Phonophoresis in Physiotherapy: Mechanisms, Applications, and Emerging Trends for Enhanced Drug Delivery and Therapeutic Efficacy

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Abstract. Phonophoresis, a widely utilized treatment in physiotherapy, combines topically applied gel or cream-based medications with ultrasonic therapy to enhance percutaneous absorption of pharmacological agents. The procedure employs ultrasound frequencies of 0.7 to 1.1 MHz with intensities ranging from 0.0 to 3.0 Watts per cm². Indications for phonophoresis span various inflammatory, deformative, dermatological, and rheumatic/neurological conditions. Recent studies suggest its clinical efficacy in pain relief and improved function, especially in conditions like lateral epicondylitis and osteoarthritis. The mechanism of action involves both thermal and non-thermal effects, with cavitation playing a key role in enhancing transdermal transport. Phonophoresis offers a non-invasive alternative for drug delivery, bypassing hepatic metabolism and minimizing systemic side effects. Various medicinal gels, particularly diclofenac, are used for transdermal drug delivery through phonophoresis. Low frequency phonophoresis has gained attention for enhancing transdermal transport, especially for macromolecules. Its applications extend beyond physiotherapy to include ocular drug delivery, nail therapy, gene therapy, and sports sciences. Clinical studies demonstrate the effectiveness of phonophoresis in conditions like anterior knee pain, tuberculous lymphadenitis, acute low back pain, and latent myofascial trigger points. Dosage considerations emphasize optimizing thermal effects without causing tissue damage. Studies highlight the potential of phonophoresis in relieving pain and improving function, particularly in knee osteoarthritis. Additionally, phonophoresis with Phyllanthus amarus nanoparticle gel shows promise in reducing pain and enhancing functional capacity in symptomatic knee osteoarthritis. In summary, phonophoresis stands as a valuable modality in physiotherapy, showcasing diverse applications and demonstrating clinical efficacy in various musculoskeletal and inflammatory conditions. Further research is warranted to explore its full potential and optimize treatment protocols.

1 Introduction

Phonophoresis treatment is widely used in the field of physiotherapy, where the topically applied gel or cream-based medicines are being used along with ultrasonic therapy to accelerate the effects of ultrasound [1]. Phonophoresis, also known as sonophoresis, has been claimed to intensify the percutaneous absorption of certain pharmacological agents such as anti-inflammatory steroids and local anesthetics from intact skin into the underlying subcutaneous structures by ultrasound, thereby improving their effectiveness. This procedure is commonly used in physical therapy practices. The procedure generally utilizes an ultrasound apparatus that produces frequencies of 0.7 to 1.1 MHz. The ultrasound intensities that are being employed usually range from 0.0 to 3.0 Watts per cm^2. Both continuous-mode as well as pulse-mode applications are utilized, and most treatments last from 5 to 8 mins, with the exception of treatments of larger areas (greater than 36 cm^2) requiring more than 8 mins[2].

1.1 Indications and therapeutic effect of phonophoresis

Diseases and conditions treated with ultrasound include inflammatory (arthritis), deformative (contractures, spondylitis), dermatological (eczema, warts), and rheumatic/neurological (sciatica, lumbago, myalgia, neuralgia) entities[3]. There are varying results regarding the therapeutic benefits of phonophoresis (such as pain relief and improved range of motion) when it was used to treat lateral epicondylitis, temporomandibular joint pain, and osteoarthritic conditions. Recent studies have shown that, when compared with placebo treatments or ultrasound alone, phonophoresis provides clinical improvement by decreasing pain and increasing function [4].Phonophoresis has been suggested by early studies to enhance the absorption of analgesics and anti-inflammatory agents. Therapeutic ultrasound has two main modes: continuous and pulsed output. Continuous ultrasound has thermal effects, and pulsed ultrasound has mechanical effects such as cavitation, acoustic streaming, microstreaming, increased skin pore size, and increased pore numbers and intercellular space[5].Therefore, the tissues undergo several changes via their interaction with therapeutic ultrasound waves. 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[6].This may also be due to thermal effects.It has been demonstrated that cavitation (creation of tiny air bubbles by splitting molecules within keratinocytes through the use of ultrasound) may have a greater role than transient hyperthermia; this is induced by the thermal effects of ultrasound and is not usually significant. Oscillation of small gas bubbles can augment transdermal transport by perturbing the lipid bilayer molecules of the stratum corneum . The small cavitation bubbles, which oscillate in a steady manner, generate mechanical stress in the blood vessel walls in the vicinity without causing any tissue damage. Therefore, the permeation of vessels is enhanced both structurally and physiologically.

Phonophoresis is the application of ultrasound waves to administer the therapeutic agents to muscles without causing pain and irritation. It is a non-invasive method drug administration through the topicalroute. Most ofthe drugs administered through the application of phonophoresis are anti-inflammatory, analgesics and muscle relaxants to the subcutaneous tissues. It can serve as a painless and non-invasive alternative to injections for the cure of common inflammation, sprains, strains, bursitis, and tendinitis. Apart from its applications in drug delivery it has also been widely utilized in the field of physiotherapy to improve the healing of the muscle injury[7]. The topical drug administration occurs under the influence of ultrasound due to the thermal, non-thermal and chemical effects.

Phonophoresis is a process of local administration of topical medicines under the influence of ultrasound. Thermal, non-thermal, and chemical effects generated by the ultrasound, drive the drug molecules into the tissues causing an enhanced penetration The use of ultrasonic waves to induce topical medicine is considered painless, noninvasive and has fewer side effects as it is administered locally at the site of pain[8].

Phonophoresis is the use of ultrasound energy to enhance percutaneous penentration of topically applied drugs .Ultrasound therapy is widely used by physiotherapists in the management of a range of conditions, in particular,musculoskeletal conditions and soft tissue injuries. Ultrasound enerygy is not directly transmitted through the skin on direct application, therefore the standard treatment procedure involves application of a coupling agent to transmit the ultrasound energy from the ultrasound transducer to the treatment site[9].

