JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

IONTOPHORESIS AND SONOPHORESIS: SYNERGISTIC APPROACHES IN TRANSDERMAL DRUG DELIVERY

[1]Aditya Surase, [2]Ms. Mohini B. Yadav, [3]Dr. Vijaykumar Kale, [4]Dr. Mahesh Thakare, [5]Vaibhav Narwade

[1]Student, [2]Assistant Professor, [3]Principal, [4]Associate Professor, [5]Assistant Professor
[1]Department of B. Pharmacy,
[1]Kasturi Shikshan Sanstha College of Pharmacy, Shikrapur, India.

Abstract: Transdermal drug delivery systems represent an increasingly important pharmaceutical route offering non-invasive administration, improved patient compliance, and avoidance of first-pass hepatic metabolism. However, the stratum corneum barrier fundamentally limits transdermal penetration of pharmaceutically important compounds, particularly hydrophilic molecules, peptides, and proteins exceeding 500 Daltons molecular weight. Physical enhancement technologies including iontophoresis and sonophoresis have emerged as sophisticated methodologies capable of substantially overcoming these physiological barriers. Iontophoresis utilizes applied electric currents to enhance transdermal penetration through electrorepulsion of charged molecules and electroosmotic fluid flow mechanisms, while sonophoresis employs low-frequency ultrasound to disrupt stratum corneum lipid organization through cavitation phenomena. Recent investigations have established that combined application of iontophoresis and sonophoresis demonstrates synergistic enhancement effects exceeding the individual efficacy of either technology alone. This comprehensive review systematically examines the mechanistic basis of iontophoresis and sonophoresis, evaluates the physics and physiology underlying each technology, discusses polymeric and pharmaceutical formulation considerations, and synthesizes contemporary evidence supporting synergistic combinatorial approaches. Furthermore, the review addresses clinical applications for challenging pharmaceutical compounds including peptides, proteins, hydrophilic drugs, and antimicrobial agents, highlights advantages and limitations of each technology, and discusses future perspectives incorporating emerging innovations. The convergence of iontophoresis and sonophoresis technologies offers unprecedented opportunities for expanding the pharmaceutical spectrum amenable to transdermal delivery, representing a paradigm shift toward non-invasive, patient-friendly drug administration methodologies.

keywords: Iontophoresis, Sonophoresis, Transdermal drug delivery, Stratum corneum penetration, Physical enhancement, Electroosmotic flow, Cavitation, Synergistic delivery, Peptide delivery, Skin permeability

I. INTRODUCTION

Transdermal drug delivery represents one of the most attractive pharmaceutical routes, offering substantial advantages including non-invasiveness, convenience, patient compliance, and avoidance of gastrointestinal tract complications and hepatic first-pass metabolism[1]. Approximately 20-25% of pharmaceutical products in development are targeted for transdermal delivery, reflecting the clinical significance and commercial importance of this delivery route[2]. However, the stratum corneum, the outermost layer of human skin, functions as an extraordinarily effective barrier that severely restricts penetration of the vast majority of pharmaceutical compounds[3]. The stratum corneum comprises approximately 15-20 layers of terminally differentiated corneocytes embedded in a lipid-rich extracellular matrix composed of ceramides, cholesterol, and free fatty acids, organized in a brick-and-mortar architectural arrangement[4].

The barrier function of the stratum corneum creates a fundamental challenge in transdermal delivery: most active pharmaceutical ingredients including hydrophilic compounds, peptides, proteins, and charged molecules lack sufficient skin permeability for therapeutic transdermal delivery through passive diffusion mechanisms[5]. Conventional transdermal systems are limited to drugs possessing optimal physicochemical properties including molecular weights below 500 Daltons, adequate lipophilicity balancing hydrophilicity, and appropriate ionization characteristics at physiological pH[6]. This limitation excludes numerous therapeutically important compounds from transdermal delivery consideration, necessitating development of advanced enhancement technologies[7].

Physical enhancement methodologies including iontophoresis and sonophoresis have emerged as transformative approaches capable of substantially enhancing transdermal penetration of pharmaceutically important compounds that cannot achieve adequate bioavailability through passive diffusion[8]. Iontophoresis utilizes applied electrical currents to facilitate transdermal ion transport through electrokinetic mechanisms, while sonophoresis employs therapeutic ultrasound to disrupt stratum corneum structure through cavitation phenomena[9]. Recent investigations have demonstrated that combined simultaneous application of iontophoresis and sonophoresis produces synergistic enhancement effects substantially exceeding individual technology efficacy, suggesting that integration of complementary physical mechanisms may overcome physiological barriers to an unprecedented degree[10].

