A Review on Ultrasound Parameters and Methods of Application in Transdermal Drug Delivery

Sreeraj S R¹, Bharati Bellare², Ipseeta Ray³

¹Research Scholar in Physiotherapy, ²Professor, MGM School of Physiotherapy, Sector 1, Kamothe, Navi Mumbai. ³Professor, Department of Pharmacology, MGM Medical College, Sector 1, Kamothe, Navi Mumbai.

Corresponding Author: Sreeraj S R

Received: 26/03/2015 Revised: 18/04/2015 Accepted: 30/04/2015

ABSTRACT

The transdermal route of drug delivery has attracted medical and pharmacological researchers due to its advantages over other methods of drug delivery. However, the stratum corneum acts as a barrier that limits the penetration of substances through the skin. Application of ultrasound to the skin believed to increase its permeability and enables the delivery of various substances into and through the skin. The use of ultrasound for the delivery of drugs to, or through, the skin is commonly known as phonophoresis or sonophoresis. Despite a wide usage of phonophoresis in physical therapy, doubts persist as to the relevance, efficacy and conditions underlying the efficacy of phonophoresis treatment. Although phonophoresis utilize ultrasound to increase the skin penetration of permeants, the mechanisms associated with this physical enhancer are not well understood in physiotherapeutic point of view. Specifically, mechanisms responsible for skin permeability enhancement and the location of these effects. In this review, we will discuss the mechanisms associated with penetration enhancement by phonophoresis and the effects of various ultrasound parameters like Frequency, Mode, Time and Intensity and the methods of phonophoresis application to skin. Background on the relevant physics associated with ultrasound transmitted through aqueous media along with implications of these phenomena on Sonophoresis will also be discussed.

Keywords: Phonophoresis, Ultrasound, Physiotherapy, Transdermal drug delivery

INTRODUCTION

Transdermal Drug Delivery

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. The delivery of drugs through the skin ("Transdermal Drug Delivery" or "TDD") provides many advantages; primarily, such a means of delivery is a comfortable, convenient and non-invasive way of administering drugs. The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. [1] The success of a dermatological drug to be used for drug delivery depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve the desired therapeutic effect. [2] The skin is
made up of several layers including stratum corneum, viable epidermis and dermis, and it contains appendages that include sweat glands, sebaceous glands, and hair follicles. The stratum corneum is the outermost layer of the skin and epidermis, the dermis, and the subcutaneous tissues falls in subsequent orders. The stratum corneum, located on the outer surface of the skin contains only 20% of water, is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix or a highly lipophilic membrane that provides the primary barrier to drug delivery into skin. The epidermis below is a viable tissue devoid of blood vessels. Just below the dermal-epidermal junction, the dermis contains capillary loops that can take up transdermally administered drugs for systemic distribution. Of the various skin layers, it is the stratum corneum that is the rate-limiting barrier to percutaneous drug transport. In fact, the stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes.

Despite its barrier properties there has been a growing interest in intact skin as a port of drug administration. This is because topically applied drugs avoid the risks and inconveniences of intravenous therapy, bypass the liver in terms of elimination, provide less chance of an overdose or under dose, allow easy termination (e.g., remove the drug from the skin), and permit both local and systemic treatment effects.

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages; through the intercellular lipid domains; or by a transcellular route. Importantly, the intercellular spaces contain structured lipids and a diffusing molecule has to cross a variety of lipophilic and hydrophilic domains before it reaches the junction between the stratum corneum and the viable epidermis. Transport of hydrophilic or charged molecules is especially difficult attributable to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein, and only 20% water. Transport of lipophilic drug molecules is facilitated by their dissolution into intercellular lipids around the cells of the stratum corneum. Absorption of hydrophilic molecules into skin can occur through ‘pores’ or openings of the hair follicles and sebaceous glands, but the relative surface area of these openings is barely 1% of the total skin surface.

