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Phonophoresis in animals- A review

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ABSTRACT

Phonophoresis is a transdermal drug-delivery system that uses ultrasound to enhance the delivery of topically-applied drugs. Use of ultrasound in therapeutics and drug delivery has gained importance in recent years in human-medicine while it is still a new frontier in veterinary medicine. The primary challenge in developing these systems is rooted in the wide differences in skin structure and function seen in species ranging from cats to cows. The following review focuses on the mechanism of phonophoresis and encompasses a discussion on the possible applications of phonophoresis, phonophoretic-systems used in humans and future trends to develop a drug and species-specific phonophoretic-systems. The paper concludes with a section detailing the scope of research in future in veterinary medicine. The purpose of this article is to build a theoretical foundation for understanding phonophoresis and review the efficacy of phonophoresis as a clinical treatment in physical-therapy in humans as well as in animals.

Key words: Animals, Cavitation, Phonophoresis, Transdermal, Ultrasound.

In veterinary medicine, topical application of a wide range of pharmaceutical agents is a useful alternative to more traditional routes of drug administration. Advantages include: (i) a reduction in first pass metabolism by the liver; (ii) non-invasiveness; (iii) avoidance of the gastric route, reducing the potential for both degradation of the drug and gastric irritation, and (iv) improved owner compliance with drug administration (Roberts *et al.*, 2002). There is an increasing number of pharmaceutical products being registered and marketed for veterinary topical application, although limited information is available about the percutaneous penetration of the active ingredient/s or their vehicles in the intended species. More importantly, many of the topical preparations currently used in veterinary clinical practice, including fentanyl patches, sunscreens and anti-inflammatories, are prescribed off-label and based on human kinetic data with no information available about the penetration of drug (or vehicle) through animal skin (Mills and Cross, 2006).

Anatomy and function of the skin: Skin is one of the largest organs of the body, accounting for more than 10% of body mass and having a complex structure that reflects its myriad of biological functions. It has important protective and homeostatic roles and is generally regarded as a critical protective barrier to the external environment (Walters and Roberts, 2002). The function most pertinent to its role in transdermal delivery is that of being a barrier to the outside environment. The skin is considered to be an efficient barrier to prevent penetration, and thus systemic absorption, of most hydrophilic and ionic compounds (Riviere and Papich, 2001). Investigation of human skin has revealed that it is composed of three layers and a number of distinct appendages. The skin consists of the epidermis, the dermis and the subcutis or subcutaneous tissue which anchors the skin to underlying tissues. Each layer is physically and functionally distinct with appendages, including hair follicles, sweat ducts and sebaceous glands, bridging between the layers and the skin surface. A more detailed account of skin structure and physiology can be found in some excellent reviews (Walters and Roberts, 2002). The major resistance to drug penetration is the outermost layer, the stratum corneum (SC). Several theories have been proposed for drug passage through the stratum corneum into the viable epidermis and dermis, including the "bricks and mortar" theory, representing keratinocytes held together by a lipid bilayer (Menon and Elias, 1997). However, differences in skin thickness, density of appendages (hair follicles and glands), vascularity and metabolic enzymes mean that different regions of skin in the same individual display different pharmacokinetics of percutaneous drug penetration. More importantly, extrapolation of percutaneous penetration data between species is not practical (Walters and Roberts, 1993) and use of products in veterinary practice without consideration of these interspecies variations in risky.

Species differences in skin structure: Marked species differences have been reported in each of the skin layers and appendages and it is these differences that probably account for the observed significant differences in transdermal drug penetration. The SC thickness (Table 1) varies in many domestic animal species, with thinner SC structures found in small laboratory animals and values

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Table 1: Physicochemical characteristics of the skin from several mammalian species.