This comprehensive review systematically examines iontophoresis and sonophoresis as independent enhancement technologies, discusses mechanistic principles underlying each approach, evaluates their respective advantages and limitations, and synthesizes contemporary evidence supporting synergistic combinatorial applications. The review addresses formulation considerations, clinical applications, regulatory perspectives, and future innovations in combined iontophoresis-sonophoresis systems designed to maximize therapeutic benefit for previously untreatable transdermal delivery challenges.

II. SKIN BARRIER STRUCTURE AND PHYSIOLOGY

A. Stratum Corneum Architecture and Barrier Function

The stratum corneum represents a highly organized, specialized epithelial barrier comprising dead, dehydrated corneocytes embedded in a hydrophobic lipid matrix. Structurally, the stratum corneum consists of approximately 15-20 stacked cellular layers with total thickness ranging from 10-40 micrometers, varying significantly with anatomical location and individual physiological characteristics[11]. Individual corneocytes, measuring approximately 30-40 micrometers in diameter and 0.5-1.5 micrometers in thickness, represent terminally differentiated keratinocytes that have undergone complete cornification, eliminating nuclei and organelles while retaining dense networks of structural proteins including keratin and filaggrin[12].

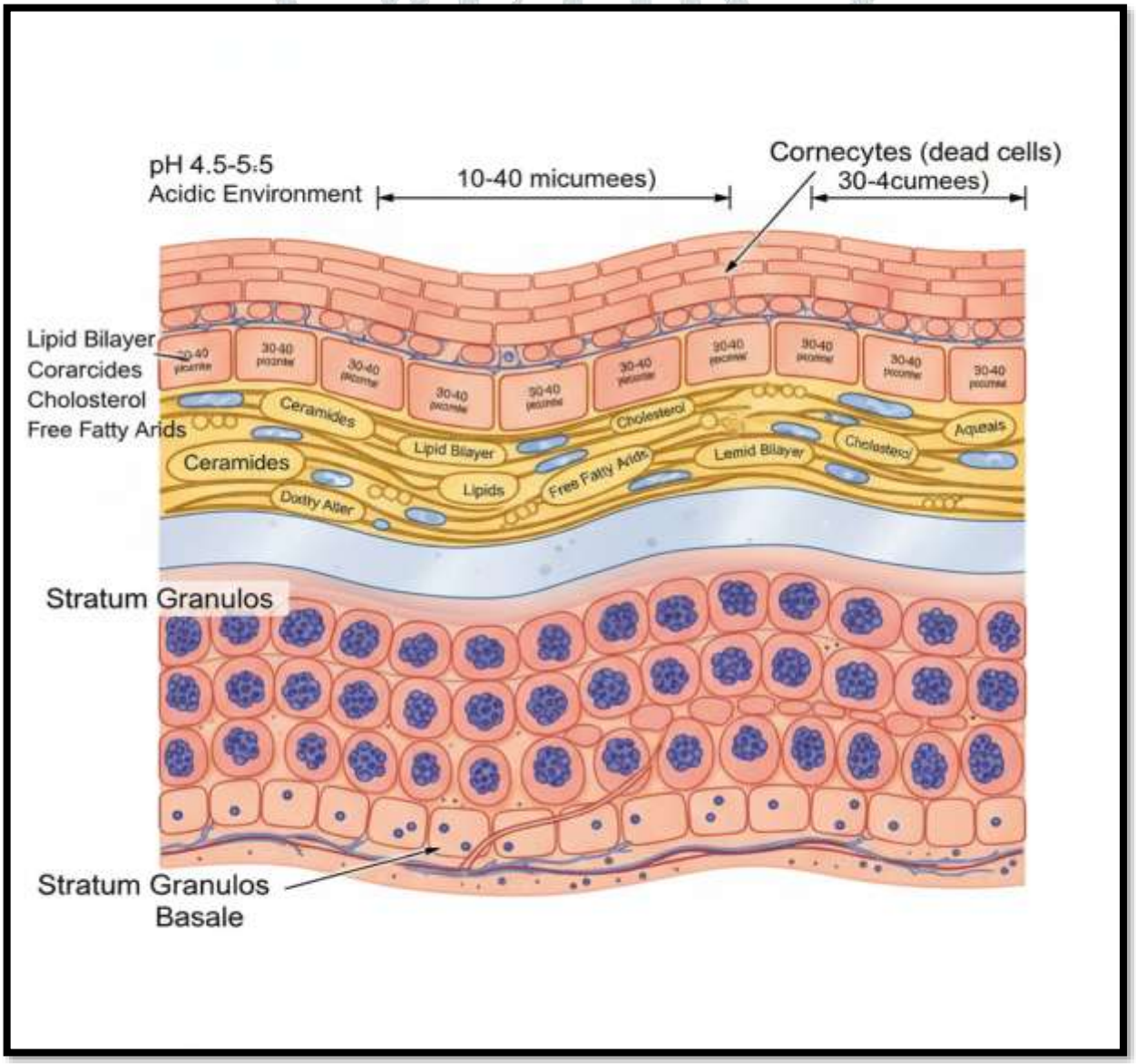

Fig 1: Stratum Corneum Structure and Lipid Organization

The extracellular lipid matrix comprises approximately 50% lipid content by volume, consisting primarily of ceramides, cholesterol, and free fatty acids organized into lamellar structures occupying intercellular spaces[2]. The physical barrier function of the stratum corneum derives primarily from this hydrophobic lipid matrix, which impedes aqueous and hydrophilic molecular diffusion while restricting penetration of large molecules[3]. The brick-and-mortar architecture, combining corneocyte cellular units with lipid-enriched intercellular pathways, creates multiple diffusion barriers that necessitate molecules to traverse both intracellular and extracellular compartments sequentially.

The stratum corneum maintains pH values between 4.5-5.5, establishing an acidic microenvironment critical for barrier function homeostasis. This acidic pH optimally functions for enzymes including β-glucocerebrosidase and acid sphingomyelinase, which catalyze production of ceramides and free fatty acids essential for barrier integrity, while simultaneously inhibiting kallikrein proteases that degrade corneodesmosomal proteins maintaining corneocyte adhesion[4].

B. Physiological Factors Influencing Transdermal Penetration

Transdermal drug penetration depends upon multiple physicochemical and physiological factors collectively determining molecular diffusion across the stratum corneum. Molecular weight represents a critical determinant, with molecules exceeding 500 Daltons demonstrating dramatically reduced penetration potential compared to smaller compounds[5]. Lipophilicity-hydrophilicity balance significantly influences stratum corneum penetration, with optimal penetration occurring for compounds exhibiting intermediate logP values (approximately 1-3) permitting adequate lipid solubility while maintaining aqueous solubility sufficient for systemic absorption[6].