**Phonophoresis**

Ultrasound is frequently used in the rehabilitation of soft tissue injuries. The technique of applying ultrasound includes the use of a coupling agent to facilitate the penetration of sound waves into body tissue. Ultrasound may also be used to introduce medication into the tissue by a technique known as phonophoresis. Phonophoresis/Sonophoresis is administered in the same manner as ultrasound, except that medication is used in the coupling agent or applied topically prior to or after ultrasound application. This procedure is used to administer medication without the pain and discomfort which can accompany injections. Phonophoresis is usually performed with anti-inflammatory medications, such as cortisol, dexamethasone, and salicylates, and with anesthetics, such as lidocaine.

Phonophoresis is used in physiotherapy, but is not exclusive to this arena, and there is lot of research studies in pharmaceutical field. A literature search will identify thousands of references, though only a relatively small proportion of them will be directly relevant to therapy type applications.
Even though there are studies relevant to physiotherapy, the efficacy of phonophoresis has not been conclusively established. Some studies have shown drug penetration, [15,17-27] but other studies have cast doubt on these findings. [16,28-37] This means despite the frequency phonophoresis is used in physical therapy clinics, questions remain regarding treatment validity and effectiveness of ultrasound. The purpose of this review is to provide a discussion on the principles of phonophoresis considering various parameters like Frequency, Mode, Time and Intensity and the methods of phonophoresis application to skin. We used various databases such as Medline, Cinahl, Embase, Google Scholar and Cochrane Database and identified articles which are relevant to phonophoresis for identifying common trends in the application.

**Ultrasound Parameters**

The extent of enhancement through transdermal phonophoresis is determined by four principal acoustic variables; frequency, duty cycle, intensity and duration.

**Frequency**

Commonly used frequencies for sonophoresis are generally separated into two groups: (i) low-frequency phonophoresis, which includes frequencies in the range 20 - 100 kHz, and (ii) high frequency phonophoresis, which includes frequencies in the range 700 KHz - 16 MHz [13] but most commonly used in physiotherapy practice are 1-3 MHz.

Ultrasound is a longitudinal pressure wave inducing sinusoidal pressure variations in the skin, which, in turn, induce sinusoidal density variation. It is generally accepted that the main mechanisms responsible for skin permeability enhancement by phonophoresis is acoustic cavitation. [9,25,38-44] Collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue. This cavitation leads to the disordering of the lipid bilayers and formation of aqueous channels in the skin through which drugs can permeate. [39,45,46,47] The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity. [39] At frequencies greater than 1 MHz, the density variations occur so rapidly that a small gaseous nucleus cannot grow and cavitational effects cease. But other effects due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium, may continue to occur. Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayer permeability. This increase is, however, non-significant and hence mechanical effects do not play an important role in therapeutic sonophoresis. Thus cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport. [39]

It is important to stress that the resonant radius of cavitation bubbles exhibits an inverse relationship with the applied ultrasound frequency. 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. Therefore, cavitation within the skin is much more likely to occur with high frequency phonophoresis, when the resonant bubble radius is on the order of microns or smaller, rather than with low frequency phonophoresis in KHz. [38,47] Another mechanisms enhances skin permeability in phonophoresis have been thermal effects of ultrasound. It was also proven that the lower the frequency, the faster and greater the...
heating regardless of the depth.\textsuperscript{[48]} The general result is that skin permeability is enhanced by the augmented mechanical stress and/or by creation of permanent or temporary cavities through corneocytes and keratinocytes.\textsuperscript{[25,49]} This may also be due to thermal effects.\textsuperscript{[11,42,49,50]} The progression of the ultrasonic wave in the tortuous channel of intercorneocyte spaces of stratum corneum and the reflection of the wave by the corneocytes could induce mechanical and thermal disturbance within the intercellular lipid bilayers.\textsuperscript{[49]}