Phonophoresis is the use of ultrasound to enhance percutaneous absorption of a drug. Phonophoresis provides an advantage as it bypasses the hepatic first-pass metabolism and avoids the side effects in absorption that occur with oral administration[4].Phonophoresis has been claimed to enhance the percutaneous absorption of certain pharmacological agents such as anti-inflammatory steroids and local anesthetics from intact skin into the underlying subcutaneous structures by ultrasound, therefore improving their effectiveness. This procedure is commonly used in physical therapy practices[10][4]. The main purpose of this method is to achieve a suitable and fast concentration of drug in the tissues without inactivating the drug molecules and with no side effects. In this efficient method, which has had wide utility in physical therapy and sports medicine, the drug is applied locally at the target site and massaged with a therapeutic ultrasound applicator[6]. It is theamount of drug molecules contained in a coupling medium through the skin under the influence of ultrasound, has been studied in clinical conditions. It is well documented to practically increase skin permeation of corticosteroids[11]. Phonophoresis or sonophoresis, which was shown to enhance the transport of many drugs, can be defined as the migration of drug molecules through skin under influence of ultrasound[12].Therapeutic ultrasound is normally generated by a transducer that converts electrical energy to ultrasound by utilizing the piezoelectric principle is shown in the Fig. 1-3.

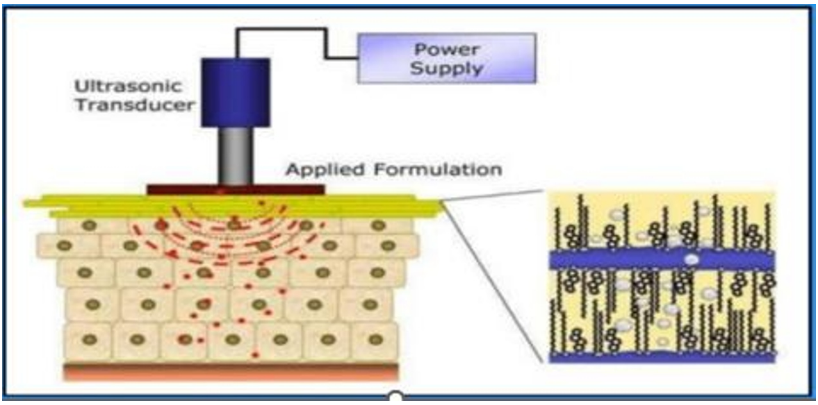

Fig. 1 Generation of ultrasound waves

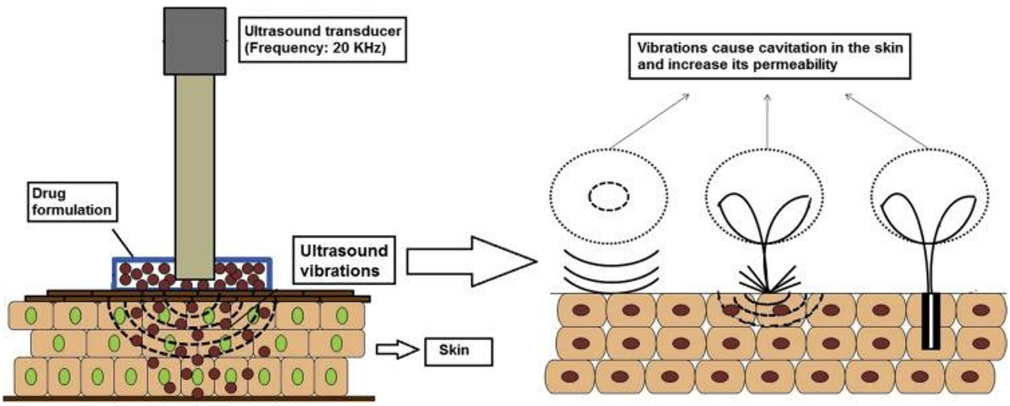

Fig. 2 Transdermal drug delivery flashcards

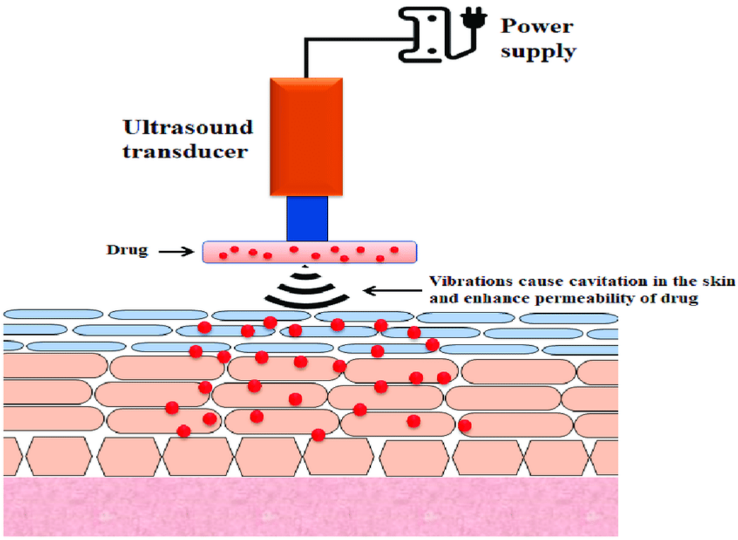

Fig. 3. Illustration of sonophoretic delivery devices

1.1 Application

Phonophoresis involves placing of the topical phonophoresis agent on the skin and massaging by the ultrasound head or transducer. The main aim of this method is attaining a fast and suitable amount of drug in the tissue without inactivating the drug molecules or no side effect. The therapeutic ultrasound, which is used for phonophoresis works on two main modes: continuous and pulsed output. The continuous ultrasound is known to have thermal effects, whereas pulsed mode has mechanical effects such as cavitation, microstreaming, acoustic streaming, increased skin pore size and number and the intercellular space. This leads to several changes in the tissues due to their interaction with the therapeutic ultrasound waves[5].

Taking into consideration there are various medicinal gels that are used for the trans dermal drug delivery by the phonophoresis. The effectiveness and penetrating power vary according to the properties of the gel. Cardero et al. indicated that diclofenac has the highest transdermal penetration among NSAIDs such as indomethacin, piroxicam, tenoxicam, ketorolac and aceclofenac. Rosim et al., also recommended that therapeutic ultrasound administration increases the percutaneous absorption of the topical diclofenac gel. According to this, diclofenac is considered to be a good agent for phonophoresis administration[13].

