a series of eleven surfactants.[33] The study included surfactants with a variety of “head” groups (cationic, anionic, nonionic, and zwitterionic) and “tail” groups (linear alkanes containing 8–16 carbons). In 10 minutes of LFS treatment, using a surfactant concentration of 1 wt% in the coupling medium, tetradecyltrimethyl ammoniumbromide (TDAB), SLS, and hexadecyltrimethyl ammoniumbromide (HDAB) yielded the highest skin conductivity enhancement ratios of 35.4, 24.5, and 15.9, respectively, of all the single surfactant solutions

considered. However, when multiple surfactants were mixed, both synergistic and antagonistic effects were observed. For example, a 50:50 mixture of TDAD and HDAB (total concentration of 1 wt%) yielded an enhancement ratio of 42.8 (greater than using either single surfactant alone at a concentration of 1 wt%), thus exhibiting synergism. On the other hand, a 50:50 mixture of SLS and glycolic acid ethoxylate 4-tert-butyl phenyl ether (ether) only showed an enhancement ratio of 1.6, much lower than the enhancement ratio corresponding to either single surfactant solution (enhancement ratio for ether alone was 5.5), thus exhibiting extreme antagonism. No mechanism was suggested to rationalize why synergistic or antagonistic effects were observed in the binary surfactant formulations. Tezel *et al.* concluded that ionic surfactants are better than nonionic surfactants at increasing skin conductivity, and that the optimum surfactant tail length to attain synergistic skin permeability enhancement with LFS is 14 carbons, compared to 12 carbons for passive enhancement.[33]

The effects of a surfactant present in the coupling medium during sonophoretic treatment can be broadly classified into two types: (i) the effect of the surfactant on ultrasound-related phenomena, and (ii) the effect of ultrasound on surfactant penetration, dispersion, and partitioning in the skin. Although these two mechanisms are strongly coupled, for simplicity, they will be discussed separately. Surfactants can affect cavitation through several mechanisms. Because of their preferential adsorption at interfaces, surfactants tend to reduce the surface tension of aqueous solutions. Surface tension has its greatest effect on the oscillation of a cavitation bubble at the beginning of its expansion and at the end of its compression, causing an increase in the rate of expansion and a decrease in the rate of compression as the surface tension decreases.[63] In general, sonochemical activity is favored in liquids possessing higher surface tensions because it leads to more violent collapse of bubbles, and consequently, more sonochemical related phenomena take place.[115] However, in addition to decreasing the surface tension, surfactants also play a role in stabilizing cavitation bubbles by inhibiting bubble coalescence and growth, especially in the case of charged surfactants (due to the electrostatic repulsions between charged bubbles). Therefore, the addition of surfactants to the coupling medium leads to a larger population of smaller cavitation bubbles.[73] If the ultrasound field is pulsed, some of these smaller bubbles have a tendency to dissolve back into the solution when the ultrasound is off due to the Laplace pressure of the bubble (see Section 2.1.2).[73] The interplay between cavitation bubble growth and coalescence inhibition depends on the surfactant concentration. Usually, in LFS-mediated transdermal drug delivery experiments, 1% w/v SLS is used in the coupling medium. At this SLS concentration, experiments have shown that shielding and stabilization effects play a more significant role than surface tension effects.[73] As a result, it is observed that when 1% w/v SLS is present in the coupling medium during LFS treatment, transient cavitation activity decreases when compared to experiments performed when SLS is not present in the coupling medium, due to the existence of a population of smaller less energetic cavitation bubbles in the presence of SLS. For example, Mitragotri *et al.* measured transient cavitation events by aluminum foil pitting and found that when 1% w/v SLS in PBS solution was used instead of just a PBS solution, the number of pits decreased from 73±20 pits, in 20 seconds, to 6±4 pits.[19] These authors also found that the average pit diameter decreased when 1% w/v SLS was present in the coupling medium. Therefore, it does not appear that a change in cavitation activity would favor synergism between LFS and surfactants, but instead, may actually inhibit it. Therefore, there must be some other mechanism to explain the synergism between surfactants and sonophoresis.

Chemical enhancers, such as surfactants, are known to increase the rate of transdermal drug delivery by: i) increasing the stratum corneum lipid fluidity, ii) changing lipid organization,[116] iii) decreasing the path length and tortuosity across the stratum corneum, iv) increasing the skin diffusion coefficient, and v) increasing the coupling medium-to-skin

partition coefficient.[117, 118] However, the barrier properties of the skin inhibit the extent to which surfactants can diffuse into and perturb the skin passively in a reasonable amount of time. Therefore, it is believed that the main role of the synergism between LFS and the surfactant is the ability of LFS to increase the concentration and dispersion of the surfactant inside the stratum corneum.[28] By carrying out a series of experiments in which skin was soaked in a solution of 1% w/v SLS for various durations between 1 minute and 24 hours, followed by the application of LFS/SLS for 10 minutes, Mitragotri *et al.* found that as the skin soaking time increased, the ratio of skin conductivity after ultrasound treatment to skin conductivity prior to ultrasound treatment decreased.[19] This result shows that the effect of LFS treatment is diminished with increased passive exposure time to SLS. From these results, the authors argued that synergism between LFS and SLS is due to the increased penetration and dispersion of the surfactant in the skin induced by LFS.[19] Another study suggested that pH changes induced in the skin during LFS may explain the synergism between LFS and SLS.[48] However, it is not clear whether the pH changes in the skin are merely a consequence of the combined LFS/SLS treatment or, in fact, play a role in the observed synergism. In spite of the findings above, no convincing physical mechanism has been proposed to date to explain why LFS causes increased uptake of surfactants. Therefore, this important topic is still an area of active research.

4.3 Synergism of Sonophoresis with Other Physical Enhancers

Early research using HFS showed that when an injection of hydrocortisone was followed by ultrasound treatment at 1 MHz, the effects of the combined treatment were superior to those of the injection alone,[3] essentially showing synergism between the injection and the therapeutic ultrasound treatment. Later, Kost *et al.* investigated synergism between HFS and electroporation, which is the process of increasing skin permeability by applying a high-voltage pulsed electric field across the skin.[119] In this study, the transport of two model permeants, calcein and sulforhodamine, were investigated in response to 10–150 V electric pulses (1 millisecond every minute) in combination with 1 MHz HFS. Although HFS alone did not increase the skin permeability to either model permeant, the combination of HFS and electroporation increased the flux of calcein by a factor of 2 and of sulforhodamine by a factor of 3, compared to the enhancement observed by electroporation alone. In addition, the lag time to steady state was decreased by 40%, relative to the case of electroporation alone, from 15 minutes to 9 minutes. However, when 3 MHz ultrasound was applied, very little synergism was observed. This led the authors to conclude that the mechanism of synergism between HFS and electroporation was cavitation-induced disordering of the skin's lipid bilayers and convection across the skin, because cavitational effects are inversely proportional to ultrasound frequency. Furthermore, convection-induced enhancement was dependent on the properties of the permeant considered. For example, the electric field played a larger role in the flux enhancement of the more highly-charged calcein (total charge of -4) than in the transport of sulforhodamine (total charge of -1) across the skin.[119]

The most common type of physical enhancer that has been studied in combination with LFS is iontophoresis, the process of increasing skin permeability by continuously applying a low voltage electric field across the skin. Le *et al.* studied the synergism of LFS at 20 kHz, through a coupling medium containing 1 wt% SLS or dodecyl pyridinium chloride (DPC), with iontophoresis applied at an energy density of 0.45 mA/cm^2.[27] Utilizing heparin, a negatively-charged biopolymer with average molecular weight of 10 kDa, as a model drug, these authors found that the skin permeability was over two-fold higher with the combination of LFS and iontophoresis (through an SLS coupling medium) than when utilizing either physical enhancer alone. Subsequently, by utilizing the positively-charged surfactant DPC, the authors were able to show that the initial (first hour) flux of the negatively-charged heparin was nearly twice that corresponding to the SLS treatment case.

[27] The authors reasoned that this was due to the fact that when the negatively-charged SLS was utilized, both SLS and heparin competed for the same current, while the opposite charges of DPC and heparin would negate this effect. However, the steady-state heparin permeability induced by SLS, in combination with LFS and iontophoresis, was still slightly higher than that attained using the same treatment with DPC. This suggests that the combined LFS treatment with SLS caused greater sustained skin perturbation than DPC. The authors concluded that the synergistic enhancement observed with LFS and iontophoresis was practically significant because it: i) allowed the delivery of a macromolecule at therapeutic levels, ii) required reduced voltage/current to achieve the desired flux, and iii) allowed for active control of transdermal transport.[27] In another study, Fang *et al.* also found that LFS (20 kHz), when combined with iontophoresis (0.5 mA/cm^2), increased permeation of sodium nonivamide acetate across nude mouse skin in a synergistic manner.[120] In a more recent study using an intermediate ultrasound frequency (270 kHz), Watanabe *et al.* demonstrated that the combined application of iontophoresis (20 V, 0.45–1.0 mA) with ultrasound can increase the delivery of hydrophilic model compounds across hairless mouse skin in a synergistic manner.[98] Specifically, despite minimal enhancing effects when ultrasound and iontophoresis were used separately, their combination increased delivery of antipyrine and sodium salicylate 10-fold. The authors suggested that the mechanism of enhancement was loosening of the connections of the stratum corneum by ultrasound, followed by increased electroosmotic flow due to iontophoresis.[98] In another study utilizing intermediate ultrasound, Hikima *et al.* studied the mechanisms of synergistic delivery of seven model permeants, ranging in size from 122–1485 Da, utilizing 300 kHz ultrasound and iontophoresis (0.32 mA/cm^2).[121] The study found that chemicals that were non-ionized or greater than 1000 Da in molecular weight showed synergistic enhancement with the combined ultrasound and iontophoresis application, whereas ionized drugs showed similar profiles in response to the iontophoretic treatment alone. The authors also conducted simulations that showed that the synergistic effect between ultrasound and iontophoresis occurred due to increased electroosmosis in the stratum corneum. Consequently, the synergistic mechanism was a result of increased skin diffusivity due to the action of ultrasound on the skin, followed by increased electroosmotic flow induced by iontophoresis.[121] Finally, Liu *et al.* demonstrated that pretreatment of rat skin with laurocapram and LFS (20 kHz), followed by electroporation of the skin samples, increased penetration of cyclosporin A by a factor of 15.[104]

Recently, LFS has also been utilized in conjunction with other physical enhancers in a clinical setting. For example, Spierings *et al.* investigated the ability of LFS, in the form of the FDA approved SonoPrep® device (Echo Therapeutics, Franklin, MA), to act synergistically with low-voltage iontophoresis, in the form of the FDA approved Phoresor PM700® device (Iomed Incorporated, Salt Lake City, UT), in delivering the topical anesthetic Iontocaine® (Abbot Laboratories, Chicago, IL).[59] The study showed that a pretreatment with LFS, followed by 2 minutes of low-voltage iontopheresis, provided statistically similar pain relief as 10 minutes of standard high-voltage iontophoresis. A similar study with higher ultrasound frequencies found that the combined treatment of iontophoresis (5 mA) and HFS (1 MHz) to deliver cortisol was effective in decreasing subjective pain complaints of patients with mild to intermediate stages of carpal tunnel syndrome.[122] Finally, a recent clinical study reported the use of microdermabrasion treatment, followed by the application of sonophoresis through a complex containing hyaluronic acid, retinol, and peptide.[123] The authors showed that the combination of the two physical skin penetration enhancement methods had beneficial effects in photorejuvenation of the skin, such as enhanced vascularity in the dermis and increased type I and III collagen formation.[123]

5. Scope of Transdermal Delivery Utilizing Sonophoresis

5.1 High-Frequency Sonophoresis

The use of therapeutic frequencies of ultrasound to increase the cutaneous penetration of cortisol, a topical steroid, was first demonstrated by Fellinger and Schmid in 1954.[2] Additional research on sonophoresis during the same time period showed beneficial effects of therapeutic ultrasound after injection of drugs[3, 124, 125] and the treatment of localized disorders with ultrasound treatment alone, such as in the treatment of pain, scars, arthritis, epicondylitis, keloid growth, and bursitis.[126–131] The popularity of delivering therapeutic compounds with ultrasound increased over the following decades, with at least 150 independent reports to-date describing the use of ultrasound frequencies greater than 0.7 MHz in the delivery of permeants transdermally. These studies are summarized in Table 1.

Nearly all studies involving HFS have utilized the simultaneous treatment protocol, that is, the drug being delivered is included in the coupling medium (typically a gel) during ultrasound treatment. Therefore, in addition to cavitational effects within the skin[12] that can increase skin permeability, thermal and convective effects can also play a role in increasing solute partitioning into the stratum corneum of the skin and subsequent mobility therein (see Section 3 for more details). The additional enhancement resulting from this combination of mechanisms is beneficial, because enhancement by HFS is usually modest (1- to 10-fold) when compared to enhancements observed with LFS.[4, 6–8] However, this level of enhancement may be sufficient for the applications that HFS has been used for, which usually entail topical or regional delivery of therapeutics (for example, topical steroids for inflammatory conditions or arthritic joints, see Table 1). Systemic delivery is not a common goal with HFS. Furthermore, most compounds delivered by HFS are small molecules, with only a handful of drugs having molecular weights greater than 1000 Da tested (see Table 1). This is consistent with the assertion that HFS does not change the structure of the skin greatly, and therefore, can only operate by increasing the penetration of molecules that would likely penetrate the skin in lesser amounts under passive conditions. Nevertheless, the fact that HFS does not induce large changes to the skin barrier is also a strength of this treatment method, as it is generally considered to be a very safe technology, and is frequently utilized in other widespread applications, such as in sports and physical therapy. Furthermore, because many ultrasound devices that operate in the range 0.7 – 3.0 MHz are FDA approved, it is much easier to initiate human trials of such therapies, as evidenced by the large number of *in vivo* human studies presented in Table 1 (in comparison, far fewer *in vivo* studies are summarized in Table 2 in the case of LFS). Therefore, as evidenced by the nearly 90 compounds tested with HFS listed in Table 1, the use of therapeutic and high-frequency ultrasound for skin penetration enhancement has a rather large scope, with interest in the technology continuing to the present day.[81–85, 132]

5.2 Low-Frequency Sonophoresis

LFS is at a disadvantage relative to HFS in that it has been studied extensively only over the past two decades. Therefore, LFS has been investigated in fewer studies and currently lacks the historical track record of safety that HFS enjoys. The first investigations devoted *solely* to the use of LFS for transdermal delivery were conducted by Tachibana and Tachibana in the early 1990s,[89, 261, 262] and involved the use of 48 kHz and 105 kHz ultrasound for the delivery of insulin and lidocaine to mice and rabbits. Surprisingly, a review of the literature shows that Griffen *et al.* used LFS at 90 kHz, *in 1965*,[180] and demonstrated that the penetration of cortisol into subcutaneous pig nerves was higher for the 90 kHz treatments than those at 1MHz. However, frequencies in the range 20 – 100 kHz were seemingly forgotten for the next 25 years, until the aforementioned publications by Tachibana and Tachibana.[89, 261, 262] These studies were followed by work done by

Mitragotri *et al.*, who showed that macromolecules even larger than insulin could be delivered transdermally at therapeutic levels, including interferon-γ (17 kDa) and erythropoietin (48 kDa).[7] A subsequent investigation demonstrated that LFS is up to three orders of magnitude more effective at increasing skin penetration enhancement of compounds transdermally than HFS.[8] From these beginnings, research on low-frequency ultrasound-mediated transdermal drug delivery has exploded, with dozens of different groups working on applications of this technology (see Table 2). All types of permeants, from small hydrophobic compounds, such as salicylic acid, to highly hydrophilic compounds, such as vasopressin, to proteins, such as insulin, and even vaccines or nanoparticles, have been delivered transdermally with LFS. All the permeants that have been delivered by LFS through varying skin models, to-date, are listed in Table 2. Note the wide range of molecules that have been delivered by LFS, including those that are either hydrophilic (negative octanol-water partition coefficient, log $K_{o/w}$) or hydrophobic (positive log $K_{o/w}$), and those that are low-molecular weight (< 1000 Da molecular weight, MW) or high-molecular weight (≥ 1000 Da MW). LFS has truly increased both the type and the extent to which molecules can be delivered through the skin at therapeutic levels, compared to HFS, which is typically limited to lower molecular weight compounds. Therefore, the scope of LFS may be even greater than that of HFS, although LFS faces more regulatory hurdles than HFS treatments, due to the current lack of historical precedence of safety.

