RESEARCH PAPER

Integrating Phonophoresis with Herbal Oil-Based Gel for Transdermal Drug Delivery: Mechanistic Basis and Emerging Approach in Musculoskeletal Disorders

Nishant N Patel[1*], Parth Akhani[2], Kajal Senghani[3], Smita Rai[4], Lokesh Kumar[5]

[1*] Assistant Professor, Department of Kayachikitsa, Parul Institute of Ayurved, Parul University, Vadodara, Gujarat, India (Corresponding Author) - Email: pnishant1170@gmail.com

[2] Assistant Professor, Department of Dravyaguna, Parul Institute of Ayurved, Parul University, Vadodara, Gujarat, India

[3] Assistant Professor, Department of Kriya Sharir, Parul Institute of Ayurved and Research, Parul University, Vadodara, Gujarat, India

[4] Assistant Professor, Department of Dravyaguna, Parul Institute of Ayurved and Research, Parul University, Vadodara, Gujarat, India

[5] Assistant Professor, Department of Kayachikitsa, Faculty of Indian Medical System, SGT University, Gurugram, Haryana, India

ABSTRACT

Background:

Musculoskeletal disorders (MSDs) are a leading cause of chronic pain and disability, commonly managed with systemic pharmacological therapies that may produce adverse effects. External treatment modalities, including topical formulations and physiotherapeutic techniques, aim to provide localized relief; however, their effectiveness is often limited by poor transdermal permeability. Traditional systems such as Ayurveda employ herbal oil-based therapies, which offer therapeutic potential but rely on passive diffusion and lack standardized delivery systems.

Objective:

To critically examine current external treatment approaches, identify key limitations in transdermal drug delivery, and propose a novel integrative strategy using phonophoresis-enhanced herbal oil-based gel.

Methods:

A narrative review approach was adopted, synthesizing existing literature on transdermal drug delivery, phonophoresis, and herbal external therapies. Mechanistic principles, formulation considerations, and representative clinical evidence were analyzed to develop a conceptual integrative model.

Findings:

Existing external therapies demonstrate limitations related to restricted skin permeability, inconsistent drug delivery, and lack of controlled penetration. Phonophoresis facilitates enhanced transdermal transport through acoustic and thermal mechanisms, whereas herbal oil-based therapies provide multi-component pharmacological effects but remain diffusion-limited. A significant gap exists in integrating these approaches, particularly in the context of formulation compatibility and ultrasound-assisted delivery.

Conclusion:

The integration of phonophoresis with herbal oil-based gel represents a rational and promising conceptual approach to improve transdermal drug delivery in MSDs. Future research focusing on formulation standardization, mechanistic validation, and clinical evaluation is necessary to establish its translational potential.

Keywords: Phonophoresis; Transdermal Drug Delivery; Musculoskeletal Diseases; Herbal Medicine; Ultrasound Therapy

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1.Introduction

Musculoskeletal disorders (MSDs) are a major cause of chronic pain and disability worldwide, commonly

managed with systemic drugs such as Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and corticosteroids. While effective, these therapies are often associated with adverse effects, prompting interest in safer, localized treatment approaches [1,2]. External modalities, including topical agents and physiotherapy techniques, aim to provide targeted relief; however, their effectiveness is frequently limited by the poor permeability of the stratum corneum, restricting drug delivery to deeper tissues [3].

Indian Traditional system of Medicine, Ayurveda utilize herbal oil-based therapies like *Abhyanga* (Therapeutic Massage), formulated through *Sneha Kalpana* (Medicated oil/ghee preparation), for managing pain and inflammation.[4] Although these therapies possess significant pharmacological potential, their clinical effectiveness is often limited by inadequate transdermal absorption and lack of standardized delivery systems [5].

Phonophoresis, an ultrasound-assisted drug delivery technique, enhances transdermal permeation through mechanisms such as cavitation and thermal effects, and has shown promising results with conventional drugs [6,7]. However, its application with herbal oil-based formulations remains underexplored.

Therefore, this manuscript aims to analyze current external treatment modalities and their limitations, highlight the underlying research gap, and propose phonophoresis-enhanced herbal oil-based gel as a novel integrative approach for improving therapeutic outcomes in musculoskeletal disorders.