Species	Lipids *a* (lg/cm^2)	Epider-mis *b* (lm)	Stratum corneum *b* (lm)	Skin blood perfusion (mL/min/100 g) *b*	
				BUT *c*	VAB *d*
Mouse	212.40	9.70 ± 2.30	3.00 ± 0.30	3.88 ± 0.92	38.85 ± 8.14
Rat	273.30	11.60 ± 1.00	4.60 ± 0.60	4.20 ± 1.05	11.35 ± 5.53
Pig	130.00	46.80 ± 2.00	14.90 ± 1.90	3.08 ± 0.48	10.68 ± 2.14
Dog	NR	22.50 ± 2.40	8.60 ± 1.90	2.21 ± 0.67	8.78 ± 1.40
Horse	NR	29.10 ± 5.00	7.00 ± 1.10	3.16 ± 1.22	8.90 ± 1.46
Cow	NR	27.40 ± 2.60	8.10 ± 0.60	6.03 ± 1.84	10.49 ± 2.13

NR - not reported.
a- Sato *et al.* (1991).
b- Monteiro-Riviere *et al.* (1990).
c- BUT, skin over right femoroiliac area of the buttocks.
d- VAB, skin of the ventral abdomen midway between the umbilicus and xiphoid.

approaching those of humans (3–5 lm) in the pig (Monteiro-Riviere *et al.*, 1990). Similarly, the epidermis is substantially thicker in pigs, while relatively thin in rabbits, rats and mice. It should be noted that rats, mice and pigs are often used as models to investigate transdermal drug penetration in development of formulations for human use. The extrapolation of these data to humans is controversial due to marked species differences in the transdermal penetration of a number of drugs, with the pig emerging as the model of choice to investigate potential topical formulations for human use (Mills and Cross, 2006).

For veterinarians, hair could be considered the initial barrier to topical application of medications in many species because it can reduce skin contact with the applied formulation. For example, there are up to 10,000 follicles/cm^2 in some regions of Merino sheep (Ryder, 1957), whereas there are comparatively fewer hair follicles in cattle (890 follicles/cm^2) and humans (40–70 follicles/cm^2) (Pitman and Rostas, 1981). Significant differences exist among different body regions within a species. For example, in humans it is accepted that the rate of penetration for most non-ionized compounds is: scrotal> forehead> axilla/scalp> back/abdomen> palmar and plantar (Feldman and Maibach, 1967). The palmar and plantar regions are highly cornified due to their functions which involve constant abrasion. Similarly, regional differences in transdermal penetration in humans have been reported for nitroglycerine (Moe and Armstrong, 1986), ketoprofen (Shah *et al.*, 1996), testosterone (Oriba *et al.*, 1996) and various organic compounds (Rougier *et al.*, 1987). In addition to thickness, hair follicle density, structure and arrangement vary greatly across different body regions (Monteiro-Riviere, 1998). Finally, cutaneous blood flow varies among the different body regions (Monteiro-Riviere *et al.*, 1990).

The rank order of the extent of absorption is mouse>> rats/rabbits> humans> pigs> primates. In general, pigs and monkeys have similar absorption characteristics as humans. This is due to similar anatomy, relatively sparse hair coats (abdomen of monkeys), and biochemically similar com positions of stratum corneum lipids. Unfortunately, similar studies have not been conducted in veterinary species except for one excellent review on topical delivery to cattle and sheep (Pitman and Rostas, 1981).

Penetration of molecules through the skin: There are two possible routes of drug penetration across the intact skin, namely the trans-epidermal and trans-appendegeal pathways. The trans-epidermal pathway involves the passage of molecules through the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Trans-epidermal penetration can be termed intra- or inter-cellular (Schuetz *et al.*, 2005). The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the transport of hydrophilic or polar solutes. Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles (Shahzad *et al.*, 2015).

Techniques for enhancement of skin permeabilisation: Technologies used to modify the barrier properties of the stratum corneum can be divided into passive/chemical or active/physical methodologies. Passive methods include the influencing of drug and vehicle interactions and optimization of formulation, in order to modify the stratum corneum structure (Chen *et al.*, 2006). Passive methods are relatively easy to incorporate into transdermal patches such as chemical enhancers and emulsions (Rehman and Zulfakar, 2013). However, the main drawback of passive methods may be a lag time in drug release incurred with obvious negative influence on rapid onset drugs, such as insulin. The active methods for skin permeabilisation include ultrasound, electrically assisted methods (electroporation and iontophoresis), velocity based devices (powder injection, jet injectors), thermal approaches (lasers and radio-frequency heating) and mechanical methodologies such as microneedles

(MN) and tape stripping (Han and Das, 2015). These techniques greatly expand the range of drugs that can be delivered effectively across the skin. In addition, active methods also offer more reproducible control over the delivery profiles of the medications, thus overcoming lag times between the application and the drug reaching the systemic circulation when compared to passive methods (Arora *et al.,* 2008).

