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Quantitative Assessment of Therapeutic Ultrasound-Assisted Phonophoresis Using Infrared Thermography: The T0–T1–T2 Thermal Response Framework, Standardization, And Clinical Translation in Rehabilitation

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ABSTRACT

Phonophoresis is a transdermal delivery approach in which therapeutic ultrasound energy is used to enhance the transport of topically applied agents across the skin barrier. The biophysical basis of ultrasound-mediated skin permeability has been associated particularly with acoustic cavitation, alterations in stratum corneum lipid organization, acoustic streaming/microstreaming, and thermal effects (Ramadon, et al. 2021). However, robust mechanistic findings from low-frequency sonophoresis cannot be directly generalized to therapeutic phonophoresis at 1–3 MHz as used in rehabilitation (Yu, et al. 2021). The clinical phonophoresis literature also exhibits substantial heterogeneity in the active agent, vehicle system, ultrasound dose, application duration, and clinical population (Jeong, et al. 2021). Infrared thermography (IRT) is a functional imaging technique that enables non-contact, non-invasive, repeated quantification of skin surface temperature. However, IRT does not directly measure transdermal drug penetration, tissue drug concentration, deep tissue temperature, or perfusion. Accordingly, interpreting thermal changes observed after phonophoresis as direct indicators of pharmacokinetic or clinical efficacy is scientifically unjustified. The aim of this structured review is to integrate the biophysical foundations of phonophoresis with the measurement characteristics of IRT and propose the T0–T1–T2 Thermal Response Framework for standardized investigation of post-phonophoresis surface thermal responses.

Within the framework, T0 represents the standardized baseline measurement, T1 the early post-application response, and T2 the delayed/recovery response. Principal quantitative outcomes are ROI-based ΔT, bilateral thermal asymmetry, and ΔTpeak, Tpeak, recovery time, and thermal AUC parameters potentially derived from dense time series in future studies. The novelty of the proposed approach lies not in using three time points, but in integrating standardized acoustic exposure, topical formulation, IRT protocol, ROI-based within-subject change analysis, appropriate control conditions, and staged physiological/pharmacokinetic validation within the same translational research architecture. At present, T0–T1–T2 is not a diagnostic or therapeutic algorithm but a hypothesis-generating biomedical research framework requiring prospective validation.

Keywords: Phonophoresis; Sonophoresis; Therapeutic Ultrasound; Infrared Thermography; Transdermal Drug Delivery; Rehabilitation; Thermal Imaging

Abbreviations: IRT: Infrared Thermography; ERA: Effective Radiating Area; BNR: Beam Nonuniformity Ratio; ICC: Intraclass Correlation Coefficient; SEM: Standard Error of Measurement; MDC: Minimal Detectable Change

Introduction

The stratum corneum constitutes the principal biological barrier to transdermal drug delivery (Yang, et al. [1]). The protective function of the skin restricts passive penetration of many molecules applied for systemic or local treatment. Consequently, physical penetration-enhancement methods have become an important area of transdermal drug delivery research. Ultrasound-mediated sonophoresis/phonophoresis is one such approach. The sonophoresis literature indicates that acoustic energy may increase molecular transport by producing transient structural and functional changes, particularly in the stratum corneum. Nevertheless, sonophoresis is not a uniform intervention. Low-frequency sonophoresis, generally performed at approximately 20–100 kHz, differs considerably from therapeutic ultrasound, commonly applied at 1–3 MHz in rehabilitation, in terms of cavitation behavior, energy absorption, and effects on skin permeability. Therefore, the marked permeabilization effects demonstrated in low-frequency systems cannot be directly transferred to therapeutic MHz applications (Liu, et al. 2024). The clinical phonophoresis literature is also heterogeneous. A systematic review and meta-analysis of knee osteoarthritis included nine randomized controlled trials involving 423 patients and reported some favorable findings for pain and function, while identifying considerable differences among protocols and active agents (Yang, et al. [1]).

