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● *Original Contribution*

EFFECT OF PHONOPHORESIS ON SKIN PERMEATION OF COMMERCIAL ANTI-INFLAMMATORY GELS: SODIUM DICLOFENAC AND KETOPROFEN

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Abstract—This study evaluated the use of ultrasound in combination with the commercial anti-inflammatory drugs ketoprofen and sodium diclofenac, according to the parameters used in physiotherapy. Ketoprofen and sodium diclofenac were used in the Franz diffusion cell model adapted to an ultrasound transducer in three conditions: no ultrasound, one application of ultrasound and two applications of ultrasound. High-performance liquid chromatography was used to quantify the total amount of drug permeating skin per unit area, as well as flux and latency. The results showed that for ketoprofen, the amount of drug permeating skin and flux increased with two ultrasound applications. Permeation of sodium diclofenac decreased in the presence of ultrasound. Ultrasound parameters and drug properties must be considered in the use of phonophoresis. (E-mail: jaquelinesz@yahoo.com.br) **© 2013 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Phonophoresis, Ketoprofen, Sodium diclofenac, Permeation.**

INTRODUCTION

The major limitation when using a transdermal or dermatological medication is passage through the skin surface, in particular the layer known as *stratum corneum,* which is composed of condensed and ordered structures of cells known as keratinocytes. These lie within an intercellular lipid matrix that functions as a protective barrier for the body (Benson 2005; Park et al. 2007; Trommer and Neubert 2006). Different vehicles using liposomes and chemical enhancers and physical penetration methods such as ultrasound have been developed to facilitate drug transport through the skin (Benson 2005; Lavon and Kost 2004; Park et al. 2007; Trommer and Neubert 2006).

Use of ultrasound to facilitate the delivery of transdermal or dermatological drugs is known as phonophoresis and is a scientifically proven clinical practice (Koeke et al. 2005; Silveira et al. 2010; Yang et al. 2005). However, the results in the literature related to the use of phonophoresis are highly variable and dependent on wave characteristics (frequency, mode, intensity) (Machet and Boucaud 2002).

It is generally accepted that there are at least three ways to promote skin permeation: (1) convection (acoustic streaming and resulting boundary layer reduction) (Brucks et al. 1989; Mitragotri et al. 1996; Simonin 1995); (2) cavitation (Mitragotri et al. 1996; Polat et al. 2011; Tezel and Mitragotri 2003) and (3) thermal effects (Polat et al. 2011; Simonin 1995). The most common cause of skin permeation is acoustic cavitation, defined as the process by which gas bubbles interact at acoustic pressure and oscillate around an equilibrium radius (non-inertial cavitation or stable), eventually leading to their collapse (inertial cavitation or transient) (Dalecki 2004; Polat et al. 2011; Tezel and Mitragotri 2003). The effects of cavitation are inversely related to the frequency and directly related to the intensity of the acoustic wave (Dalecki 2004; Escobar-Chavez et al. 2009; Humphrey 2007; Machet and Boucaud 2002; O'Brien 2007; Somaglino et al. 2011). The literature indicates that cavitation (inertial and non-inertial) can induce the skin to be permeable to the drug being applied (Smith 2007; Sundaram et al. 2003; Tezel et al. 2002). At low ultrasound frequency, it is primarily inertial cavitation that is responsible for the

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skin's permeability to drugs (Tang et al. 2002a, 2002b; Tezel et al. 2002), whereas at high frequency, such as 1 MHz, primarily non-inertial cavitation is responsible (O'Brien 2007; Silveira et al. 2010).

The effectiveness of ultrasound in facilitating delivery of several drugs such as corticoids (triamcinolone acetonide), anesthetics (lidocaine), immunosuppressive agents (cyclosporine), hormones (insulin) and anti-inflammatory agents (diclofenac, dimethylsulfoxide) has been investigated (Kim et al. 2007; Liu et al. 2006; Miyatake 2008; Park et al. 2007; Silveira et al. 2010; Yang et al. 2005). Anti-inflammatory drugs promote reversible inhibition of cyclooxygenases 1 and 2, which reduces formation of prostaglandin precursors (inflammatory mediators), but their oral administration causes gastrointestinal side effects such as abdominal pain, ulceration and irritation of the gastric mucosa, rendering these drugs more suitable for transdermal application (Herwadkar et al. 2012; Maestrelli et al. 2006; Rahusen et al. 2004). Because of the need to increase local access to anti-inflammatory drugs, there has been increased interest in studying the transdermal mechanisms influenced by ultrasound.