Ultrasound as an enhancer of transcutaneous drug delivery (phonophoresis, sonophoresis or ultrasonophoresis): Phonophoresis or sonophoresis uses ultrasound energy for the skin penetration enhancement of drugs. Even though ultrasound has been used extensively over the last three decades for medical diagnostics and physical therapy, it has only recently become popular as an enhancer of drug delivery (Kost *et al.,* 1990). The first published report on the use of ultrasound for increasing drug flux across the skin appeared in 1954 (Fellinger and Schmid, 1954). Numerous studies (Bommannan *et al.,* 1992a; Bommannan *et al.,* 1992b) have since demonstrated that ultrasound is generally safe, with no negative long- or short-term side effects, but the mechanisms by which ultrasound works as an enhancer are less clearly understood. There are three distinct sets of ultrasound conditions based on frequency range and applications (Suslick, 1988):

- *High frequency (3–10 MHz) or diagnostic ultrasound*: For Clinical imaging.
- *Medium frequency (0.7–3 MHz) or therapeutic ultrasound:* For Physical therapy
- *Low frequency (18 to 100 KHz) or power ultrasound:* For lithotripsy, cataract emulsification, liposuction, cancer therapy, dental descaling and ultrasonic scalpels.

Phonophoresis: a historical perspective: The literature describing the development of phonophoresis in humans is extensive, but there is little development and even less literature in the veterinary field. One of the earliest reports of the interaction between ultrasound and biological tissue can be traced back to the 1920s and the post-World War I experiments of Professor Paul Langévin (Graff, 1981). The first published report on phonophoresis dates back to 1950's. Fellinger and Schmidt (1954) reported successful treatment of polyarthritis of the hand's digital joints using hydrocortisone ointment with Phonophoresis. In a series of publications, Griffin *et al.* showed improved treatment of elbow epicondylitis, bicipital tendonitis, shoulder osteoarthritis, shoulder bursitis and knee osteoarthritis by combined application of hydrocortisone and ultrasound (Griffin and Touchstone, 1972). Bommannan *et al.* (1992I; 1992II) hypothesized that since the absorption coefficient of the skin varies directly with the ultrasound frequency, high frequency ultrasound energy would concentrate more in the epidermis, thus leading to higher enhancements.

Mechanism of phonophoresis: It is believed that there are two types of mechanisms which are commonly invoked to explain the effects produced by therapeutic ultrasound, and the biophysical effects of therapeutic ultrasound are generally divided into two sides: thermal and non-thermal (Baker *et al.,* 2001).

Thermal effects: The energy transported by an ultrasonic beam is attenuated as it passes through tissues, energy scattered out of the beam may be absorbed elsewhere in the tissue. As the energy within the sound wave is passed down into the tissues, it will cause oscillation of the particles (Watson, 2008). The increase in the molecular vibration in the tissue can result in heat generation, and the ultrasound can then produce thermal changes in the tissues. Usually, the temperatures that higher than 42°C are thought to be toxic to cells, while temperatures that lower than 41.8°C are thought to be beneficial in pain relief, changes in blood flow, and decrease in muscle spasm (Draper *et al.,* 2010). Most authorities currently attribute a greater importance to the non-thermal effects of ultrasound as a result of several investigative trials in the last 15 years or so.

Non-thermal effects: The non-thermal effects of therapeutic ultrasound are typically considered to be a combination of cavitation, acoustic streaming, and micromassage (Baker *et al.,* 2001; Ter Haar, 2007). There appears to be little by way of convincing evidence to support the notion of micromassage though it does sound rather appealing.

The role played by each individual phenomenon associated with application of ultrasound to the skin and its relative importance in phonophoresis is elucidated below:

Micromassage: Micromassage is a mechanical effect which appears to have been attributed less importance in recent years. Micromassage is the effect of molecules vibrating when the sound wave travelling through the medium, which can possibly affect tissue fluid interchange and tissue mobility (Xin *et al.,* 2016). There is little, if any hard evidence for this often cited principle.

