International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

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

Sreeraj S R[1], Bharati Bellare[2], Ipseeta Ray[3]

[1]Research Scholar in Physiotherapy, [2]Professor, MGM School of Physiotherapy, Sector 1, Kamothe, Navi Mumbai.
[3]Professor, 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. [3-5] 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. [6] 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. [7-10]

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. [11]

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. [12] 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. [10]

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. [13-16] 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. [1]

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. [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. [25,49] This may also be due to thermal effects. [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. [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. [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. [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. [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. [48,53] Mechanistically, phonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue. [54-56] While the cavitational 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 [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. [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. [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. [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 [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^2 to 2 W/cm^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/cm^2, continuous mode, 10 minutes). A second-degree burn was observed macroscopically at the higher intensities (7 W/cm^2 in continuous and 12.3 W/cm^2 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/cm^2 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. Ultrsound 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/cm^2 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/cm^2 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 Wcm^2) 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. [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.[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. [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

1. Inayat B P, C Mallikarjuna S, Chemical Penetration Enhancers for Transdermal Drug Delivery Systems, Tropical Journal of Pharmaceutical Research 2009; 8 (2): 173-179
2. Kanikkannan N, Kandimalla K, Lamba SS, Singh M. Structures activity relationship of chemical penetration enhancers in transdermal drug delivery. Current Medicinal Chemistry 1999; 7(6): 593-608.
3. Forslind B.A. Domain Mosaic Model of Skin Barrier. ActaDermVenereol. 1994; 74:1-6,
4. Potts RO, Guy RH. Predicting skin permeability. Pharm. Res. 1992; 9(5): 663-669.
5. Walters K.A, Roberts M.S. Dermatological and Transdermal Formulations. New York:Marcel Dekker, Inc. 2002; 1-39.
6. Prausnitz M R, Mitragotri S, Langer R. Current Status and Future Potential of Transdermal Drug Delivery. Nature Reviews Drug Discovery 2004; 3(2): 115-124
7. Ratna Mehta. Topical and Transdermal Drug Delivery: What a Pharmacist Needs to Know. College of Pharmacy – Midwestern University Glendale, Arizona 2004; 2, Available from http://www.inetce.com/archivedArticles.asp
8. Margetts L, Sawyer R. Transdermal Drug Delivery: Principles and Opioid Therapy. Continuing Education in Anaesthesia, Critical Care & Pain 2007; 7(5): 171 – 176
9. Morrow D.I.J, McCarron P.A, Woolfson A.D, Donnelly R.F. Innovative