Thus, phonophoresis should be regarded as a multivariable biophysical system: Phonophoresis response = f(acoustic dose × active agent × formulation × tissue × time × patient). This heterogeneity has increased interest in measurement tools that objectively and reproducibly characterize the biological response following phonophoresis. Infrared thermography (IRT) detects infrared radiation emitted by the skin and allows non-contact quantification of the surface temperature distribution. IRT has been investigated in musculoskeletal medicine, sports medicine, and rehabilitation for thermal asymmetry, physiological responses, and treatment monitoring (Lubkowska & Pluta, 2022). Nevertheless, the physiological meaning of IRT must be carefully defined. IRT does not directly measure anatomical structures, drug concentrations, intramuscular temperature, or microcirculation; its primary measured variable is skin surface temperature (Viegas, et al. 2020). Accordingly, a temperature change after phonophoresis cannot in itself establish that drug penetration increased or that treatment was effective (Carvalho, et al. 2021). This review addresses the gap between these two bodies of literature. Its central research question is: Can the surface thermophysiological response following phonophoresis be characterized by IRT as a standardized, quantitative, time-dependent research outcome? To address this question, the T0–T1–T2 Thermal Response Framework is proposed.

Scope of the Review and Literature Approach

This study was designed as a structured translational literature review and does not claim to be a systematic review or meta-analysis. Its purpose is not to estimate a pooled effect size for a particular intervention, but to integrate the literature on phonophoresis, ultrasound biophysics, and medical thermography into a testable research framework. The synthesis focused on four related evidence domains:

1. Ultrasound-mediated transdermal drug delivery and sonophoresis;
2. The thermal and mechanical biophysical effects of therapeutic ultrasound;
3. Infrared thermography measurement science and standardization; and
4. Applications of phonophoresis and IRT in musculoskeletal conditions and rehabilitation.

Randomized controlled trials, experimental human studies, in vitro and ex vivo mechanistic investigations, systematic reviews, meta-analyses, methodological studies, and relevant consensus documents were prioritized. Evidence was considered at three distinct levels: mechanistic evidence → transdermal transport evidence → clinical efficacy evidence. A favorable finding at one level was not considered direct proof at another. Likewise, IRT-detected thermal changes were methodologically distinguished from pharmacokinetic and clinical outcomes. This approach seeks particularly to prevent overgeneralization across sonophoresis frequencies and misinterpretation of thermal change as a marker of penetration.

Biophysical Foundations of Therapeutic Ultrasound and Phonophoresis

Acoustic Exposure

Therapeutic ultrasound is based on converting electrical energy into mechanical acoustic energy through a piezoelectric transducer. Frequencies of 1 and 3 MHz are commonly used in rehabilitation. Biological effects are determined not by frequency alone, but jointly by intensity, duty cycle, application duration, effective radiating area (ERA), beam nonuniformity ratio (BNR), transducer movement, treatment area, and the acoustic properties of the tissue (Suzuki, 2017). Consequently, reporting only limited device parameters, such as "1 MHz and 1.5 W/cm^2," is insufficient to characterize actual acoustic exposure (Miller, et al. 2008). A proportion of ultrasound energy may be absorbed by biological tissues and converted into heat. Experimental studies in human muscle have shown that continuous ultrasound at 1 and 3 MHz can increase intramuscular temperature and that thermal effects are closely related to acoustic dose (Draper, et al. [2]). However, surface temperature and deep tissue temperature are not the same variable. Therefore, the distinction $\Delta T_{skin} \neq \Delta T_{deep\ tissue}$ must be maintained (Draper, et al. [3]).

Cavitation and the Skin Barrier

Acoustic cavitation is among the strongest mechanistic explanations of sonophoresis (UEDA, et al. 2009). Oscillation or collapse of gas bubbles within an acoustic pressure field can produce mechanical

effects at the skin surface, particularly at low frequencies (UEDA, et al. 2009). These effects may transiently alter stratum corneum lipid organization and enhance molecular transport pathways (UEDA, et al. 2009). Studies of low-frequency sonophoresis have demonstrated that permeabilization is not homogeneous across the skin surface but may be concentrated in areas termed "localized transport regions." (Oberli, et al. 2014) This suggests that transdermal transport is a spatial process that cannot be explained by average acoustic energy alone. Acoustic streaming and microstreaming may also contribute to molecular delivery toward the skin surface and to local convective transport (Sirsi & Borden 2014). Thus, transport during sonophoresis should be understood as an interaction among cavitation + barrier perturbation + diffusion + convective transport.

Distinguishing Low-Frequency Sonophoresis from Therapeutic Phonophoresis

A central methodological distinction in this review is that low-frequency sonophoresis and clinical therapeutic phonophoresis should not be treated as the same biophysical intervention. Mechanistic evidence for cavitation and stratum corneum permeabilization is strong in low-frequency sonophoresis. By contrast, findings concerning transdermal transport and clinical efficacy with 1–3 MHz therapeutic phonophoresis are more heterogeneous (Polat [4]). Accordingly, mechanistic plausibility in low-frequency sonophoresis ≠ established clinical efficacy of MHz therapeutic phonophoresis. This distinction must also guide interpretation of the T0–T1–T2 framework.