Cavitation: Although all the mechanisms responsible for skin permeability enhancement by phonophoresis are not fully understood, it is generally accepted that the main contributor is cavitation. Cavitation is the formation of gaseous cavities in a medium ultrasound exposure. The primary cause of cavitation is ultrasound-induced pressure variation in the medium. Cavitation involves either the rapid growth or collapse of a bubble (inertial cavitation), or the slow oscillatory motion of a bubble in an ultrasound field (stable cavitation). Collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue (Clarke *et al.,* 2004). Ultrasound can generate violent microstreams, which increase the bioavailability of the drugs (Tachibana and Tachibana, 1999). Tissues contain air pockets that are trapped in the fibrous

structures that act as nuclei for cavitation upon ultrasound exposure. Cavitation might be important when low-frequency ultrasound is used, gassy fluids are exposed or when small gas-filled spaces are exposed. Cavitation occurs due to the nucleation of small gaseous cavities during the negative pressure cycles of ultrasound, followed by the growth of these bubbles throughout subsequent pressure cycles. This cavitation leads to the disordering of the lipid bilayers and formation of aqueous channels in the skin through which drugs can permeate (Tang *et al.,* 2001).

Acoustic streaming: Acoustic streaming is a phenomenon known to affect diffusion rates and membrane permeability. Sodium ion permeability is altered resulting in changes in the cell membrane potential. Calcium ion transport is modified which in turn leads to an alteration in the enzyme control mechanisms of various metabolic processes, especially concerning protein synthesis and cellular secretions (Watson, 2008).

The result of the combined effects of stable cavitation and acoustic streaming is that the cell membrane becomes 'excited' (up regulates), thus increasing the activity levels of the whole cell. The US energy acts as a 'trigger' for this process, but it is the increased cellular activity which is in effect responsible for the therapeutic benefits of the modality (Leung *et al*., 2004).

Phonophoretic system: Ultrasound is generated using a device referred to as a sonicator. It consists of an electrical signal generated which generates an electrical AC signal at the desired frequency and amplitude. This signal is applied across a piezo-electrical crystal (transducer) to generate ultrasound the thickness of the operating frequency. For phonophoresis delivery, the desired drug is dissolved in a solvent and applied on the skin. Ultrasound is applied by contacting the transducer with the skin through a coupling medium to ensure a proper contact between the transducer and the skin. This medium can be the same as the solvent used to dissolve the drug or it can be a commercially available ultrasound coupling gel (for e.g. Aquasonic, Polar, NJ) (Pahade *et al.,* 2010). Drug is placed on the skin beneath the ultrasonic probe. Ultrasound pulses are passed through the probe, and it is hypothesised that drug molecules move into the skin by a combination of physical wave pressure and permeabilisation of intercellular bilayers. As the ultrasound energy interacts with the tissue it traverses, it will be encounter changes in density, pH and chemical constituents in the different layers. Structural changes in the skin barrier layer are the result of various acoustic phenomena taking place at the skin–transducer junction, such as refraction, reflection, absorption and scattering. This leads to cause-effect phenomena like perturbation of bio membrane lipid–protein configurations, bubble formation, cavitation and even micro-streaming after long exposures at high intensities of ultrasound exposure (Rao and Nanda, 2009).

Commercial phonophoretic systems: Since there have been no commercial phonophoretic systems specifically developed for veterinary species, it is prudent to briefly review human development for insights in to design and potential candidates for veterinary applications.

SonoPrep Skin Permeation Device: Sontra has developed a novel non-invasive and painless skin permeation technique that uses ultrasound to permeate the skin (Rao and Nanda, 2009). This device provides a convenient way to enhance permeability through a short (15 s) well-controlled burst of low-frequency (compared with diagnostic imaging) ultrasonic energy to the skin that allows sustained permeability for up to 24 h. The transport properties of the stratum corneum are greatly improved after skin permeation and the technique opens up the potential for non-invasive transdermal diagnostics and the enhanced delivery of drugs through the skin. The SonoPrep device consists of a battery operated power and control unit, a handpiece containing the ultrasonic horn and the disposable coupling medium cartridge, and a return electrode. Ultrasonic horn vibrates 55,000 times per second applying energy to skin and creates cavitation bubbles that expand and contract which disrupts lipid bilayer creating reversible microchannels in skin through which large drug molecules can be delivered.

Initial studies in the area of transdermal drug delivery suggest that ultrasound-mediated skin permeation can enhance transport rates across the skin up to 100-fold for both small and large compounds. Sontra is investigating the delivery of several large proteins and peptides by incorporating the use of the SonoPrep device in combination with transdermal patches to deliver the drug transdermally (Becker *et al.,* 2005). Sontra Medical is developing a vaccine against dengue fever for the US army using the SonoPrep ultrasonic skin permeation device.