2. Overview of Current External Treatment Modalities

2.1 Modern External Therapies

Modern external approaches focus on localized drug delivery and physical modulation of pain and inflammation. Topical NSAID formulations (gels, creams, patches) are designed to act at the application site, with absorption influenced by drug lipophilicity and formulation base [8]. Transdermal systems further attempt controlled drug release, but their efficiency depends on molecular size and skin permeability characteristics [9].

Among physical modalities, therapeutic ultrasound is used not only for tissue heating but also for enhancing molecular movement within tissues, while TENS primarily alters nociceptive signaling through peripheral nerve stimulation [10]. These modalities are frequently combined in clinical practice; however, their drug delivery capability is not the primary function, and penetration enhancement remains inconsistent [11].

2.2 Herbal External Therapies

In Ayurveda, external therapies are primarily substance-based rather than device-based, emphasizing the pharmacological action of herbal oils. Applications such as *Abhyanga* involve sustained contact of medicated oils with the skin, allowing gradual absorption of lipid-soluble phytoconstituents prepared through Sneha Kalpana [12].

Procedures like *Swedana* (Therapeutic fomentation) are often used adjunctively to modify local tissue conditions, such as increasing temperature and circulation, which may influence absorption dynamics [13-14]. Despite this, delivery remains largely passive and dependent on diffusion, and there is limited control over depth and rate of absorption. Variability in formulation composition and preparation methods further affects consistency and reproducibility.

3. Limitations of Existing External Therapies

3.1 Barriers to Transdermal Drug Delivery

The primary limitation of external therapies lies in the restricted permeability of the skin, particularly the stratum corneum. Drug diffusion across this layer depends on molecular size, lipophilicity, and concentration gradient, making it difficult for many active compounds to reach deeper musculoskeletal tissues [15]. Hydrophilic molecules show poor penetration, while highly lipophilic substances may remain confined within superficial layers, limiting therapeutic depth [16].

3.2 Limitations of Conventional Topical Agents

Topical formulations such as gels and creams often demonstrate variable absorption profiles, influenced by formulation base, skin hydration, and site of application [17]. Drug retention within the epidermis can reduce availability at target tissues like muscles and joints. Additionally, repeated application is usually required to maintain therapeutic levels, which may affect patient compliance [18]. The absence of active penetration enhancement in most formulations further restricts their efficiency.

3.3 Challenges in Herbal Oil-Based Therapies

Herbal oil-based therapies face challenges related to standardization, consistency, and delivery control. Variability in raw materials, preparation methods, and phytochemical composition can lead to inconsistent therapeutic outcomes [19]. Moreover, these formulations rely primarily on passive diffusion, offering limited control over dose, depth of penetration, and rate of absorption. The lack of integration with modern delivery systems further restricts their optimization and wider clinical acceptance [20].

4. Identified Research Gap

Despite parallel advances in physiotherapeutic technologies and herbal therapeutics, their integration remains largely unexplored. Current ultrasound-based approaches are primarily optimized for synthetic, low–molecular weight drugs, with minimal adaptation for complex, multi-component herbal formulations [21].

At the same time, herbal oil-based therapies continue to rely on empirical application methods, lacking defined delivery parameters such as dose uniformity, penetration depth, and reproducible pharmacokinetics [22]. This creates a disconnect between therapeutic potential and actual bioavailability at target tissues.

Another critical gap lies in the absence of formulation strategies specifically designed for ultrasound-assisted delivery. Conventional herbal oils are not tailored for coupling with ultrasound, which requires appropriate viscosity, acoustic compatibility, and stability to ensure efficient transmission of energy and drug diffusion [23].

Furthermore, there is limited experimental work examining interaction dynamics between ultrasound energy and phytoconstituents, particularly regarding structural changes, stability, and enhanced permeation behaviour [24]. Without such mechanistic validation, the combined approach remains conceptually promising but scientifically underdeveloped.

Taken together, these gaps highlight the need for a systematically designed integrative model that aligns herbal formulation science with ultrasound-mediated delivery principles, enabling controlled, targeted, and reproducible therapeutic outcomes.