6. Emerging Trends in Sonophoresis

6.1 High-Frequency Sonophoresis

The future of HFS appears to be very similar to its past, that is, in its utilization for the treatment of topical or regional disorders. A review of publications in the last two years reveals that the most common types of drugs delivered with HFS are anti-inflammatory medications for joint and muscle pain, as well as ointments for local skin or muscle conditions. However, while historically the most common types of anti-inflammatory medications used with HFS have been topical steroids, such as cortisol, dexamethasone, or prednisolone (see Table 1), a shift has been seen in recent years to non-steroidal anti-inflammatory drugs (NSAIDs). These include: i) diclofenac, used to alleviate knee pain or arthritis,[199, 200], ii) ibuprofen, used to treat pain and inflammation in arthritis and other ailments,[84, 200] iii) ketoprofen, used in treating pain of the knee and termporomandibular joints,[82], iv) ketorolac, used for post-operative pain and inflammation,[223] v) nimesulide, used for acute pain, such as that associated with osteoarthritis,[81] and vi) piroxicam, used to treat symptoms of arthritis.[85, 200, 239] This trend is likely due to the fact that oral NSAIDs commonly cause gastrointestinal (GI) side-effects, such as nausea, heartburn, GI ulcers, GI inflammation, nonspecific colitis, relapse of inflammatory bowel disease, and GI bleeding, among others.[292, 293] Meanwhile, common uses of oral NSAIDs include local joint conditions such as arthritis, that may be equally, or more, effective if administered topically, while greatly mitigating systemic side-effects.[294] In fact, it has been shown that treating GI-related side-effects of NSAID usage adds, on average, nearly 46% to the total cost of patient care.[295, 296] Therefore, creating a dependable and usable topical NSAID treatment method is clearly an area of need, and is a current and emerging trend with HFS.

Other recent studies that have utilized HFS for increased percutaneous absorption to treat local ailments include: i) aloe vera, a common skin moisturizer or skin healing agent,[83] ii) *Arnica montana*, a plant extract used to treat inflammatory muscle lesions,[135] iii) dimethylsulfoxide, for the treatment of local muscle damage and oxidative stress,[132] panax notoginseng, an herbal extract used to increase strength of local ligament repair,[233] and v) sinomenine, a morphinan derivative used in the treatment of rheumatism and arthritis.[111] In nearly all of these studies, the combination of HFS treatment with the active agent showed increased benefit over passive treatment with the drug alone. Therefore, because of

its track-record of safety and its ability to increase the epidermal penetration of topical ointments, it is likely that HFS will continue to emerge as a viable method for the delivery of low-molecular weight drugs (<1000 Da) for local and regional ailments.

6.2 Low-Frequency Sonophoresis

Unlike HFS, LFS is not restricted as severely by the size of the molecules that it can deliver, since proteins, vaccines, and even nanoparticles have been demonstrated to be deliverable by LFS (see Table 2). Therefore, emerging trends with LFS include the delivery of therapeutics for systemic, regional, or local conditions. Arguably the most exciting application is the use of LFS for transdermal vaccination. Transcutaneous administration of vaccines is already known to act as an immunization adjuvant, by targeting the Langerhans cells of the viable epidermis.[297, 298] Even ultrasound itself, without exposure to an antigen, has been shown to elicit an immune response and to activate Langerhans cells.[53, 299] Furthermore, it has been demonstrated that LFS can be utilized to deliver high-molecular weight vaccines, such as tetanus toxoid, and can offer equal protection as intramuscular injection.[53, 291] Therefore, it is of no surprise that transdermal vaccination by LFS is an area of increased research interest. Transdermal vaccination has the added safety benefits of decreased risk of needle misuse, abuse, or re-use, especially in lower income areas and nations where these types of issues can be a problem.[101, 300] Moreover, an equal immune response can be achieved by transdermal application of antigens, as injection, but with the body being exposed to a far smaller concentration of antigen. For example, Tezel *et al.* have shown that just 1.3 μg of tetanus toxoid delivered to the Langerhans cells after LFS treatment elicited an immune response equivalent to that of 10 μg injected subcutaneously in mouse models.[53] This clearly demonstrates the ability of LFS to deliver vaccines effectively.

Another interesting area of research is the use of LFS to transdermally deliver drug carriers, which could be used for targeted or systemic delivery of agents. For example, several groups have recently shown the ability of LFS to deliver nanoparticles as large as ~100 nm through the stratum corneum, the primary barrier of the skin, into the viable epidermal and dermal skin layers.[35, 39, 42, 287] Specifically, Lopez *et al.* have utilized functionalized quantum dots (QDs), to mimic drug delivery vehicles, in order to understand optimum surface chemistry for the delivery of nano-carriers through LFS-treated skin.[287] Their findings showed that cationic, neutral, and anionic QDs, ranging in size from 10 – 22 nm, could be delivered into the dermal layers of LFS-treated skin. They found that, unexpectedly, the cationic-functionalized QD with the highest charge did not penetrate to the greatest extent through LFS-treated skin. Therefore, it is likely that an optimal cationic surface charge exists when designing transdermal drug delivery vehicles.[287] Therefore, with further research in this area, one could design drug delivery carriers that could be administered through LFS-treated skin for applications such as transdermal vaccination, the delivery of drugs for treatment of skin disorders, or even possibly for systemic delivery.

Other areas in which LFS has been utilized in emerging technologies include: i) blood glucose monitoring,[29, 30, 301–305], protein delivery,[225, 271, 275, 278, 279], and in clinical allergy testing.[274] Glucose-monitoring, coupled with transdermal insulin delivery, [225, 275, 278, 279] is especially exciting because it may permit the creation of a closed-loop system that allows for on-demand delivery of insulin, based on a patient's continuous blood-glucose measurements.[305] The miniaturization of LFS horns, to the size of 3 – 6 cm wearable devices, has brought this goal even closer to reality. [275, 278–280, 282, 289, 304, 305] Needless to say, there are many emerging LFS technologies on the horizon that may change how doctors administer, and patients receive, drug therapies in the future.

7. Conclusions

The use of ultrasound for the transdermal delivery of drugs has been investigated extensively. Mechanisms of skin permeabilization induced by low-frequency ultrasound (low-frequency sonophoresis, LFS) and by therapeutic and high-frequency ultrasound (high-frequency sonophoresis, HFS) are different. With LFS, the primary mechanism of enhancement has been conclusively shown to be transient acoustic cavitation above the skin membrane, likely as microjets impinging on the skin surface. With HFS, cavitation within the skin, either in skin appendages or at locations near the kerotinocytes of the stratum corneum, is the main contributor to skin permeability enhancement, although other mechanisms may play more minor roles. In general, HFS is more effective at increasing the skin penetration of small molecular weight compounds, such as NSAIDs and topical steroids. Moreover, because HFS has a long track-record of safety and use in patients for physical therapy, HFS also has the advantage of being more readily usable in human trials. On the other hand, LFS has shown a much greater capacity to deliver high-molecular weight compounds, including proteins, hormones, vaccines, and nanoparticles. However, clinical uses of LFS are in their infancy, with only a few current applications in patients, due to the relatively shorter time frame in which LFS-mediated transdermal delivery has been investigated. Regardless, both HFS and LFS technologies are being utilized to an increasing extent, and provide the potential to improve how drugs are administered to patients clinically.

Acknowledgments

The authors thank Jennifer Seto for her useful feedback in the preparation of this review. This work was funded by the National Institutes of Health (Grant# EB-00351) and the U.S. Army Research Office through the Institute for Soldier Nanotechnologies at MIT (Grant# DAAD-19-02-D-002). The contents of this manuscript represent solely the views of the authors and do not necessarily reflect the position of the U.S. Government. No official endorsement should be inferred.

References

1. Mitragotri S. Sonophoresis: a 50-year journey. Drug Discov Today. 2004; 9(17):735–736. [PubMed: 15450237]
2. Fellinger, K.; Schmid, J. Klinik und Therapie des chronischen Gelenkrheumatismus. Maudrich, Vienna, Austria: 1954.
3. Newman M, Kill M, Frampton G. Effects of ultrasound alone and combined with hydrocortisone injections by needle or hypo-spray. Amer J Physical Med. 1958; 37(4):206–209.
4. Tyle P, Agrawala P. Drug delivery by phonophoresis. Pharm Res. 1989; 6(5):355–361. [PubMed: 2664754]
5. Bommannan D, Menon G, Okuyama H, Elias P, Guy R. Sonophoresis. II. Examination of the mechanism (s) of ultrasound-enhanced transdermal drug delivery. Pharm Res. 1992; 9(8):1043–1047. [PubMed: 1409375]
6. Byl N. The use of ultrasound as an enhancer for transcutaneous drug delivery: phonophoresis. Phys Ther. 1995; 75(6):539. [PubMed: 7770499]
7. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science. 1995; 269(5225):850–853. [PubMed: 7638603]
8. Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using low-frequency sonophoresis. Pharm Res. 1996; 13(3):411–420. [PubMed: 8692734]
9. Apfel R. Acoustic cavitation: a possible consequence of biomedical uses of ultrasound. Br J Cancer. 1982; (Suppl 5):140–146. [PubMed: 7059457]
10. Kost, J.; Levy, D.; Langer, R. Ultrasound effect on transdermal drug delivery; International Symposium Controlled Release; 1986. p. 177-178.

11. Levy D, Kost J, Meshulam Y, Langer R. Effect of ultrasound on transdermal drug delivery to rats and guinea pigs. J Clin Invest. 1989; 83(6):2074. [PubMed: 2498396]
12. Mitragotri S, Edwards D, Blankschtein D, Langer R. A mechanistic study of ultrasonically-enhanced transdermal drug delivery. J Pharm Sci. 1995; 84(6):697–706. [PubMed: 7562407]
13. Gaertner W. Frequency Dependence of Ultrasonic Cavitation. J Acoust Soc Am. 1954; 26(6):977–980.
14. Baroli B. Penetration of nanoparticles and nanomaterials in the skin: Fiction or reality? J Pharm Sci. 2010; 99(1):21–50. [PubMed: 19670463]
15. Cevc G, Vierl U. Nanotechnology and the transdermal route:: A state of the art review and critical appraisal. J Control Release. 2010; 141(3):277–299. [PubMed: 19850095]
16. Polat B, Blankschtein D, Langer R. Low-frequency sonophoresis: application to the transdermal delivery of macromolecules and hydrophilic drugs. Expert Opin Drug Del. 2010; 7(12):1415–1432.
17. Leighton T. What is ultrasound? Prog Biophys Mol Bio. 2007; 93(1–3):3–83. [PubMed: 17045633]
18. Pointon A. Piezoelectric devices. IEE Proc-A. 1982; 129(5):285–307.
19. Mitragotri S, Ray D, Farrell J, Tang H, Yu B, Kost J, Blankschtein D, Langer R. Synergistic effect of low-frequency ultrasound and sodium lauryl sulfate on transdermal transport. J Pharm Sci. 2000; 89(7):892–900. [PubMed: 10861590]
20. Boucaud A, Montharu J, Machet L, Arbeille B, Machet M, Patat F, Vaillant L. Clinical, histologic, and electron microscopy study of skin exposed to low-frequency ultrasound. Anat Rec Part A. 2001; 264(1):114–119.
21. Tang H, Mitragotri S, Blankschtein D, Langer R. Theoretical description of transdermal transport of hydrophilic permeants: application to low-frequency sonophoresis. J Pharm Sci. 2001; 90(5): 545–568. [PubMed: 11288100]
22. Tang H, Wang C, Blankschtein D, Langer R. An investigation of the role of cavitation in low-frequency ultrasound-mediated transdermal drug transport. Pharm Res. 2002; 19(8):1160–1169. [PubMed: 12240942]
23. Alvarez-Román R, Merino G, Kalia Y, Naik A, Guy R. Skin permeability enhancement by low frequency sonophoresis: lipid extraction and transport pathways. J Pharm Sci. 2003; 92(6):1138–1146. [PubMed: 12761803]
24. Kushner J, Kim D, So P, Blankschtein D, Langer R. Dual-channel two-photon microscopy study of transdermal transport in skin treated with low-frequency ultrasound and a chemical enhancer. J Invest Dermatol. 2007; 127(12):2832–2846. [PubMed: 17554365]
25. Polat B, Figueroa P, Blankschtein D, Langer R. Transport Pathways and Enhancement Mechanisms Within Localized and Non-Localized Transport Regions in Skin Treated with Low-Frequency Sonophoresis and Sodium Lauryl Sulfate. J Pharm Sci. (in press).
26. Wolloch L, Kost J. The importance of microjet vs shock wave formation in sonophoresis. J Control Release. 2010; 148(2):204–211. [PubMed: 20655341]
27. Le L, Kost J, Mitragotri S. Combined effect of low-frequency ultrasound and iontophoresis: applications for transdermal heparin delivery. Pharm Res. 2000; 17(9):1151–1154. [PubMed: 11087051]
28. Mitragotri S. Synergistic effect of enhancers for transdermal drug delivery. Pharm Res. 2000; 17(11):1354–1359. [PubMed: 11205727]
29. Mitragotri S, Coleman M, Kost J, Langer R. Transdermal extraction of analytes using low-frequency ultrasound. Pharm Res. 2000; 17(4):466–470. [PubMed: 10870992]
30. Mitragotri S, Kost J. Low-frequency sonophoresis: a noninvasive method of drug delivery and diagnostics. Biotechnol Prog. 2000; 16(3):488–492. [PubMed: 10835253]
31. Tang H, Blankschtein D, Langer R. Effects of low-frequency ultrasound on the transdermal permeation of mannitol: comparative studies with in vivo and in vitro skin. J Pharm Sci. 2002; 91(8):1776–1794. [PubMed: 12115805]
32. Terahara T, Mitragotri S, Langer R. Porous resins as a cavitation enhancer for low-frequency sonophoresis. J Pharm Sci. 2002; 91(3):753–759. [PubMed: 11920760]

