Journal of Neonatal Surgery
ISSN (Online): 2226 -0439
Vol. 14, Issue 8 (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Enhancement of Transdermal Absorption of drugs via Phonophoresis and TENS: An *in vitro* Study

Roopika Sabharwal[1*], Amandeep Singh[1], Nitin Kumar Saluja[2], Thakur Gurjeet Singh[3], Debarshi Ghosh[4]

[1*]Chitkara School of Health Sciences, Chitkara University, Punjab, India

[2]Chitkara University Institute of Engineering and Technology, Chitkara University, Punjab, India

[3]Chitkara College of Pharmacy, Chitkara University, Punjab, India

[4]Chitkara University Institute of Engineering and Technology, Chitkara University, Punjab, India

Corresponding Author:

Roopika Sabharwal,

[1*]Chitkara School of Health Sciences, Chitkara University, Punjab, India

Cite this paper as: Roopika Sabharwal, Amandeep Singh, Nitin Kumar Saluja, Thakur Gurjeet Singh, Debarshi Ghosh, (2025) Enhancement of Transdermal Absorption of drugs via Phonophoresis and TENS: An *in vitro* Study. *Journal of Neonatal Surgery*, 14 (8), 290-294.

ABSTRACT

Background: Neuromusculoskeletal pain is a complex condition often requiring multifaceted approaches for effective management. Gabapentin is frequently prescribed for such conditions due to its ability to modulate nerve transmission. However, systemic administration may lead to significant side effects. Enhancing transdermal drug delivery via non-invasive modalities presents a novel strategy for local pain control with minimized systemic risks.

Objective: The aim of this study was to compare the effectiveness of Phonophoresis (ultrasound-assisted) and Transcutaneous Electrical Nerve Stimulation (TENS)-assisted techniques in enhancing transdermal drug absorption using an in vitro model, to support their application in pain management.

Methods: A 5% gel formulation of gabapentin was prepared using Carbopol 934, ethanol, and standard gelling agents. Hairless mouse skin was used for the in vitro permeation study using Franz diffusion cells. Three intervention arms were tested: (1) Control (topical gabapentin only), (2) Phonophoresis with ultrasound (1 MHz and 3 MHz), and (3) TENS at varying frequencies (50 Hz, 100 Hz, 150 Hz). For Phonophoresis, ultrasound was applied in pulsed mode at intensities of 0.8 and 1.0 W/cm² for 5 minutes. For TENS, stimulation was provided using a trapezoidal sweep pattern for 10 minutes. Samples were collected at 0, 1, 2, and 3 hours and analyzed using HPLC.

Results: The 1 MHz, 1.0 W/cm² Phonophoresis condition resulted in the highest permeation (35.0 ± 2.3 µg/cm² at 3 hours), followed by TENS at 150 Hz (30.0 ± 1.8 µg/cm²), and then control (12.0 ± 1.2 µg/cm²). Statistically significant differences ($p < 0.05$) were observed between all groups via ANOVA. Drug permeation was time-dependent and enhanced markedly by both active methods compared to passive application.

Discussion: Ultrasound at 1 MHz penetrates deeper tissues, aligning well with the needs of neuromusculoskeletal pain management. The mechanical and thermal effects of ultrasound, such as cavitation and acoustic streaming, likely contributed to enhanced permeability. Although 3 MHz ultrasound is generally preferred for superficial applications, this study confirms the benefit of 1 MHz for deeper tissue targeting. TENS demonstrated moderate but meaningful enhancement in drug permeation, likely through improved local circulation and neural modulation. These findings reinforce the rationale for using 1 MHz Phonophoresis for pain control.

Limitations include the use of hairless mouse skin instead of human samples, and the lack of long-term retention or penetration depth analysis. Future work should explore in vivo validation and examine therapeutic outcomes on pain scores and functional recovery.

Conclusion: This study confirms that Phonophoresis using 1 MHz ultrasound significantly enhances transdermal drug delivery, outperforming both TENS and control groups. These findings support the integration of ultrasound-assisted transdermal therapy in physiotherapeutic pain management regimens. Further clinical research is warranted.