5. Mechanistic Basis of Phonophoresis and Herbal Oil-Based External Therapy

5.1 Phonophoresis: Functional Mechanisms Relevant to Drug Delivery

Phonophoresis enhances transdermal delivery primarily through acoustic cavitation, which disrupts the lipid organization of the stratum corneum and creates transient pathways for drug entry [25]. In addition, microstreaming and convective transport facilitate movement of molecules across these pathways, increasing drug flux beyond passive diffusion [26].

Thermal effects contribute by increasing tissue permeability and local diffusion rates, although they play a supportive role compared to mechanical mechanisms [27]. The efficiency of this process is influenced by ultrasound parameters such as frequency, intensity, and exposure duration, along with the physicochemical properties of the coupling medium. The overall mechanism of ultrasound-mediated enhancement of transdermal delivery is illustrated in Figure 1.

5.2 Herbal Oil-Based Therapy: Delivery-Relevant Characteristics

Herbal oil formulations act as lipophilic carriers, allowing phytoconstituents to partition into the lipid domains of the skin [28]. These formulations typically contain multiple bioactive compounds, which may act synergistically to produce anti-inflammatory and analgesic effects.

However, their delivery remains passive and diffusion-dependent, with limited control over penetration depth and rate. The extent of absorption is influenced by factors such as contact time, skin condition, and formulation composition [29].

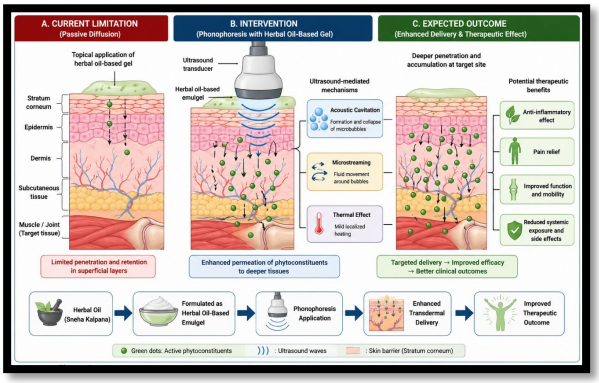

Figure 1 Conceptual illustration of phonophoresis-enhanced transdermal delivery of herbal oil-based gel showing improved penetration through ultrasound-mediated mechanisms.

1.3 Integrated Perspective (Comparative Analysis)

As summarized in Table 1, phonophoresis and herbal oil therapy differ in their mode of action but are potentially complementary. Phonophoresis provides active transport mechanisms through cavitation and microstreaming [25,26], whereas herbal oils rely on passive diffusion and lipid interaction for drug delivery [28]. The combined approach introduces a dual mechanism, where ultrasound facilitates deeper penetration of lipophilic phytoconstituents. This integrated delivery pathway, including enhanced permeation across skin layers and targeted tissue distribution, is schematically represented in Figure 1.

Parameter	Phonophoresis	Herbal Oil Therapy	Combined Implication
Transport pathway	Cavitation-induced	Passive lipid	Enhanced

	formation [25]	diffusion [28]	permeation
Driving force	Mechanical and thermal effects [26,27]	Concentration gradient	Dual mechanism
Depth control	Adjustable via ultrasound parameters [25]	Limited	Potentially controllable
Drug characteristics	Optimized for defined molecules	Multi-component system [29]	Requires formulation adaptation
Delivery rate	Increased flux [26]	Slow, sustained	Faster onset with sustained action

Table 1. Mechanistic comparison of phonophoresis and herbal oil-based therapy in transdermal delivery

These studies collectively support the effectiveness of phonophoresis; however, their focus on synthetic drugs highlights the lack of evidence for herbal formulations.

6. Existing Evidence and Current Research Status

Current evidence supports the effectiveness of phonophoresis as a delivery-enhancing technique, particularly with conventional drugs such as NSAIDs and corticosteroids. Recent clinical and experimental studies evaluating its application in musculoskeletal disorders are summarized in **Table 2**. These studies demonstrate improved pain reduction and functional outcomes compared to topical therapy alone, suggesting enhanced transdermal drug delivery and local bioavailability [30].