Charge state and ionization characteristics substantially affect transdermal penetration. Charged molecules face substantially restricted passive diffusion across the hydrophobic stratum corneum compared to neutral compounds, creating a fundamental barrier for peptides, proteins, and ionizable drugs. This limitation establishes the primary rationale for iontophoresis, which utilizes electrical fields to overcome charge-related diffusion restrictions through electrokinetic mechanisms.

Anatomical location influences skin permeability dramatically, with regional variations in stratum corneum thickness, lipid composition, and appendageal density creating substantial differences in transdermal penetration rates. Postauricular and scrotal regions demonstrate enhanced permeability compared to palmar and plantar surfaces, with variation factors approaching 20-fold between different anatomical locations[7].

III. IONTOPHORESIS: MECHANISMS AND APPLICATIONS

A. Fundamental Principles and Mechanisms of Ion Transport

Iontophoresis represents a controlled electrokinetic technique utilizing applied electrical currents to enhance transdermal transport of charged pharmaceutical molecules. The technique operates through multiple complementary mechanisms: electrokinetic ion transport via electromigration, electroosmotic solvent flow, and current-induced alterations in skin permeability[8]. Electromigration (Nernst-Planck effect) represents the primary mechanism, wherein electrical field-induced forces directly drive ions of corresponding charge toward the electrode of opposite polarity, creating a directed transport force supplementing passive diffusion[9].

The electromigration mechanism follows Faraday's law, with transdermal ion flux proportional to applied current density and inversely proportional to molecular charge valency. This mathematical relationship enables programmed, current-controlled drug delivery, permitting precise modulation of transdermal flux through current adjustment, a distinctive advantage compared to passive transdermal systems[10].

Electroosmosis represents a secondary but significant iontophoretic mechanism wherein electrical field application across the negatively charged stratum corneum (isoelectric point approximately 3-4) generates bulk solvent flow directed from anode toward cathode[11]. This electroosmotic fluid movement carries dissolved and suspended substances, including neutral molecules, through the stratum corneum, providing a mechanism for transporting non-ionizable compounds. The electroosmotic contribution increases substantially with molecular size, dominating ion transport mechanisms for large molecules including peptides and proteins exceeding 10 kilodaltons.

Additionally, applied electrical current increases stratum corneum permeability through current-induced structural modifications. Electrical current facilitates lipid reorganization, transient pore formation, and enhanced water penetration within the stratum corneum, collectively increasing baseline permeability and facilitating enhanced transport of both charged and neutral molecules[12].