ImaRx Sonoderm Device: Sonoderm Technology is an ultrasound-assisted transdermal transport useful for many drugs, particularly large molecules such as insulin which cannot be administered orally and have to be injected frequently. ImaRx has developed novel ultrasound-enhanced transdermal drug delivery systems (Rao and Nanda, 2009). ImaRx is now developing SonoLysis which involves the administration of their MRX-801 microbubbles and ultrasound with or without thrombolytic drug to break up blood clots and restore blood flow to oxygen-deprived tissues.

Ekos Microlysis Device: The Microlysis developed by Ekos is designed to deliver ultrasound and thrombolytic (clot-dissolving) drug directly into the area of a brain clot (Rao and Nanda, 2009). The Microlysis device is a miniature catheter that is inserted into an artery in the brain until it reaches the clot. Drug is infused through the catheter to the tip, where a tiny ultrasound transmitter is located. The ultrasound and drug are designed to be administered simultaneously because it has been shown that ultrasound

energy induces a temporary change in the structure of a clot that allows the drug to penetrate more efficiently into the inner reaches of the blockage.

Ekos is currently focusing its research and development efforts in the areas of ultrasound enhanced thrombolysis for treatment of stroke and peripheral vascular occlusion, and gene therapy for prevention of coronary re-stenosis. Ekos developed the EkoSonic Endovascular System (EkoSonic ES) with rapid pulse modulation for the dissolution of vascular blood clots. This is the only endovascular system that can deliver microsonic energy and thrombolytic drugs simultaneously, providing a safer, faster and more complete way to remove clots by accelerating dissolution. The EkoSonic ES recently received approval by the US Food and Drug Administration.

Patch-Cap and U-strip applicator device: In June 2005, Dermisonics obtained the patent for the ultrasonic Patch-Cap and a flexible patch for transdermal delivery of drugs via ultrasound (Rao and Nanda, 2009). This has resulted in the U-strip drug delivery system, which incorporates a transdermal patch in combination with microelectronics and ultrasonic technology (Redding and Bruce, 2005). The U-strip Insulin System is the first wearable, programmable and non-invasive drug delivery system that eliminates painful needles and promises improved compliance with the automatic 'set-in and forget- it' design of the system. The U-strip Insulin Patch is an ultrasonic drug delivery system using an alternating sonic transmission to effect pore dilation and deposit large-molecule drugs into the dermis.

Applications of phonophoresis: The applications of certain phonophoresis techniques in the transdermal drug delivery system are given as follows:

- Treatment of wide varieties of injuries such as tennis elbow, tendon problems, repairing damaged ligaments, muscle spasms, stiff joints, fractured bones and cartilage. Also used in healing of wounds, damaged skin, skin rejuvenation, nerve stimulation, and improving the strength and elasticity of scar tissues (Sampath Kumar *et al.,* 2013).

- Ocular delivery of drugs for enhancement of corneal permeability to glaucoma drugs of different lipophilicity (Zderic *et al.,* 2004).

- To enhance the permeability of the nails to topically applied drugs for ultrasound guided nail drug delivary (Torkar *et al.,* 2007).

- Another application for ultrasound as a topical enhancer lies in the field of topical gene therapy (Vogel, 2000). Significantly better transfection is achieved in the presence of cavitation (Price and Kaul, 2002). Enhanced gene transfer is found either when the exposed bubbles are in the vicinity of the genetic material or when genes are encapsulated within or bound to the bubbles.

- The application of phonophoresis in drug and gene delivery to the brain is used to deliver a wide variety of small and large molecules to the brain for imaging and therapy in other neurogenerative disorders (Raymond *et al.,* 2008).

- There has been increasing interest in the use of needle-free immunization technologies in human and veterinary medicine due to practical considerations and the role of the epidermis as a sensitive immune organ. Particle mediated epidermal delivery (PMED) uses particles of gold, coated with DNA or protein, that are accelerated into the epidermis by a similar device to that used to deliver DNA and protein vaccines (Dean *et al.,* 2003).

- Topical delivery of vaccines such as the tetanus toxoid offers several advantages over needle-based immunisations, including ease of administration (Tezel *et al.,* 2005).

- Phonophoresis can be effectively used in transdermal hormone replacement therapy (Henzl, 2002).