Keywords: *Neuromusculoskeletal Pain, Phonophoresis, TENS, Transdermal Drug Delivery, Franz Diffusion Cell, Ultrasound Therapy.*

Pain is an uncomfortable sensory experience that indicates presence of damage in the tissues due to a noxious stimulus. Due to the activation of nociceptors, pain signals are generated which are transmitted to the Central Nervous System via the Peripheral Nervous System. Brain receives these signals where processing occurs inside the Thalamus and certain areas of the cortex. Further, motor responses are generated which involve certain reflexive and voluntary movements aiming to minimize pain.[1] Neuropathic pain also involves a specific sensorimotor mechanism. Certain pathophysiological mechanisms at the nerve roots such as mechanical compression, inflammation, ischemia and peripheral sensitization result in hyperexcitation of nociceptors thereby generating noxious stimuli. After the brain processes these noxious stimuli, the body exhibits involuntary motor responses such as withdrawal reflex (flexor reflex response), muscle hyperactivity leading to spasm and cramps and altered reflex activity such as hyperreflexia or hyporeflexia. Patients may also make voluntary adjustments to minimise the pain such as adopting guarding and protective postures, either restricting movement of the affected limb or incorporating tricky movements to execute the tasks. [2]When the lower limbs are involved, gait abnormalities may also be seen. Other manifestations may include muscle atrophy, weakness, tremors and dystonic movements depending upon the severity of the neuropathy. Neuropathic pain is common in certain conditions such as Diabetic neuropathy, postherpetic neuralgia, sciatica, complex regional pain syndrome, and trigeminal neuralgia, etc. The common treatment for neuropathic pain involves intake of Neuropathic pain agents like gabapentin, pregabalin and Non steroidal anti inflammatory drugs like Diclofenac, ibuprofen, etc. Clinical evidence suggests that these drugs provide significant relief within the first week when taken at doses between 150 to 600 mg twice daily. However, continued usage of such high doses can lead to risk of kidney failure and liver damage.[3,4] Topical application of these drugs, which must be applied at least four times a day, offers a lower rate of symptom relief. To address this limitation, alternative drug delivery techniques are being explored to improve absorption and therapeutic effectiveness. This study examines two separate transdermal drug delivery methods—therapeutic ultrasound (phonophoresis) and TENS (Transcutaneous Electrical Nerve Stimulation)—to enhance drug penetration and efficacy.[5]Phonophoresis is a non-invasive technique that utilizes ultrasonic waves to facilitate drug delivery through the skin. These waves generate mechanical effects, such as acoustic cavitation, which involves the formation and oscillation of microbubbles in body fluids. This process increases skin permeability, allowing for deeper and more efficient absorption of topically applied medications. Phonophoresis is particularly useful in targeted drug delivery, promoting pain relief, reducing inflammation, and enhancing tissue healing, while minimizing systemic side effects.[6,7,16]

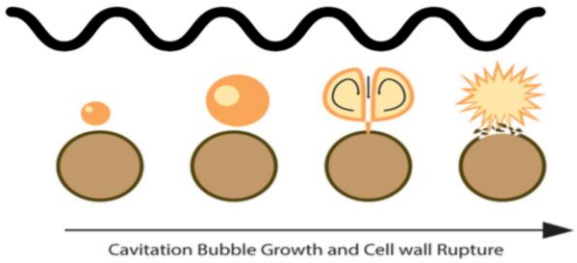

Figure 1: Acoustic Streaming causing expansion and compression of bubbles.

TENS, on the other hand, is an electrical stimulation technique commonly used for pain management. While primarily known for its analgesic effects, TENS may also influence skin permeability and drug absorption by modulating local circulation and nerve activity. Its potential role in transdermal drug delivery requires further exploration.[7,8,19,20]

This study aims to evaluate both phonophoresis and TENS independently in enhancing topical Gabapentin absorption, improving bioavailability, and accelerating pain relief. By comparing these two modalities, the findings may offer valuable insights into optimizing non-invasive drug delivery techniques for neuromusculoskeletal pain management.

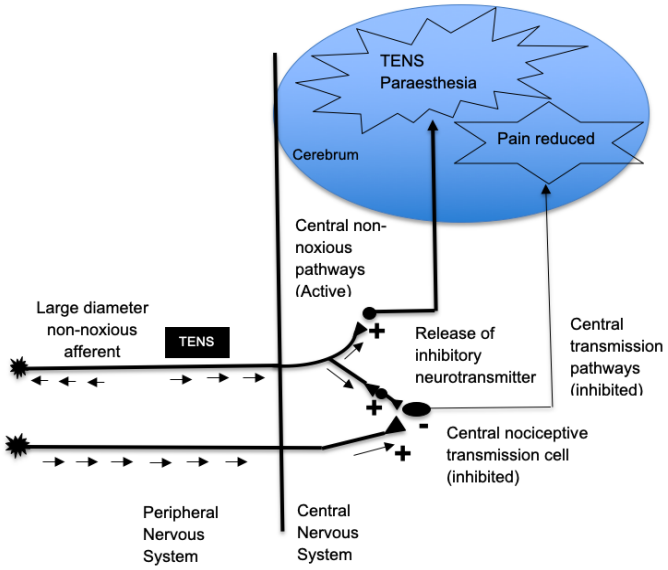

Figure 2: Pain Gate Mechanism

2. Materials and Methods

2.1 Study Design and Objective

This study utilized an in vitro experimental design with three comparative arms: control (passive application), phonophoresis, and TENS-assisted application. Skin samples from hairless mice were mounted on Franz diffusion cells, simulating physiological conditions[7,8].