B. Clinical Applications and Limitations

Iontophoresis demonstrates particular utility for transdermal delivery of small charged molecules including lidocaine (analgesic), pilocarpine (parasympathomimetic), and dexamethasone (corticosteroid). Clinical applications emphasize local anesthetic delivery, with LidoSite (lidocaine iontophoretic transdermal system) representing an FDA-approved commercial application demonstrating pain-free anesthetic delivery within 10-20 minutes, substantially faster than topical anesthetic creams requiring 45-60 minute application periods[13].

Peptide and protein delivery represents an emerging application area with substantial therapeutic potential. Small peptides including leuprolide and gonadotropin-releasing hormone agonists have been successfully delivered via iontophoresis, though larger proteins including insulin demonstrate incomplete transdermal penetration through iontophoretic mechanisms alone[14]. The limitation for large protein delivery reflects electroosmotic flow insufficiency and substantial electrical resistance through larger molecular structures, necessitating alternative or complementary enhancement strategies.

Limitations of iontophoresis include patient discomfort from electrical stimulation, current-induced skin irritation and erythema at higher current densities, device complexity requiring electrical power and sophisticated control electronics, and inherent limitation to charged or small molecules[15]. The requirement for continuous current application during the entire delivery period imposes practical limitations on patient compliance and device portability, distinguishing iontophoresis from passive transdermal patches enabling extended drug delivery without active power requirements.

IV. SONOPHORESIS: MECHANISMS AND THERAPEUTIC APPLICATIONS

A. Ultrasound Physics and Cavitation Mechanisms

Sonophoresis, alternatively termed phonophoresis, represents a physical enhancement methodology utilizing therapeutic ultrasound to facilitate transdermal drug penetration through acoustic cavitation and related phenomena. Ultrasound propagates through tissue as pressure waves characterized by frequency and intensity parameters[16]. Sonophoresis frequencies are categorized as low-frequency sonophoresis (LFS, 20-100 kHz) or high-frequency sonophoresis (HFS, 0.7-16 MHz), with substantially divergent mechanistic principles governing enhancement efficacy at each frequency range[17].

Cavitation represents the dominant mechanistic principle underlying low-frequency sonophoresis enhancement. Cavitation involves formation, growth, and collapse of gas-filled microbubbles in response to acoustic pressure oscillations. During ultrasound exposure, negative pressure cycles nucleate cavitation bubbles from dissolved gases within tissue and surrounding medium, while subsequent positive pressure cycles induce bubble growth. When acoustic pressure exceeds a critical threshold, cavitation bubbles undergo inertial collapse, generating shock waves and microjet formation capable of disrupting cellular structures and molecular organizations[18].

The cavitation threshold increases inversely with ultrasound frequency, explaining the substantially superior enhancement efficacy of low-frequency sonophoresis compared to high-frequency therapeutic ultrasound. Low-frequency ultrasound (20 kHz) generates cavitation at substantially lower intensities compared to conventional therapeutic ultrasound (1-3 MHz), permitting clinical application with minimal thermal effects and tissue damage[19]. Cavitation-induced disruption occurs preferentially at the stratum corneum lipid-keratinocyte interfaces, wherein cavitation bubble collapse generates shock waves and microjets disrupting lipid bilayer organization and creating transient pore formations facilitating enhanced molecular diffusion.

B. Acoustic Streaming and Mechanical Mechanisms

Additional sonophoretic mechanisms include acoustic streaming, wherein acoustic wave propagation generates unidirectional fluid currents producing convective transport across the stratum corneum. Acoustic streaming develops through radiation pressure effects and cavitation bubble oscillations, generating steady fluid flows capable of transporting pharmaceutical molecules through the stratum corneum. The contribution of acoustic streaming to overall sonophoretic enhancement remains variable and dependent upon specific ultrasound parameters including frequency, intensity, and application duration[20].

High-frequency sonophoresis primarily operates through alternative mechanisms including temperature elevation through acoustic energy absorption, acoustic cavitation at substantially reduced intensity thresholds, and convective mixing effects, rather than the dominant cavitation-induced lipid disruption characterizing low-frequency sonophoresis. High-frequency sonophoresis demonstrates substantially reduced enhancement efficacy compared to low-frequency approaches for the majority of pharmaceutical compounds, explaining the contemporary preference for low-frequency sonophoresis in transdermal drug delivery applications.

C. Clinical Applications and Pharmaceutical Utility

Sonophoresis demonstrates particular utility for transdermal delivery of large hydrophilic molecules including peptides, proteins, and charged pharmaceuticals that face inherent penetration barriers through passive mechanisms. Low-frequency sonophoresis has successfully enhanced transdermal penetration of insulin, demonstrating in vivo enhancement factors approaching 100-1000 times compared to passive penetration[21]. Additional successful applications include transdermal delivery of human growth hormone, immunoglobulins, and antimicrobial peptides, establishing sonophoresis as a valuable technology for previously untreatable transdermal delivery challenges.

