INTRODUCTION

There are numerous methods of administering drugs to the body, both passive and active. Active methods include the use of penetration enhancers and assisted drug delivery (phonophoresis and iontophoresis). A recent review of the literature on phonophoresis reports that 75% of the studies reviewed reported positive effects of ultrasound on local subcutaneous drug diffusion, with some systemic effects being reported. This current article discusses the use of ultrasound (phonophoresis) as a method of drug administration and sample formulations that are routinely used.

ULTRASOUND

Ultrasound consists of inaudible, acoustic, high-frequency vibrations that may produce either thermal or non-thermal physiologic effects. Traditionally, it is used for the purpose of elevating tissue temperatures and is referred to as a deep-heating modality. Ultrasound is unlike traditional electrical modalities because it involves the longitudinal waveform associated with sound and is not electromagnetic in nature. Sound waves represent a compression and refraction of a vibrating medium and require a medium for transmission, whereas electromagnetic waveforms can be transmitted across a vacuum. Sound waveforms obey rules of physics concerning reflection, absorption, refraction and dispersion.

Ultrasound uses a high-frequency generator that provides an electrical current through a coaxial cable to a transducer contained within an applicator wand or device. The ultrasonic waves are actually produced by a piezoelectric crystal within the transducer converting electrical energy to acoustic energy through a mechanical deformation process via the piezoelectric effect.

Ultrasound energy can travel through body tissues as a beam that is focused but non-uniform in intensity. The actual intensity delivered is dependent upon the quantity of energy delivered to the applicator or wand head. The energy is expressed as the number of watts per square centimeter (W/cm²), ranging from about 0.1 to 3 W/cm² in medicine.

GOALS AND OBJECTIVES

Goal: To provide information on the ultrasound, phonophoresis and the basics of compounding formulations for phonophoresis administration.

Objectives: After reading and studying the article, the reader will be able to:

1. Explain the theory behind ultrasound and the phonophoresis process.
2. Discuss the basic requirements for phonophoresis therapy.
3. Describe the variables that affect phonophoresis.
4. Discuss various formulations of phonophoresis gels.

Loyd V. Allen, Jr., Ph.D., R.Ph., Professor Emeritus, University of Oklahoma, HSC College of Pharmacy, Oklahoma City, OK 73190
The ultrasound emitted from the unit is actually sound waves that are outside the normal human hearing range. The ultrasonic unit sound transducer head is generally set to emit energy at 1 MHz at 0.5 to 1 W/cm². As ultrasound waves, they can be reflected, refracted and absorbed by the medium, just like regular sound waves. Ultrasound can induce four basic physiologic effects in the body, including chemical reactions, biologic responses, mechanical responses and thermal effects. Enhancement of chemical reactions by ultrasound can result in enhanced healing. Biologic responses are enhanced when ultrasound increases the transfer of fluids and nutrients into the tissues. Mechanical responses involve cavitation and tendons extensibility and the thermal effects include treatment referred to as ultrasonic diathermy. Ultrasound has been indicated in tissue healing, acute and chronic inflammation, joint contractures, muscle spasm, scar tissue, trigger points, myositis ossificans and plantar warts. Due to potential heat buildup, ultrasound can be administered in a pulsed mode, rather than continuous. The use of pulsed ultrasound results in a reduced average heating of the tissues. Interestingly enough, either pulsed or continuous low intensity ultrasound can produce nonthermal or mechanical effects that are associated with soft-tissue healing. Another modality should be mentioned for completeness; that of infrasonic therapy. Normal human hearing is in the range of 60 to 20,000 Hz; ultrasound uses the frequencies of 3 and 5 MHz; infrasonic therapy uses the frequencies below the hearing range, at 8 to 14 Hz. Infrason is used primarily as a therapeutic modality.

**Phonophoresis**

When ultrasound is used to drive molecules of a topically applied medication, it is called phonophoresis. Iontophoresis primarily involves delivery of "ions" (as well as some molecules through the process of electroendosmosis) whereas phonophoresis involves the delivery of "molecules". Although the exact mechanism is not known, drug absorption may involve a disruption of the stratum corneum lipids allowing the drug to pass through the skin. Phonophoresis (therapeutic ultrasound, sonophoresis, ultrasonophoresis, ultraphonophoresis) is actually a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. It is widely used by physiotherapists. Generally, it is said that phonophoresis will result in greater depth of penetration than iontophoresis; ultrasound waves have been reported to penetrate up to 4 to 6 cm into the tissues. Both pulsed and continuous ultrasound are used in phonophoresis. Phonophoresis is commonly used in the treatment of muscle soreness, tendonitis and bursitis.