- Chemical activation of drugs by ultrasound energy for the treatment of cancer is termed 'sonodynamic therapy' (Rosenthal *et al.,* 2004). Application of ultrasound to growing tumour enhances intracellular delivery of anti-cancerous drugs after intra-peritoneal or intra-tumoral administration, thereby potentiating their cytotoxicity (Larkin *et al.,* 2008).

- An interesting application for therapeutic sonography is the thrombolytic effect of ultrasound (Singh *et al.,* 2003; Pfaffenberger *et al.,* 2005).

- Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means (Husseini and Pitt, 2008).

- Phonophoresis has a major application in cardiovascular therapy. Ultrasound-targeted microbubble destruction is a method that could combine low invasiveness with possibly higher gene transfer efficiency as well as high organ specificity. The development of myocardial contrast echocardiography was an essential milestone in this process, as the use of ultrasound-targeted microbubble destruction for local drug and gene delivery is broadly based on tools that were developed for this technique (Mayer and Bekeredjian, 2008).

- In the treatment of sick fish by University of Maryland's Center of Marine Biotechnology. The current method uses intraperitoneal injections which are costly and highly labour intensive. In this experiment, ultrasound was applied to water containing fish and compound of interest. The ultrasound waves increased the permeability of compound into the tissues of the skin and gills (Sampath Kumar *et al.,* 2013).

Future trends in phonophoresis: Ultrasound-mediated drug therapy has immense future and scope for further

research in human and veterinary medicine. Unfortunately to date most of this treatment has been conducted on a rather subjective and non-quantitative basis and is plagued by lack of use of proper controls, incomplete accounts of dosimetry and vagueness in designing experimental protocols (Skauen and Zentner, 1986). The conflicting data have resulted from the fact that different research groups have used different ultrasonic parameters (i.e. frequency, intensity, duration, mode), different skin membranes and different vehicles. In addition, the presence and absence of cooling systems, processing of membranes used, distance between skin and transducer, size of transducer, quantity and type of coupling medium used, and end point evaluation techniques all affect the sonophoretic skin permeation rates (Dahlan *et al.*, 2005). Ultrasound can reflect back on itself at a tissue-bone interface in vivo or at a vessel wall-solution interface in vitro to produce a standing wave. Another factor that must not be neglected is the effect of ultrasound on drug stability (Dahlan *et al.*, 2005). Degradation of drugs in the presence of ultrasound has been studied and reported in only a few cases, for example, oligonucleotides, insulin, fentanyl and caffeine (Boucaud *et al.*, 2002). No degradation was reported. However, this important aspect should be studied as a part of preformulation studies for any drug to be used through phonophoretic delivery. Further work is required in this area using ultrasound but it is now thought in human transdermal research that the transfollicular routes of solute delivery may have greater prominence than initially thought and may rely on formulations designed to optimize solute passage (Lauer, 1999), particularly for drugs whose pharmacological target lies in or around the follicle itself. Importantly, the significantly higher and more generalised follicular density in animals would appear to make this area of research more attractive.

Further work is needed as the effect of site on the efficacy and/or toxicity of topical drug administration in veterinary medicine is rarely considered. The ease of administration of topical formulations encourages compliance with prescribed dosing recommendations in humans and in veterinary species. However, there are significant differences in transdermal drug penetration between species (Sato *et al.*, 1991), meaning that topical products should be formulated for the target species, whereas efficacy and/or toxicity cannot be assumed from studies in other species. Importantly, there is increasing interest in physical enhancement of transdermal drug penetration, hopefully increasing the range of drugs available to topical application and/ or increasing the efficacy of drugs currently used in topical formulations. With the advent and development of ultrasound mediated transdermal transport, phonophoretic devices may soon become the name of the game. It is important that veterinarians recognize the limitations of applying drug formulations to the skin, yet understand the potential advantages of this rapidly developing field of drug delivery. The development of phonophoretic systems specifically for veterinary medicine appears to be a feasible scenario for the future. However, before extensive product development occurs, considerable experimental investigations are required in the primary target species to define some basic parameters of drug absorption and ultrasound. The data reviewed to date leave many questions unanswered. Phonophoretic delivery is feasible as demonstrated by the use of the process in nearly all the species. It is obvious that development of the systems will be drug and species specific. With the rapid advancement of phonophoretic technology for humans, the know-how is presently available to develop effective phonophoretic systems for at least canine and feline therapeutics.

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