Strategies for Enhancing Topical and Transdermal Drug Delivery. The Open Drug Delivery Journal, 2007; 1: 36-59
10. Gaur P K, Mishra S, Purohit S, Dave K. Transdermal Drug Delivery System: A Review. Asian Journal of Pharmaceutical and Clinical Research 2009; 2(1): 14 – 20
11. Byl NN. The Use of Ultrasound as an Enhancer for Transcutaneous Drug Delivery: Phonophoresis. Physical Therapy 1995; 75(6): 539-553.
12. Oziomek RS, Perrin DH, Herold DA, Denegar CR. Effect of Phonophoresis on Serum Salicylate Levels. Medicine and Science in Sports and Exercise, 1991; 23(4): 397-401.
13. Polat BE, Hart D, Langer R, Blankschtein D. Ultrasound-Mediated Transdermal Drug Delivery: Mechanisms, Scope, and Emerging Trends. J Control Release. 2011; 152(3): 330–348. doi:10.1016/j.jconrel.2011.01.006.
14. Ogura M, Paliwal S, Mitragotri S. Low-Frequency Sonophoresis: Current Status and Future Prospects. Adv Drug Deliv Rev. 2008; 60(10): 1218–1223 doi: 10.1016/j.addr.2008.03.006.
15. Kaya K, Delialouglu S, Babadag M, Duleroglu D, Ozel S, Culha C, Gorgun S. Combined Physiotherapy in Patients with Arthrogenous Pain of Temporomandibular Joint. J PMR Sci. 2010; 13: 6–14.
16. Klaiman MD, Shrader JA, Danoff JV, Hicks JE, Pesce WJ, Ferland J. Phonophoresis Versus Ultrasound in the Treatment of Common Musculoskeletal Conditions. Med.ScL Sports Exerc. 1998; 30(9), 1349-1355
17. Wing M. Phonophoresis with Hydrocortisone in the Treatment of Temporomandibular Joint Dysfunction. Physical Therapy 1982; 62(1): 32-33
18. Levy D, Kost J, Meshulam Y, Langer R. Effect of Ultrasound on Transdermal Drug Delivery to Rats and Guinea Pigs. J Clin Invest.1989; 83(6): 2074-2078
19. Clccone CD, Leggin BG, Callamaro JJ. Effects of Ultrasound and Trolamine Salicylate Phonophoresis on Delayed-Onset Muscle Soreness. Physical Therapy 1991; 71(9): 666-675
20. Byl NN, McKenzie A, Halliday B, Wong T, O'Connell J. The Effects of Phonophoresis with Corticosteroids: A Controlled Pilot Study. J Orthop Sports. Physical Therapy 1993; 18(5): 590-600
21. Cagnie B, Vinck E, Rimbaut S, Vanderstraeten G. Phonophoresis Versus Topical Application of Ketoprofen: Comparison Between Tissue and Plasma Levels. Physical Therapy 2003; 83(8): 707-712
22. Rosim GC, Barbieri CH, Lancas FM, Mazzer N. Diclofenac Phonophoresis in Human Volunteers. Ultrasound in Med. & Biol. 2005; 31(3): 337-343. doi: 10.1 0161j.ultrasmedbio.2004.11.012
23. Saliba S, Mistry DJ, Perrin DH, Gieck J, Weltman A. Phonophoresis and the Absorption of Dexamethasone in the Presence of an Occlusive Dressing. Journal of Athletic Training 2007; 42(3): 349–354
24. Yildiz N, Atalay NS, Gungen GO, Sanal E, Akkaya N, Topuz O. Comparison of Ultrasound and Ketoprofen Phonophoresis in the Treatment of Carpal Tunnel Syndrome. Journal of Back and Musculoskeletal Rehabilitation 2011; 24(1): 39–47. doi: 10.3233/BMR20110273
25. Ebrahimi S, Abbasnia K, Motealleh A, Kooroshfard N, Kamali F, Ghaffarinezhad F. Effect of Lidocaine Phonophoresis on Sensory Blockade: Pulsed or Continuous Mode of Therapeutic Ultrasound?. Physiotherapy 2012; 98(1): 57–63. doi: 10.1016/j.physio.2011.01.009
26. Luksurapan W, Boonhong J. Effects of Phonophoresis of Piroxicam and Ultrasound on Symptomatic Knee Osteoarthritis. Arch Phys Med Rehabil. 2013; 94(2): 250-5. doi: 10.1016/j.apmr.2012.09.025.