Infrared Thermography: Measurement Principles and Limitations

IRT radiometrically images the surface temperature distribution by detecting infrared radiation emitted by human skin. Many medical thermography systems operate in the long-wave infrared range of approximately 8–14 μm (Zhang, et al. 2020). The high infrared emissivity of human skin enables quantitative evaluation of surface temperature under appropriate conditions. However, skin temperature is not the product of a single biological mechanism. Cutaneous blood flow, the autonomic nervous system, local metabolic activity, inflammatory processes, subcutaneous tissue properties, sweating, evaporation, and environmental heat exchange can influence surface temperature (Hildebrandt, et al. 2012). Therefore, single-variable interpretations such as "high temperature = inflammation" or "low temperature = impaired circulation" should be avoided. Similarly, IRT does not directly measure drug concentration, depth of transdermal penetration, intramuscular temperature, synovial temperature, tissue perfusion, or inflammatory mediators (Fujimasa, et al. 2000). Four distinctions must therefore be preserved within the T0–T1–T2 framework: ΔTskin ≠ deep tissue temperature; ΔTskin ≠ perfusion; ΔTskin ≠ transdermal penetration; ΔTskin ≠ clinical efficacy (Fujimasa et al., 2000). The principal advantage of IRT is instead its ability to measure the time-dependent surface thermal response of the same anatomical region non-invasively and repeatedly.

The T0–T1–T2 Thermal Response Framework

Core Structure

The T0–T1–T2 approach is based on repeated evaluation of the same anatomical region of interest (ROI) under standardized conditions before and after phonophoresis.

T0 — Baseline: The standardized thermogram obtained after acclimatization and before the intervention.

T1 — Early response: The thermal measurement obtained during the early post-application period following phonophoresis.

T2 — Delayed/recovery response: A subsequent measurement assessing persistence of the early thermal response or the tendency to return toward the baseline profile.

The principal change parameters may be defined as $\Delta T_1 = T1 - T0$; $\Delta T_2 = T2 - T0$; and $\Delta T_{2-1} = T2 - T1$.

For bilateral anatomical regions, thermal asymmetry may also be evaluated as ΔTasymmetry = |Tright − Tleft|. In controlled studies, intervention-specific change can be strengthened using the difference-in-differences approach: ΔΔT = ΔTintervention − ΔTcontrol (Christensen, et al. 2012).

Why three Time Points?

The thermal response after phonophoresis need not be static. Early surface cooling, rewarming, maximal response, and return to baseline may occur at different times. Consequently, a simple before → after comparison may fail to capture the temporal characteristics of the response. Nevertheless, the use of T0, T1, and T2 time points is not itself novel. The framework's contribution lies not in serial thermography alone, but in integrating a standardized phonophoresis protocol, standardized IRT measurements, within-subject ΔT analysis, bilateral comparison, appropriate control arms, and an advanced validation pathway into a single research architecture.

T1 and T2 Should Not Be Fixed a Priori

Current evidence is insufficient to establish universal T1 and T2 time points applicable to all interventions (Median, et al. 1995). Initial validation studies may therefore benefit from denser thermal sampling, for example T0 → P0 → P5 → P10 → P15 → P30. Such time series could be used to calculate peak temperature change (ΔTpeak), time to peak (Tpeak), recovery slope, recovery time, and thermal area under the curve (AUC). T1 and T2 could subsequently be selected as two clinically feasible representative points based on empirical thermal kinetic data. This shifts the framework from assumed timing to data-driven selection.

Standardization

The scientific value of the T0–T1–T2 approach depends on distinguishing true biological changes in ΔT from measurement variability.

Standardization should encompass five principal domains: participant preparation, environment, IRT acquisition, ultrasound exposure, and topical formulation (Bhardwaj, et al. 2024) (Table 1).

Table 1.