33. Tezel A, Sens A, Tuchscherer J, Mitragotri S. Synergistic effect of low-frequency ultrasound and surfactants on skin permeability. J Pharm Sci. 2002; 91(1):91–100. [PubMed: 11782900]
34. Kushner J, Blankschtein D, Langer R. Experimental demonstration of the existence of highly permeable localized transport regions in low-frequency sonophoresis. J Pharm Sci. 2004; 93(11): 2733–2745. [PubMed: 15389675]
35. Paliwal S, Menon G, Mitragotri S. Low-frequency sonophoresis: ultrastructural basis for stratum corneum permeability assessed using quantum dots. J Invest Dermatol. 2006; 126(5):1095–1101. [PubMed: 16528354]
36. Kushner J, Blankschtein D, Langer R. Evaluation of the porosity, the tortuosity, and the hindrance factor for the transdermal delivery of hydrophilic permeants in the context of the aqueous pore pathway hypothesis using dual-radiolabeled permeability experiments. J Pharm Sci. 2007; 96(12): 3263–3282. [PubMed: 17887176]
37. Kushner J, Blankschtein D, Langer R. Heterogeneity in skin treated with low-frequency ultrasound. J Pharm Sci. 2008; 97(10):4119–4128. [PubMed: 18240305]
38. Kushner J, Blankschtein D, Langer R. Evaluation of hydrophilic permeant transport parameters in the localized and non-localized transport regions of skin treated simultaneously with low-frequency ultrasound and sodium lauryl sulfate. J Pharm Sci. 2008; 97(2):906–918. [PubMed: 17887123]
39. Seto J, Polat B, Lopez R, Blankschtein D, Langer R. Effects of ultrasound and sodium lauryl sulfate on the transdermal delivery of hydrophilic permeants: Comparative in vitro studies with full-thickness and split-thickness pig and human skin. J Control Release. 2010; 145(1):26–32. [PubMed: 20346994]
40. Merino G, Kalia Y, Delgado-Charro M, Potts R, Guy R. Frequency and thermal effects on the enhancement of transdermal transport by sonophoresis. J Control Release. 2003; 88(1):85–94. [PubMed: 12586506]
41. Terahara T, Mitragotri S, Kost J, Langer R. Dependence of low-frequency sonophoresis on ultrasound parameters; distance of the horn and intensity. Int J Pharm. 2002; 235(1–2):35–42. [PubMed: 11879737]
42. Lee S, Choi K, Menon G, Kim H, Choi E, Ahn S, Lee S. Penetration Pathways Induced by Low-Frequency Sonophoresis with Physical and Chemical Enhancers: Iron Oxide Nanoparticles versus Lanthanum Nitrates. J Invest Dermatol. 2010; 130(4):1063–1072. [PubMed: 19940858]
43. Tezel A, Mitragotri S. Interactions of inertial cavitation bubbles with stratum corneum lipid bilayers during low-frequency sonophoresis. Biophys J. 2003; 85(6):3502–3512. [PubMed: 14645045]
44. Tezel A, Sens A, Mitragotri S. A theoretical analysis of low-frequency sonophoresis: dependence of transdermal transport pathways on frequency and energy density. Pharm Res. 2002; 19(12): 1841–1846. [PubMed: 12523663]
45. Tezel A, Sens A, Mitragotri S. Investigations of the role of cavitation in low-frequency sonophoresis using acoustic spectroscopy. J Pharm Sci. 2002; 91(2):444–453. [PubMed: 11835204]
46. Tezel A, Sens A, Mitragotri S. Description of transdermal transport of hydrophilic solutes during low-frequency sonophoresis based on a modified porous pathway model. J Pharm Sci. 2003; 92(2):381–393. [PubMed: 12532387]
47. Ueda H, Mutoh M, Seki T, Kobayashi D, Morimoto Y. Acoustic Cavitation as an Enhancing Mechanism of Low-Frequency Sonophoresis for Transdermal Drug Delivery. Biol Pharm Bull. 2009; 32(5):916–920. [PubMed: 19420764]
48. Lavon I, Grossman N, Kost J. The nature of ultrasound-SLS synergism during enhanced transdermal transport. J Control Release. 2005; 107(3):484–494. [PubMed: 16165244]
49. Lavon I, Grossman N, Kost J, Kimmel E, Enden G. Bubble growth within the skin by rectified diffusion might play a significant role in sonophoresis. J Control Release. 2007; 117(2):246–255. [PubMed: 17197050]
50. Mitragotri S, Farrell J, Tang H, Terahara T, Kost J, Langer R. Determination of threshold energy dose for ultrasound-induced transdermal drug transport. J Control Release. 2000; 63(1–2):41–52. [PubMed: 10640579]

51. Mitragotri S, Kost J. Transdermal delivery of heparin and low-molecular weight heparin using low-frequency ultrasound. Pharm Res. 2001; 18(8):1151–1156. [PubMed: 11587487]
52. Tezel A, Dokka S, Kelly S, Hardee G, Mitragotri S. Topical delivery of anti-sense oligonucleotides using low-frequency sonophoresis. Pharm Res. 2004; 21(12):2219–2225. [PubMed: 15648253]
53. Tezel A, Paliwal S, Shen Z, Mitragotri S. Low-frequency ultrasound as a transcutaneous immunization adjuvant. Vaccine. 2005; 23(29):3800–3807. [PubMed: 15893617]
54. Tezel A, Sens A, Tuchscherer J, Mitragotri S. Frequency dependence of sonophoresis. Pharm Res. 2001; 18(12):1694–1700. [PubMed: 11785688]
55. Morimoto Y, Mutoh M, Ueda H, Fang L, Hirayama K, Atobe M, Kobayashi D. Elucidation of the transport pathway in hairless rat skin enhanced by low-frequency sonophoresis based on the solute-water transport relationship and confocal microscopy. J Control Release. 2005; 103(3):587–597. [PubMed: 15820406]
56. Katz N, Shapiro D, Herrmann T, Kost J, Custer L. Rapid onset of cutaneous anesthesia with EMLA cream after pretreatment with a new ultrasound-emitting device. Anesth Analg. 2004; 98(2):371. [PubMed: 14742372]
57. Becker B, Helfrich S, Baker E, Lovgren K, Minugh P, Machan J. Ultrasound with topical anesthetic rapidly decreases pain of intravenous cannulation. Acad Emerg Med. 2005; 12(4):289–295. [PubMed: 15805318]
58. Brown M, Martin G, Jones S, Akomeah F. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv. 2006; 13(3):175–187. [PubMed: 16556569]
59. Spierings E, Brevard J, Katz N. Two-minute skin anesthesia through ultrasound pretreatment and iontophoretic delivery of a topical anesthetic: A feasibility study. Pain Med. 2008; 9(1):55–59. [PubMed: 18254767]
60. Tang H, Blankschtein D, Langer R. Prediction of steady-state skin permeabilities of polar and nonpolar permeants across excised pig skin based on measurements of transient diffusion: Characterization of hydration effects on the skin porous pathway. J Pharm Sci. 2002; 91(8):1891–1907. [PubMed: 12115816]
61. Ghosh S, Blankschtein D. The role of sodium dodecyl sulfate (SDS) micelles in inducing skin barrier perturbation in the presence of glycerol. Int J Cosmetic Sci. 2007; 30:73.
62. Brennen, C. Cavitation and bubble dynamics. USA: Oxford University Press; 1995.
63. Margulis, M. Sonochemistry and Cavitation. Taylor & Francis; 1995.
64. Crum, L. Sonochemistry and sonoluminescence. Springer Netherlands; 1999.
65. Fong S, Klaseboer E, Turangan C, Khoo B, Hung K. Numerical analysis of a gas bubble near bio-materials in an ultrasound field. Ultrasound Med Biol. 2006; 32(6):925–942. [PubMed: 16785014]
66. Leighton T, Walton A, Pickworth M. Primary Bjerknes forces. Eur J Phys. 1990; (1):47.
67. Leighton T. An introduction to acoustic cavitation. Med Sci Ser. 1998:199–223.
68. Simonin J. On the mechanisms of in vitro and in vivo phonophoresis. J Control Release. 1995; 33(1):125–141.
69. Hsieh D, Plesset M. Theory of Rectified Diffusion of Mass into Gas Bubbles. J Acoust Soc Am. 1961; 33(2):206–215.
70. Eller A, Flynn H. Rectified diffusion during nonlinear pulsations of cavitation bubbles. J Acoust Soc Am. 1965; 37:493.
71. Naji Meidani A, Hasan M. Mathematical and physical modelling of bubble growth due to ultrasound. Appl Math Model. 2004; 28(4):333–351.
72. Jones S, Evans G, Galvin K. Bubble nucleation from gas cavities -- a review. Adv Colloid Interfac. 1999; 80(1):27–50.
73. Lee J, Kentish S, Matula T, Ashokkumar M. Effect of surfactants on inertial cavitation activity in a pulsed acoustic field. J. Phys. Chem. B. 2005; 109(35):16860–16865. [PubMed: 16853145]
74. Mason, T.; Peters, D. Practical sonochemistry: Uses and applications of ultrasound. Horwood Publishing Limited; 2002.
75. Pelekasis N, Gaki A, Doinikov A, Tsamopoulos J. Secondary Bjerknes forces between two bubbles and the phenomenon of acoustic streamers. J Fluid Mech. 2004; 500:313–347.

76. Mettin R, Akhatov I, Parlitz U, Ohl CD, Lauterborn W. Bjerknes forces between small cavitation bubbles in a strong acoustic field. Phys Rev E. 1997; 56(3):2924.
77. Mettin, R.; Koch, P.; Lauterborn, W.; Krefting, D. Modeling acoustic cavitation with bubble redistribution. Sixth International Symposium on Cavitation; Wageningen; The Netherlands. 2006.
78. Mettin, R.; Krefting, D.; Appel, J.; Koch, P.; Lauterborn, W. Stereoscopic high- speed recording of bubble structures. Proceedings of the 3rd Conference on Ultrasound in Processing; Paris, France. 2001. p. 199-203.
79. Appel J, Koch P, Mettin R, Krefting D, Lauterborn W. Stereoscopic high-speed recording of bubble filaments. Ultrason Sonochem. 2004; 11(1):39–42. [PubMed: 14624986]
80. Ogura M, Paliwal S, Mitragotri S. Low-frequency sonophoresis: current status and future prospects. Adv Drug Deliv Rev. 2008; 60(10):1218–1223. [PubMed: 18450318]
81. Barja, P.; Veloso, D. Photoacoustic study of the penetration kinetics of nimesulid into human skin; International Conference on Photoacoustic and Photothermal Phenomena; 2010. p. (214) 012017IOP Publishing
82. Kaya K, Delialouglu S, Babadag M, Duleroglu D, Ozel S, Culha C, Gorgun S. Combined Physiotherapy in Patients with Arthrogenous Pain of Temporomandibular Joint. J PMR Sci. 2010; 13:6–14.
83. Maia Filho ALM, Villaverde AB, Munin E, Aimbire F, Albertini R. Comparative Study of the Topical Application of Aloe Vera Gel, Therapeutic Ultrasound and Phonophoresis on the Tissue Repair in Collagenase-Induced Rat Tendinitis. Ultrasound Med Biol. 2010; 36(10):1682–1690. [PubMed: 20800944]
84. Meshali M, Abdel-Aleem H, Sakr F, Nazzal S, El-Malah Y. Effect of gel composition and phonophoresis on the transdermal delivery of ibuprofen: In vitro and in vivo evaluation. Pharm Dev Technol. 2010 (in press).
85. Silveira F, Barja P, Acosta-Avalos D. Photoacoustic evaluation of the penetration of piroxicam gel applied with phonophoresis into human skin. International Conference on Photoacoustic and Photothermal Phenomena. 2010:(214) 012022.IOP Publishing
86. Riesz P, Kondo T. Free radical formation induced by ultrasound and its biological implications. Free Radical Bio Med. 1992; 13(3):247–270. [PubMed: 1324205]
87. Meidan V, Walmsley A, Irwin W. Phonophoresis is it a reality? Int J Pharm. 1995; 118(2):129–149.
88. Julian T, Zentner G. Mechanism for ultrasonically enhanced transmembrane solute permeation. J Control Release. 1990; 12(1):77–85.
89. Tachibana K, Tachibana S. Use of ultrasound to enhance the local anesthetic effect of topically applied aqueous lidocaine. Anesthesiology. 1993; 78(6):1091. [PubMed: 8512102]
90. Lenart I, Ausländer D. The effect of ultrasound on diffusion through membranes. Ultrasonics. 1980; 18(5):216–218. [PubMed: 7414742]
91. Brucks R, Nanavaty M, Jung D, Siegel F. The effect of ultrasound on the in vitro penetration of ibuprofen through human epidermis. Pharm Res. 1989; 6(8):697–701. [PubMed: 2813262]
92. Bommannan D, Okuyama H, Stauffer P, Guy R. Sonophoresis. I. The use of high-frequency ultrasound to enhance transdermal drug delivery. Pharm Res. 1992; 9(4):559–564. [PubMed: 1495903]
93. Machluf M, Kost J. Ultrasonically enhanced transdermal drug delivery. Experimental approaches to elucidate the mechanism. J Biomat Sci-Polym E. 1993; 5(1–2):147–156.
94. Ueda H, Sugibayashi K, Morimoto Y. Skin penetration-enhancing effect of drugs by phonophoresis. J Control Release. 1995; 37(3):291–297.
95. Skauen D, Zentner G. Phonophoresis. Int J Pharm. 1984; 20(3):235–245.
96. Sundaram J, Mellein B, Mitragotri S. An experimental and theoretical analysis of ultrasound-induced permeabilization of cell membranes. Biophys J. 2003; 84(5):3087–3101. [PubMed: 12719239]
97. Isselin J, Alloncle A, Autric M. On laser induced single bubble near a solid boundary: Contribution to the understanding of erosion phenomena. J Appl Phys. 1998; 84:5766.

98. Watanabe S, Takagi S, Ga K, Yamamoto K, Aoyagi T. Enhanced transdermal drug penetration by the simultaneous application of iontophoresis and sonophoresis. Drug Del Sci Tech. 2009; 19(3): 185–189.

99. Joshi A, Raje J. Sonicated transdermal drug transport. J Control Release. 2002; 83(1):13–22. [PubMed: 12220834]

100. Pahade M, Jadhav M, Kadam M. Sonophoresis: An Overview. Int J Pharm Sci Res. 2010; 3(2): 24–32.

101. Prausnitz M, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004; 3(2):115–124. [PubMed: 15040576]

102. Johnson M, Mitragotri S, Patel A, Blankschtein D, Langer R. Synergistic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery. J Pharm Sci. 1996; 85(7): 670–679. [PubMed: 8818988]

103. Meidan V, Docker M, Walmsley A, Irwin W. Phonophoresis of hydrocortisone with enhancers: an acoustically defined model. Int J Pharm. 1998; 170(2):157–168.

104. Liu H, Li S, Pan W, Wang Y, Han F, Yao H. Investigation into the potential of low-frequency ultrasound facilitated topical delivery of Cyclosporin A. Int J Pharm. 2006; 326(1–2):32–38. [PubMed: 16949776]

105. Tiwari S, Pai R, Udupa N. Influence of ultrasound on the percutaneous absorption of ketorolac tromethamine in vitro across rat skin. Drug Deliv. 2004; 11(1):47–51. [PubMed: 15168791]

106. Xu X, Zhu Q, Sun C. Combined effect of ultrasound-SLS on skin optical clearing. IEEE Photonic Tech L. 2008; 20(24):2117–2119.

107. Xu X, Zhu Q, Sun C. Assessment of the effects of ultrasound-mediated alcohols on skin optical clearing. J Biomed Opt. 2009; 14(3) 034042.

108. Xu X, Zhu Q, Sun C. Assessment of the effects of ultrasound-mediated alcohols on skin optical clearing. J Biomed Opt. 2009; 14 034042.

109. Zhong H, Guo Z, Wei H, Guo L, Wang C, He Y, Xiong H, Liu S. Synergistic Effect of Ultrasound and Thiazone–PEG 400 on Human Skin Optical Clearing In Vivo. Photochem Photobiol. 2010; 86(3):732–737. [PubMed: 20202160]

110. Zhong H, Guo Z, Wei H, Zeng C, Xiong H, He Y, Liu S. In vitro study of ultrasound and different-concentration glycerol--induced changes in human skin optical attenuation assessed with optical coherence tomography. J Biomed Opt. 2010; 15(3) 036012.