27. Toopchizadeh V, Javadi R, Sadat BE. Therapeutic Efficacy of Dexamethasone Phonophoresis on Symptomatic Knee Osteoarthritis in Elderly Women. Int J Women's Health Reproduction Sci 2014; 2(3): 168-177. doi: 10.15296/ijwhr.2014.25
28. Mc Elnay JC, Matthews MP, Harland R, Mc Cafferty DF. The Effect of Ultrasound on the Percutaneous Absorption of Lignocaine. Br. J. clin. Pharmac. 1985; 20(4): 421-424
29. Benson H A, McElnay J C, Harland R. Use of Ultrasound to Enhance Percutaneous Absorption of Benzydamine. Physical Therapy 1989; 69(2): 113 – 118
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 Determinedby Serum Cortisol Concentrations. Physical Therapy 1996; 76(7): 738 – 745
31. Darrow H, Schulthies S, Draper D, Ricard M, Measom GJ. Serum Dexamethasone Levels After Decadron Phonophoresis. Journal of Athletic Training 1999; 34(4): 338-341
32. Kozanoglu E, Basaran S, Guzel R, Uysal FG. Short Term Efficacy of Ibuprofen Phonophoresis versus Continuous Ultrasound Therapy in Knee Osteoarthritis. Swiss Med Wkly 2003; 133(23-24): 333-338
33. Kuntz A K, Griffiths C M, Rankin J M, Armstrong C W, Mc Loughlin T J. Cortisol Concentrations in Human Skeletal Muscle Tissue After Phonophoresis With 10% Hydrocortisone Gel. J Athl Train. 2006; 41(3): 321–324
34. Hsieh Y. Effects of Ultrasound and Diclofenac Phonophoresis on Inflaniniatory Pain Relief: Suppression of Inducible Nitric Oxide Synthase in Arthritic Rats. Physical Therapy 2006; 86(1): 39-49
35. Nagrale AV, Herd CR, Ganvir S, Ramteke G. Cyriax Physiotherapy Versus Phonophoresis with Supervised Exercise in Subjects with Lateral Epicondylalgia: A Randomized Clinical Trial. J Man ManipTher 2009; 17(3): 171-178
36. Barja PR, Veloso DJDV. Photoacoustic study of the penetration kinetics of nimesulid into human skin. Journal of Physics: Conference Series 214. 2010; 1-4 doi:10.1088/1742 6596/214/1/012017
37. Saime AY, Dogan SK, Evcik D, Baser OC. Comparison the Efficacy of Phonophoresis and Ultrasound Therapy in Myofascial Pain Syndrome. Rheumatol Int 2011; 31(9): 1203–1208. doi: 10.1007/s00296-010-1419-0
38. Tang H, Wang C, Blankschtein D, Langer R. An Investigation of the Role of Cavitation in Low frequency ultrasound-Mediated Transdermal Drug Transport. Pharm Res. 2002; 19(8): 1160–1169.
39. Chavez JJE, Martinez DB, Gonzalez MAV, Cruz IMR, Delgado CLD. The Use of Sonophoresis in the Administration of Drugs Throughout the Skin. J Pharm Pharmaceut Sci 2009; 12(1): 88 – 115
40. Tiwary AK, Sapra B, Jain S. Innovations in Transdermal Drug Delivery: Formulations and Techniques. Recent Patents on Drug Delivery & Formulation 2007; 1(1): 23-36
41. Tezel A, Mitragotri S. Interactions of Inertial Cavitation Bubbles with Stratum Corneum Lipid bilayers During Low-Frequency Sonophoresis. Biophys J. 2003; 85(6): 3502–3512.
42. Boucaud A, Montharu JRM, Machet L, Arbeille B, Machet MC, Patat FDR, Vaillant LC. Clinical, Histologic, and Electron Microscopy Study of Skin Exposed to Low-Frequency Ultrasound. The Anatomical Record 2001; 264(1): 114–119
43. Sarheed O, Bazigha K, Rasool A. Development of an Optimised Application Protocol For Sonophoretic Transdermal Delivery of a Model