2.2 Drug Formulation

Topical gabapentin was formulated for neuropathic pain relief in the laboratory using a gel-based formulation. Gabapentin (5%) was accurately weighed and dissolved in ethanol (10%). A gelling agent, carbopol 934 (2%), was added to form the gel base. Triethanolamine (1%) was used to neutralize the carbopol and adjust the pH to ensure proper gel consistency. Methylparaben (0.15%) and propylparaben (0.05%) were incorporated as preservatives. The ingredients were mixed thoroughly to achieve a uniform gel. The gel was then tested for viscosity, drug content, and stability.[9]

2.3 Preparation of Skin Samples

The Franz diffusion cell method (Hanson Research) was employed to assess skin permeability. Hairless mouse skin was prepared, ensuring the dermal side was mounted upwards to facilitate effective contact with the diffusion medium. Donor area taken was of 4 cm^2 and the receptor compartment was filled with Phosphate Buffer Solution (PBS) to mimic physiological conditions.[10] Magnetic stirrer was placed beneath the Franz Diffusion Cell for homogenization of the samples along with hotplate to maintain the temperature at 37 degrees Celsius mimicking the human body temperature conditions.

2.4 Intervention Parameters

In this in vitro study, the control group received passive topical application of gabapentin gel over excised hairless mouse skin mounted on Franz diffusion cells, simulating physiological conditions. For the phonophoresis groups, ultrasound was applied in pulsed mode (1:2) using frequencies of 1 MHz and 3 MHz at intensities of 0.8 W/cm^2 and 1.0 W/cm^2, respectively, for a duration of 5 minutes.

The gel was mixed with a coupling medium in a 2:1 ratio before application. In the TENS group, electrical stimulation was delivered using a continuous mode with a trapezoidal sweep pattern at 150 Hz for 10 minutes, following similar gel application. Five independent Franz diffusion cell experiments were conducted using rat skin for each group, with receptor fluid samples collected at 0 hour (baseline), and subsequently at 1, 2, and 3 hours, and analyzed by HPLC[12].

2.5 Sampling and Analysis

Samples were collected from the receptor medium at 0, 1, 2, and 3 hours. Analysis was performed using HPLC with C18 column, methanol:buffer (63:37, pH 2.8) as mobile phase, flow rate 1.0 mL/min, detection at 210 nm.[13,14,15]

3. Results

Table 1. **Comparison of mean drug permeation (µg/cm²) at 3 hours across intervention groups with standard deviation.**

Group	Ultrasound Frequency (MHz)	Ultrasound Intensity (W/cm²)	TENS Frequency (Hz)	Mean Permeation at 3h (µg/cm²)	Standard Deviation (SD)
Control (Topical only)	–	–	–	12.0	1.2
TENS 150 Hz	–	–	150	30.0	1.8
Phonophoresis	3.0	1.0	–	32.0	2.2
Phonophoresis	1.0	0.8	–	30.0	2.0
Phonophoresis	1.0	1.0	–	35.0	2.3

Table 1 presents the comparative permeation data for gabapentin gel across five groups, including a control group (topical application only), TENS-assisted transdermal delivery, and phonophoresis at varied ultrasound frequencies and intensities.

All values represent mean cumulative drug permeation per square centimeter at the 3-hour time point (n=5). One-way ANOVA revealed statistically significant differences among all experimental groups ($p < 0.05$), indicating that both TENS and phonophoresis significantly enhance transdermal drug delivery compared to passive diffusion.

3.1 Comparison and Key Findings

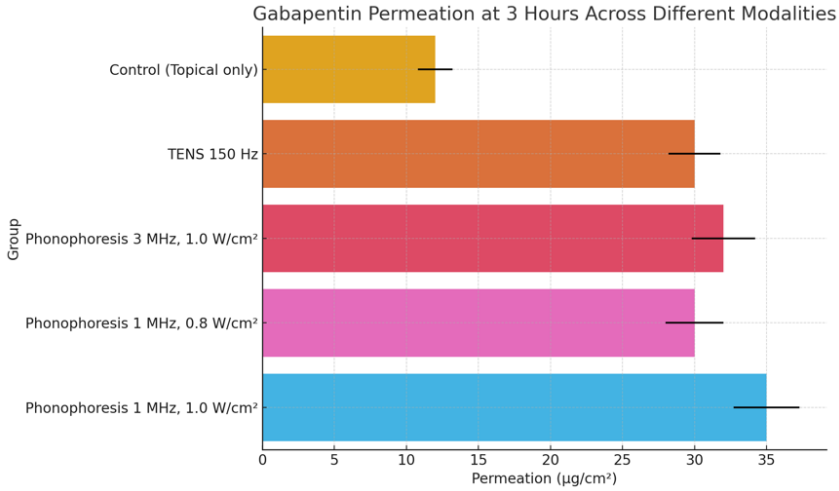

Figure 3: Comparative graph of gabapentin permeation (µg/cm²) at 3 hours across intervention groups.

