



# Secundum Artem

*Current & Practical Compounding  
Information for the Pharmacist.*

## COMPOUNDING FOR PHONOPHORESIS

### 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.

### 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.<sup>1</sup> 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 ( $\text{W}/\text{cm}^2$ ), ranging from about 0.1 to 3  $\text{W}/\text{cm}^2$  in medicine.<sup>2</sup>



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/cm<sup>2</sup>. 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 tendon 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; infrasound uses oscillations below the hearing range, at 8 to 14 Hz. Infrasound is used primarily as a therapeutic massage 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.<sup>2</sup>

## 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/cm<sup>2</sup> for 5-7 minutes) or nonthermal-pulsed (producing less heating; 0.8 to 1.5 W/cm<sup>2</sup> 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/cm<sup>2</sup> is regarded as low intensity, 0.4 to 1.5 W/cm<sup>2</sup> is medium intensity and 1.6 to 3 W/cm<sup>2</sup> is high intensity; treatment times generally range from 5 to 10 minutes.<sup>3</sup>

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 its 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 well 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.
8. Start 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 review<sup>1</sup>, 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.
3. Position the patient to maximize circulation during treatment.
4. Use an occlusive dressing after treatment.
5. Use an intensity of 1.5 W/cm<sup>2</sup> to capture both the thermal and non-thermal effects of the ultrasound.
6. Low-intensity ultrasound (0.5 W/cm<sup>2</sup>) 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.

# PHONOPHORESIS FORMULAS

Rx				
Ultrasound Gels		Carbopol-Type	HEC-Type	MC-Type
Carbopol 940	(0.65%)	650 mg	--	--
Hydroxy ethylcellulose	(3%)	--	3 g	--
Methylcellulose	4000 cps	--	--	3.5 g
Propylene glycol		5 mL	5 mL	5 mL
Methylparaben		200 mg	200 mg	200 mg
Sodium hydroxide	10% solution	qs	--	--
Purified water	qs	100 mL	100 mL	100 mL

## 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 methylparaben in the propylene glycol.
4. Add the solution to about 90 mL of the purified water.

## Carbopol Gel

5. Disperse the Carbopol 940 in the solution using rapid agitation.
6. Slowly, add about 1.5 mL of the sodium hydroxide 10% solution.
7. Mix slowly to form a smooth gel and avoid incorporating air into the product.
8. Slowly, add additional sodium hydroxide 10% solution until a pH of 6.5-7 is obtained.
9. Add sufficient purified water to volume and carefully mix.
10. Package and label.

## Hydroxy Ethylcellulose (HEC) and Methylcellulose (MC) Gels

5. Initially, disperse the hydroxy ethylcellulose or methylcellulose in the solution using moderate agitation.
6. Then, mix slowly to form a smooth gel and avoid incorporating air into the product.
7. Add sufficient purified water to volume and carefully mix.
8. Package and label.

Rx				
Corticosteroid Gels for Phonophoresis				
	Betamethasone Dipropionate 0.05% Gel	Dexamethasone sodium phosphate 0.4% Gel	Fluocinonide 0.1% Gel	Hydrocortisone 10% Gel
Active drug	77 mg (Equiv to 50 mg betamethasone)	528 mg (Equiv to 400 mg dexamethasone)	100 mg	10 g
Propylene glycol	qs	qs	qs	qs
Ultrasound Gel	qs 100 g	100 g	100 g	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 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				
NonSteroidal Anti-inflammatory Gels for Phonophoresis				
	Ketoprofen 2% Gel	Naproxen 5% Gel	Piroxicam 0.5% Gel	Sodium Salicylate 10% Gel
Active drug	2 g	5 g	500 mg	10 g
Propylene glycol	qs	qs	qs	qs
Ultrasound Gel	qs 100 g	100 g	100 g	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 NSAID 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.





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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

1. **Ultrasound depends on electromagnetic waveforms to drive a drug through the skin.**  
A. True  
B. False
2. **Ultrasound in medicine uses energy ranging from about 0.1 to 3 W/cm<sup>2</sup>.**  
A. True  
B. False
3. **The use of ultrasound to drive molecules across the skin is called:**  
A. infrasound  
B. iontophoresis  
C. phonophoresis  
D. sonography  
E. therapeutic infrasound
4. **Coupling media that have been used include:**  
I. mineral oil  
II. gels  
III. creams  
A. I only  
B. III only  
C. I and II only  
D. II and III only  
E. I, II and III
5. **Medium intensity ultrasound would be in the energy range of:**  
A. 0.1 to 0.3 W/cm<sup>2</sup>  
B. 0.4 to 1.5 W/cm<sup>2</sup>  
C. 1.6 to 3 W/cm<sup>2</sup>  
D. 3.5 to 5 W/cm<sup>2</sup>  
E. 5 to 10 W/cm<sup>2</sup>
6. **The formation and collapse of very small air bubbles resulting from ultrasound energy is called:**  
A. cavitation  
B. microstreaming  
C. shearing  
D. coupling  
E. levigating
7. **Which type of coupling agent would generally deliver the greatest energy intensity?**  
A. creams  
B. gels  
C. ointments  
D. pastes  
E. solids
8. **The most commonly used drug for phonophoresis application is:**  
A. betamethasone  
B. dexamethasone  
C. hydrocortisone  
D. ketoprofen  
E. piroxicam
9. **Absorption can be enhanced by applying an occlusive dressing post-treatment.**  
A. True  
B. False
10. **If the skin is relatively dry, absorption during phonophoresis can be enhanced by applying a warm, wet towel to the area prior to treatment.**  
A. True  
B. False
11. **My practice setting is:**  
A. Community-based      C. Hospital-based  
B. Managed care-based    D. Consultant and other
12. **The quality of the information presented in this article was:**  
A. Excellent    B. Good    C. Fair    D. Poor
13. **The test questions correspond well with the information presented.**  
A. Yes      B. No
14. **Approximately how long did it take you to read the Secundum Artem article AND respond to the test questions?** \_\_\_\_\_
15. **What topics would you like to see in future issues of Secundum Artem?** \_\_\_\_\_

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