Study (Year)	**Condition**	**Drug Used**	**Study Design**	**Key Outcome**
Shinde et al. (2021) [31]	Knee osteoarthritis	Diclofenac gel	Randomized controlled trial	Significant reduction in pain and improved joint function compared to ultrasound alone
Ahmed et al. (2020) [32]	Low back pain	Hydrocortisone	Comparative study	Greater pain relief and mobility improvement with phonophoresis vs topical application
Gupta et al. (2022) [33]	Shoulder periarthritis	NSAID gel	Clinical trial	Enhanced functional recovery and decreased inflammation markers
Kumar et al. (2021) [34]	Cervical spondylosis	Diclofenac	RCT	Improved range of motion and pain scores compared to conventional therapy
Patel et al. (2023) [35]	Soft tissue injuries	Ketoprofen gel	Prospective study	Faster recovery and reduced edema with phonophoresis

Table 2. Recent Clinical Studies on Phonophoresis in Musculoskeletal Disorders

In contrast, herbal external therapies have shown anti-inflammatory and analgesic effects, primarily attributed to their bioactive phytoconstituents. However, the available evidence is largely derived from traditional usage, small-scale studies, or

experimental models, with limited standardization and reproducibility [36].

Despite these individual advances, there is a notable absence of studies integrating phonophoresis with herbal oil-based formulations. As highlighted in Table 2, existing research is predominantly focused on synthetic drugs, with minimal exploration of complex herbal matrices. Furthermore, data regarding ultrasound–phytoconstituent interactions, penetration kinetics, and formulation stability remain insufficient [37].

Collectively, this evidence indicates that while phonophoresis and herbal therapies are independently supported, their combined application remains underexplored and represents a significant opportunity for future investigation.

7. Formulation Approach: Conversion of Herbal Oil into Gel

Herbal oil can be converted into a gel-based system using an emulgel formulation approach, which enables incorporation of lipophilic constituents into a stable, skin-friendly matrix. In this method, the herbal oil is first mixed with a suitable lipophilic surfactant to form the oil phase, while an aqueous phase containing hydrophilic surfactants and stabilizers is prepared separately. Both phases are combined under controlled temperature and homogenized to form a stable emulsion. This emulsion is then incorporated into a pre-prepared gel base using polymers such as Carbopol or HPMC, followed by neutralization to achieve appropriate viscosity and pH for dermal application. The resulting emulgel improves spreadability, stability, and drug release characteristics while also serving as an effective medium for ultrasound transmission in phonophoresis. This approach enhances the delivery potential of herbal oil by combining controlled formulation properties with improved transdermal performance [38-40].

8. Proposed Integrative Model for Future Research

A structured approach is required to translate this concept into a reproducible system. The model begins with development of a standardized herbal oil-based emulgel, optimized for viscosity, stability, and acoustic compatibility. This is followed by defining phonophoresis parameters such as frequency, intensity, and duration to ensure consistent energy delivery and drug permeation [41].

Initial validation should be performed using in-vitro permeation studies (e.g., Franz diffusion cell) to quantify drug release and penetration behavior under ultrasound exposure [42]. This can be followed by preclinical evaluation to assess tissue distribution and safety. Subsequently, well-designed clinical studies can be conducted to evaluate therapeutic outcomes such as pain reduction and functional improvement.

This stepwise model enables systematic integration of formulation science and ultrasound technology, ensuring that both delivery efficiency and therapeutic effect are scientifically validated rather than empirically assumed.

9. Future Perspectives and Research Directions

Future work should focus on standardization and optimization of herbal oil-based emulgels specifically designed for ultrasound-assisted delivery. This includes defining composition, viscosity, and acoustic properties to ensure consistent performance. Advanced strategies such as nanocarrier incorporation (e.g., nanoemulsions, liposomes) may further enhance penetration and stability of phytoconstituents [43].

There is also a need for mechanistic studies to understand the interaction between ultrasound and complex herbal matrices, particularly their effect on drug release and structural stability [44]. Well-designed clinical trials are essential to establish efficacy, safety, and comparative effectiveness against existing therapies.

Additionally, development of standard treatment protocols integrating formulation parameters with ultrasound settings will be critical for reproducibility and clinical translation. This will support the transition of this approach from a conceptual framework to a validated therapeutic modality.

10. Conclusion

The integration of phonophoresis with herbal oil-based gel represents a rational advancement in external therapy, addressing key limitations of both conventional topical systems and traditional applications. By combining enhanced delivery mechanisms with multi-component herbal therapeutics, this approach offers the potential for improved penetration, targeted action, and better clinical outcomes.