2Mechanism

2.1 Thermal effects

Ultrasound cannot propagate through tissue without some of its associated energy being deposited as heat. This heat will result in increased temperature of the tissue if its rate of input exceeds the capacity of that tissue to dissipate it. Thermal effects are important with high-intensity continuous-wave ultrasound and are prominent when the irradiated tissue has high protein content or includes bony regions, and when the vascular supply to the area is poor[8].

In thermal mode, it will be most effective in heating the dense collagenous tissues and will require a relatively high intensity, preferably in continuous mode to achieve this effect. Many papers have concentrated on the thermal effectiveness of ultrasound, and much as it can be used effectively in this way when an appropriate dose is selected (continuous mode >0.5 W cm2),the focus of this paper will be on the non-thermal effects. Both Nussbaum (1998) and ter Haar (1999) have provided some useful review material with regards the thermal effects of ultrasound.

Comparative studies on the thermal effects of ultrasound have been reported by several authors (e.g., Draper et al., 1993, 1995a, b) with some interesting, and potentially useful results. It is too simplistic to assume that with a particular treatment application there will either be thermal or non-thermal effects. It is almost inevitable that both will occur, but it is furthermore reasonable to argue that the dominant effect will be influenced by treatment parameters, especially the mode of application i.e. pulsed or continuous[14].

Baker et al., (2001) have argued the scientific basis for this issue coherently. Lehmann (1982) suggests that the desirable effects of therapeutic heat can be produced by US. It can be used to selectively raise the temperature of tissues due to its mode of action. Among the more effectively heated tissues are periosteum, collagenous tissues (ligament, tendon & fascia) & fibrotic muscle (Dyson 1981). If the temperature of the damaged tissues is raised to 40-45°C, then hyperemia will result, the effect of which will be therapeutic. In addition, temperatures in this range are also thought to help in initiating the resolution of chronic inflammatory states (Dyson & Suckling 1978). Having made these comments, most authorities currently attribute a greater importance to the non-thermal effects of U/S as a result of several investigative trials in the last 15 years or so.

2.2Non-Thermal Effects

2.2.1 Cavitation

Cavitation is the result of the pressure changes associated with the propagation of a compressional wave (which is the only wave that can propagate for large distances through soft tissues). This may lead to structural disordering of the stratum corneum lipids, due to oscillations of the ultrasound-induced cavitation bubbles near the keratinocyte lipid bilayer interfaces. Cavitation bubbles also generate shock waves upon collapse, and this may also contribute to the structure-disordering effect. The diffusion of permeants through a disordered bilayer phase would naturally be higher than that through normal bilayers[15].

Cavitation is defined as the physical forces of the sound waves on micro environmental gases within fluid. As the sound waves propagate through the medium, the characteristic compression and rarefaction causes microscopic gas bubbles in the tissue fluid to contract and expand. It is generally thought that the rapid changes in pressure (caused by the leading and lagging edges of the sound wave), both in and around the cell, may cause damage to the cell. Substantial injury to the cell can occur when microscopic gas bubbles expand and then collapse rapidly, causing a "micro explosion." Although true micro explosions, referred to as unstable cavitation, are not thought to commonly occur at therapeutic levels of ultrasound, pulsation of gas bubbles may disrupt cellular activity, altering the function of the cell[16].

2.2.2 Micro Streaming effect

The streaming effect becomes more important when continuous-wave application is used, and the fluid is free to move in a biological medium whose acoustic impedance is different from its surroundings. The rate at which ultrasonic energy is supplied to the tissue, that is, the intensity of the beam (which is one of the main parameters) appears to determine the biological effects that will result from that exposure[4], is described as a small scale eddying of fluids neara vibratingstructuresuch as cell membranes & the surface of stable cavitation gas bubble (Burns 1981, Dyson & Suckling 1978). This phenomenon is known to affect diffusion rates & 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 & cellular secretions.

2.2.2.1 Dosage

Several authors have analyzed the optimal rise in surface temperature of the skin that is required for the increased absorption of the drugs. Miyazaki et al. (1991) concluded that there is a rise of 6 °C with 1 MHz for a low intensity of 0.25 W/cm2and 12°C rise at an intensity of 0.75 W/cm2., which suggests that the rise in skin temperature is an important factor. On the other hand, there are various in vitro studies which used 1-MHz continuous US at spatial peak doses equal to or higher than 1 W/cm2, which led to cell damage due to cavitation. Use of high intensity US application may also generate a feeling of warmth and cause pain. The choice of US dose should be in accordance in order to optimize beneficial thermal effects and avoid tissue damage [7].

2.2.3 Low frequency phonophoresis

There has been extensive research on Low frequency phonophoresis the last 15 years. In the early 1990's Tachibana et al. reported that application of low-frequency ultrasound (48 kHz) enhances transdermal transport of lidocaine and insulin. Another study by Mitragotri et al. applied ultrasound at even lower frequencies (20 kHz) which showed to enhance the transdermal transport of various proteins including insulin, γ-interferon and erythropoeitin across human skin in vitro. There are several other studies which demonstrated the ability of low-frequency ultrasound to deliver macromolecules across the skin [11].

3 Application of Sonophoresis in Medical Sciences and Physiotherapy

Phonophoresis is being used for various purposes including ocular drug delivery, nailtherapy, gene therapy, sport sciences and more importantly in physiotherapy practice etc.In a double blinded, randomized clinical trial, Nakhostin-Roohi et al., (2016) evaluated the effects of virgin olive oil phonophoresis on female athletes' anterior knee pain (AKP). A total of 93 female athletes suffering from AKP voluntarily participated in this study. Patients were randomly assigned into olive oil (n = 31), piroxicam (n = 31) or base gel phonophoresis (n = 31) groups. At the baseline visit, the Western Ontario, and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire was filled by subjects who were then treated with olive oil, piroxicam or pure phonophoresis for 12 sessions. After 6 and 12 sessions of physiotherapy, subjects filled the questionnaire again. Main outcomes were significant improvement in pain, stiffness, physical function, and total WOMAC scores. The authors concluded that it could be proposed that phonophoresis with virgin olive oil is as effective as piroxicam gel on lowering WOMAC scores of AKP in female athletes and has several beneficial properties including faster effect and shorter duration of therapy.