In the present study, we investigated the effect of ultrasound in facilitating delivery of anti-inflammatory drugs similar to those used in clinical practice. We used pulsed ultrasound at a frequency of 1 MHz together with the commercial drugs ketoprofen and sodium diclofenac. In addition, in contrast to traditional phonophoresis studies, in which ultrasound is applied immediately after drug application, we used ultrasound at two points: at the time of drug application and 3 h afterward.

METHODS

Chemicals

The two non-steroidal anti-inflammatory drugs sodium diclofenac (gel formulation, 10 mg/g, EMS, São Bernardo do Campo, São Paulo, Brazil) and ketoprofen (gel formulation, 25 mg/g, Medley, Campinas, São Paulo, Brazil) were applied with and without ultrasound. Transdermal sodium diclofenac was composed of isopropyl alcohol, cetomacrogol, liquid petrolatum, caprylic capric triglyceride, carbopol, sodium sulfite, diethylamine, methyl paraben, propyl paraben, disodium edentate, quality essence, propylene glycol and purified water. Ketoprofen contained ethyl alcohol, carbomer, essence of Venice, propylene glycol, trolamida and deionized water. All chemicals used were of either analytical or pharmaceutical grade. The standard materials sodium diclofenac salt and ketoprofen were obtained from Pharma Nostra (Rio de Janeiro, Rio de Janeiro, Brazil; imported from origin India/Germany). Acetonitrile and methanol were acquired from Tedia (Fairfield, CA, USA), and phosphoric acid was from Merck (Darmstadt, Bundesland, Germany).

Sodium diclofenac ($C_{14}H_{10}Cl_2NNaO_2$), molecular weight 318.13, is hygroscopic and poorly soluble in water (log P [partition coefficient] = 4.4, pK_a = 3.78) (Martindale 2009; Su et al. 2003; U.S.P. U.S. Pharmacopeial Convention 2007). Ketoprofen ($C_{16}H_{14}O_3$), molecular weight 254.28, is not hygroscopic, is considered a weak acid, is practically insoluble in water (log P = 0.97, pK_a = 4.5) and is freely soluble in alcohol (Beetge et al. 2000; Martindale 2009; U.S.P. U.S. Pharmacopeial Convention 2007).

Permeation experiments and ultrasound parameters

Permeation experiments with Franz diffusion cells were carried out using a circulating water bath with magnetic stirring (DIST Indústria Comércio e Serviços, Florianópolis, Santa Catarina, Brazil); porcine ear skin was used as a membrane, as previously described (Garcia et al. 2006; Argemi et al. 2011), with modifications to adapt the ultrasound transducer. This model is a common method used to evaluate skin permeation *in vitro* (Argemi et al. 2011). Pig ears were donated by a local slaughterhouse (Pig Production Cooperative of Superior Caí, Harmonia, Rio Grande do Sul, Brazil) and cleaned under cold running water; the hair, subcutaneous fat tissue and whole skin membranes were removed from the underlying cartilage within 48 h of death. The membranes were stored wrapped in aluminum foil at −20°C until further use, but for no longer than 3 mo. On the day of experiments, skins were stored at room temperature and were then mounted on the glass Franz diffusion cell, which consists of a donor chamber and a receptor chamber, as illustrated in Figure 1. The skin membranes were mounted with the stratum corneum toward the donor chamber, leaving an available diffusion area of 1.75 cm^2. The two cell compartments were held

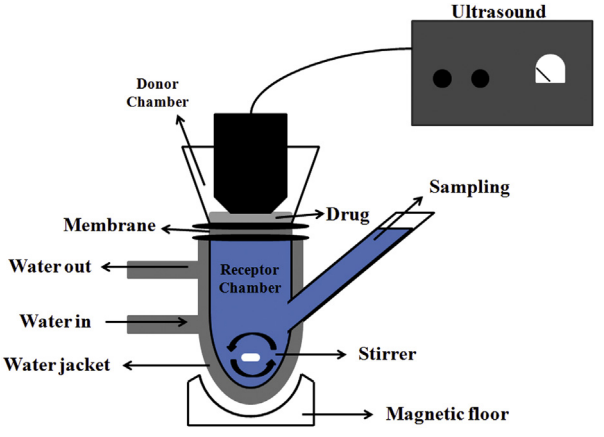

Fig. 1. Schematic of the diffusion cell.