111. Li-an L, Hong W, Xin-Ping L, Jian-Qing G. Effect of Sonophoresis Combined with Chemical Enhancer on Transdermal Delivery of Sinomenine Hydrochloride Gel in Vitro. Chin Arch Trad Chin Med. 2009

112. Fang J, Fang C, Hong C, Chen H, Lin T, Wei H. Capsaicin and nonivamide as novel skin permeation enhancers for indomethacin. Eur J Pharm Sci. 2001; 12(3):195–203. [PubMed: 11113638]

113. Mutalik S, Parekh H, Davies N, Udupa N. A combined approach of chemical enhancers and sonophoresis for the transdermal delivery of tizanidine hydrochloride. Drug Deliv. 2009; 16(2): 82–91. [PubMed: 19267299]

114. Dahlan A, Alpar H, Murdan S. An investigation into the combination of low frequency ultrasound and liposomes on skin permeability. Int J Pharm. 2009; 379(1):139–142. [PubMed: 19539736]

115. Shah, Y.; Pandit, A.; Moholkar, V. Cavitation reaction engineering. Plenum Pub Corp; 1999.

116. Golden G, McKie J, Potts R. Role of stratum corneum lipid fluidity in transdermal drug flux. J Pharm Sci. 1987; 76(1):25–28. [PubMed: 3585718]

117. Yu B, Dong C, So P, Blankschtein D, Langer R. In vitro visualization and quantification of oleic acid induced changes in transdermal transport using two-photon fluorescence microscopy. J Invest Dermatol. 2001; 117(1):16–25. [PubMed: 11442745]

118. Yu B, Kim K, So P, Blankschtein D, Langer R. Visualization of oleic acid-induced transdermal diffusion pathways using two-photon fluorescence microscopy. J Invest Dermatol. 2003; 120(3): 448–455. [PubMed: 12603859]

119. Kost J, Pliquett U, Mitragotri S, Yamamoto A, Langer R, Weaver J. Synergistic effect of electric field and ultrasound on transdermal transport. Pharm Res. 1996; 13(4):633–638. [PubMed: 8710759]

120. Fang J, Hwang T, Huang Y, Tsai Y. Transdermal iontophoresis of sodium nonivamide acetate: V. Combined effect of physical enhancement methods. Int J Pharm. 2002; 235(1–2):95–105. [PubMed: 11879744]

121. Hikima T, Ohsumi S, Shirouzu K, Tojo K. Mechanisms of Synergistic Skin Penetration by Sonophoresis and Iontophoresis. Biol Pharm Bull. 2009; 32(5):905–909. [PubMed: 19420762]

122. Dakowicz A, Latosiewicz R. The value of iontophoresis combined with ultrasound in patients with the carpal tunnel syndrome. Rocz Akad Med Bialymst. 2005; 50:196–198. [PubMed: 16119664]

123. Dudelzak J, Hussain M, Phelps R, Gottlieb G, Goldberg D. Evaluation of histologic and electron microscopic changes after novel treatment using combined microdermabrasion and ultrasound induced phonophoresis of human skin. J Cosmet Laser Ther. 2008; 10(4):187–192. [PubMed: 19012051]

124. Coodley E. Bursitis and post-traumatic lesions: management with combined use of ultrasound and intra-articular hydrocortisone. Am Pract. 1960; 11:181–187.

125. Mune O, Thorseth K. Ultrasonic treatment of subcutaneous infiltrations after injections. Acta Orthop Scand. 1963; 33(1–4):347–349.

126. Aldes J. Ultrasonic radiation in the treatment of epicondylitis. GP. 1956; 13(6):89. [PubMed: 13318162]

127. Aldes J, Jadeson W. Ultrasonic therapy in the treatment of hypertrophic arthritis in elderly patients. Ann West Med Surg. 1952; 6(9):545. [PubMed: 12977082]

128. Aldes J, Klaras T. Use of ultrasonic radiation in the treatment of subdeltoid bursitis with and without calcareous deposits. West J Surg Obstet Gynecol. 1954; 62(7):369–376. [PubMed: 13179503]

129. Bierman W. Ultrasound in the treatment of scars. Arch Phys Med Rehabil. 1954; 35(4):209–214. [PubMed: 13149318]

130. Kuitert J, Davis M, Brittis A, Aldes J. Control of keloid growth with ultrasonic energy; a report of two cases. Am J Phys Med. 1955; 34(3):408–412. [PubMed: 14376517]

131. Mune O, Thorseth K. Ultrasonic Treatment of Cicatricalgia. Acta Orthop Scand. 1963; 33(1–4): 342–346. [PubMed: 14106858]

132. Silveira P, Victor E, Schefer D, Silva L, Streck E, Paula M, Pinho R. Effects of Therapeutic Pulsed Ultrasound and Dimethylsulfoxide (DMSO) Phonophoresis on Parameters of Oxidative Stress in Traumatized Muscle. Ultrasound Med Biol. 2010; 36(1):44–50. [PubMed: 19900747]

133. Meidan V, Docker M, Walmsley A, Irwin W. Low intensity ultrasound as a probe to elucidate the relative follicular contribution to total transdermal absorption. Pharm Res. 1998; 15(1):85–92. [PubMed: 9487552]

134. Romanenko I, Aravi ski R. Comparative levels of amphotericin B in the skin and subcutaneous fatty tissue after cutaneous application of amphotericin ointment by phonophoresis and with preliminary treatment by dimethyl sulfoxide. Antibiot Khimioter. 1991; 36(9):29. [PubMed: 1781707]

135. Alfredo P, Anaruma C, Pião A, João S, Casarotto R. Effects of phonophoresis with Arnica montana onto acute inflammatory process in rat skeletal muscles: An experimental study. Ultrasonics. 2009; 49(4–5):466–471. [PubMed: 19152953]

136. Glushchenko L. Phonophoresis of thiamin and ascorbic acid. Zdravookhr Beloruss. 1977; 11:80–81.

137. Hakozaki T, Takiwaki H, Miyamoto K, Sato Y, Arase S. Ultrasound enhanced skin-lightening effect of vitamin C and niacinamide. Skin Res Technol. 2006; 12(2):105–113. [PubMed: 16626384]

138. Williams AR. Phonophoresis: An in vivo evaluation using three topical anaesthetic preparations. Ultrasonics. 1990; 28(3):137–141. [PubMed: 2339470]

139. Chatterjee D. A double-blind clinical study with benzydamine 3% cream on soft tissue injuries in an occupational health centre. J Int Med Res. 1977; 5(6):450–458. [PubMed: 338395]

140. Benson H, McElnay J, Whiteman J, Harland R. Lack of effect of ultrasound on the percutaneous absorption of benzydamine. J Pharm Pharmacol. 1986; 38

141. Benson H, McElnay J, Harland R. Use of ultrasound to enhance percutaneous absorption of benzydamine. Phys Ther. 1989; 69(2):113. [PubMed: 2913579]
142. Hofmann D, Moll F. The effect of ultrasound on in vitro liberation and in vivo penetration of benzyl nicotinate. J Control Release. 1993; 27(3):185–192.
143. Indkevich P. Experience in the treatment of hidradenitis with biomycin phonophoresis. Vestn Dermatol Venerol. 1971; 44:75–77.
144. Indkevich P. Use of biomycin phonophoresis in the treatment of suppurative skin diseases. Vestn Dermatol Venerol. 1972; 37:266–267.
145. Famaey J. Sonophoresis with non-steroidal antiinflammatory drugs. A survey of the problem (author's transl). J Belge Rhumatol Med Phys. 1975; 30(3):129–141. [PubMed: 1083388]
146. Monti D, Giannelli R, Chetoni P, Burgalassi S. Comparison of the effect of ultrasound and of chemical enhancers on transdermal permeation of caffeine and morphine through hairless mouse skin in vitro. Int J Pharm. 2001; 229(1–2):131–137. [PubMed: 11604265]
147. Choi EH, Kim MJ, Yeh B-I, Ahn SK, Lee SH. Iontophoresis and Sonophoresis Stimulate Epidermal Cytokine Expression at Energies That Do Not Provoke a Barrier Abnormality: Lamellar Body Secretion and Cytokine Expression Are Linked to Altered Epidermal Calcium Levels. J Invest Dermatol. 2003; 121(5):1138–1144. [PubMed: 14708617]
148. Wanet G, Dehon N. Clinical study of ultrasonophoresis with a topical preparation combining phenylbutazone and alpha-chymotrypsin. J Belge Rhumatol Med Phys. 1976; 31(2):49–58. [PubMed: 1002717]
149. Gatev S, Vatsov E. Attempt to treat essential pruritus vulvae and some inflammatory gynecologic diseases with hydrocortisone phonophoresis. Akush Ginekol. 1966; 5(2):123.
150. Safiulina S, Pushkareva A. Experience in the phonophoresis treatment with hydrocortisone of patients with diseases of the musculoskeletal system. Vopr Kurortol Fizioter Lech Fiz Kult. 1967; 32(6):485–488. [PubMed: 5609008]
151. Nagovitsyn E. Comparative evaluation of the effectiveness of hydrocortisone injections and phonophoresis in the treatment of diseases of the support-motor apparatus. Vestn Khir Im I I Grek. 1970; 104(3):54–55. [PubMed: 5505927]
152. Nagovitsyn E, Vakhatova I. Hydrocortisone phonophoresis for various diseases of the locomotor apparatus. Vopr Kurortol Fizioter Lech Fiz Kult. 1971; 36(2):180. [PubMed: 5095458]
153. Bel'ts E, Bondarenko M. The use of ultrasound and phonophoresis with hydrocortisone in chronic psoriasis. Vestn Dermatol Venerol. 1971; (45):70–72. [PubMed: 5122563]
154. Burgudzhieva T. The treatment of pruritus vulvae essentialis with ultrasound and hydrocortisone ointment as well as phonophoresis with hydrocortisone ointment. Akush Ginekol. 1971; 10(3): 231–234.
155. Burgudzhieva T. Comparative data on histological changes in the external genitalia in patients with pruritus vulvae essentialis before and after treatment by phonophoresis with unguentum hydrocortisone. Akush Ginekol. 1971; 10(16):477–482.
156. Burgudzhieva T. Histological changes in external genital organs in patients with kraurosis vulvae, treated by phonophoresis and hydrocortisone ointment. Akush Ginekol. 1971; 10(4):287–291.
157. Burgudzhieva T. Comparative study of treatment of kraurosis vulvae (lichen scleroatrophicus vulvae) with ultrasound, hydrocortisone ointment and phonophoresis with hydrocortisone ointment. Akush Ginekol. 1972; 11(3):246–251.
158. Burgudzhieva T. Effect of ultrasonics, hydrocortisone ointment and phonophoresis of hydrocortisone ointment on indices of sensory chronaximetry of kraurosis vulvae, lichen scleroatrophicus vulvae and pruritis vulvae essentialis. Vopr Kurortol Fizioter Lech Fiz Kult. 1974; (3):267–269. [PubMed: 4536573]
159. Grinshtein A, Shevchenko S. Rheoencephalographic studies of facial neuritis in treatment by ultrasonics and hydrocortisone phonophoresis. Vopr Kurortol Fizioter Lech Fiz Kult. 1973; 38(3):230. [PubMed: 4747478]
160. Grinshtein A, Tolmacheva A, Khriptulov V. The effectiveness of hydrocortisone phonophoresis in facial nerve neuritis according to strength-duration findings. Vopr Kurortol Fizioter Lech Fiz Kult. 1971; 36(6):528–530. [PubMed: 5140399]

161. Bioarintseva T, Grushlavski I. Hydrocortisone phonophoresis treatment of various diseases of the weight bearing-locomoter apparatus. Vrach Delo. 1972; (11):119–120.
162. Blinova N, Ishchenko M. The effect of hydrocortisone phonophoresis in the androgenic and glucocorticoid function of the adrenal cortex in patients with lumbosacral radiculitis. Vopr Kurortol Fizioter Lech Fiz Kult. 1972; (37):220–223. [PubMed: 5048107]
163. Antropova M. Use of hydrocortisone phonophoresis in the treatment of facial nerve neuritis. Zh Nevropatol Psikhiatr Im S S Korsakova. 1974; (7):506–511. [PubMed: 4545221]
164. Kornienko A. Use of hydrocortisone phonophoresis in the treatment of allergic rhinitis. Vestn Otolorinolaringol. 1974; (1):55–57.
165. Braginski M. Treatment of certain dermatoses by hydrocortisone phonophoresis. Sov Med. 1975; (7):145.
166. Bratslavskaia E, Vitushkina S. Hydrocortisone phonophoresis in trauma and diseases of the locomotor system in athletes. Med Sestra. 1975; 34:34–36. [PubMed: 1038536]
167. Kharitonov R, Gol'dblat V, Anisimov A. Hydrocortisone phonophoresis in complex conservative treatment of arthrosis deformans of the knee joint. Ortop Traumatol Protez. 1975; (2):22–26.
168. Artamonova V, Nikitana T. Use of ultrasound and hydrocortisone phonophoresis in the complex treatment of children with rheumatoid arthritis. Vopr Kurortol Fizioter Lech Fiz Kult. 1977; (42): 29–33. [PubMed: 860416]
169. Dozhanskaia V. Hydrocortisone and cuprenil phonophoresis in the therapy of scleroderma. Vestn Dermatol Venerol. 1980; (10):50–51.
170. Pottenger F, Karalfa B. Utilization of hydrocortisone phonophoresis in United States Army Physical Therapy Clinics. Mil Med. 1989; 154(7):355. [PubMed: 2503775]
171. Griffin J, Echternach J, Price R, Touchstone J. Patients treated with ultrasonic driven hydrocortisone and with ultrasound alone. Phys Ther. 1967; 47(7):595–601.
172. Bare A, McAnaw M, Pritchard A, Struebing J, Smutok M, Christie D, Domenech M, Bare M, Bloodworth M, Seal L. Phonophoretic delivery of 10% hydrocortisone through the epidermis of humans as determined by serum cortisol concentrations. Phys Ther. 1996; 76(7):738. [PubMed: 8677278]
173. Koeke P, Parizotto N, Carrinho P, Salate A. Comparative study of the efficacy of the topical application of hydrocortisone, therapeutic ultrasound and phonophoresis on the tissue repair process in rat tendons. Ultrasound Med Biol. 2005; 31(3):345–350. [PubMed: 15749557]
174. Kleinkort J, Wood F. Phonophoresis with 1 percent versus 10 percent hydrocortisone. Phys Ther. 1975; 55(12):1320–1324. [PubMed: 1197356]
175. Kuntz A, Griffiths C, Rankin J, Armstrong C, McLoughlin T. Cortisol concentrations in human skeletal muscle tissue after phonophoresis with 10% hydrocortisone gel. J Athl Training. 2006; 41(3):321.
176. Byl N, McKenzie A, Halliday B, Wong T, O'Connell J. The effects of phonophoresis with corticosteroids: a controlled pilot study. J Orthop Sports Phys Ther. 1993; 18(5):590. [PubMed: 8268961]
177. Griffin J, Touchstone J. Ultrasonic movement of cortisol into pig tissues. I. Movement into skeletal muscle. Amer J Physical Med. 1963; 42:77–85.
178. Griffin J, Touchstone J. Low-intensity phonophoresis of cortisol in swine. Phys Ther. 1968; 48(12):1336. [PubMed: 5704952]
179. Griffin J, Touchstone J. Effects of ultrasonic frequency on phonophoresis of cortisol into swine tissues. Amer J Physical Med. 1972; 51(2):62–78.
180. Griffin J, Touchstone J, Liu A. Ultrasonic movement of cortisol into pig tissue. II. Movement into the paravertebral nerve. Amer J Physical Med. 1965; 44:20–25.
181. Popov N, Kudriashov V, Pristupa L. 17-oxycorticosteroids in levels in blood and skin of rabbits after hydrocortisone phonophoresis. Voprosy kurortologii, fizioterapii, i lechebno fizichesko kultury. 1970; 35(4):295–297.
182. Tsitlanadze V. Changes in the metabolism of trace elements and the comparative effectiveness of treating infectious non-specific polyarthritis with ultrasound and hydrocortisone phonophoresis. Vopr Kurortol Fizioter Lech Fiz Kult. 1971; 36(2):158–161. [PubMed: 5095450]

183. Tsitlanadze V. Morphohistochemical changes during experimental arthritis in rabbits caused by hydrocortisone phonophoresis. Soobshch Akad Nauk Gruz SSR. 1971; (63):237–240.