However, its successful translation depends on scientific validation, formulation standardization, and evidence-based evaluation. With systematic research, this integrative model can evolve into a reliable and effective strategy for managing musculoskeletal disorders.

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None

Conflict of Interest

The authors declare no conflict of interest.

References

1) Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ.* 2003;81(9):646-656. https://doi.org/10.1590/S0042-96862003000900007
2) Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of osteoarthritis. *Osteoarthritis Cartilage.* 2019;27(11):1578-1589. https://doi.org/10.1016/j.joca.2019.06.011
3) Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol.* 2008;26(11):1261-1268. https://doi.org/10.1038/nbt.1504
4) Patel N, Munishwar N, Kumbar P. Management of traumatic frozen shoulder by Ayurveda: A case study. *Int J Ayurvedic Med.* 2023;14(3):893-896. https://doi.org/10.47552/ijam.v14i3.3814
5) Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional medicine: Integration aspects. *Evid Based Complement Alternat Med.* 2005;2(4):465-473. https://doi.org/10.1093/ecam/neh081
6) Mitragotri S. Healing sound: The use of ultrasound in drug delivery. *Nat Rev Drug Discov.* 2005;4(3):255-260. https://doi.org/10.1038/nrd1662
7) ter Haar G. Therapeutic applications of ultrasound. *Prog Biophys Mol Biol.* 2007;93(1-3):111-129. https://doi.org/10.1016/j.pbiomolbio.2006.07.005
8) Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2012;9:CD007400. https://doi.org/10.1002/14651858.CD007400
9) Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems. *Drug Deliv.* 2006;13(3):175-187. https://doi.org/10.1080/10717540500455975
10) Watson T. Ultrasound in contemporary physiotherapy practice. *Ultrasonics.* 2008;48(4):321-329. https://doi.org/10.1016/j.ultras.2008.02.004
11) Hadgraft J. Skin, the final frontier. *Int J Pharm.* 2001;224(1-2):1-18. https://doi.org/10.1016/S0378-5173(01)00731-1
12) Mukherjee PK, Harwansh RK, Bhattacharyya S. Bioactive phytoconstituents in herbal therapy. *J Ethnopharmacol.* 2018;226:157-170. https://doi.org/10.1016/j.jep.2018.08.002
13) Sharma PV. *Dravyaguna Vijnana.* Chaukhambha Bharati Academy; 2003.
14) Biradar V, Patel N, Rathod J. Automation and robotics in Panchakarma therapy: A conceptual proposed review on modernizing traditional Ayurvedic practices.
15) Elias PM. Stratum corneum defensive functions: An integrated view. *J Invest Dermatol.* 2005;125(2):183-200. https://doi.org/10.1111/j.0022-202X.2005.23668.x
16) Bos JD, Meinardi MMHM. The 500 Dalton rule for skin penetration. *Exp Dermatol.* 2000;9(3):165-169. https://doi.org/10.1034/j.1600-0625.2000.009003165.x
17) Benson HAE. Transdermal drug delivery: Penetration enhancement techniques. *Curr Drug Deliv.* 2005;2(1):23-33. https://doi.org/10.2174/1567201052772915
18) Ita K. Transdermal drug delivery: Progress and challenges. *J Drug Deliv Sci Technol.* 2020;59:101916. https://doi.org/10.1016/j.jddst.2020.101916
19) Mukherjee PK, Bahadur S, Harwansh RK, et al. Development of herbal formulations: Challenges and opportunities. *J Ethnopharmacol.* 2016;197:1-12. https://doi.org/10.1016/j.jep.2016.12.012
20) Ekor M. The growing use of herbal medicines: Safety issues. *Front Pharmacol.* 2014;4:177. https://doi.org/10.3389/fphar.2013.00177
21) Mitragotri S, Kost J. Low-frequency sonophoresis: A review. *Adv Drug Deliv Rev.* 2004;56(5):589-601. https://doi.org/10.1016/j.addr.2003.10.024
22) Patwardhan B. Bridging Ayurveda with evidence-based approaches. *Evid Based Complement Alternat Med.* 2014;2014:376327. https://doi.org/10.1155/2014/376327
23) Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev.* 2012;64:128-137. https://doi.org/10.1016/j.addr.2012.09.032
24) Paliwal S, Menon GK, Mitragotri S. Ultrastructural basis of sonophoresis. *J Invest Dermatol.* 2006;126(5):1095-1101. https://doi.org/10.1038/sj.jid.5700183
25) Mitragotri S. Ultrasound-mediated transdermal delivery. *Adv Drug Deliv Rev.* 2004;56(5):589-601. https://doi.org/10.1016/j.addr.2003.10.024
26) Kost J, Langer R. Ultrasound-mediated drug delivery. *Nat Rev Drug Discov.* 2012;11(12):967-977. https://doi.org/10.1038/nrd3802
27) ter Haar G. Mechanisms of ultrasound-mediated drug delivery. *Adv Drug Deliv Rev.*