Chen et al (2016) stated that electro-phonophoresis (EP) has been used in various clinical fields. These researchers evaluated the skin permeability of isoniazid (INH) and rifampicin (RIF) in patients with tuberculous lymphadenitis with the aid of EP to validate the clinical applications of this transdermal delivery system for the treatment of superficial extra-pulmonary tuberculosis. Isoniazid and RIF solutions were delivered trans dermally, with or without EP, in the surrounding tissue of the lesion for 30 minutes. The authors concluded that EP can effectively enhance the skin permeability of INH and RIF in patients with tuberculous lymphadenitis. The increase in drug concentrations in the lesions could help eradication of the germs; shorten the treatment course and increase the cure rate of patients with tuberculous lymphadenitis.

In a prospective, double-blind, randomized clinical study, Altan and colleagues (2019) examined the effect of phonophoresis with the combination of non-steroidal anti-inflammatory drugs (NSAID's) and myorelaxant versus routine ultrasound (US) treatment with non-therapeutic gel on the patients with acute low back pain (LBP). A total of 60 patients with acute LBP were randomly assigned into 2 groups. The authors concluded that these findings showed that phonophoresis was superior to conventional US therapy in the short-term in the treatment of patients with acute LBP. The relatively small sample sizes (n = 30 in each group) and the short-term follow-up (6 weeks) were the main drawbacks of this trial. These researchers suggested that further studies with larger patient groups are needed for better understanding of the effects of phonophoresis in acute and chronic LBP[17].

Tabatabaiee and associates (2019) stated that latent myofascial trigger point (LMTP) is a small hypersensitive area in skeletal muscles that becomes painful under compression or stimulation; and LMTPs are relevant for various musculoskeletal disorders. Although several treatments have been introduced to treat LMTP, the most efficient one is yet to be found. These researchers compared the effectiveness of pressure release, phonophoresis of betamethasone and dry needling in treating upper trapezius LMTP. A total of 60 subjects (mean ± SD age of 23.6 ± 2.1 years), with at least 1 LMTP in the upper trapezius muscle, participated in this study. The authors concluded that considering the significant, positive effects of all 3 methods, dry needling and phonophoresis appeared to be more effective than pressure release in treating upper trapezius LMTP[18].

In a systematic review and meta-analysis, Wu, and colleagues (2019) examined the safety and effectiveness of therapeutic US with sham US on pain relief and functional improvement in patients with knee osteoarthritis (OA). As phonophoresis is a unique therapeutic US, these researchers also compared the effects of phonophoresis with conventional non-drug US. PubMed, Embase, and the Cochrane Library were systematically searched for RCTs from inception up to June 2019; RCTs comparing therapeutic US with sham US in knee OA patients were included. Phonophoresis in the experimental and control groups were compared through conventional US, and corresponding trials were also included; 2 reviewers independently identified eligible studies and extracted data. Risk of bias assessments and therapeutic US safety assessments were also performed. A total of 15 studies including 3 phonophoresis-related studies with 1,074 patients were included. Meta-analyses demonstrated that therapeutic US significantly relieved pain ($p < 0.00001$) and reduced the WOMAC physical function score ($p = 0.03$). In addition, therapeutic US increased the active ROM ($p < 0.00001$) and reduced the Lequesne index ($p < 0.00001$). Subgroup analysis of phonophoresis US showed significant differences on the visual analogue scale (VAS; $p = 0.009$), but no significant differences on WOMAC pain subscales ($p = 0.10$), and total WOMAC scores were observed ($p = 0.30$). There was no evidence to suggest that US was an unsafe treatment. The authors concluded that therapeutic US is a safe treatment to relieve pain and improve physical function in patients with knee OA. However, phonophoresis did not produce additional benefits to functional improvement, but may relieve pain compared to conventional non-drug US.

In a double-blind RCT, Pinkaew and colleagues (2020) examined the effects of treatment with Phyllanthus amarus (P. amarus) nanoparticle gel applied by phonophoresis (PP) and US therapy (UT) in patients with symptomatic knee OA. Patients with knee OA (n = 40; mean age ± SD, 64.30 ± 9.71 years), who had VAS scores for knee pain intensity of 68.00 ± 9.58 (UT group) and 71.00 ± 8.74 (PP group, respectively) before treatment, were randomly allocated into 2 groups. Both groups were treated with a US program in continuous mode, 1.0 W/cm2, 10 mins/session for 10 sessions. Nanoparticles of P. amarus were used in the PP group, whereas a non-drug coupling gel was used in the UT group. The 6-min walk test (6MWT) was carried out to examine functional capacity. The VAS and the 6MWT were evaluated before and after 10 treatment sessions in both groups using a double-blind procedure. VAS and 6-MWT showed significant improvement after treatment in both groups ($p < 0.05$). The PP group showed more significant effects than the UT group, in terms of both reducing the VAS pain score ($p < 0.05$) and improving 6MWT ($p < 0.05$). The authors concluded that PP was suggested as an effective method for the treatment of symptomatic knee OA for reducing pain and improving functional capacity. This was a relatively small study (total of 40 subjects) with no follow-up.

Ramakrishnan and Aswath (2019) examined the efficacy of phonophoresis in patients with temporomandibular disorders (TMDs). A total of 50 patients diagnosed clinically and radiographically as TMD were randomly assigned into either of the 2 groups: Group A - plain US, and Group B - phonophoresis. Acoustic gel containing no pharmacological agent was applied in the US group, whereas a gel containing aceclofenac was applied in the phonophoresis group. Each group was treated thricelyweekly for 2 weeks. The assessment of pain and inflammation both before and after treatment were carried out using the VAS and C-reactive protein (CRP). Inter-group comparison was performed and analyzed statistically using independent t-test. Intra-group comparison was carried out using paired t-test. A significant difference in VAS scores and CRP levels before and following treatment were observed within both US and phonophoresis groups. No significant difference was observed statistically between US and phonophoresis group. The authors concluded that the findings of this study suggested that although plain US as well as phonophoresis with aceclofenac gel were effective in the management of TMD, phonophoresis was found be slightly superior as evident in VAS scores and CRP levels though not statistically significant.