**Drug Application**

Two different approaches are used for actual drug delivery. Originally, the drug-containing coupling agent was applied to the skin immediately followed by the ultrasound treatment. Today, generally the product is applied to the skin and a period of time allowed for the drug to begin absorption into the skin; then, the ultrasound is applied. Drug penetration is most likely in the 1 to 2 mm depth range.

**Contraindications**

Contraindications and/or precautions for the use of ultrasound and phonophoresis include infection, cancer, heart problems/pacemaker, implants (metal, silicone, saline), acute and post-acute injury, epiphyseal areas, pregnancy, thrombophlebitis, impaired sensation and around the eyes.

**Coupling Medium**

A coupling medium is required to provide an airtight contact between the skin and the ultrasound head. The coupling medium should form a slick, low-friction surface for the ultrasound head to glide over. In phonophoresis, the coupling medium can also serve as the drug vehicle. Agents used as coupling media include mineral oil, water-miscible creams and gels. The pseudoplastic rheology flow exhibited by gels is advantageous as gels are "shear-thinning", decreasing viscosity and friction when stress is applied. In the immersion method, water is the best medium. The immersion method is best used for areas that are small or irregularly shaped. In this method, the drug is applied in a suitable vehicle prior to immersion into water and the application of the ultrasound.

**Variables**

Variables involved in phonophoresis include energy levels, cavitation, microstreaming, coupling efficiency and transmissivity of the vehicle, extent of skin hydration, use of an occlusive dressing post-treatment and type of drug. Energy levels are attenuated as the ultrasound waves are transmitted through the tissues due to either absorption of the energy by the tissues or by dispersion and scattering of the waves. Ultrasound used for therapeutics is generally in the frequency range between 0.75 and 3.0 MHz; 1 MHz is transmitted through the more superficial tissues into the deeper tissues (3-5 cm) and is more useful in individuals with a higher percent of body fat and 3 MHz energy is absorbed more in the superficial tissues (1-2 cm). Delivery of ultrasound can be either
thermal-continuous (producing more thermal heating; intensity of 1.0 to 1.5 W/cm² for 5-7 minutes) or nonthermal-pulsed (producing less heating; 0.8 to 1.5 W/cm² with a duty cycle of 20%-60% for 5-7 minutes). Another variable affecting dosage is the energy of application; 0.1 to 0.3 W/cm² is regarded as low intensity, 0.4 to 1.5 W/cm² is medium intensity and 1.6 to 3 W/cm² is high intensity; treatment times generally range from 5 to 10 minutes.³

Effects produced by ultrasound, other than heating, include cavitation and acoustic micro-streaming. Cavitation involves the formation and collapse of very small air bubbles in a liquid in contact with ultrasound waves due to the pressure changes induced in the tissue fluids. Cavitation can actually cause an increased fluid flow around these vibrating "bubbles". Microstreaming, closely associated with cavitation, results in efficient mixing by inducing eddies in small volume elements of a liquid; this may enhance dissolution of suspended drug particles resulting in a higher concentration of drug near the skin for absorption. It is actually a movement of fluids in one direction along cell boundaries that results from the mechanical pressure wave in an ultrasonic field. Microstreaming can alter the structure of the cell membrane and it's function as a result of changes in permeability to sodium and calcium ions. Ultrasound apparently also contributes to protein synthesis, fibroblastic activity, blood flow, vascular permeability and decreased edema. The amount of drug absorbed is related to the amount of protein in the tissues, water content of tissues and the frequency and intensity of the ultrasound resulting in increased molecular motion.

The actual tissue penetration also is dependent upon the impedance or acoustic properties of the media or the efficiency of the coupling agent. The vehicle containing the drug must be formulated to provide good conduction of the ultrasonic energy to the skin. The product must be smooth and non-gritty as it will be rubbed into the skin by the head of the transducer. The product should be of relatively low viscosity for ease of application and ease of movement of the transducer head during the ultrasound process. Gels work very well as a medium. Emulsions have been used but the oil:water interfaces in emulsions can disperse the ultrasonic waves, resulting in a reduction of the intensity of the energy reaching the skin. It may also cause some localized heating. Air should not be incorporated into the product as air bubbles may disperse the ultrasound waves resulting in heating at the liquid:air interface.