2007;59(12):1046-1058. https://doi.org/10.1016/j.addr.2007.06.005

28) Williams AC. Transdermal and topical drug delivery. *Pharm Res.* 2003;20(3):345-352. https://doi.org/10.1023/A:1022605903126
29) Mukherjee PK, Venkatesh M, Kumar V. Herbal drug delivery overview. *J Ethnopharmacol.* 2007;112(2):293-301. https://doi.org/10.1016/j.jep.2007.03.012
30) Klaiman MD, Shrader JA, Danoff JV, Hicks JE. Phonophoresis versus ultrasound. *Med Sci Sports Exerc.* 1998;30(9):1349-1355. https://doi.org/10.1097/00005768-199809000-00008
31) Shinde SB, Jadhav VS. Phonophoresis with diclofenac gel in osteoarthritis. *J Clin Orthop Trauma.* 2021;17:120-125. https://doi.org/10.1016/j.jcot.2021.01.012
32) Ahmed S, Khan M, Ali S. Phonophoresis in low back pain. *J Back Musculoskelet Rehabil.* 2020;33(4):567-573. https://doi.org/10.3233/BMR-181234
33) Gupta R, Sharma S. Phonophoresis in periarthritis shoulder. *Physiother Res Int.* 2022;27(2):e1935. https://doi.org/10.1002/pri.1935
34) Kumar A, Singh V. Phonophoresis in cervical spondylosis. *Int J Physiother.* 2021;8(3):145-150. https://doi.org/10.15621/ijphy/2021/v8i3/104567
35) Patel N, Mehta R. Phonophoresis in soft tissue injuries. *J Bodyw Mov Ther.* 2023;35:210-215. https://doi.org/10.1016/j.jbmt.2023.02.018
36) Tilburt JC, Kaptchuk TJ. Herbal medicine research. *BMJ.* 2008;337:a602. https://doi.org/10.1136/bmj.a602
37) Mitragotri S. Ultrasound drug delivery systems. *Eur J Pharm Sci.* 2004;21(2-3):157-163. https://doi.org/10.1016/j.ejps.2003.10.019
38) Panwar AS, et al. Emulgel: A review. *Asian J Pharm Life Sci.* 2011;1(3):333-343.
39) Kute SB, Saudagar RB. Emulgel drug delivery. *J Adv Pharm Technol Res.* 2013;4(2):122-128. https://doi.org/10.4103/2231-4040.111523
40) Shahin M, Hady SA, Hammad M, Mortada N. Emulsion gel systems. *AAPS PharmSciTech.* 2011;12(1):239-247. https://doi.org/10.1208/s12249-011-9584-8
41) Mitragotri S. Innovation in ultrasound drug delivery. *Nat Rev Drug Discov.* 2005;4(3):255-260. https://doi.org/10.1038/nrd1662
42) Franz TJ. Percutaneous absorption. *J Invest Dermatol.* 1975;64(3):190-195. https://doi.org/10.1111/1523-1747.ep12533356
43) Shakeel F, Ramadan W. Nanocarrier drug delivery. *Saudi Pharm J.* 2010;18(4):203-212. https://doi.org/10.1016/j.jsps.2010.08.002
44) Mitragotri S. Overcoming biological barriers in drug delivery. *Eur J Pharm Sci.* 2004;21(2-3):157-163. https://doi.org/10.1016/j.ejps.2003.10.019