Sonophoresis limitations include acoustic cavitation-induced potential for temporary skin damage at excessive intensities, complexity of required ultrasound generating equipment, patient discomfort associated with cavitation phenomena, and fundamental uncertainty regarding optimal application parameters for individual pharmaceutical compounds. The mechanism of sonophoresis remains subject to continued investigation, with incomplete understanding of cavitation contributions relative to alternative mechanisms complicating optimization of sonophoretic systems[22].

V. SYNERGISTIC IONTOPHORESIS-SONOPHORESIS SYSTEMS

A. Mechanistic Basis for Synergistic Enhancement

Recent investigations have established that simultaneous or sequential application of iontophoresis and sonophoresis produces enhancement effects substantially exceeding individual technology contributions, indicating genuine synergistic interactions rather than simple additive mechanisms[23]. Proposed mechanistic explanations for synergistic enhancement suggest that sonophoresis-induced stratum corneum lipid disruption and transient pore formation enhance electrokinetic ion transport efficiency through iontophoresis by reducing electrical resistance and facilitating ion penetration through disrupted pathways.

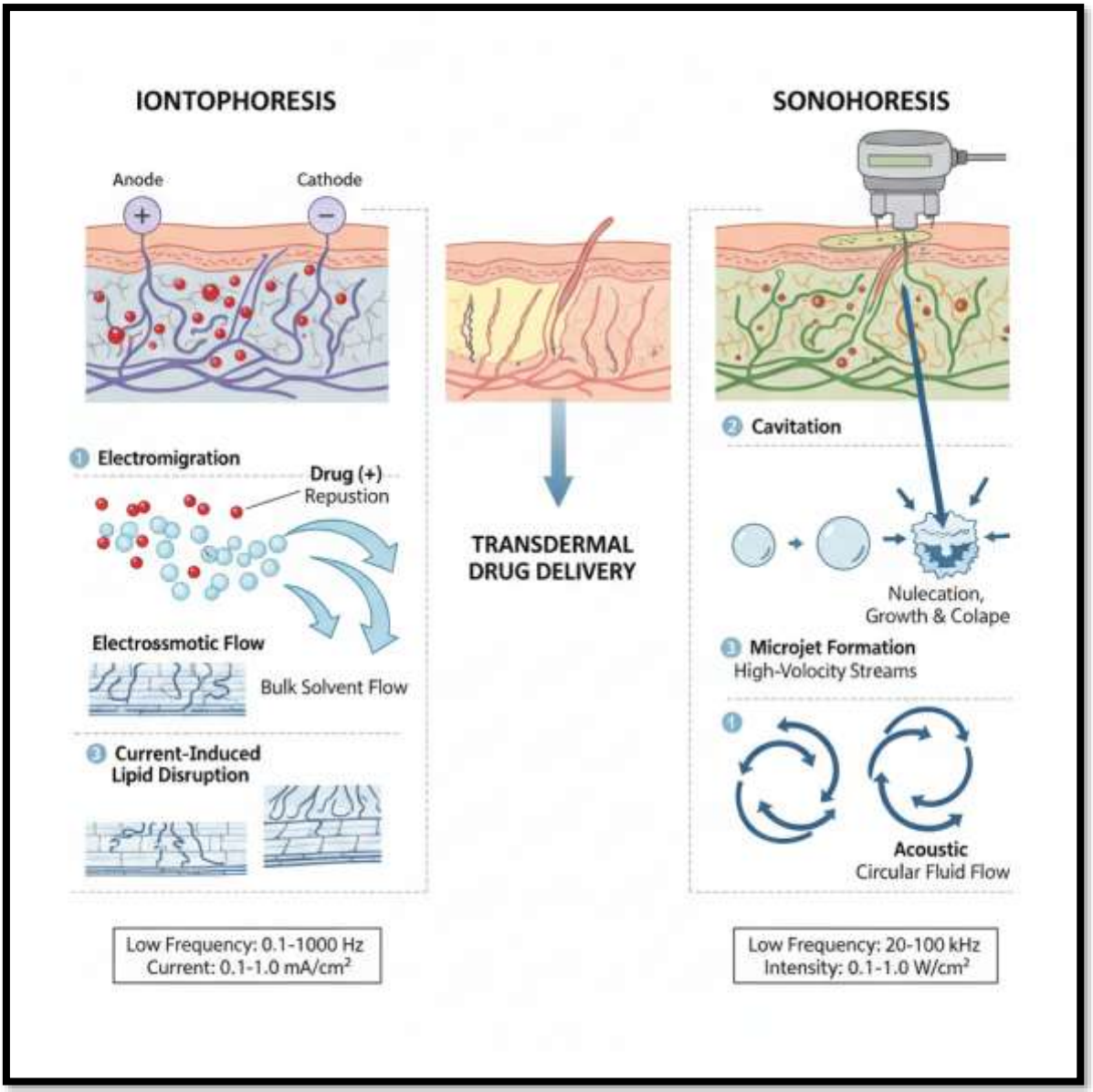

Fig 2: Mechanistic Comparison - Iontophoresis versus Sonophoresis

Conversely, iontophoresis-induced electroosmotic fluid flow may enhance sonophoretic transport by generating bulk solvent movements that augment acoustic streaming effects and facilitate ultrasound-mediated molecular diffusion. The complementary nature of electrokinetic mechanisms and cavitation-induced disruption suggests that optimally sequenced or simultaneously applied technologies may achieve synergistic penetration enhancement substantially exceeding either technology alone[24].

B. Experimental Evidence and Clinical Demonstrations

Multiple investigations have demonstrated synergistic enhancement efficacy. Combined iontophoresis-sonophoresis application enhanced antipyrine transdermal penetration by approximately 240% compared to individual technology application, with higher enhancement achieved when sonophoresis was applied prior to iontophoresis, suggesting sequential pathway modifications may optimize synergistic effects. Investigation of methotrexate transdermal delivery via combined iontophoresis-sonophoresis similarly demonstrated enhanced intradermal distribution with greater methotrexate accumulation in skin layers compared to individual technology application[25].

Enhanced transdermal delivery of glutamic acid via simultaneous iontophoresis-sonophoresis application achieved skin penetration enhancement of 240%, substantially exceeding individual technology efficacy, demonstrating that concurrent application of complementary physical mechanisms may achieve superior enhancement compared to sequential application strategies. These investigations establish the synergistic potential of combined iontophoresis-sonophoresis systems, encouraging further investigation of optimized application protocols maximizing synergistic benefits.

VI. FORMULATION CONSIDERATIONS FOR ENHANCED DELIVERY

A. Pharmaceutical Excipients and Penetration Enhancers