184. Tsitlanadze V. The mechanism of action of hydrocortisone phonophoresis in rabbits with adjuvant arthritis. Voprosy revmatizma. 1973; 12(4):19–22. [PubMed: 4664906]

185. Davick JP, Martin RK, Albright JP. Distribution and Deposition of Tritiated Cortisol Using Phonophoresis. Phys Ther. 1988; 68(11):1672–1675. [PubMed: 3186792]

186. Muir W, Magee F, Longo J, Karpman R, Finley P. Comparison of ultrasonically applied vs. intra-articular injected hydrocortisone levels in canine knees. Orthop Rev. 1990; 19(4):351. [PubMed: 2333223]

187. Machet L, Cochelin N, Patat F, Arbeille B, Machet M, Lorette G, Vaillant L. In vitro phonophoresis of mannitol, oestradiol and hydrocortisone across human and hairless mouse skin. Int J Pharm. 1998; 165(2):169–174.

188. Safiulina S, Proskurova G. Phonophoresis of hydrocortisone. Vopr Kurortol Fizioter Lech Fiz Kult. 1970; 35(4):293–295. [PubMed: 5490839]

189. Gatev S. Effect of ultrasonic phonophoresis on passage of hydrocortisone through the skin of Rana ridibunda. Eksp Med Morfol. 1972; 11(4):231–236. [PubMed: 4659912]

190. Quillin W. Ultrasonic phonophoresis. Phys Sportsmed. 1982; 10:211.

191. Conner-Kerr T, Franklin M, Kerr J, Smith S, Franklin R. Phonophoretic delivery of dexamethasone to human transdermal tissues: a controlled pilot study. Eur J Phys Rehab Med. 1998; 8(1):19–23.

192. Moll M. A new approach to pain: lidocaine and decadron with ultrasound. USAF Med Serv Dig. 1979; 30:8–11.

193. Darrow H, Schulthies S, Draper D, Ricard M, Measom G. Serum dexamethasone levels after Decadron phonophoresis. J Athl Training. 1999; 34(4):338.

194. Saliba S, Mistry D, Perrin D, Gieck J, Weltman A. Phonophoresis and the Absorption of Dexamethasone in the Presence of an Occlusive Dressing. J Athl Training. 2007; 42(3):349.

195. Alballa S. Effect of phonophoretic application of diclofenac gel on localized musculoskeletal disorders. Curr Ther Res. 1994; 55(11):1382–1390.

196. Barja P, Acosta-Avalos D, Rompe P, Dos Anjos F, Marciano F, da Silva M. In vivo evaluation of drug delivery after ultrasound application: A new use for the photoacoustic technique. J. Phys. IV France. 2005; 125:789–791.

197. Rosim G, Barbieri C, Lanças F, Mazzer N. Diclofenac phonophoresis in human volunteers. Ultrasound Med Biol. 2005; 31(3):337–343. [PubMed: 15749556]

198. Hsieh Y-L. Effects of Ultrasound and Diclofenac Phonophoresis on Inflammatory Pain Relief: Suppression of Inducible Nitric Oxide Synthase in Arthritic Rats. Phys Ther. 2006; 86(1):39–49. [PubMed: 16386061]

199. Sharma D, Hanesh M, Yahya A, Mohamed M. Phonophoresis with Diclofenac versus Ketoprofen for Knee Joint Injuries. Middle East J Int Med. 2009; 2(2):9–12.

200. Meshali M, Abdel-Aleem H, Sakr F, Nazzal S, El-Malah Y. In vitro phonophoresis: effect of ultrasound intensity and mode at high frequency on NSAIDs transport across cellulose and rabbit skin membranes. Pharmazie. 2008; 63(1):49–53. [PubMed: 18271303]

201. Machet L, Pinton J, Patat F, Arbeille B, Pourcelot L, Vaillant L. In vitro phonophoresis of digoxin across hairless mice and human skin: Thermal effect of ultrasound. Int J Pharm. 1996; 133(1–2): 39–45.

202. Benson HAE, McElnay JC, Harland R, Hadgraft J. Influence of Ultrasound on the Percutaneous Absorption of Nicotinate Esters. Pharm Res. 1991; 8(2):204–209. [PubMed: 2023868]

203. Benson HAE, McElnay JC, Harland R. Phonophoresis of lignocaine and prilocaine from Emla cream. Int J Pharm. 1988; 44(1–3):65–69.

204. Wu, Y.; Chen, W.; Luh, J.; Chong, F. Thermal Effect of Sonophoresis for Accelerating the Analgesic Effect of Local Anesthetics on Rat Tail Nerve. International IEEE EMBS Conference; Vancouver, BC. 2008. p. 2504-2507.

205. Vainshtein E, Lutsker L, Zobina L, Tartakovskaia A. Electro-and phonophoresis of fibrinolysin. Vestn Oftalnol. 1975; (4):74–76.

206. Hippius M, Uhlemann C, Smolenski U, Schreiber U, Reissig S, Hoffmann A. In vitro investigations of drug release and penetration: enhancing effect of ultrasound on transmembrane transport of flufenamic acid. Int J Clin Pharm Th. 1998; 36(2):107–111.

207. Uhlemann C, Reißig S, Hippius M, Smolenski U, Schreiber T. Phonophorese mit Flufenaminsäure in Abhängigkeit von Parametern der Ultraschalldosis Phonophoresis of flufenamin acid dependent on parameters of dose of ultrasound. Phys Rehab Kur Med. 2000; 10:86–93.

208. Chirkin A, Kozin V. Enzymatic activity of the pentosephosphate pathway of carbohydrate conversion in the experimental therapy of dermatitis in rats. Vopr Med Khim. 1976; 22(4):448–451. [PubMed: 1027227]

209. Kozin V. Morphological changes in the skin of rats under experimental therapy for dermatitis. Zdravookhr Beloruss. 1976; (4):81–82.

210. Kozin V, Chirkin A, Griaditski I. Histamine and serotonin content in the blood and skin in experimental therapy of dermatitis in rats. Fiziol Zh. 1976; 22(3):390–394. [PubMed: 1278478]

211. McElnay JC, Kennedy TA, Harland R. The influence of ultrasound on the percutaneous absorption of fluocinolone acetonide. Int J Pharm. 1987; 40(1–2):105–110.

212. Klaiman M, Shrader J, Danoff J, Hicks J, Pesce W, Ferland J. Phonophoresis versus ultrasound in the treatment of common musculoskeletal conditions. Med Sci Sport Exer. 1998; 30(9):1349.

213. Meidan V, Walmsley A, Docker M, Irwin W. Ultrasound-enhanced diffusion into coupling gel during phonophoresis of 5-fluorouracil. Int J Pharm. 1999; 185(2):205–213. [PubMed: 10460916]

214. Kafas P. Ghicosaminoglycan Phonophoresis of the TMJ in the Symptomatic Treatment of Internal Derangement. J Med Sci. 2007; 7(1):158–160.

215. Park D, Yoon J, Park J, Jung B, Park H, Seo J. Transdermal Drug Delivery Aided by an Ultrasound Contrast Agent: An In Vitro Experimental Study. Open Biomed Eng J. 2010; 4:56–62. [PubMed: 20448793]

216. Klare V, Kury W. On phonophoresis treatment with hirudoid. Wien Med Wschr. 1960; 110:701–702. [PubMed: 13756555]

217. Park SR, Jang KW, Park S-H, Cho HS, Jin CZ, Choi MJ, Chung SI, Min B-H. The effect of sonication on simulated osteoarthritis. Part I: Effects of 1 MHz ultrasound on uptake of hyaluronan into the rabbit synovium. Ultrasound Med Biol. 2005; 31(11):1551–1558. [PubMed: 16286032]

218. Kozanoglu E, Basaran S, Guzel R, Guler-Uysal F. Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis. Swiss Med Wkly. 2003; 133(23–24):333–338. [PubMed: 12923684]

219. Asano J, Suisha F, Takada M, Kawasaki N, Miyazaki S. Effect of pulsed output ultrasound on the transdermal absorption of indomethacin from an ointment in rats. Biol Pharm Bull. 1997; 20(3): 288–291. [PubMed: 9084890]

220. Miyazaki S, Mizuoka H, Kohata Y, Takada M. External control of drug release and penetration. VI. Enhancing effect of ultrasound on the transdermal absorption of indomethacin from an ointment in rats. Chem Pharm Bull. 1992; 40(10):2826. [PubMed: 1464116]

221. Bumin G, Can F. Effects of iontophoresis and phonophoresis methods on pain in cases with shoulder periarthritis. Pain Clinic. 2001; 13(2):159–162.

222. Cagnie B, Vinck E, Rimbaut S, Vanderstraeten G. Phonophoresis Versus Topical Application of Ketoprofen: Comparison Between Tissue and Plasma Levels. Phys Ther. 2003; 83(8):707–712. [PubMed: 12882611]

223. Yang J-H, Kim T-Y, Lee J-H, Yoon S-W, Yang K-H, Shin S-C. Anti-hyperalgesic and anti-inflammatory effects of Ketorolac Tromethamine gel using pulsed ultrasound in inflamed rats. Arch Pharm Res. 2008; 31(4):511–517. [PubMed: 18449510]

224. Wei L, Xinping L, Gang W. Sonophoresis Induces the Enhanced Permeation of Drug and Its Effect on Stratum Corneum. Chin JMAP. 2009; 26(6):510–513.

225. McElnay J, Matthews M, Harland R, McCafferty D. The effect of ultrasound on the percutaneous absorption of lignocaine. Brit J Clin Pharmaco. 1985; 20(4):421.

226. Kim T, Jung D, Kim Y, Yang J, Shin S. Anesthetic effects of lidocaine hydrochloride gel using low frequency ultrasound of 0.5 MHz. J Pharm Pharm Sci. 2007; 10(1):1–8. [PubMed: 17498388]

227. Novak E. Experimental Transmission of lidocaine through intact skin by ultrasound. Arch Phys Med Rehab. 1964; 45:231–232.

228. Ashton D, Draper D, Myrer J. Temperature rise in human muscle during ultrasound treatments using Flex-All as a coupling agent. J Athl Training. 1998; 33(2):136.

229. Cameroy B. Ultrasound enhanced local anesthesia. Am J Orthaped. 1966; 8(47)

230. Glushchenko L. Quantitative study of analgin phonophoresis. Vopr Kurortol Fizioter Lech Fiz Kult. 1976; (41):20–23. [PubMed: 1014449]

231. McElnay JC, Benson HAE, Harland R, Hadgraft J. Phonophoresis of Methyl Nicotinate: A Preliminary Study to Elucidate the Mechanism of Action. Pharm Res. 1993; 10(12):1726–1731. [PubMed: 8302758]

232. Mortimer A, Trollope B, Villeneuve E, Roy O. Ultrasound-enhanced diffusion through isolated frog skin. Ultrasonics. 1988; 26(6):348–351. [PubMed: 3263724]

233. Ng GYF, Wong RYF. Ultrasound Phonophoresis of Panax Notoginseng Improves the Strength of Repairing Ligament: A Rat Model. Ultrasound Med Biol. 2008; 34(12):1919–1923. [PubMed: 18692299]

234. Zague V, Polacow M, Pires-de-Campos M, Leonardi G. Evaluation of the ultrasound influence in the cutaneous penetration of d-panthenol: test in vitro. J Cosmet Dermatol. 2005; 4(1):29–33. [PubMed: 17134419]

235. Kost J, Leong K, Langer R. Ultrasonically controlled drug delivery in vivo. Proc. Int. Symp. Controlled Release Bioact. Mater. 1987; Vol. 14:186–187. Controlled Release Society.

236. Dynnik T, Garbar A. Use of antibiotic phonophoresis in purulent inflammatory skin diseases. Vrach Delo. 1977; (8):115–116. [PubMed: 583634]

237. Brondolo W. Phenylbutazone with ultrasonics in some cases of arthrosynovitis of the knee. Arch Orthoped. 1960; (73):532–540.

238. Chung K, Kim Y, Yang J. Phonophoretic delivery of piroxicam. J Korean Pharm Sci. 2002; 32(4):259–266.

239. Shiran M, Motevalian M, Ravanfar R, Bohlouli S. The effect of bubble surface charge on phonophoresis: implications in transderaml piroxicam delivery. Iran J Pharm Ther. 2008; 7(1): 15–19.

240. Hikima T, Hirai Y, Tojo K. Effect of Ultrasound Application on Skin Metabolism of Prednisolone 21-Acetate. Pharm Res. 1998; 15(11):1680–1683. [PubMed: 9833987]

241. Yamashita A, Hirai Y, Tojo K. Effect of ultrasound on rate of drug absorption through skin. j Chem Eng Jpn. 1996; 29(5):812–816.

242. Dohnalek J, Hrazdira I, Cecava J, Novak F, Svoboda J. Penetration of radioiodine through the skin enhanced by ultrasonics. Cesk Derm. 1965; 40:173–178. [PubMed: 14348554]

243. Klare V. Experiences with Reparil. Iontophoretic, phonophoretic and oral application. Ther Ggw. 1968; 107(2):240. [PubMed: 5752738]

244. Doweck, I.; Nachum, Z.; Dachir, S.; Spitzer, O.; Gordon, C.; Gonen, A.; Levy, A.; Shupak, A. Enhancement of transdermal scopolamine absorption using sonophoresis. International Congress of Aviation and Space Medicine; Jerusalem, Israel. 1996.

245. Frenkel V, Kimmel E, Iger Y. Ultrasound-facilitated transport of silver chloride (AgCl) particles in fish skin. J Control Release. 2000; 68(2):251–261. [PubMed: 10925133]

246. Fyfe MC, Chahl LA. The effect of ultrasound on experimental oedema in rats. Ultrasound Med Biol. 1980; 6(2):107–111. [PubMed: 7404841]

247. Ragelis S. Penicillin and streptomycin penetration into tissue by a modified electrophoretic method. Antibiotiki. 1981; 26(9):699–703. [PubMed: 7294763]

248. Brawner T, Senne J, Fahim M. A combined chemical-physical treatment for herpes simplex lesions in guinea pigs. Arch Dermatol Res. 1979; 265(1):71–77. [PubMed: 475446]

249. Fahim M, Brawner T, Hall D. New treatment for herpes simplex virus type 2 [ultrasound and zinc, urea and tannic acid ointment]. Part II: Female patients. J Med. 1980; 11(2–3):143–167. [PubMed: 6931874]

250. Fahim M, Brawner T, Millikan L, Nickell M, Hall D. New treatment for herpes simplex virus type 2 [ultrasound and zinc, urea, and tannic acid ointment]. Part I--Male patients. J Med. 1978; 9(3):245–264. [PubMed: 283170]

251. El-Kamel A, Al-Fagih I, Alsarra I. Effect of sonophoresis and chemical enhancers on testosterone transdermal delivery from solid lipid microparticles: an in vitro study. Curr Drug Deliv. 2008; 5(1):20–26. [PubMed: 18220547]

252. Parikov V. Injection of tetracyline into the tissues of cow udders by ultrasonics. Veterinariia. 1966; 43(6):88–91. [PubMed: 6011241]

253. Ragelis S. Tetracycline penetration into tissue by modified electro-and phonophoretic methods. Antibiotiki. 1981; 26(9):699. [PubMed: 7294763]

254. Yang J, Kim D, Kim T, Kim G, Shin S. Anti-inflammatory effects by transdermal application of triamcinolone acetonide gel using phonophoresis in rats. Int J Pharm. 2005; 302(1–2):39–46. [PubMed: 16098696]

255. Yang J, Kim D, Yun M, Kim T, Shin S. Transdermal delivery system of triamcinolone acetonide from a gel using phonophoresis. Arch Pharm Res. 2006; 29(5):412–417. [PubMed: 16756087]

256. Grinshtein A, Tolmacheva A, Khriptulov V. Phonophoresis of Trilon B. Vopr Kurortol Fizioter Lech Fiz Kult. 1972; 37(3):223–225. [PubMed: 4625899]

257. Kamrash L, Mal'tseva M, Tigeev V. Trylon B phonophoresis in the rehabilitation of patients with stable contractures of extremity joints. Ortop Traumatol Protez. 1974; (9):79–80.