US Mode

Another experimental variables that are important in sonophoresis is the Ultrasound mode/duty cycle (ratio of the time that ultrasound is on). Apart from a continuous mode various pulsed modes are used in experiments with phonophoresis. Typical pulse ratios are 1:1 and 1:4 though others are available. In 1:1 mode, the machine offers an output for 2 ms followed by 2 ms rest. In 1:4 mode, the 2 ms output is followed by a 8 ms rest period.\textsuperscript{[13,51]} 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.\textsuperscript{[13,52]} In phonophoresis, thermal effects is considered as one of the mechanisms responsible for skin permeability enhancement along with cavitation, convection (acoustic streaming and resulting boundary-layer reduction), mechanical or radiation pressure effects, lipid extraction and increase in the solution-membrane interfacial transfer rate.\textsuperscript{[11,42]} A continuous mode of insonation delivered a greater and faster rise in temperature than a pulsed energy delivery for the same intensity at the same depth. The smaller the frequency, the greater the increase in temperature. The mean rise in temperature per minute is as expected greater and faster in a continuous mode than a pulsed one and this for each US frequency, intensity and depth.\textsuperscript{[48,53]} Mechanistically, phonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue.\textsuperscript{[54-56]} While the cavitation effects as a principal mechanism of phonophoresis, the role of the accompanying thermal effect has not been deduced. Given that skin permeability can increase significantly with temperature\textsuperscript{[44]} and that phase transitions of the intercellular lipids of the stratum corneum can occur at temperatures close to physiological, it is clearly possible that thermal changes can contribute to sonophoretically enhanced transdermal transport.\textsuperscript{[56,57]}

Moreover, the skin displayed capillaries and muscle necrosis when ultrasound was applied in high intensity continuous mode which is due to excess heat buildup.\textsuperscript{[42]} Thus it can be that the increase in the skin temperature resulting from the absorbance of ultrasound energy may increase the skin permeability coefficient because of an increase in the permeant diffusion coefficient.\textsuperscript{[58]}

The skin permeability increases significantly, almost 2 times when heated to 42.6 °C and it suggests that for every 10°C increase in temperature leads to doubling of skin permeability\textsuperscript{[43]} thus the thermal effects of continuous mode ultrasound may also act as a secondary contributor to transport enhancement.

Intensity

There is a wide variety of intensities used in physiotherapeutic ultrasound ranging from 0.1W/cm\textsuperscript{2} to 2 W/cm\textsuperscript{2}. The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity. The intensity and the time of application were found to play an important role in the transdermal phonophoretic delivery system. Ultrasound exposure at a given frequency varies directly with the
intensity and exposure time.\[39,59,60\] When applying ultrasound caution should be taken as obvious histologic modifications such as detachment of the epidermis and dermal necrosis were seen with higher intensity (4 W/cm², continuous mode, 10 minutes). A second-degree burn was observed macroscopically at the higher intensities (7 W/cm² in continuous and 12.3 W/cm² in pulsed mode). These findings indicate that even at low-frequency (20 kHz) ultrasound a high-intensity can cause severe skin lesions and intensities lower than 2.5 W/cm² at same frequency seems to have no effect on human skin in vitro.\[42\] Further low-frequency ultrasound at low intensities appears safe for use to enhance the topical delivery of medications, producing only minimal urticarial reactions.\[61\] Higher-intensity conditions resulted in second-degree burns, most likely attributable to localized heating.\[60\] So it is viable to assume that as the frequency of ultrasound is higher the intensity need to be controlled. Ultrasound energy transfer is converted into heat proportional to the intensity of the US. If this heat is not dissipated by physiological means, a localized increase in temperature will occur and thermal therapeutic effects may arise. If the dissipation of heat equals the generation of it, any effect is said to be non-thermal. It is believed that such effect could be achieved by low intensities or a pulsed output of ultrasonic energy.\[48\]