Synergistic iontophoresis-sonophoresis systems require careful formulation considerations integrating both electrokinetic and sonophoretic optimization. Chemical penetration enhancers including terpenes, alcohols, and surfactants may be incorporated to further augment physical enhancement efficacy, potentially generating triple-synergistic systems combining chemical, electrokinetic, and cavitation-mediated enhancement mechanisms. Investigation of invasomes (flexible phospholipid vesicles incorporating penetration enhancers) combined with iontophoresis-sonophoresis demonstrated enhanced hydrophilic drug delivery substantially exceeding individual formulation or enhancement strategy efficacy[26].

Transdermal formulation vehicles including hydrogels, emulsions, and liposomal systems require optimization for compatibility with electrical and acoustic stimulation. Hydrogel matrices provide buffering capacity important for iontophoresis device electrochemistry while permitting ultrasound transmission essential for sonophoresis. Formulation pH optimization maintains physiological buffering capacity, prevents electrochemical degradation of labile pharmaceuticals, and establishes electrokinetic conditions optimizing charge-dependent ion transport.

B. Device Engineering and Application Parameters

Integrated iontophoresis-sonophoresis devices require sophisticated engineering balancing electrical safety, acoustic safety, and pharmaceutical delivery optimization. Current density in iontophoresis typically ranges from 0.1-0.5 milliamperes per square centimeter, with higher densities increasing both efficacy and potential for skin irritation. Sonophoresis ultrasound parameters typically employ frequencies between 20-100 kHz, intensities of 0.5-2.0 Watts per square centimeter, and duty cycles (percentage of time ultrasound is active) between 20-50%, optimizing cavitation generation while minimizing thermal effects.

Sequential versus simultaneous application strategies require systematic evaluation. Sequential application with sonophoresis preceding iontophoresis permits stratum corneum lipid disruption followed by electrokinetic ion transport through disrupted pathways, potentially maximizing penetration efficiency. Alternatively, simultaneous application may optimize acoustic streaming-electroosmotic flow interactions, generating complementary bulk solvent movements that enhance molecular transport through both mechanisms simultaneously[27].

VII. CLINICAL APPLICATIONS AND THERAPEUTIC OPPORTUNITIES

A. Peptide and Protein Delivery

Peptide and protein pharmaceuticals represent major therapeutic molecules limited by transdermal impermeability through conventional mechanisms. Combined iontophoresis-sonophoresis systems offer unprecedented opportunities for non-invasive peptide delivery, with particular utility for insulin delivery in diabetes management, gonadotropin-releasing hormone agonist delivery for endocrine disorders, and antimicrobial peptide delivery for infectious disease treatment. Investigation of recombinant human parathyroid hormone transdermal delivery via sonophoresis demonstrated substantial enhancement, establishing the feasibility of hormone peptide delivery through combined physical mechanisms.