Hydrophilic Drug. The Open Biomedical Engineering Journal 2011; 5: 14-24. doi: 10.2174/1874120701105010014
44. Mitragotri S, Edwards D, Blankschtein D, Langer R. A Mechanistic Study of Ultrasonically Enhanced Transdermal Drug Delivery. J Pharm Sci. 1995; 84(6): 697–706.
45. Bommannan D, Menon GK, Okuyama H, Elias PM, Guy RH. Sonophoresis. II. Examination of The Mechanism(S) of Ultrasound-Enhanced Transdermal Drug Delivery, Pharmaceutical Research. 1992; 9(8): 1043-1047
46. Mitragotri, S., Kost J. Low-Frequency Sonophoresis: A Noninvasive Method of Drug Delivery and Diagnostics. Biotechnol. Prog 2000; 16(3): 488–492
47. Tang H., Mitragotri S., Blankschtein D., Langer R. Theoretical Description of Transdermal Transport of Hydrophilic Permeants: Application to Low Frequency Sonophoresis. J. Pharm. Sci. 2001; 90(5): 543–566
48. Cambier D, D'Herde K, Witvrouw E, Beck M, Soenens S, Vanderstraeten G. Therapeutic Ultrasound: Temperature Increase at Different Depths by Different Modes in a Human Cadaver. J Rehab Med 2001; 33(5): 212–215
49. Machet L, Boucaud A. Phonophoresis: Efficiency, Mechanisms and Skin Tolerance. International Journal of Pharmaceutics 2002; 243(1-2): 1–15
50. Kima TY, Junga DI, Kimb YI, Yangc JH, Shind SC. Anesthetic Effects of Lidocaine Hydrochloride Gel Using Low Frequency Ultrasound of 0.5 MHz. J Pharm Pharm Sci. 2007; 10(1): 1-8.
51. Electrotherapy on Web: Educational resources for practitioners, students and educators. Pulsed Ultrasound. 1995-2014. Available from: http://www.electrotherapy.org/
52. Asano J, Suisha F, Takada M, Kawasaki N, Miyazaki S. Effect of Pulsed Output Ultrasound on the Transdermal Absorption of Indomethacin from an Ointment in Rats. Biol Pharm Bull 1997; 20(3): 288–91.
53. Nanda S, Saroha K, Sharma B. Sonophoresis: An Eminent Advancement for Transdermal Drug Delivery System. IJPT 2011; 3(3): 1285-1307. Available Online through www.ijptonline.com
54. Aldwaikat M, Alarjah M, Willis J, Mason T. Sonophoresis Effect on the Permeation of Metronidazole Using 3D Skin Equivalent IJPSR, 2013; 4(1): 205-214
55. Kumar KPS, Bhowmik D, Komala M. Transdermal Sonophoresis Technique - An Approach for Controlled Drug Delivery. Indian Journal of Research in Pharmacy and Biotechnology 2013; 1(3): 379-381
56. Sivakumar M, Tachibana K, Pandit AB, Yasui K, Tuziuti T, Towata A, Iida Y. Transdermal Drug Delivery Using Ultrasound-Theory, Understanding And Critical Analysis. Cell Mol Biol 2005; 51: 767-784. doi: 10.1170/91
57. Merino G, Kalia YN, Delgado-Charro MB, Potts RO, Guy RH. Frequency and Thermal Effects on the Enhancement of Transdermal Transport by Sonophoresis. J. Control Release 2003, 88(1): 85-94.
58. Pahade A, Jadhav VM, Kadam VJ. Sonophoresis: An Overview. International Journal of Pharmaceutical Sciences Review and Research 2010; 3(2): 24-32
59. Verma R, RS Jadon RS. Phonophoresis: Transdermal drug transport by ultrasound [Internet]. 2008 [submitted 10/27/2008]. Available from: http://www.pharmainfo.net/pharma-student-magazine/phonophoresis-transdermal-drug-transport-ultrasound
60. Miyazaki S, Mizuoka H, Kohata Y, Takada M. External Control of Drug Release and Penetration. Enhancing Effect of Ultrasound on the Transdermal Absorption of Indomethacin from an Ointment in Rats. Chem Pharm Bull 1992; 40(10): 2826-2830.

61. Singer AJ, Homan CS, Church AL, McClain SA. Low-Frequency Sonophoresis: Pathologic and Thermal Effects in Dogs. Acad Emerg Med.1998; 5(1): 35-40.
62. Szczypiorowska BG, Zajac L, Izdebska RS. Evaluation of Factors Influencing the Quality and Efficacy of Ultrasound and Phonophoresis Treatment. Ortopedia Traumatologia Rehabilitacja. 2007; 5(6): 449-458
63. Benson H. Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery 2005; 2(1): 23-33
64. Luksurapan W, Boonhong J. Effects of Phonophoresis of Piroxicam and Ultrasound on Symptomatic Knee Osteoarthritis. Archives of Physical Medicine and Rehabilitation 2013; 94(2): 250-5. doi: 10.1016/j.apmr.2012.09.025
65. Griffin JE, Touchstone JC. Ultrasonic Movement of Cortisol into Pig Tissues, I: Movement into Skeletal Muscle. Am J Phys Med 1963; 42: 77-85.
66. Bommannan D, Okujama H, Stauffer P, Guy RU. Sonophoresis I: The Use of High Frequency Ultrasound to Enhance Transdermal Drug Delivery. Pharmaceutical Research 1992; 9(4): 559-564.
67. Riesz P, Kondo T. Free Radical Formation Induced By Ultrasound and Its Biological Implications. Free Radical Bio Med. 1992; 13(3): 247–270.

How to cite this article: Sreeraj SR, Bellare B, Ray I. A review on ultrasound parameters and methods of application in transdermal drug delivery. Int J Health Sci Res. 2015; 5(5):476-485.

****