Domain	Principal variables requiring standardization
Participant	Physical activity, rest, caffeine/nicotine, topical products, position
Environment	Room temperature, humidity, airflow, radiant heat sources
IRT	Camera, emissivity, distance, angle, calibration, ROI
Ultrasound	Frequency, intensity, duty cycle, duration, ERA, BNR, transducer movement
Formulation	Active substance, concentration, amount, vehicle, temperature, viscosity

Participant and Environment

Before thermography, participants must acclimatize to a controlled environment. Because different acclimatization periods have been used in the literature, no single duration should be regarded as a universal standard for all anatomical regions. Room temperature, relative humidity, airflow, and radiant heat sources should be kept as constant as possible during measurement and reported (Tejedor, et al. 2020). Factors that may alter skin temperature—including physical activity, massage, hot/cold applications, showering, topical products, caffeine, nicotine, and alcohol—should be controlled or documented in the protocol (Tejedor, et al. 2020).

Camera and ROI

Camera-to-participant distance, camera height, imaging angle, and anatomical position should remain consistent across T0, T1, and T2 (Zendron, et al. 2025). Whenever possible, ROI analysis should be based on anatomical landmarks, and the same ROI geometry, size, and analytical method should be maintained across serial images (Zendron, et al. 2025). Mean ROI temperature (Tmean) is an appropriate candidate primary thermal endpoint. Tmax, Tmin, standard deviation, thermal heterogeneity, and bilateral asymmetry may be considered secondary measures. Image registration and semi-automated/automated segmentation should be evaluated in future studies to reduce operator dependence associated with manually redrawing ROIs.

Quantifying Measurement Error

A statistically significant ΔT does not necessarily indicate a genuine biological change. For example, a difference of 0.2°C may be statistically significant, yet its physiological interpretation remains limited if the uncertainty of the measurement system is of comparable magnitude. Validation studies should therefore determine the intraclass correlation coefficient (ICC), standard error of measurement (SEM), minimal detectable change (MDC), and Bland–Altman limits of agreement. The fundamental question should be whether |ΔT| exceeds measurement uncertainty. The distinction MDC ≠ MCID must also be maintained. A change exceeding measurement error is not necessarily clinically meaningful to the patient.

Interpretation of the Thermal Response Following Phonophoresis

The thermal response observed after phonophoresis is a multifactorial physiological phenomenon. Surface temperature may arise from the interaction of acoustic energy absorption + local thermal effects + vascular response + mechanical effects + topical preparation + evaporation + thermoregulation. Accordingly, interpretation of T0–T1–T2 data can be organized into four levels.

i. Level I — Measurement finding: "ROI temperature increased by 0.8°C from T0 to T1." This is a direct measurement.

ii. Level II — Thermal phenotype: "An early temperature increase followed by a partial return toward baseline at T2 was observed." This describes a temporal pattern.

iii. Level III — Physiological hypothesis: "The thermal change may be associated with a local perfusion response." This is a hypothesis requiring additional physiological validation, not direct evidence.

iv. Level IV — Pharmacological/clinical inference: "Transdermal penetration increased" or "the treatment was effective." Neither conclusion can be drawn from IRT data alone.

This interpretive hierarchy is a central safeguard of the T0–T1–T2 framework against causal overinterpretation of thermographic findings.

Clinical Translation

Phonophoresis has been investigated in various musculoskeletal conditions (Bhardwaj, et al. 2024). However, initial validation of T0–T1–T2 should preferably use clinical models that are anatomically accessible, suitable for bilateral comparison, and supported by an existing phonophoresis literature. Knee osteoarthritis is one potential starting point. The knee permits relatively straightforward identification of superficial anatomical landmarks, standardized ROI delineation, and contralateral comparison (Alfieri, et al. 2020). Clinical literature is also available for both phonophoresis and thermography in this condition (Marziani, et al. [5]). Nevertheless, clinical translation should not begin by attempting to "measure treatment success using IRT." Technical and biological validity must first be demonstrated. The proposed evidence pathway is: technical reliability → thermal kinetics → mechanistic differentiation → physiological validation → association with transdermal penetration → association with clinical outcomes → external validation → clinical utility. A favorable finding at one stage does not automatically establish the next stage.

Evidence Gaps and Proposes Experimental Design

The principal gap in the current literature is the unknown direct relationship between post-phonophoresis IRT responses, actual transdermal transport, and clinical outcomes. (Table 2) A four-arm controlled design is particularly valuable for mechanistic differentiation:

1. Sham application;
2. Topical preparation alone;
3. Ultrasound with an inert coupling medium; and
4. Ultrasound with an active preparation.

This design may help distinguish the contributions of transducer movement/contact, the preparation, ultrasound, and the actual phonophoresis combination to the thermal response.

Table 2.