In a randomized clinical trial, Taheri, and colleagues (2021) examined the effects of using extra-corporeal shock wave therapy (ECSWT) and phonophoresis therapy on pain and neck disability in patients with neck myofascial pain syndrome (MPS). A total of 40 eligible patients were randomly divided into 2 groups of ECSWT (received 3sessions of ECSWT, onceweekly for 3 weeks) and phonophoresis (received US using hydrocortisone gel 1 % over the trigger point on trapezius muscle, 3 times a week for 3 weeks). Patients in both groups received the same stretching exercise program and drug regimen during the intervention. Pain and NDI scores in both groups were significantly improved at the end of the treatment and 4 weeks later. At the end of the treatment, the pain score was similar between the groups. Four weeks after the treatment, the pain score in the ECSWT group was significantly lower than in the phonophoresis group ($p = 0.030$). The NDI score was not significantly different between the groups at the end of the treatment. However, 4 weeks after the treatment, the NDI score was significantly lower in the ECSWT group than in the phonophoresis group ($p = 0.032$). The trend of changes in the pain and NDI scores was not significantly different between the groups. The authors concluded that both phonophoresis and ECSWT groups effectively decreased pain and neck disability in patients with MPS, with the superiority of ECSWT with a more lasting effect for a month after the end of the treatment. Moreover, these researchers stated that further studies may elucidate the effects of ECSWT and phonophoresis in MPS treatment. Other than physiotherapy phonophoresis can be used and is applicable in other medical sciences as well as explained below.

3.1 Ocular delivery

For many years, ultrasound has been widely used in ophthalmology for diagnostic imaging A-mode ocular biometry is frequently performed before cataract surgery for intraocular lens power calculation. B-mode echography of 8 to 20 MHz allows visualization of the posterior segment of the eye, even in cases in which the ocular media are not optically transparent (cataract, vitreous hemorrhage, corneal opacities, etc.), and are used for many applications such as ocular tumors or retinal detachment diagnosis. High frequency (20 to 50 MHz) ultrasound, which is known as ultrasound biomicroscope, is used to perform high resolution imaging of the anterior segment. Therapeutic ultrasound, although less well known than ultrasound for ocular imaging, has become a topic of growing interest in ophthalmology. High intensity focused ultrasound (HIFU) for the treatment of glaucoma, and ultrasonic drug delivery are the two main areas of research and potential clinical applications[19].

Ultrasound is known to improve the efficiency of gene transfer in cell culture. In in vitro models of odontoblasts,8skeletal muscle cellsand muscular arteries,92 ultrasound enhances the delivery of reparative transgenes. Yet, while the beneficial effects of ultrasound on genetransfer are well appreciated in multiple tissue types, the impacts ofultrasound and contrast agent exposure in the eye are less under-stood. A seminal study by Sonoda et al.15 demonstrated that 1 MHzultrasound exposure in cultured rabbit corneal epithelial cells andin vivo rabbit cornea significantly improves ($p < 0.05$) gene deliveryefficiency, as measured by fluorescence microscopy[20].

Ocular delivery Ultrasound has the potential to provide an efficient andminimally invasive method for drug delivery into the eye.Application of 1 s bursts of 20 kHz ultrasound at spatial-average pulse-average intensity of 14 W/cm2(spatial-averagetemporal-averageintensity2 W/cm2),for enhancement of corneal permeability to glaucoma drugs ofdifferent lipophilicity (atenolol, carteolol, timolol andbetaxolol), was investigated. The permeability of rabbitcornea increased by 2.6 times for atenolol, 2.8 for carteolol,1.9 for timolol and 4.4 times for betaxolol (all$P< 0.05$) after60 min ultrasound exposureinvitro. The differences between the treatment and control experiments weresignificant after 10–30 min ultrasound exposure for all fourdrugs. In the treatment of corneal infections, the application of 880 kHz ultrasound resulted in up to a 10-fold increase incorneal permeability for sodium fluorescein whilst producingonly minor and reversible changes in the cornealstructure[21].

The most convincing evidence for the utility of ultrasound in oculardrug delivery stems from studies of ultrasound in animal eyes.Gatifloxacin, a fluoroquinolone antibiotic used to treat ocular infection, has limited clinical efficacy due to poor corneal penetration.About 1 MHz ultrasound applied to mouse cornea 10 min priorto gatifloxacin treatment improves corneal delivery and extends itshalf-life as measured by two-photon microscopy, suggesting thatultrasound is beneficial for anterior segment drug delivery. Otherstudies of ultrasound-mediated drug delivery to rabbit cornea ,demonstrate enhanced transcorneal penetration of topically applieddrugs, as measured by confocal and light microscopy[22].

3.2 Nail Therapy

It was recently reported that ultrasound can also be used for nail delivery of drugs. Torkar and colleagues reported that low-frequency ultrasound enhanced the permeability of the model nail plate to topically applied drugs. Studies to optimize the ultrasound parameters (sonication time, intensity, duty cycle, probe shape, size, and distance of horn from the membrane used), which are expected to increase the drug permeation, are underway to understand the mechanisms involved.

The two most common disorders of the nail are onychomycosis (fungal infections of the nail plate and/or bed) and psoriasis. Onychomycosis is usually treated with oral antifungals, while psoriasis necessitates repeated monthly injections of corticosteroids into the nail folds. Ideally, these diseases would be treated topically to eliminate the inherent side effects of the current treatments such as pain, systemic adverse events, and drug interactions, and to increase patient compliance. The effectiveness of topical therapy is, however, limited mainly by the very poor permeability of drugs in the nail plate. So far, only a few ungual enhancers, such as N-acetyl cysteine, mercaptoethanol, N-(2-mercaptopropionyl) glycine, have beenidentified[23].

In Magdalena et al. study, in the US examination, in patients with nail psoriasis after six months of treatment with acitretin, the thickness of the matrix and nail bed decreased. The reduction of the thickness of the nail plates was statistically insignificant but it was still greater than in the control group. Acitretin treatment did not affect the thickness of the extensor tendon or the reduction of increased blood supply in the extensor tendon attachment. Thisindicates, on the one hand, the ineffectiveness of the treatment of subclinical enthesopathy of the nail apparatus with acitretin and, on the other hand, the potential usefulness of US examination of the nail apparatus inthe selection of therapy in patients with ultrasound features of enthesopathy[24].