258. Ciccone CD, Leggin BG, Callamaro JJ. Effects of Ultrasound and Trolamine Salicylate Phonophoresis on Delayed-Onset Muscle Soreness. Phys Ther. 1991; 71(9):666–675. [PubMed: 1881957]

259. Pelucio-Lopes C, Machet L, Vaillant L, Patat F, Lethiecq M, Furet Y, Pourcelot L, Lorette G. Phonophoresis of azidothymidine (AZT). Int J Pharm. 1993; 96(1–3):249–252.

260. [accessed September 30, 2010] Syracuse Research Corporation, Interactive PhysProp Database Demo. http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

261. Tachibana K. Transdermal Delivery of Insulin to Alloxan-Diabetic Rabbits by Ultrasound Exposure. Pharm Res. 1992; 9(7):952–954. [PubMed: 1438012]

262. Tachibana K, Tachibana S. Transdermal delivery of insulin by ultrasonic vibration. J Pharm Pharmacol. 1991; 43(4):270–271. [PubMed: 1676740]

263. Tezel A, Sens A, Mitragotri S. Incorporation of lipophilic pathways into the porous pathway model for describing skin permeabilization during low-frequency sonophoresis. J Control Release. 2002; 83(1):183–188. [PubMed: 12220849]

264. Ueda H, Isshiki R, Ogihara M, Sugibayashi K, Morimoto Y. Combined effect of ultrasound and chemical enhancers on the skin permeation of aminopyrine. Int J Pharm. 1996; 143(1):37–45.

265. Santoianni P, Nino M, Calabro G. Intradermal drug delivery by low-frequency sonophoresis (25 kHz). Dermatol Online J. 2004; 10(2):24. [PubMed: 15530314]

266. Ueda H, Ogihara M, Sugibayashi K, Morimoto Y. Change in the electrochemical properties of skin and the lipid packing in stratum corneum by ultrasonic irradiation. Int J Pharm. 1996; 137(2):217–224.

267. Maruani A, Boucaud A, Perrodeau E, Gendre D, Giraudeau B, Machet L. Low-frequency ultrasound sonophoresis to increase the efficiency of topical steroids: A pilot randomized study of humans. Int J Pharm. 2010; 395:84–90. [PubMed: 20472045]

268. Boucaud A, Machet L, Arbeille B, Machet M, Sournac M, Mavon A, Patat F, Vaillant L. In vitro study of low-frequency ultrasound-enhanced transdermal transport of fentanyl and caffeine across human and hairless rat skin. Int J Pharm. 2001; 228(1–2):69–77. [PubMed: 11576769]

269. Mutoh M, Ueda H, Nakamura Y, Hirayama K, Atobe M, Kobayashi D, Morimoto Y. Characterization of transdermal solute transport induced by low-frequency ultrasound in the hairless rat skin. J Control Release. 2003; 92(1–2):137–146. [PubMed: 14499192]

270. Fang J-Y, Fang C-L, Sung KC, Chen H-Y. Effect of low frequency ultrasound on the in vitro percutaneous absorption of clobetasol 17-propionate. Int J Pharm. 1999; 191(1):33–42. [PubMed: 10556738]

271. Katikaneni S, Li G, Badkar A, Banga A. Transdermal delivery of a~ 13 kDa protein—an in vivo comparison of physical enhancement methods. J Drug Target. 2010; 18(2):141–147. [PubMed: 19772395]

272. Cancel L, Tarbell J, Ben-Jebria A. Fluorescein permeability and electrical resistance of human skin during low frequency ultrasound application. J Pharm Pharmacol. 2004; 56(9):1109–1118. [PubMed: 15324479]

273. Lanke S, Kolli C, Strom J, Banga A. Enhanced transdermal delivery of low molecular weight heparin by barrier perturbation. Int J Pharm. 2009; 365(1–2):26–33. [PubMed: 18801420]

274. Maruani A, Vierron E, Machet L, Giraudeau B, Boucaud A. Efficiency of low-frequency ultrasound sonophoresis in skin penetration of histamine: A randomized study in humans. Int J Pharm. 2010; 385(37–41)

275. Park E, Dodds J, Smith N. Dose comparison of ultrasonic transdermal insulin delivery to subcutaneous insulin injection. Int J Nanomed. 2008; 3(3):335.

276. Boucaud A, Garrigue M, Machet L, Vaillant L, Patat F. Effect of sonication parameters on transdermal delivery of insulin to hairless rats. J Control Release. 2002; 81(1–2):113–119. [PubMed: 11992684]

277. Boucaud, A.; Machet, L.; Garrigue, M.; Vaillant, L.; Patat, F. A Practical Use of Low Frequency Ultrasound For Rapid and Reproducible Transdermal Delivery of Insulin. IEEE Ultrasonics Symposium; Atlanta, GA. 2001. p. 1327-1330.

278. Lee S, Snyder B, Newnham R, Barrie Smith N. Noninvasive ultrasonic transdermal insulin delivery in rabbits using the light-weight cymbal array. Diabetes Technol The. 2004; 6(6):808–815.

279. Luis J, Park EJ, Meyer JRJ, Smith NB. Rectangular cymbal arrays for improved ultrasonic transdermal insulin delivery. J Acoust Soc Am. 2007; 122(4):2022–2030. [PubMed: 17902839]

280. Park E, Werner J, Smith N. Ultrasound mediated transdermal insulin delivery in pigs using a lightweight transducer. Pharm Res. 2007; 24(7):1396–1401. [PubMed: 17443398]

281. Zhang I, Shung K, Edwards D. Hydrogels with enhanced mass transfer for transdermal drug delivery. J Pharm Sci. 1996; 85(12):1312–1316. [PubMed: 8961145]

282. Smith N, Lee S, Maione E, Roy R, McElligott S, Shung K. Ultrasound-mediated transdermal transport of insulin in vitro through human skin using novel transducer designs. Ultrasound Med Biol. 2003; 29(2):311–317. [PubMed: 12659919]

283. Skarbek-Borowska S, Becker BM, Lovgren K, Bates A, Minugh PA. Brief Focal Ultrasound With Topical Anesthetic Decreases the Pain of Intravenous Placement in Children. Pediatr Emerg Care. 2006; 22(5):339–345. [PubMed: 16714961]

284. Stowell CP, Trieu MQ, Chuang H, Katz N, Quarrington C. Ultrasound-enabled topical anesthesia for pain reduction of phlebotomy for whole blood donation. Transfusion. 2009; 49(1):146–153. [PubMed: 18954400]

285. Zempsky W, Robbins B, McKay K. Reduction of topical anesthetic onset time using ultrasound: a randomized controlled trial prior to venipuncture in young children. Pain Med. 2008; 9(7):795–802. [PubMed: 18346063]

286. Weimann L Jr, Wu J. Ultrasound induced enhancement of skin permeability to Octa L Lysine. J Acoust Soc Am. 1999; 106:2230.

287. Lopez R, Seto J, Blankschtein D, Langer R. Enhancing the transdermal delivery of rigid nanoparticles using the simultaneous application of ultrasound and sodium lauryl sulfate. Biomaterials. 2011; 32(3):933–941. [PubMed: 20971504]

288. Gou M, Wu L, Yin Q, Guo Q, Guo G, Liu J, Zhao X, Wei Y, Qian Z. Transdermal Anaesthesia with Lidocaine Nano-Formulation Pretreated with Low-Frequency Ultrasound in Rats Model. J Nanosci Nanotechno. 2009; 9(11):6360–6365.

289. Tran M, Gowda R, Sharma A, Park E, Adair J, Kester M, Smith N, Robertson G. Targeting V600EB-Raf and Akt3 using nanoliposomal-small interfering RNA inhibits cutaneous melanocytic lesion development. Cancer Res. 2008; 68(18):7638. [PubMed: 18794153]

290. Polat B, Seto J, Blankschtein D, Langer R. Application of the Aqueous Porous Pathway Model to Quantify the Effect of Sodium Lauryl Sulfate on Ultrasound-Induced Skin Structural Perturbation. J Pharm Sci.

291. Dahlan A, Alpar H, Stickings P, Sesardic D, Murdan S. Transcutaneous immunisation assisted by low-frequency ultrasound. Int J Pharm. 2009; 368(1–2):123–128. [PubMed: 19013510]

292. Bjarnason I, Hayllar J, MacPherson A, Russell A. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology. 1993; 104(6):1832. [PubMed: 8500743]

293. Rainsford KD. Profile and mechanisms of gastrointestinal and other side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Am J Med. 1999; 107(Supplement 1)(6):27–35.

294. Heyneman C, Lawless-Liday C, Wall G. Oral versus topical NSAIDs in rheumatic diseases: a comparison. Drugs. 2000; 60(3):555–574. [PubMed: 11030467]

295. Bloom B. Risk and cost of gastrointestinal side effects associated with nonsteroidal anti-inflammatory drugs. Arch Intern Med. 1989; 149(5):1019–1022. [PubMed: 2719496]

296. Bloom BS. Direct medical costs of disease and gastrointestinal side effects during treatment for arthritis. Am J Med Eng. 1988; 84(Supplement 1)(2):20–24.

297. Karande P, Mitragotri S. Transcutaneous immunization: an overview of advantages, disease targets, vaccines, and delivery technologies. Annu Rev Chem Biomol Eng. 2010; 1:175–201. [PubMed: 22432578]

298. Mikszta J, Alarcon J, Brittingham J, Sutter D, Pettis R, Harvey N. Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery. Nat Med. 2002; 8(4):415–419. [PubMed: 11927950]

299. Scarponi C, Nasorri F, Pavani F, Madonna S, Sestito R, Simonacci M, De Pità O, Cavani A, Albanesi C. Low-Frequency Low-Intensity Ultrasounds Do Not Influence the Survival and Immune Functions of Cultured Keratinocytes and Dendritic Cells. J Biomed Biotechnol. 2009

300. Prausnitz M, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008; 26(11):1261–1268. [PubMed: 18997767]

301. Chuang H, Taylor E, Davison T. Clinical evaluation of a continuous minimally invasive glucose flux sensor placed over ultrasonically permeated skin. Diabetes Technol The. 2004; 6(1):21–30.

302. Chuang H, Trieu M, Hurley J, Taylor E, England M, Nasraway S Jr. Pilot Studies of Transdermal Continuous Glucose Measurement in Outpatient Diabetic Patients and in Patients during and after Cardiac Surgery. J Diabetes Sci Technol. 2008; 2(5):595–602. [PubMed: 19885235]

303. Kost J, Mitragotri S, Gabbay R, Pishko M, Langer R. Transdermal monitoring of glucose and other analytes using ultrasound. Nat Med. 2000; 6(3):347–350. [PubMed: 10700240]

304. Park E, Werner J, Beebe J, Chan S, Smith N. Noninvasive Ultrasonic Glucose Sensing with Large Pigs (200 Pounds) Using a Lightweight Cymbal Transducer Array and Biosensors. J Diabetes Sci Technol. 2009; 3(3):517–523. [PubMed: 20144290]

305. Pishko M, Smith N, Gabbay R, Werner J. Closed-Loop Noninvasive Ultrasound Glucose Sensing and Insulin Delivery. Storming Media. 2006

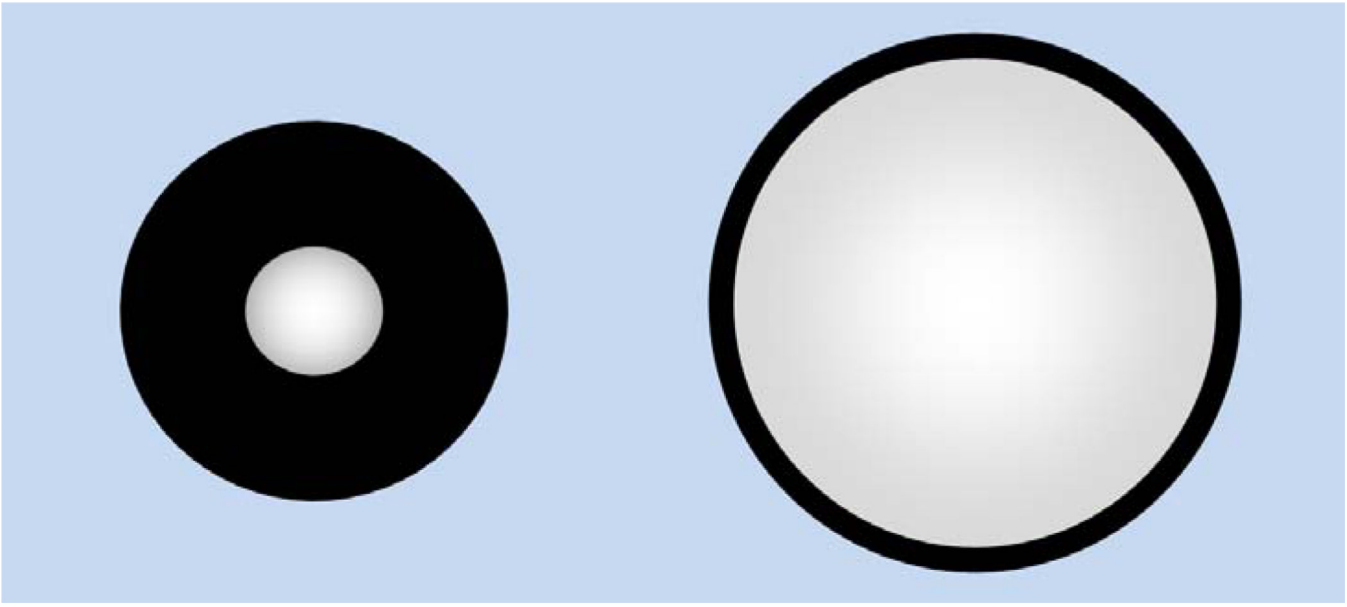

Figure 1.
Relative thickness of the diffusion boundary layer (in black) of a spherical cavitation bubble in the collapsed state (in the compression cycle, left) and in the expanded state (in the rarefaction cycle, right).