Evidence gap	Current problem	Proposed validation
T1/T2 timing	Optimal timing unknown	Dense thermal time series
IRT reliability	Measurement error may affect ΔT	ICC, SEM, MDC, Bland–Altman
Acoustic dose	Heterogeneous protocols	Complete acoustic-dose reporting
Preparation effect	May independently influence temperature	Preparation-only control
Ultrasound effect	Not separated from preparation effect	Ultrasound + inert gel
Sham effect	Transducer movement/contact effect	Standardized sham
ΔT–perfusion	Direct association unknown	LDF/LSCI/NIRS/Doppler
ΔT–penetration	Insufficient direct evidence	Analytical penetration measurement
ΔT–clinical outcome	Clinical significance unknown	Prospective clinical correlation
ROI	Operator dependence	Registration/automated segmentation
Device agreement	Differences among cameras	Multidevice comparison
Generalizability	Limited populations	Multicenter validation

Future Research: A Staged Validation Roadmap

The T0–T1–T2 framework cannot be validated for clinical research by a single study. A staged validation program is more appropriate.

Phase I — Technical Validation

The objective is to establish the reliability of the IRT measurement system. Key outcomes include ICC, SEM, MDC, Bland–Altman agreement, and ROI reproducibility.

Phase II — Thermal Kinetics

The post-phonophoresis temperature response should be monitored using dense time series. The objective is to determine ΔTpeak, Tpeak, recovery slope, recovery time, and thermal AUC, and to select T1/T2 times on an empirical basis.

Phase III — Mechanistically Controlled Study

Sham, preparation-only, ultrasound with inert gel, and active phonophoresis arms should be compared to distinguish the components of the thermal response.

Phase IV — Multimodal Physiological Validation

IRT should be compared concurrently with methods assessing microcirculation or hemodynamics, for example: IRT + LDF/LSCI → microcirculation; IRT + NIRS → oxygenation/hemodynamic response; and IRT + Doppler → vascular response. This phase moves from asking "Does ΔT occur?" to asking "Which physiological process is associated with ΔT?".

Phase V — Validation Against Transdermal Penetration

This stage constitutes the most critical experimental test of the T0–T1–T2 framework in phonophoresis research. Within the same experiment, IRT ΔT(t) should be compared with direct measurements of actual transdermal penetration. If a meaningful and reproducible association is identified, the potential of IRT as a non-invasive surrogate marker may be investigated further. Failure to identify an association would also be scientifically informative, supporting the interpretation of IRT as a measure of thermophysiological responses independent of penetration.

Phase VI — Clinical and Multicenter Validation

The final stage should evaluate associations between thermal parameters and pain, function, patient-reported outcomes, and clinical response. The model should not be used for clinical decision support until external validation across different centers, cameras, and operators has been completed.

Discussion

This review identifies an important but as yet unvalidated research opportunity at the intersection of three scientific fields. First, the sonophoresis literature provides strong mechanistic evidence that ultrasound energy can alter the skin barrier and enhance transdermal transport (Yu, et al. 2021). However, a substantial proportion of this evidence comes from low-frequency sonophoresis research. It cannot therefore be assumed that effects of the same magnitude occur with 1–3 MHz therapeutic phonophoresis used in rehabilitation. Second, although some favorable findings have been reported in clinical phonophoresis studies, protocol heterogeneity is considerable (Martín-Vega, et al. 2022). Acoustic dose, active agent, concentration, vehicle system, treatment area, and clinical population may influence outcomes. The clinical phonophoresis literature should therefore not be interpreted as an evidence base for a single uniform intervention. Third, the principal advantage of IRT is its ability to measure surface temperature non-invasively and serially (Strasse, et al. 2021). This property is valuable for investigating dynamic responses following phonophoresis. However, it is essential to remember that IRT measures skin surface temperature. Two parallel biological pathways must therefore be distinguished: acoustic energy → alteration of the skin barrier → transdermal transport; and acoustic energy → thermal/mechanical/vascular response → change in surface temperature. Although both pathways may be influenced by the same physical intervention, they are not biologically equivalent.