Phonophoresis with 1 MHz ultrasound significantly improves transdermal drug delivery in an in vitro model, offering a promising adjunct for localized pain management. TENS shows moderate efficacy. These non-invasive techniques may serve as effective complements or alternatives to systemic therapies.

4. Discussion

The 1 MHz ultrasound provided the deepest penetration and highest cumulative drug permeation. These outcomes are particularly relevant for pain affecting muscles, joints, and nerves beneath the dermal layer[16]. Literature supports these findings, with studies citing 1 MHz as effective for deep-tissue penetration[17,18]. TENS, while less potent than phonophoresis, still improved drug delivery, possibly due to increased vascular perfusion[19].

5. Conclusion

Phonophoresis with 1 MHz ultrasound significantly improves transdermal drug delivery in an in vitro model, offering a promising adjunct for localized pain management. TENS shows moderate efficacy. These non-invasive techniques may serve as effective complements or alternatives to systemic therapies.

6. Limitations and Future Scope

This study was conducted under in vitro conditions using hairless mouse skin, which may not fully replicate human skin characteristics. Future studies should include in vivo testing on human volunteers to evaluate clinical efficacy, safety, and pharmacodynamic responses. Additionally, drug retention in skin layers and pain-alleviation outcomes were not assessed in this phase. Clinical trials involving patients with conditions such as sciatica or lumbar radiculopathy are warranted. The promising results of gabapentin delivery through phonophoresis suggest the next step: evaluating a combinatorial gel of gabapentin and NSAIDs like diclofenac. This dual-therapy gel will be tested using similar transdermal setups and subsequently validated in clinical pain and function score assessments.

REFERENCES

1. Baron R. Mechanisms of disease: neuropathic pain. Nat Clin Pract Neurol. 2006;2(2):95–106.
2. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. Curr Pharm Des. 2001;7(5):451–64.
3. Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237–51.
4. Nair AB, Shah J. Role of transdermal drug delivery system in pain management. Curr Drug Ther. 2020;15(2):121–133.
5. Mitragotri S. Innovation—device-mediated transdermal drug delivery. Nat Rev Drug Discov. 2009;8(1):99–110.
6. Banga AK. Transdermal and Intradermal Delivery of Therapeutic Agents. CRC Press; 2011.
7. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–8.
8. Finnin BC, Morgan TM. Transdermal penetration. J Pharm Sci. 1999;88(10):955–8.
9. Aggarwal S et al. Formulation and evaluation of topical gel of gabapentin. Int J Curr Pharm Res. 2015;7(1):40–3.
10. Wester RC et al. In vitro percutaneous absorption of model compounds using human cadaver skin. Fundam Appl Toxicol. 1993;20(1):65–70.
11. Kim MJ et al. Evaluation of in vitro skin permeation of gabapentin. Drug Dev Ind Pharm. 2017;43(10):1670–7.
12. Polat BE, Blankschtein D, Langer R. Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends. J Control Release. 2011;152(3):330–48.
13. Jain A et al. HPLC method for estimation of gabapentin in transdermal formulations. J Appl Pharm Sci. 2012;2(6):123–6.
14. Kapoor D et al. Quantitative analysis of gabapentin using RP-HPLC method. Int J Pharm Pharm Sci. 2015;7(4):405–9.
15. Rani S et al. Development and validation of HPLC method for gabapentin analysis. Int J Pharm Sci Res. 2016;7(9):3777–83.
16. Petrofsky JS et al. Effect of ultrasound on skin permeability. Med Sci Monit. 2008;14(3):CR112–6.
17. Draper DO et al. Therapeutic ultrasound and its application in sports medicine. Sports Med. 1995;20(1):17–26.
18. Baker KG et al. A review of therapeutic ultrasound: biophysical effects. Phys Ther Sport. 2001;2(3):135–49.
19. Ferreira CL et al. Influence of TENS on blood flow and skin temperature. Braz J Phys Ther. 2015;19(1):35–42.
20. Johnson MI. Transcutaneous Electrical Nerve Stimulation (TENS) and Pain Relief: Past, Present and Future. Pain Rev. 2014;1(2):91–6.