**APPLICATION**

For greater efficiency of both the ultrasound and phonophoresis, the skin should be will hydrated. Lack of moisture impedes sound transfer; the skin can be rehydrated using a warm, moist towel for about 10-15 minutes prior to the treatment. After treatment is completed, an occlusive dressing will help to maintain skin hydration, warmth and capillary dilatation; it will also keep the drug (residing on the skin surface) in intimate contact with the skin for further absorption. There are numerous steps involved in successful treatment using phonophoresis, as follows:

1. Determine if phonophoresis is indicated and that no contraindications are present.
2. Clean and hydrate (if necessary) the body part.
3. Determine the drug to be used.
4. Determine the coupling method {direct (determine coupling agent) or water immersion} to be used.
5. Determine the frequency.
6. Determine the intensity.
7. Determine the time of treatment.
9. If local, move the sound head at approximately 4 cm/sec, with an overlap one-half the width of the sound head.
10. Determine the number of treatments per day.
11. Record the necessary parameters.
12. Clean the unit and the treated area.
13. Apply an occlusive dressing if desired.

In summary, drug delivery can be maximized by controlling these variables. According to a phonophoresis research review⁴, special attention should be to the following:

1. Both the drug and the coupler (or vehicle) should efficiently transmit ultrasound.
2. Pretreat the skin using ultrasound, heat, moisture or by shaving.
4. Use an occlusive dressing after treatment.
5. Use an intensity of 1.5 W/cm² to capture both the thermal and non-thermal effects of the ultrasound.
6. Low-intensity ultrasound (0.5 W/cm²) should be used when treating open wounds or acute injuries.

**DRUGS USED**

Numerous drugs have been administered using phonophoresis. Hydrocortisone is the drug most often administered using phonophoresis in concentrations ranging from 1% to 10%. Other drugs administered include betamethasone dipropionate, chymotrypsin alpha, dexamethasone, fluocinonide, hyaluronidase, iodine, ketoprofen, lidocaine, mecholyl, naproxen, piroxicam, sodium salicylate, trypsin, and zinc.
### Corticosteroid Gels for Phonophoresis

<table>
<thead>
<tr>
<th>Active Drug</th>
<th>Betamethasone Dipropionate 0.05% Gel</th>
<th>Dexamethasone Sodium Phosphate 0.4% Gel</th>
<th>Fluocinonide 0.1% Gel</th>
<th>Hydrocortisone 10% Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>77 mg (Equiv to 528 mg betamethasone)</td>
<td>528 mg (Equiv to 400 mg dexamethasone)</td>
<td>100 mg</td>
<td>10 g</td>
</tr>
<tr>
<td>Ultrasound Gel</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
</tr>
</tbody>
</table>

### NonSteroidal Anti-inflammatory Gels for Phonophoresis

<table>
<thead>
<tr>
<th>Active Drug</th>
<th>Ketoprofen 2% Gel</th>
<th>Naproxen 5% Gel</th>
<th>Piroxicam 0.5% Gel</th>
<th>Sodium Salicylate 10% Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>2 g</td>
<td>5 g</td>
<td>500 mg</td>
<td>10 g</td>
</tr>
<tr>
<td>Ultrasound Gel</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
</tr>
</tbody>
</table>

### Method of Preparation

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Mix the corticosteroid powder with sufficient propylene glycol to form a smooth paste.
4. Carefully, add the ultrasound gel without incorporating air into the product.
5. Mix until uniform.
6. Package and label.
**Rx DEXAMETHASONE 1.5% AND LIDOCAINE HCl 4% ULTRASOUND GEL**

Dexamethasone sodium phosphate 1.98 g  
(Equiv to 1.5 g dexamethasone)  
Lidocaine hydrochloride 4 g  
Propylene glycol 10 mL  
Hydroxy Ethylcellulose Ultrasound Gel qs 100 g

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.  
2. Accurately weigh/measure each ingredient.  
3. Mix the powders with the propylene glycol to form a smooth mixture.  
4. Carefully, add the ultrasound gel without incorporating air into the product.  
5. Mix until uniform.  
6. Package and label.

**Rx IODINE ULTRASOUND OINTMENT**

Iodine 4 g  
Oleic acid 5 mL  
White petrolatum qs 100 g

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.  
2. Accurately weigh/measure each ingredient.  
3. Dissolve the iodine in the oleic acid.  
4. Incorporate the white petrolatum and stir until uniform.  
5. Package and label. Protect from light.

**Rx ZINC OXIDE 20% GEL**

Zinc oxide 20 g  
Pluronic F127 30% gel 80 g

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.  
2. Accurately weigh/measure each ingredient.  
3. Add the zinc oxide powder, previously comminuted, in small portions to the Pluronic F127 Gel.  
4. Mix until uniform being careful not to incorporate air into the product.  
5. Package and label.

**REFERENCES**