One of the most important experimental questions for the future T0–T1–T2 framework is whether these pathways are related. The novelty of the proposed framework does not stem from acquiring three images designated T0, T1, and T2. Serial thermal imaging has previously been used in physiological and rehabilitation research (Procházka, et al. 2018). Its original contribution is the integration of standardized acoustic exposure, standardized formulation, standardized IRT measurement, within-subject ΔT analysis, bilateral asymmetry, thermal kinetics, appropriate control conditions, and multimodal/pharmacokinetic validation within a unified translational architecture. Focusing on within-subject change is an important methodological feature. Absolute skin temperature can be influenced by age, body composition, anatomical region, vascular status, environmental conditions, and autonomic thermoregulation (Marins, et al. 2014). Using each participant's T0 value as a reference may reduce some of this variability. However, a within-subject design does not completely eliminate environmental or technical confounders. Thermal kinetics may be more informative than a single post-application ΔT value. Two individuals with identical ΔTpeak values may differ in response duration and recovery behavior. Future combined assessment of ΔTpeak, Tpeak, recovery slope, recovery time, and thermal AUC may therefore provide more comprehensive thermal phenotyping.

The framework's principal methodological challenge is the need to standardize two technological platforms simultaneously. For IRT, participant preparation, environment, camera, geometric positioning, and ROI must be controlled; for phonophoresis, frequency, intensity, duty cycle, duration, ERA, BNR, transducer movement, coupling medium, and preparation properties require control. The coupling medium may be an important confounder, particularly in early thermal measurements (Escobar-Chávez, et al. 2009). The preparation's initial temperature, water content, evaporation, and residual surface layer can alter the T1 thermogram. Preparation-only and ultrasound-plus-inert-gel control arms are therefore important for mechanistic differentiation. The scientific value of the T0–T1–T2 framework does not depend on obtaining positive findings. Failure to observe a thermal difference between phonophoresis and sham, lack of reproducibility of ΔT, or absence of associations between thermal response and penetration or clinical outcomes would not constitute failure of the framework, but rather empirical determination of its limits. At present, the model is not a diagnostic method, a drug penetration test, a treatment success test, a patient selection algorithm, or a phonophoresis dose-setting system.

More precisely, T0–T1–T2 is a proposed translational measurement framework intended to quantitatively characterize temporal changes in skin surface temperature after standardized phonophoresis and prospectively investigate their relationships with biophysical, physiological, pharmacokinetic, and clinical outcomes [6-31].

Limitations

This review has several important limitations. First, the subject lies at the intersection of pharmaceutical sciences, rehabilitation, biomedical engineering, and thermal imaging; directly comparable studies are therefore limited. Second, phonophoresis studies are heterogeneous in ultrasound parameters, topical agents, formulations, and clinical populations (Median, et al. 1995). Third, much of the robust experimental evidence supporting the mechanistic basis of sonophoresis comes from low-frequency ultrasound studies and cannot be directly generalized to MHz therapeutic phonophoresis (Liu, et al. 2024). Fourth, the IRT literature shows differences in standardization of environmental conditions, acclimatization, camera characteristics, imaging geometry, and ROI analysis (Tejedor, et al. 2020). Fifth, evidence directly linking the thermal response after phonophoresis to actual transdermal penetration remains insufficient (Jeong, et al. 2021). Finally, T0–T1–T2 is a hypothesis-generating translational research framework proposed in this review, not a prospectively validated clinical algorithm.

Conclusion

Therapeutic ultrasound-assisted phonophoresis has the potential to modulate transdermal transport through interactions between acoustic energy and the skin and underlying tissues. However, current evidence does not permit direct generalization of permeabilization mechanisms demonstrated in low-frequency sonophoresis to MHz therapeutic phonophoresis used in rehabilitation. The clinical pho-

nophoresis literature is also heterogeneous with respect to acoustic dose, active agents, vehicle systems, and clinical populations. Because IRT can quantify skin surface temperature non-invasively and repeatedly, it may provide a suitable measurement platform for investigating thermophysiological responses after phonophoresis. Nevertheless, temperature changes measured by IRT are not direct indicators of transdermal penetration, tissue drug concentration, perfusion, or clinical efficacy. The T0–T1–T2 Thermal Response Framework proposed in this review aims to quantitatively assess standardized baseline conditions (T0), the early post-application response (T1), and the delayed/recovery response (T2) within the same anatomical ROI. The framework's original value lies not in three time points, but in combining standardized acoustic exposure + standardized formulation + standardized IRT + within-subject ΔT + thermal kinetics + appropriate control conditions + multimodal validation within one translational research architecture.

Future studies should establish technical reliability, thermal kinetics, mechanistic differentiation, physiological validity, and relationships with actual transdermal penetration and clinical outcomes in stages. Until this validation pathway has been completed, T0–T1–T2 should be regarded not as a tool for clinical decision-making or assessing treatment efficacy, but as a testable and falsifiable translational biomedical research framework for standardized characterization of surface thermophysiological responses following phonophoresis.

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