3.3 Gene therapy

Another future application for ultrasound as a topical enhancer that seems to show promise lies in the field of topical gene therapy. There is considerable interest in facilitating the transfer of genes into diseased tissues and organs. The main aim is to increase the delivery efficiency of exogenous nucleic acid to the intended target. The ideal system would enhance gene expression in the target while having no effect in non-target tissues. Ultrasound might be able to provide this localization. Ultrasound has been shown to enhance gene transfer into cells in vitroand in vivo.Significantly better transfection is achieved in the presence of cavitation. 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. Both strategies have been investigated in vitroand in vivo.Ultrasound-enhanced gene therapy is a rapidly evolving field. The exposure levels required to destroy microbubbles lie in the diagnostic range. This is one of the most rapidly expanding fields of ultrasound therapy research; its future utility is of course closely related to the success of gene therapy treatments more widely. A recent themed issue in Advanced Drug Delivery Reviews discussed ultrasound in gene and drug delivery in detail in its reviews[25].

Animal and human studies have shown that relatively efficient gene expression can be achieved by direct injection of a gene into muscle. Muscle cells appear able to take up exogenous genes and produce the protein from the gene. However, direct injection of naked (uncoated) DNA has generally been less successful in other tissues. Furthermore, direct injection is invasive and technically difficult to achieve in some tissues such as the heart. A variety of coating materials has been tested to improve delivery of genetic materials. Ultrasound has a direct effect on gene expression that may be used to enhance gene expression without the use of exogenous micro-bubbles. A synergistic effect is attained with the use of microbubbles and ultrasound and cavitation is a likely mechanism. Acoustically active materials, microbubbles, and gaseous precursor agents have been developed that bind or entrap genetic materials. Targeting ligands have also been incorporated onto the surface of these agents for cell-specificdelivery[26].

Su et al. reported on a new approach for remote high intensity ultrasound-guided delivery of poly-(lactic-co-glycolic acid) (PLGA) microparticles to promote prolonged sustained targeted therapy. The authors observed a sustained release of therapeutics for up to two weeks after ultrasound-guided implantation of microparticles with increased therapeutic-load compared to controls, highlighting the potential of this technique in the enhancement of high intensity ultrasound applications in tumor tissue[27].

3.4 Drug and gene delivery to brain

According to Raymond and colleagues, low-intensity focused ultrasound with a microbubble contrast agent can be used to transiently disrupt the blood–brain barrier, allowing non-invasive localized delivery of imaging fluorophores and therapeutic/immunotherapeutic agents directly to amyloid plaques in mouse models of Alzheimer's disease. This approach should aid preclinical drug screening and the development of imaging probes. Furthermore, this technique may be used to deliver a wide variety of small and large molecules to the brain for imaging and therapy in other neurogenerative disorders[28].

Recently, focused ultrasound (FUS) in combination with microbubble (MB) contrast agent, have been used as a non-invasive method to induce BBB disruption (BBBD) for spatially targeted drug delivery to the brain. Inside the blood vessel, under the influence of the FUS beam, MBs expand and contract via inertial cavitation or stable cavitation processes These physical activities exert mechanical forces (i.e., shear and circumferential stresses) onto proximal capillary walls leading to increased paracellular transport through widened tight junctions , and/or increased transcellular transport through activation of carrier proteins or pore formation[29].

3.5 Vaccines

Topical delivery of vaccines such as the tetanus toxoid offersseveral advantages over needle-based immunizations, including ease of administration. Tezel and colleagues used low-frequency ultrasound (20 kHz, 2.4 W/cm2) to deliver tetanustoxoid (150 kDa) in mice and generated a robustimmune response. Specifically, low-frequency ultra-sound delivered 1.3mg toxoid into skin, which generatedthe same immunoglobulin G antibody titres generated by5mg subcutaneous injections of tetanus toxoid, sufficient toprotect against a lethal dose of tetanus toxin. A study by tezel et al., Using tetanus toxoid as a model vaccine, the results presented here demonstrate that ultrasound-mediated TCI generates a strong systemic immune response. Ultrasound conditions used in these studies have been utilized for systemic transdermal delivery of macromolecules and studieshave reported on clinical acceptance of ultrasound application procedure in human volunteers under similar conditions. Ultrasound thus offers a safe and painless adjuvant for TCI and constitutes a potential alternative toneedle-basedvaccinations[30].

3.6Sports medicine

A new direction for ultrasound therapy has been revealed by recent research demonstrating a beneficial effect of ultra-sound on injured bone. During fresh fracture repairs, ultrasound reduced healing times by 30–38%. When applied to non-united fractures, it stimulated union in 86% of cases. These benefits were generated using low-intensity (<0.1 W/cm2) pulsed ultrasound. Though currently developed for intervention in bone injuries, low-intensity pulsed ultrasound has the potential for use on other tissues and conditions more commonly encountered in sports medicine[31].

3.7Hormone replacement therapy

Kost and colleagues suggested the feasibility of ultrasound as a possible approach to externally affect the release rates of implantable contraceptive delivery systems.Poly(lactide-co-glycolide) microspheres loaded with, nor ethister-one were exposed for 2 h to ultrasound at 3 W/cm2(1 MHz,20% duty cycle) for six consecutive days, resulting in depletion times fourfold shorter than with microspheres that were not exposed to ultrasound. Henzl discussed passive transdermal delivery systems and the possibility of using active transdermal delivery systems including sonophoretic drug delivery for transdermal hormone replacement therapy[26].

3.8Sonoporation and sonodynamic therapy (related to cancer cell)

Chemical activation of drugs by ultrasound energy for the treatment of cancer is another new field recently termed‘sonodynamic therapy.Husseini and colleagues demonstrated that cavitation can also aid delivery of drug contained within Pluronicmicelles. They used doxorubicin inside the hydrophobic core and showed that the amount of drug released correlated well in sub harmonic emissions (70 KHz,0.28 W/cm2). Larkin and colleagues showed that application of low-intensity ultrasound to growing tumor enhances intracellular delivery of bleomycin after intraperitoneal or intra tumoral administration, thereby potentiating its cyto-toxicity.Ultrasound parameters for in-vivo bleomycin delivery were optimized, and an effective anti-tumor effect was demonstrated in solid tumors of both murine and human cell lines. Cell death after treatment was shown to occur by an apoptotic mechanism. The results achieved in these experiments were equivalent to those achieved using electro chemotherapy[32].