**Duration**

According to a review by Szczypiorowska et al.\[62\] the duration of the procedure and the forms of drugs, are factors influencing the efficacy of phonophoresis technique. Duration and frequency of treatment were chosen based on standard clinical practice with the use of ultrasound. A continuous mode at a frequency of 1 MHz and intensity of 1-1.5 W/cm² with treatment duration of 8-10 minutes is ideal dosimetry as per various suggestions.\[16,31,42,63,64\] When a pulsed mode is used the duration has to be increased to gain the thermal effect of ultrasound.\[18,42\] It is already mentioned that the use of ultrasound as an aid to increasing skin permeability is based on its non thermal bio effects, mostly cavitation. The increase in the skin temperature resulting from the absorbance of ultrasound energy may increase the skin permeability coefficient because of an increase in the permeant diffusion coefficient.\[58\] It was also expected that drug flux could be proportional to the solution strength and duration of exposure.\[40\]

Prolonged use of phonophoresis with intensities of between 0.1 and 3.0 W/cm² and frequencies up to 3.6 MHz and durations of 5 to 51 minutes increases tissue penetration in experiments but also caused considerable thermal damage to the skin, and would be inappropriate for clinical use.\[29,45,65,66\] Low-intensity phonophoresis (0.3 and 0.1 W/cm²) was also examined by Griffin and Touchstone\[66\] but, because of the low intensities, longer treatment times were indicated.

**Methods of Application to Skin.**

Phonophoresis is applied to skin in three ways:

i) as a pretreatment of the skin prior to ultrasound application,\[16,18,21,24,26,27,3-33,35,37\]

ii) as a simultaneous application of ultrasound through a coupling medium containing the drug\[19,23,25,30,34\]

iii) as a post treatment after the application of ultrasound.\[22\] Simultaneous treatment causes enhancement of drug transport through structural changes to the skin and convection related mechanisms that occur only when ultrasound is applied. In the pretreatment and post treatment methods enhancement of drug transport happens through structural changes to the skin because the drug applied is not utilizing the convection related mechanisms during the application of ultrasound. Out of the three
the most common method applied in clinical set up is pre treatment and simultaneous method.\textsuperscript{[13]} But it is argued that the action of ultrasound on drugs, or other active ingredients, can cause degradation of the molecules or other chemical reactions can result in loss of activity or effectiveness of the therapeutic compound.\textsuperscript{[67]} A post treatment drug application can be a viable idea considering that that the direct interaction of the oscillating cavitation bubbles induces disordering of the stratum corneum lipid bilayers, causing an increase in skin permeability.\textsuperscript{[13,44]}

CONCLUSION
Phonophoresis aims to achieve therapeutically relevant concentrations of the transdermally introduced drug in the tissues subjected to the procedure by the use of ultrasound waves. The quality and efficacy of phonophoresis depends on factors like frequency and intensity of the ultrasound waves, duration and technique of the procedure and possibility of occurrence of physical phenomena like cavitation, convection related mechanisms, thermal effects and their effects on skin lipid barrier. Instead of traditional belief that ultrasound drives molecules through the skin, it should be understood that ultrasound causes disturbances in the skin structure (barrier properties of skin) to cause increased drug permeability through the skin. The physicochemical properties of the transdermally introduced drugs like vehicle, concentration and molecular weight of the drug are not explored in this review which requires more research evidence. The use of ultrasound for the transdermal delivery of drugs has been investigated extensively but the parameters used in majority are not consistent with physiotherapeutic applications. Even though there are studies relevant to physiotherapy, the efficacy of phonophoresis has not been conclusively established. Despite its extensive usage, the principles of phonophoresis remain elusive to practitioners and academicians. There is lack of insight about the reason for using a particular parameter and the researchers seem to follow a common trend in the parameter selection.

REFERENCES


30. Bare AC, Christie DS, Mc Anaw MB, Domenech MA, Pritchard AE, Bare MA et al. Phonophoretic Delivery of 1 0%Hydrocortisone Through the Epidermis of Humans as Determined by Serum Cortisol Concentrations. Physical Therapy 1996; 76(7): 738 – 745
43. Sarheed O, Bazigha K, Rasool A. Development of an Optimised Application Protocol For Sonophoretic Transdermal Delivery of a Model