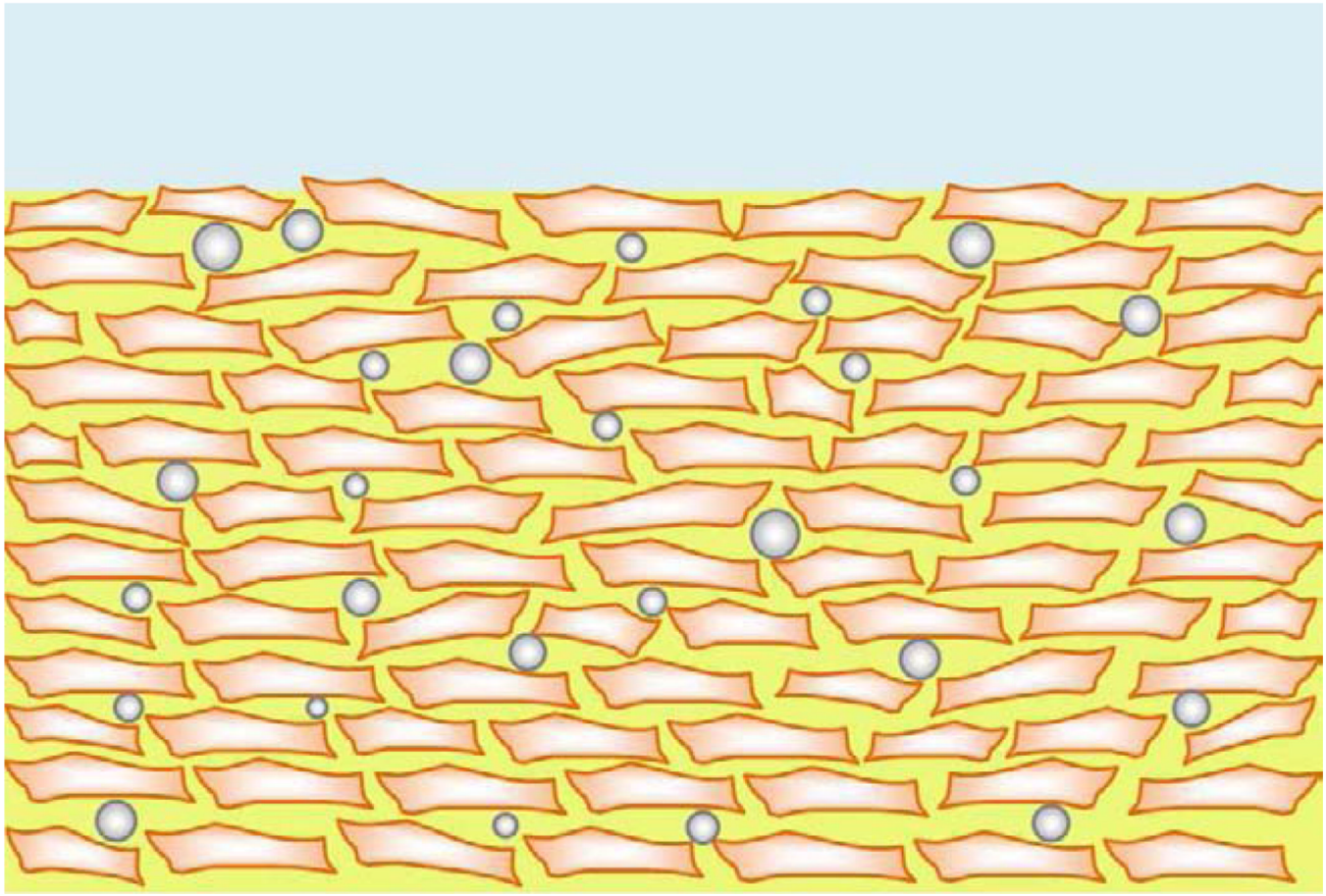

Figure 2.
Illustration of cavitation bubbles inducing disordering within the stratum corneum under HFS. Legend: Keratinocytes ( ), cavitation bubbles ( ), lipid bilayers ( ), and coupling medium ( ).

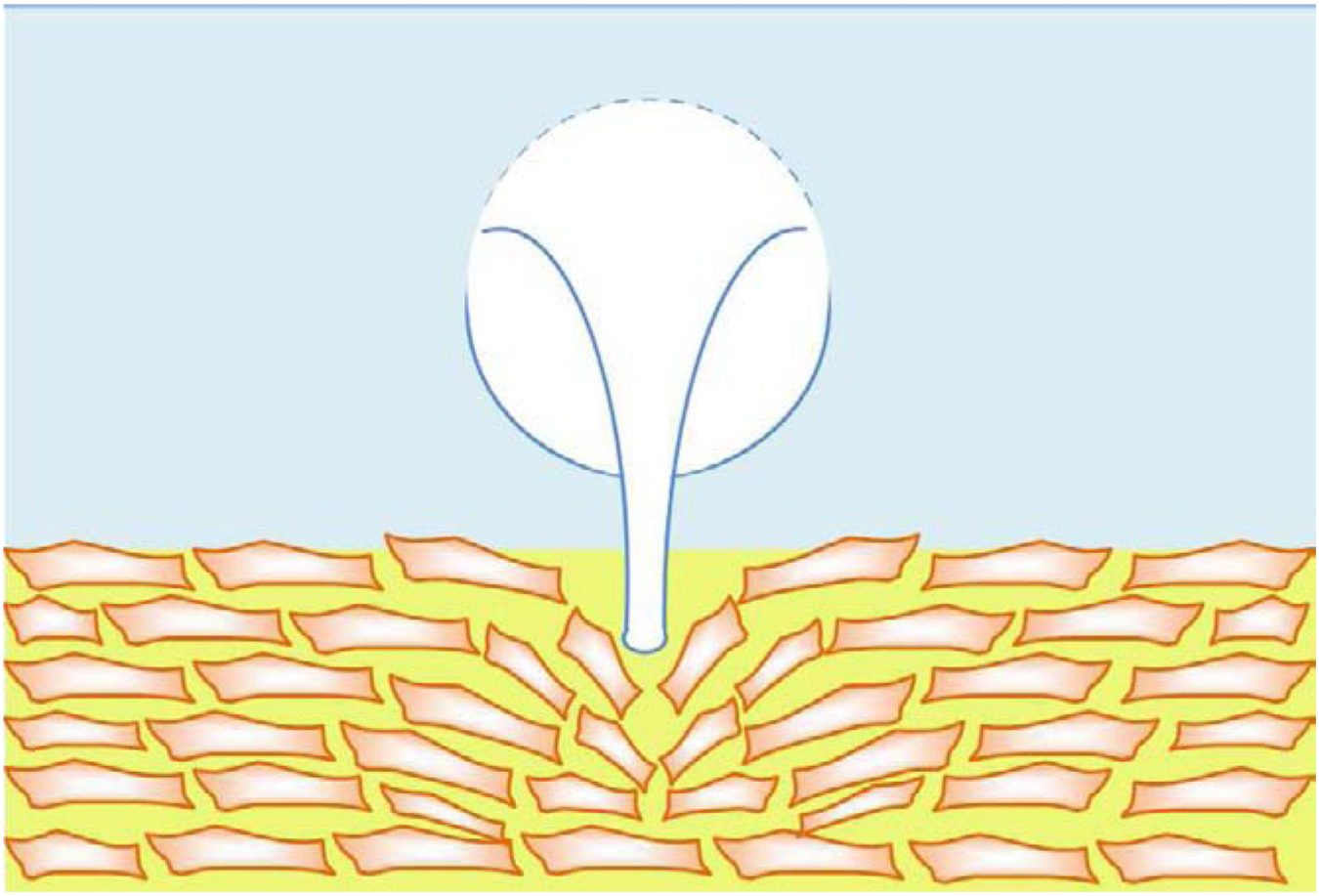

Figure 3.
Illustration of a cavitation bubble asymmetrically collapsing into the stratum corneum as a microjet under LFS. Legend: Keratinocytes ( ), lipid bilayers ( ), and coupling medium ( ).

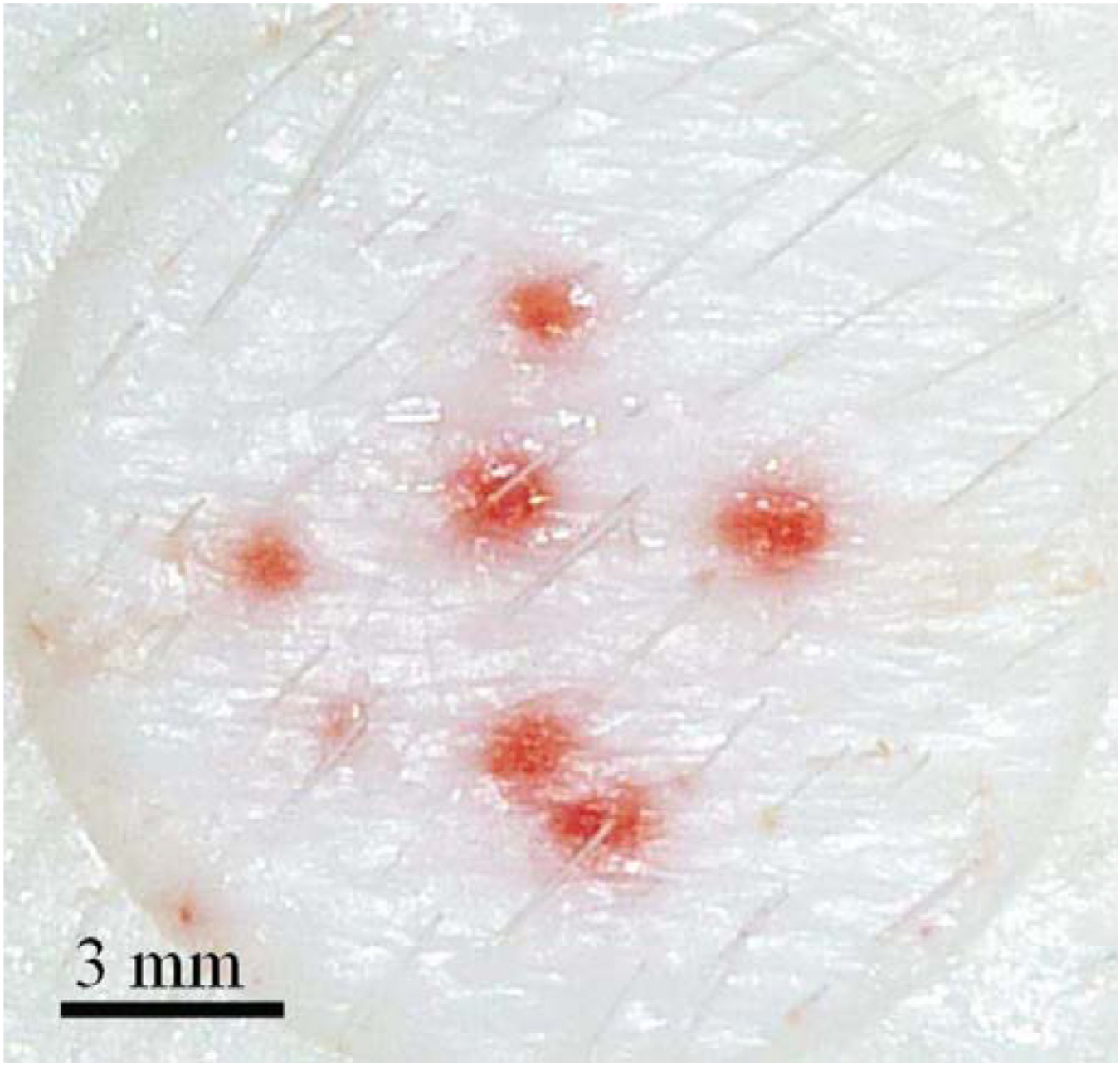

Figure 4.
LTRs formed on the surface of pig skin treated with 20 kHz LFS and a surfactant. LTRs are stained with allura red.

Table 1

Molecules that have been delivered transdermally with therapeutic and high-frequency ultrasound.

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Aloe vera gel	-	-	1.0	0.5	*in vivo*	rat	[83]
Aminopyrine	231	1.00	3.5	0.1–2.0	*in vitro*	rat FTS	[133]
Amphotericin B	924	−2.80	2.64	1.0	*in vivo*	gp	[134]
Arnica montana extract	-	-	1.0	0.5	*in vivo*	rat	[135]
Ascorbic acid	176	−1.85	0.88, 5	0.3–1.0	*in vivo*	human	[136, 137]
Benzene	78	2.13	1.0–3.0	0–2.0	*in vitro*	h FTS	[12]
Benzocaine, benzethonium mixture	165 448	1.86 4.00	1.1	0.25	*in vivo*	human	[138]
Benzydamine	309	4.21	*c*	*c*	*in vivo*	human	[139, 140]
			0.75–3.0	0–3.0	*in vivo*	human	[141]
Benzyl nicotinate	213	2.40	3.0	0.2–1.0	*in vivo*	human	[142]
Biomycin	451	−3.60	*c*	*c*	*in vivo*	human	[143, 144]
Bufexamac	223	2.08	3.0	0.1–3.0	*in vivo*	human	[145]
Butanol	74	0.88	1.0–3.0	0–2.0	*in vitro*	h FTS	[12]
Caffeine	194	−0.07	1.0–3.0	0–2.0	*in vitro*	h FTS	[12]
			1.0–3.0	0.01–2.0	*in vitro*	m FTS	[93, 146]
Calcein	623	-	1.0–3.0	1.4	*in vitro*	h FTS	[119]
Calcium	42	−0.57	1.0	0.3	*in vivo*	mouse	[147]
Chymotrypsin	25k	-	*c*	*c*	*in vivo*	human	[148]
Corticosterone	346	1.94	1.0–3.0	0–2.0	*in vitro*	h FTS	[12, 102]

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Cortisol (hydrocortisone)	362	1.61	*c*	*c*	*in vivo*	human	[2, 149–170]
			0.5–1.0	0–3.0	*in vivo*	human	[122, 171–176]
			0.09–3.6	1.0–3.0	*in vivo*	pig	[177–180]
			c	*c*	*in vivo*	rabbit	[181–184]
			0.87–1.0	0.5–2.75	*in vivo*	dog	[185, 186]
			1.1	1.5	*in vitro*	h FTS	[187]
			1.1–3.5	0.1–2.5	*in vitro*	rat FTS	[103, 133]
			1.0	3.0	*in vitro*	m FTS	[187]
			c	*c*	*in vitro*	frog	[188, 189]
Dexamethasone	392	1.83	*c*	*c*	*in vivo*	human	[190, 191]
			0.87	*c*	*in vivo*	human	[192]
			1.0–3.0	1.0	*in vivo*	human	[193, 194]
			1.0	1.5	*in vivo*	pig	[176]
			1.0	1.4	*in vitro*	h FTS	[102]
Dibucaine (cinchocaine)	343	4.40	1.1	0.25	*in vivo*	human	[138]
Diclofenac	296	4.51	1.0–3.0	0.5–1.5	*in vivo*	human	[195–199]
			0.8	0.5–3.0	*in vitro*	r FTS	[200]
Digoxin	781	1.26	3.3	1.0, 3.0	*in vitro*	h FTS	[201]
					in vitro	m FTS	
Dimethyl sulfoxide	78	−1.35	1.0	0.8	*in vivo*	rat	[132]
Ethyl nicotinate	151	1.32	3.0	1.0	*in vivo*	human	[202]
EMLA (lidocaine, prilocaine mixture)	234	2.44	0.75–3.0	0.25–1.5	*in vivo*	human	[138, 203]
	220	2.11	1.0	2.0	*in vivo*	rat	[204]
Estradiol	272	4.01	1.0–3.0	0–2.0	*in vitro*	h FTS	[12, 102, 187]
Fibrinolysin	13.8k	-	*c*	*c*	*in vivo*	human	[205]

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Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Flufenamic acid	281	5.25	0.8, 1.0	0.0–1.5	*in vivo*	human	[206, 207]
			0.8, 1.0	0.0–1.5	*in vitro*	h FTS	[206]
Fluocinolone acetonide (sinalar)	452	2.48	c	0.2	*in vivo*	rat	[208–210]
			0.87	2.0	*in vivo*	human	[211]
Fluocinonide	495	3.19	1.0	1.5	*in vivo*	human	[212]
5-Fluorouracil	130	−0.89	3.5	0.1–2.0	*in vitro*	rat FTS	[133, 213]
Glucosamine	179	−4.23	1.0	0.3	*in vivo*	human	[214]
Glucose	180	−3.24	10	0.2, 2.0	*in vitro*	p FTS	[40]
Glycerol	92	−1.76	1.0	*f*	*in vitro*	p FTS	[215]
Heparinoid	5–40k [d]	-	*c*	*c*	*in vivo*	human	[216]
Hexyl nicotinate	207	3.51	3.0	1.0	*in vivo*	human	[202]
Hyaluronan	1–3k	-	1.0	0.4	*in vivo*	rabbit	[217]
Ibuprofen	206	3.97	1.0	1.0	*in vivo*	human	[218]
			1.0	1.0	*in vitro*	h HSS	[91]
			0.8	0.5–3.0	*in vitro*	r FTS	[84, 200]
Indomethacin	358	4.27	1.0	0.25–2.5	*in vivo*	rat	[219, 220]
Inulin	5k	-	1.0	1.5–3.0	*in vivo*	gp, rat	[11]
Iodex pomade (Iodine, methyl salicylate mixture)	127 152	2.49 2.55	c	1.5	*in vivo*	human	[221]
Ketoprofen	254	3.12	1.0–3.0	1.0–1.5	*in vivo*	human	[82, 199, 222]
Ketorolac tromethamine	255	2.32	1.0	1.0–3.0	*in vitro*	rat FTS	[105, 223]
Lappaconitine HBr	666	-	0.8–1.0	0.7–0.75	*in vitro*	rat FTS	[224]