3.9Sonothrombolysis

Despite several successful studies using ultrasound on its own, it was found that more enhancement is achieved when ultrasound exposure is combined with fibrinolytic drugs such as streptokinase, urokinase or tissue plasminogen activator.An interesting application for therapeutic sonography is the thrombolytic effect of ultrasound. A positive effect of ultrasound on clot dissolution was first reported byTrubestein and colleagues.Three different therapeutic options based on ultrasound alone are currently in use: transcutaneous non-invasive ultrasound thrombolysis,catheter-delivered transducer-tipped ultrasound thrombolysis and catheter-delivered ultrasound transducer for thrombolysis.All of them use physicalproperties of ultrasound such as acoustic streaming, shear stress and thermal effects to increase mechanical fragmentation of the thrombus or the enzymatic activity of the applied thrombolytics.

3.10Nanoparticles

New technologies combine the use of nanoparticles with acoustic power for both drug and gene delivery. Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective for treating tumors in vivo. Ultrasound releases drug from micelles most probably via shear stress and shock waves fromcollapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genesin vitroandin vivo. The small packaging allows nanoparticles to penetratetumour tissues. 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[33].

3.11Cardiovascular therapy

Ultrasound-targeted microbubble destruction is a promising new method that could combine low invasiveness with possibly higher gene transfer efficiency as well as high organ specificity. It is based on the development of second-generation ultrasound contrast agents. These are microbub-bles that are stable for several minutes in the human circulation and can pass through the pulmonary capillaries; they can be visualized and destroyed by conventional echocardiography devices. 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.Ultrasound-targeted microbubble destruction has been shown to increase transfection rates of naked plasmid DNA and viral vectors by several orders of magnitude.Ultra-sound transducer-tipped catheters are being developed for treatment of cardiovascular diseases[34].

4 Devices in Market

Ultrasound waves are created when a generator produceselectrical energy that is converted to mechanical energythrough the deformation of piezoelectric material in atransducer.The waves produced are transmitted bypropagation through molecular oscillations in biologicaltissue.The piezoelectric material can be lead zirconatetitanate, polyvinyl fluoride, thin-film zinc oxide, lead titanateor the piezo-ceramic/polymer composites, lead metaniobate, barium titanate or modified lead titanate. Sonicatorsoperating at various frequencies in the range of 20 kHz to3 MHz that can be used for sonophoresis are availablecommercially.The design and construction of portable,efficient, and cost-effective devices is currently a thriving area of research in sonophoresis.

Maione and colleagues focused their research on the design and construction of a small lightweight transducer or array. To obtain the desired intensity range, a cymbal transducer design was chosen because of its light, compact structure and low resonance frequency in water. In order to increase the spatial ultrasound field for drug delivery across skin, two arrays, each comprising four cymbal transducers, were constructed[35].

Smith and colleagues explored the feasibility of using ultrasound by novel transducers for enhancing the transport of insulin across skin in vitro. They also explored the use of the cymbal transducer as both a single element and configured as an array for transdermal insulin delivery, and accurately quantified the acoustic field[36].

Yeo and Zhang developed and investigated a new sonophoresis device with dual flat flextensional ultrasound transducers.This device has a radiated acoustic intensity about 2-4 times higher than that generated by a single ultrasound transducer. The device has the capability to reduce the applied voltage at least twofold. The proposed sonophoresis devices with double ultrasound transducers weigh only 73.3 g; by comparison the ultrasonic probe from a commercial sonicator weighs about 1 kg. The authors also proposed the new concept of a highly compact sonophores is micro device to overcome some of the drawbacks of commercial equipment. Several types of sonophoresis devices have been developed in recent years[37].

Lee and colleagues demonstrated the feasibility of using short ultrasound exposure times to non-invasively deliver insulin using a lightweight (<22 g), low-profile cymbal array (f = 20 kHz). Their results indicated that ultrasound exposure times do not need to be long to deliver a clinically significant insulin dose that reduces high blood glucose.

Several different low-frequency transducer designs can be used for drug delivery, such as low-frequency extensional resonators,tonpliz transducers,and ‘thickness’-type resonators.A recent comprehensive review on ultrasound drug delivery commented on the need to develop small low-frequency transducers that patients can wear.Luis and colleagues found that circular cymbal ultrasound arrays were effective in delivering therapeutic levels of insulin in rats, rabbits and pigs.

However, a rectangular cymbal design, desired in order to achieve a broader spatial intensity field without increasing the size of the device or the spatial-peak temporal-peak intensity, improved the efficiency of drug delivery. Park and colleagues investigated the feasibility of a lightweight cymbal transducer array as a practical device for non-invasive transdermal insulin delivery in large pigs.Their findings indicated the feasibility of ultrasound-mediated transdermal insulin delivery using the cymbal transducer array in animals of similar size and weight to humans[38]. The patents granted on the phonophoresis devices have been provided in table 1.

Table.1 Patents available related to phonophoresis.

Title of the patent	**Patent number**
Topical application of medication by ultrasound with coupling agent	4309989
Disposable piezoelectric polymer bandage for percutaneous delivery of drug and method for such percutaneous delivery	4787888
Ultrasound enhancement of transdermal drug delivery	4767402
Ultrasound enhancement of membrane permeability	4780212
Ultrasound enhancement of trans buccal drug delivery	4948587
Local application of medication with ultrasound	5016615
Ultrasound-enhanced delivery of materials into and through the skin	5115805
Drug delivery by multiple frequency phonophoresis	5267985
Ultrasound-enhanced delivery of materials into and through the skin	5231975
Ultrasound-enhanced delivery of materials into and through the skin	5323769
Method for enhancing delivery of chemotherapy employing high frequency force fields	5386837
Enhancement of transdermal delivery with ultrasound and chemical enhancers	5445611
Ultrasonic transdermal drug delivery system	5421816
Enhancement of transdermal monitoring applications with ultrasound and chemical enhancers.	5458140
Sonophoretic drug delivery system	5656016
Ultrasonic method and apparatus for cosmetic and dermatological applications	5618275
Enhancement of transdermal monitoring applications with ultrasound and chemical enhancers	5722397
Transdermal protein delivery using low frequency sonophoresis	6002961
Chemical and physical enhancers and ultrasound for transdermal drug delivery	5947921
Effect of electric field and ultrasound for transdermal drug delivery	6041253
Transdermal protein delivery or measurement using low frequency sonophoresis	6018678
Method and apparatus for therapeutic treatment of skin with ultrasound	6113559
Ultrasound enhancement of percutaneous drug absorption	6030374
Sonophoresis method and apparatus	6322532
Sonophoretic enhanced transdermal transport	6190315
Ultrasound enhanced chemotherapy	6308714
Ultrasound enhancement of percutaneous drug absorption	6398753
Ultrasound enhancement of transdermal transport	6491657