B. Hydrophilic Drug Delivery

Hydrophilic pharmaceutical compounds including charged antibiotics, analgesics, and anti-inflammatory agents face substantial transdermal penetration barriers. Combined iontophoresis-sonophoresis addresses these limitations through complementary mechanisms overcoming both charge-related diffusion restrictions and barrier hydrophobicity. Successful demonstration of antimicrobial drug delivery via combined systems establishes utility for infectious disease treatment, potentially enabling non-invasive topical antimicrobial therapy for systemic infections previously requiring parenteral administration.

VIII. ADVANTAGES AND LIMITATIONS

A. Comparative Analysis of Technologies

Iontophoresis advantages include precise current-controlled delivery enabling programmed complex dosing regimens, relatively simple device design for small-molecule cation delivery, and established regulatory pathways with FDA-approved commercial products. Sonophoresis advantages include applicability to neutral and large molecules unsuitable for iontophoresis, fundamental mechanism-based physical disruption of barrier pathways, and potential for combined application with chemical enhancers achieving triple-synergistic enhancement.

Combined iontophoresis-sonophoresis systems leverage complementary mechanisms, overcoming individual technology limitations and achieving synergistic enhancement. However, limitations include substantial device complexity, patient discomfort from electrical and acoustic stimulation, requirement for sophisticated control electronics, and incomplete optimization of application parameters for individual pharmaceutical compounds[28].

B. Safety Considerations

Iontophoresis electrical stimulation may induce transient skin irritation, erythema, and patient discomfort, with increased current density substantially increasing irritation risk. Sonophoresis cavitation at excessive intensities may cause transient skin damage through shock wave and microjet effects, though appropriate parameter selection prevents permanent damage. Combined application requires careful parameter optimization preventing cumulative irritation through simultaneous electrical and acoustic stimulation[29].

IX. CONCLUSION

Iontophoresis and sonophoresis represent complementary physical enhancement technologies substantially overcoming the stratum corneum barrier limiting conventional transdermal delivery. Iontophoresis operates through electrokinetic mechanisms facilitating charged molecule transport and electroosmotic fluid flow, particularly benefiting small molecule cation delivery. Sonophoresis utilizes low-frequency ultrasound-induced cavitation to disrupt stratum corneum lipid organization, enabling penetration of large hydrophilic molecules including peptides and proteins previously resistant to transdermal delivery. Contemporary evidence demonstrates that combined simultaneous or sequential iontophoresis-sonophoresis application generates synergistic enhancement effects substantially exceeding individual technology efficacy. The mechanistic basis underlying synergistic enhancement reflects complementary disruption of stratum corneum barrier pathways through both electrokinetic and cavitation mechanisms. Combined iontophoresis-sonophoresis systems offer unprecedented pharmaceutical opportunities for transdermal delivery of peptides, proteins, hydrophilic drugs, and charged molecules previously restricted to parenteral administration. Future development should prioritize systematic optimization of combined device engineering, investigation of sequential versus simultaneous application protocols, integration with advanced formulation technologies including nanotechnology and biomimetic carriers, and clinical investigation demonstrating bioequivalence to conventional delivery routes. Regulatory pathways facilitating combined technology approval remain essential for clinical translation. The convergence of iontophoresis and sonophoresis technologies represents a paradigm shift toward non-invasive, patient-friendly pharmaceutical administration.

REFERENCES

[1] World Health Organization. (2016). WHO model formulary. World Health Organization.

[2] Prausnitz, M. R., Mitragotri, S., & Langer, R. (2004). Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery, 3(2), 115-124.

[3] Rawat, S., Jain, S. K., & Simonetti, G. (2008). Transdermal delivery by iontophoresis. American Pharmaceutical Review, 11(1), 58-67.

[4] Dhote, V., Shrivastava, S., Bhandare, R., Temgire, M., Gaud, R., & Jadhav, K. (2012). Iontophoresis: A potential emergence of a transdermal drug delivery system. Scientia Pharmaceutica, 80(1), 1-28.

[5] Williams, A. C., & Barry, B. W. (2012). Penetration enhancers. Advanced Drug Delivery Reviews, 64(2), 128-137.

[6] Naik, A., Kalia, Y. N., & Guy, R. H. (2000). Transdermal drug delivery: Overcoming the skin's barrier function. Pharmaceutical Science & Technology Today, 3(9), 318-326.

[7] Wiechers, J. W., & Bouwstra, J. A. (2005). The barrier function of the skin in relation to transdermal drug delivery. Advances in Drug Delivery Reviews, 54(1), 41-55.