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Lanthanum hydroxide	190	-	10, 16	0.2	*in vitro*	gp FTS	[5]
Lidocaine	234	2.44	0.87	c	*in vivo*	human	[192]
			0.5–1.0	2.0	*in vivo*	human	[225, 226]
			c	2.0	*in vivo*	rabbit	[227]
			1.0	1.4	*in vitro*	h FTS	[102]
Linoleic acid	280	7.05	1.0	1.4	*in vitro*	h FTS	[102]
Mannitol	182	−3.10	1.0	1.5–3.0	*in vivo*	gp, rat	[11]
			1.1	1.5	*in vitro*	h FTS	[187]
			3.5	0.1–2.0	*in vitro*	rat FTS	[133]
			10	0.2, 2.0	*in vitro*	p FTS	[40]
Menthol	156	3.40	1.0–3.0	1.5	*in vivo*	human	[228]
Mepivacaine	246	1.95	*c*	*c*	*in vivo*	human	[229]
Metamizole (analgin)	333	−4.76	*c*	*c*	*in vivo*	human	[230]
Methyl nicotinate	137	0.83	3.0	1.0	*in vivo*	human	[202], [231]
Morphine	285	0.89	1.5–3.0	0.01–2.0	*in vitro*	m FTS	[146]
Niacinamide	122	−0.37	5.0	0.7	*in vivo*	human	[137]
Niflumic acid	282	4.43	3.0	0.1–3.0	*in vivo*	human	[145]
Nimesulide	308	2.60	1.0	1.0	*in vivo*	human	[81]
Oxygen gas	32	0.65	0.97	1.0–2.0	*in vitro*	frog	[232]
Panax notoginseng	-	-	1.0	0.5	*in vivo*	rat	[233]
Panthenol	205	−1.92	3.0	0.1	*in vitro*	p FTS	[234]
Paraaminohippuric acid	194	−0.89	*c*	*c*	*in vitro*	m FTS	[235]
Penicillamine (cuprenil)	149	−1.78	*c*	*c*	*in vivo*	human	[169]

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Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Penicillin	334	1.83	*c*	*c*	*in vivo*	human	[236]
Phenylbutazone	308	3.16	3.0	0.1–3.0	*in vivo*	human	[145]
			c	*c*	*in vivo*	human	[148, 237]
Physostigmine	275	1.58	1.0	1.5–3.0	*in vivo*	gp, rat	[11]
Piroxicam	331	3.06	3.0	0.5	*in vivo*	human	[85]
			1.0–3.0	1.0–2.0	*in vitro*	h FTS	[238]
			0.8–0.87	0.5–3.0	*in vitro*	r FTS	[200, 239]
Prednisolone	360	1.62	1.0	1.50–4.32	*in vitro*	m FTS	[240, 241]
Prednisolone acetate	402	2.40	1.0	1.50–4.32	*in vitro*	m FTS	[240]
Progesterone	314	3.87	1.0–3.0	0–2	*in vitro*	h FTS	[12]
Radioiodine	131	2.49	*c*	*c*	*in vivo*	human	[242]
Reparil (mix of Aescin, Diethylamine salicylate)	1131 211	- -	*c*	*c*	*in vivo*	human	[243]
Salicylic acid	138	2.26	2.0–16	0.2	*in vivo*	gp	[92]
			1.0	3.0	*in vitro*	m FTS	[93]
Scopolamine	303	0.98	*c*	*c*	*in vivo*	human	[244]
Sinomenine	329	1.05	0.8	*c*	*in vitro*	r FTS	[111]
Silver Chloride	143	-	1.0–3.0	1.0, 2.2	*in vivo*	fish	[245]
Silver Nitrate	170	-	0.79–2.9	0.5	*in vivo*	rat	[246]
Streptomycin	582	−7.53	*c*	*c*	*in vivo*	rabbit	[247]
Sucrose	342	−3.70	3.5	0.1–2.0	*in vitro*	rat FTS	[133]
Sulforhodamine 101	607	-	1.0–3.0	1.4	*in vitro*	h FTS	[119]

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq.(MHz)	Amp.(W/cm^2)	Skin Model [b]		Ref.
Tannic acid	1.7k	−0.19	1.0	1.0	*in vivo*	human	[248–250]
Testosterone	288	3.32	1.0–3.0	0–2.0	*in vitro*	h FTS	[12, 102]
			1.0	0.5	*in vitro*	rat FTS	[251]
Tetracycline	444	−1.30	*c*	*c*	*in vivo*	cow	[252]
					in vivo	rabbit	[253]
Thiamin	337	−3.93	0.88	0.3–1.0	*in vivo*	human	[136]
Triamcinolone acetonide	434	2.53	1.0–3.0	1.0–2.5	*in vivo*	rat	[254, 255]
					in vitro	mouse	
Trilon B (Na_4EDTA [e])	380	−13.2	*c*	*c*	*in vitro*	frog	[256, 257]
Trolamine salicylate	287	-	1.0	0.5–1.5	*in vivo*	human	[258]
Urea	60	−2.11	1.0	1.0	*in vivo*	human	[248–250]
Zidovudine	266	0.05	1.1	1.5	*in vitro*	h FTS	[259]
					in vitro	m FTS	
Zinc Sulfate	65	−0.47	1.0	1.0	*in vivo*	human	[248–250]

[a] from Syracuse Research Corporation physical property database.[260]

[b] legend: h = human, p = pig, r = rabbit, m = mouse, gp = guinea pig, FTS = full-thickness skin, and HSS = heat-stripped skin.

[c] not available or not specified.

[d] estimated from references or other sources.

[e] ethylenediaminetetraacetate tetrasodium salt.

[f] 600 kPa, not reported in W/cm2.

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Table 2

Molecules that have been delivered transdermally with low-frequency ultrasound.

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq. (kHz)	Amp. (W/cm^2)	Skin Model [b]		Ref.
Acetic acid	60	−0.17	58	1.08	*in vitro*	p FTS	[263]
Aldosterone	360	1.08	20	0.125	*in vitro*	h HSS	[8]
Aminopyrine	231	1.00	150	0.111	*in vitro*	rat FTS	[94, 264]
Antipyrine	188	0.38	150	0.111	*in vitro*	rat FTS	[94]
Ascorbic acid	176	−1.85	25	0.05–0.1	*in vivo*	human	[265]
Azelaic acid	188	1.57	25	0.05–0.1	*in vivo*	human	[265]
Benzoate ion	121	−2.27	150	0.111	*in vitro*	rat FTS	[266]
Betamethasone valerate	477	3.60	36	2.72	*in vivo*	human	[267]
Bovine serum albumin	66k	–	20	*g*	*in vitro* *in vivo*	rat FTS rat	[114]
Butanol	74	0.88	20	0.125	*in vitro*	h HSS	[8]
Caffeine	194	−0.07	20	2.5	*in vitro*	rat FTS	[268]
			40	0.13–0.44	*in vitro*	m FTS	[146]
Calcein	623	-	20	1–15	*in vitro*	p FTS	[23, 25, 34]
			41 – 445	0.06–0.30	*in vitro*	rat FTS	[47, 55, 269]
Clobetasol propionate	467	3.50	20	*c*	*in vitro*	m FTS	[270]
Corticosterone	346	1.94	20	0.125	*in vitro*	h HSS	[8]
			58	1.08	*in vitro*	p FTS	[263]
Cortisol	362	1.61	90	1.0	*in vivo*	pig	[180]
Cyclobarbital	236	1.77	150	0.111	*in vitro*	rat FTS	[94, 264]

Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq. (kHz)	Amp. (W/cm^2)	Skin Model [b]		Ref.
Cyclosporin	1.2k	2.92	25	0.05–0.1	*in vivo*	human	[265]
			20	0.4–1.2	*in vitro*	rat FTS	[104]
Daniplestim	13k	-	55	≤15	*in vivo*	rat	[271]
Dextran	70k	-	58, 20	1.08, 7.0	*in vitro*	p FTS	[46, 51]
Deuterium oxide	20	−1.38	41 – 445	0.06–0.24	*in vitro*	rat FTS	[94, 264, 269]
Epinephrine	183	−1.37	55	≤15	*in vivo*	human	[59]
Erythropoeitin	48k	-	20	0–0.225	*in vitro*	h HSS	[7]
Estradiol	272	4.01	20	0.125	*in vitro*	h HSS	[8]
Fentanyl	336	4.05	20	2.5	*in vitro*	rat FTS	[268]
FITC-dextran [c]	4.4k, 38k	-	20	4.4	*in vitro*	p FTS	[26]
			41, 150	0.06–0.30	*in vitro*	rat FTS	[55, 94]
Fluorescein	332	3.35	20	0.008–0.024	*in vitro*	h FTS	[272]
5-Fluorouracil	130	−0.89	150	0.111	*in vitro*	rat FTS	[94]
Flurbiprofen	244	4.16	150	0.111	*in vitro*	rat FTS	[94]
Glucose	180	−3.24	20	*g*	*in vitro*	p FTS	[40]
Gold nanoparticles	5 nm	-	20	7.5	*in vitro*	p FTS	[39]
					in vitro	p 700	
Heparin	10k – 19k [f]	-	20	7.0, 7.4	*in vitro*	p FTS	[27, 51]
					in vivo	rat	[51]
Heparin (Low-Molecular Weight)	3.0k – 8.0k [f]	-	20	7.0	*in vivo*	rat	[51]
			20	7.0	*in vitro*	p FTS	[51]
			55	≤15	*in vitro*	rat FTS	[273]

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Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq. (kHz)	Amp. (W/cm^2)	Skin Model [b]		Ref.
Histamine	111	−0.70	36	2.72–3.5	*in vivo*	human	[274]
Ibuprofen	206	3.97	150	0.111	*in vitro*	rat FTS	[94]
Indomethacin	358	4.27	20	0.2	*in vitro*	m FTS	[112]
Interferon - γ	17k	-	20	0.0125–0.225	*in vitro*	h HSS	[7]
Insulin	5.8k	-	48	*e*	*in vivo*	mouse	[262]
			20	0–10.0	*in vivo*	rat	[7, 275–277]
			20, 32, 105	0.05–0.1, *e*	*in vivo*	rabbit	[261, 278, 279]
			20	0.1, 2.5	*in vivo*	pig	[277, 280]
			20	0.0125–1.0	*in vitro*	h HSS	[7, 281]
			20	0.173	*in vitro*	h FTS	[282]
Inulin	5.0k	-	20	1.6	*in vivo*	rat	[30]
			58, 20	1.08, 7.0	*in vitro*	p FTS	[46, 51]
			20	7.2	*in vitro*	h FTS	[36, 38]
Iron oxide particles	5 – 10 nm	-	25	0.8	*in vivo*	mouse	[42]
Isosorbide dinitrate	236	1.31	150	0.111	*in vitro*	rat FTS	[94]
Ketoprofen	254	3.12	150	0.111	*in vitro*	rat FTS	[94]
Kojic acid	142	−0.64	25	0.05–0.1	*in vivo*	human	[265]
Lanthanum nitrate	433	-	35	0.80	*in vivo*	mouse	[42]
LHRH	1.3k	-	58	1.08	*in vitro*	p FTS	[46]
Lidocaine	234	2.44	55	≤15	*in vivo*	human	[56, 57, 59, 283–285]
			48	0.17	*in vivo*	mouse	[89]
			150	0.111	*in vitro*	rat FTS	[94]
Lipid particles	~100 nm [f]	-	20	2.5–5.0	*in vitro*	rat FTS	[251]

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Molecule	MW (Da)	Log $K_{o/w}$[a]	Freq. (kHz)	Amp. (W/cm^2)	Skin Model[b]		Ref.
Liposomes	0.08 μm, 4.6 μm	-	20	*g*	*in vitro* *in vivo*	rat FTS rat	[114]
Mannitol	182	−3.10	20	1.6	*in vivo*	rat	[30]
			20	6.5	*in vivo*	pig	[31]
			20	1.6, 6.5	*in vitro*	h HSS	[21, 31]
			20	7.2	*in vitro*	h FTS	[36, 38]
			20	6.5	*in vitro*	p 700	[31]
			19 – 93	1.08–14	*in vitro*	p FTS	[19, 21, 31, 32, 44, 46, 263]
Methylprednisolone	374	1.82	55	≤15	*in vivo*	human	[265]
Microparticles	1.5–173 μm[h]	-	20	19	*in vitro* *in vitro*	h HSS h FTS	[286]
Morphine	285	0.89	40	0.13–0.44	*in vitro*	m FTS	[146]
Nile red	318	-	20	15	*in vitro*	p FTS	[23]
Oligonucleotides	7k – 10k[f]	-	20	2.4	*in vitro*	p FTS	[52]
poly-l-lysine-FITC[c]	51k	-	20	2–50	*in vitro*	h HSS	[286]
Quantum dots	10–22 nm	-	20	7.5	*in vitro*	p700	[39, 287]
			20	7.5, 2.4	*in vitro*	p FTS	[35, 39]
Octa-l-lysine-4-FITC[c]	2.5k	-	20	2–50	*in vitro*	h HSS	[286]
Polymer nanoparticles	200 nm	-	28	8	*in vivo*	rat	[288]
Prilocaine	220	2.11	55	≤15	*in vivo*	human	[56]
Raffinose	504	−6.76	20	7.2	*in vitro*	h FTS	[36, 38]
Rhodamine B	479	1.95	41	0.06–0.30	*in vitro*	rat FTS	[47, 55]

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Molecule	MW (Da)	Log $K_{o/w}$ [a]	Freq. (kHz)	Amp. (W/cm^2)	Skin Model [b]		Ref.
Rhod. B hexyl ester	627	-	20	7.2	*in vitro*	h FTS	[24]
Salicylic acid	138	2.26	20	0.125	*in vivo*	mouse	[8]
					in vitro	h HSS	
siRNA-liposomes	50 nm	-	20	0.05	*in vivo*	mouse	[289]
Sodium nonivamide acet.	373	-	20	0.20	*in vitro*	m FTS	[120]
Sucrose	342	−3.70	20	0.125, 1.6	*in vitro*	h HSS	[8, 21]
			20	7.5	*in vitro*	p 700	[39, 290]
			20	1.6, 7.5	*in vitro*	p FTS	[21, 39, 290]
Sulforhodamine B	559	−0.01	20, 58	0–7.5	*in vitro*	p FTS	[24]
Testosterone	288	3.32	20	2.5–5.0	*in vitro*	rat FTS	[251]
Tetanus Toxoid	150k	-	20	2.4, *g*	*in vivo*	mouse	[53, 291]
Tizanidine	254	-	20	10	*in vitro*	mouse	[113]
Urea	60	−2.11	20	7.2	*in vitro*	h FTS	[36, 38]
Vasopressin	1.1k	−8.37	20	0.1–1.0	*in vitro*	h HSS	[281]
Water	18	−1.38	20	0.125	*in vitro*	h HSS	[8]
			41	0.06–0.30	*in vitro*	rat FTS	[55]
			58	1.08	*in vitro*	p FTS	[263]

[a] from Syracuse Research Corporation physical property database.

[b] Legend: h = human, p = pig, r = rabbit, m = mouse, gp = guinea pig, FTS = full-thickness skin, 700 = dermatomed 700 μm skin, and HSS = heat-stripped skin.

[c] not available or not specified.

[d] estimated from references or other sources.

[e] Intensity was reported as 3000 – 8000 Pa.

[f] Molecular weight or size were estimated from references.

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[g] A setting of 10–70% was reported (VCX 400 or 500, Sonics and Materials, USA).

[h] Particles larger than 25 μm in diameter were not observed to penetrate the skin.