Title of the patent	Patent number
Method and apparatus for in-vivo transdermal and/or intradermal delivery of drugs by sonoporation	6487447
Method and apparatus for producing homogenous cavitation to enhance transdermal transport	6620123
Sonophoresis apparatus European Patent	1089788
Device for a transdermal and photophoretic combination therapy and the use thereof in a method for medical application	6868286
Method and apparatus for in-vivo transdermal and/or intradermal delivery of drugs by sonoporation	6842641
Ultrasound enhancement of percutaneous drug absorption	7004933
Ultrasound mediated transscleral drug delivery.WIPO Patent	WO/2007/081750
Apparatus and method for enhanced intravascular phonophoresis including dissolution of intravascular blockage and concomitant inhibition of restenosis	US5362309A
Sonophoretic drug delivery system	US5656016A
Portable Ultrasound Device for the Treatment of Wounds	US20080051693A1
Nozzle for ultrasound wound treatment	US6964647B1
Ultrasonic therapeutic apparatus	US20030225332A1
Method and device for ultrasound drug delivery	US6601581B1

4.1Limitations and Future implications/advancements required in the design ofsonophoresisdevices.

Ultrasound-mediated drug therapy has an immense future and scope for further research.[39] 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.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. Phonophoretic research often suffers from poor calibration in terms of the amount of ultrasound energy emitted. The problem is that as an ultrasound propagates away from its source, the beam area begins to expand after a certain critical distance. Mathematically, this is dependent on the ultrasonic wavelength, transducer radius and effects associated with constructive and destructive wave interference. Ultra-sound can reflect on itself at a tissuebone interface in vivo or at a vessel wallsolution interface in vitro to produce a standing wave.[40] However, to date no research has been published on the effect of ultrasound standing waves on drug migration, either in vivo or in vitro.[41]

Another important issue that cannot be neglected is that Physiotherapists have been using variable/unmeasured ratio of medicine and ultrasonic gel for the purpose of phonophoresis.This uneven or unmeasured ratio questions the penetration of the medicine and its effects on the underlying tissues.[42] Also, these medicinal gels are bought separately either by the patients or the therapists from the market without exactly knowing their amount to be applied along with ultrasonic gel and have a vague idea about its penetration into the tissues. There is lack of evidence which gives us the amount of medicine that should be applied for effective penetration in the underlying tissues. To maximize the effect of medicine, a proper concentration of medicine should be used for effective phonophoresis. Therefore, there is need to improvise the technique of phonophoresis, where a machine can be devised, which uses ultrasonic waves and dispenses the ointment or gel itself in an appropriate amount directly on the affected area or the area that is being treated. It would ease the treatment for physiotherapist as proper amount of solution will be used for phonophoresis. This effective dosage will maximize the effects of ultrasound It shall be beneficial to both the patient and the therapist and would upgrade the ultrasound therapy and make it more efficientand promising as physiotherapy is still a growing health care profession, we need more modalities and technique to improve the effects of physiotherapy so that the patient will find it more trust worthy, which will ultimately lead to positive growth of physiotherapy. The ultrasound is the modality which has been used in medical field since a very long time, with time the technique of phonophoresis was developed and found very effective. The same technique is used in different health care specialties one of which is physiotherapy the use of ultrasound and phonophoresis has been in practice since the begging of the physiotherapy, with time the technique of phonophoresis has develop to be more precise and is used to treat multiple condition and has shown a very positive effect in the same. But there are still a few limitations and future recommendations as mentioned above which should be addressed and take in considerations in future studies.[43]

5 Conclusion

In conclusion, phonophoresis emerges as a valuable and versatile modality within physiotherapy, demonstrating clinical efficacy across a spectrum of musculoskeletal and inflammatory conditions. The combination of topically applied gel or cream-based medications with ultrasound therapy, operating within specific frequency and intensity ranges, enhances percutaneous absorption of pharmacological agents. Recent studies underscore its effectiveness in pain relief and improved function, particularly noteworthy in conditions like lateral epicondylitis and osteoarthritis. The mechanism of action, encompassing both thermal and non-thermal effects with cavitation as a key player, underscores the intricate processes involved in enhancing transdermal transport. Phonophoresis offers a non-invasive avenue for drug delivery, bypassing hepatic metabolism and mitigating systemic side effects, making it an attractive option in various medical fields. The applications of phonophoresis extend beyond traditional physiotherapy, reaching into ocular drug delivery, nail therapy, gene therapy, and sports sciences. Low-frequency phonophoresis, in particular, gains attention for its efficacy in transporting macromolecules. Clinical studies provide compelling evidence for the effectiveness of phonophoresis in diverse conditions, including anterior knee pain, tuberculous lymphadenitis, acute low back pain, and latent myofascial trigger points. Dosage considerations underscore the importance of optimizing thermal effects without causing tissue damage. Notably, research suggests the potential of phonophoresis in relieving pain and improving function, with a specific focus on knee osteoarthritis. Furthermore, exploration into novel approaches, such as phonophoresis with Phyllanthus amarus nanoparticle gel, holds promise in enhancing its therapeutic capabilities. In summary, phonophoresis stands as a cornerstone in physiotherapy, offering a non-invasive and effective means of drug delivery with applications reaching far beyond its initial scope. Despite current successes, ongoing research is imperative to unlock the full potential of phonophoresis, refining treatment protocols and expanding its applications in diverse therapeutic contexts.

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