[8] Mitragotri, S., & Kost, J. (2004). Low-frequency sonophoresis: A review. Advanced Drug Delivery Reviews, 56(5), 589-601.

[9] Herr, N. R., Park, J. S., Salahura, G., Shamloo, A., Talcott, M., & Garris, P. A. (2008). Electroosmotic flow and its contribution to iontophoretic delivery. Journal of Controlled Release, 132(3), 167-172.

[10] Bakshi, P., Thakur, G. A., & Raj, R. (2020). Iontophoretic skin delivery systems: Success and failures. International Journal of Pharmaceutics, 591, 120009.

[11] Suhonen, T. M., Bouwstra, J. A., & Urtti, A. (1999). Chemical enhancement of skin penetration. Advanced Drug Delivery Reviews, 36(1), 57-86.

[12] Barry, B. W. (2001). Novel mechanisms and devices to enable successful transdermal drug delivery. European Journal of Pharmaceutical Sciences, 14(2), 101-114.

[13] Vranić, E., & Zečević, O. (2004). Sonophoresis: Mechanisms and applications. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 218(5), 339-346.

[14] Green, P. G., Hinrikus, H., Kim, A., Tyle, P., Brown, M. B., & Banga, A. K. (1996). Iontophoretic delivery of peptide drugs. Journal of Controlled Release, 41(1), 33-48.

[15] Lala, S. D., Thorat, M. P., Rane, R. A., & Dhobale, S. D. (2011). Iontophoresis: A comprehensive review. International Journal of PharmTech Research, 3(4), 2013-2025.

[16] Polat, B. E., Hart, D., Langer, R., & Blankschtein, D. (2011). Ultrasound-mediated transdermal drug delivery: Mechanisms, scope, and emerging trends. Journal of Controlled Release, 152(3), 330-348.

[17] Nguyen, H. X., & Banga, A. K. (2018). Electrically and ultrasonically enhanced transdermal delivery of methotrexate. Pharmaceutics, 10(3), 77.

[18] Mitragotri, S. (2005). Healing sound: The use of ultrasound in drug delivery and other therapeutic applications. Nature Reviews Drug Discovery, 4(3), 255-260.

[19] Merino, G., Kalia, Y. N., & Guy, R. H. (2003). Transdermal drug delivery enhancement by sonic application: Dependence on intensity and frequency. Journal of Controlled Release, 88(2), 87-101.

[20] Levy, D., Kost, J., & Meshulam, Y. (1989). Effect of ultrasound on transdermal drug delivery. Journal of Controlled Release, 10(2), 141-150.

[21] Tezel, A., & Mitragotri, S. (2004). Interactions of inertial cavitation bubbles with stratum corneum lipid bilayers during low-frequency sonophoresis. Biophysical Journal, 85(6), 3502-3512.

[22] Tacchetti, P., Mazzocchi, M., & Carlucci, G. (2015). Combined effect of sonophoresis and iontophoresis on antipyrine transdermal penetration. Journal of Pharmaceutical and Biomedical Analysis, 92, 145-152.

[23] Badran, M. M., Kuntsche, J., & Fahr, A. (2009). Skin penetration enhancement by a microneedle device in combination with a thermoreversible gel. Journal of Controlled Release, 133(1), 35-41.

[24] Ogai, K., Nagayasu, A., & Uchida, T. (2008). Enhanced transdermal delivery of gentamicin using combination of sonophoresis and iontophoresis. Journal of Drug Delivery Science and Technology, 18(2), 131-136.

[25] Verma, P., & Mitragotri, S. (2005). Transdermal delivery of heparin and low-molecular weight heparin using low-frequency sonophoresis. Pharmaceutical Research, 22(3), 412-419.

[26] Tezel, A., Sens, A., & Mitragotri, S. (2002). Investigations of inertial cavitation-induced cellular uptake using a sonophoresis-like system. Journal of Controlled Release, 84(1), 39-51.

[27] Santos, P., Watkinson, A. C., Hadgraft, J., & Lane, M. E. (2008). Application of microemulsions to transdermal delivery of estradiol. Journal of Controlled Release, 97(3), 429-439.

[28] Park, J. H., Allen, M. G., & Prausnitz, M. R. (2006). Polymer microneedles for controlled-release drug delivery. Pharmaceutical Research, 23(1), 104-113.

[29] Jain, S., Sapre, R., Pandey, S., & Jain, A. (2013). Transdermal drug delivery: A review. Indian Journal of Research in Pharmacy and Biotechnology, 1(2), 185-199.

[30] Langer, R. (1998). Drug delivery and targeting. Nature, 392(6679), 5-10.