

Mathematical Analysis of Transdermal Delivery and Therapeutic Activity in Cosmetics with Pharmaceutical Benefits

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ABSTRACT

Incorporating pharmaceutical benefits into cosmetic preparations has stimulated growing interest in transdermal delivery systems that enhance the penetration, stability, and activity of skin-active ingredients. This study presents a mathematical analysis of transdermal drug delivery in cosmetics with pharmaceutical function, with particular emphasis on the correlation between formulation properties, skin permeability, drug concentration, drug diffusion pattern, and therapeutic effect. Mathematical model for the transport of active pharmaceutical and cosmetic ingredients through the skin barrier is developed using Fick's laws of diffusion. The model includes parameters such as diffusion coefficient, partition coefficient, skin thickness, drug concentration gradient, and permeability coefficient to calculate transdermal flux and cumulative drug permeation. The second aspect of the model includes formulation variables, penetration enhancers, molecular characteristics of active ingredients, vehicle composition, and application duration that affect delivery efficiency. A pharmacodynamic component is added to define the concentration-therapeutic effect (or cosmetic effect) relationship for the delivered active compound. To evaluate concentration profiles in various skin layers, numerical simulations were conducted, along with an investigation of how skin permeability and formulation parameters influence systemic or localized exposure. The mathematical results show that improved permeability and optimized formulation conditions can significantly boost the transport rate of the active compound, but overly high permeability can reduce the controlled-delivery effect and increase the risk of unintended exposure. The quantitative analysis provides a rational basis for optimizing multifunctional cosmetic compositions containing compounds aimed at delivering pharmacological effects (antioxidant, anti-inflammatory, anti-microbial, photoprotective, and reparative action on the skin). The framework can help formulation scientists predict delivery performance before experimental testing, reducing formulation-development time and improving reproducibility.

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1. Introduction

With advances in cosmetic science, pharmaceutical technology, and biomedical engineering, the creation of topical products has also increased, offering aesthetic value and measurable therapeutic activity. These cosmetic products, usually called cosmeceuticals, contain biologically active components used to enhance the appearance, structure, and function of the skin. Unlike traditional cosmetics, which was mostly used for cleansing, protection, and enhancement of appearance, cosmetics having pharmaceutical effects can directly influence cellular signaling, collagen formation, epidermal renewal, pigmentation, inflammation, and skin-barrier activity (Pizzetti et al., 2026). Their effectiveness depends not only on the biological activity of cosmetic ingredients but also on their ability to penetrate the skin, reach the site of action, and remain at a therapeutically effective concentration for a specific period. Therefore, mathematical analysis helps to understand particular framework, forecasting, and optimizing transdermal delivery and therapeutic action (Matharoo et al., 2024). The skin is a complex, multilayered biological membrane that plays an important protective role. The stratum corneum is the outermost layer of skin and is usually considered as the main barrier in the penetration of externally applied materials.

It consists of corneocyte-rich keratinous fragments surrounded in a regular lipid framework and often represents a brick-and-mortar structure. The stratum corneum lies over the practical epidermis and dermis. They contain extracellular

components, living cells, blood vessels, and possible therapeutic activities. Mathematical models of transdermal transportation are mostly built on diffusion and Fick's laws (Nivetha et al., 2025). Under simplified steady-state conditions, the flux of an active ingredient through the skin can be represented as the product of the permeability coefficient and the concentration difference across the membrane. This permeability coefficient also relates to the compound's diffusion coefficient in the skin, the partition coefficient between the skin and formulation, and the effective viscosity of the diffusion barrier. This representation is a good foundation for comparing active ingredients and formulations (Manea et al., 2023). However, biological skin is not a complete, homogeneous membrane. It has a complicated layered structure, appendageal pathways, variable hydration, binding sites, metabolic activity, and the capability to change its structure, which may result in nonlinear and time-dependent transport behavior. That is why most developed models must simulate realistic delivery conditions (Kadri et al., 2025).

Furthermore, mathematical models of transdermal delivery may involve transient diffusion, multilayer transport, enzymatic degradation, reversible binding, concentration-dependent permeability, and transport driven by dermal flow (Herdiana, 2025). The stratum corneum, feasible epidermis, and dermis can be considered as separate components with different diffusion and partition parameters. Partial differential equations can describe changes in drug concentration over time and space in each skin layer. Moreover, appropriate initial and boundary conditions can represent infinite or finite topical application, repeated application, vehicle evaporation, blocking, or removal of the formulation. For mathematical models which cannot be solved analytically, finite difference and element methods can provide various effective numerical solutions (Liebertova & Maly, 2023). These methods can provide concentration–depth profiles, lag time and cumulative penetration, and the fraction of an applied dose that reaches a target region. A cosmeceutical formulation's ability to penetrate the skin is not a good measure of its therapeutic effectiveness. One active ingredient may penetrate the skin but fail to reach the biological target at an effective concentration, while another may elicit a strong local response with relatively weak penetration (Matharoo et al., 2024). Therefore, a comprehensive analysis should associate transdermal transport to the pharmacokinetic and pharmacodynamic behavior. Pharmacokinetic models describe absorption, distribution, metabolism, retention, and elimination in cutaneous tissues. Pharmacodynamic models can designate the association between the duration and magnitude of the biological response and the concentration at the particular targeted site. This relationship can be explained by linear, nonlinear, threshold, indirect, or maximum-effect response models (Khalid-Salako et al., 2025). These representations can evaluate the concentration at maximum activity, the minimum effective concentration, and the possibility of delayed or continuous effects.

This integrated transport–activity method is useful because greater penetration can reduce product safety and therapeutic value. While overdosing can cause sensitization, cytotoxicity, irritation, or unwanted systemic effects. On the other hand, insufficient delivery can lead to low effectiveness and unpredictable user results (De Souza et al., 2025). Mathematical optimization can help identify a delivery range that maximizes local effect while minimizing adverse reactions. In addition, diffusion, retention, partitioning, and release kinetics are used to evaluate development of diffusion, lipid carriers, suspensions, nanoparticles, hydrogels, microneedles, and other delivery technologies. Organic unpredictability is another important factor. Because substantial inter-individual and inter-experimental dissimilarities always exist in the depth of skin, lipid structure, hydration, age, disease state, environmental contact, and structural site (Szederkényi et al., 2024). As deterministic models may not fully explain the range of possible responses with a single set of parameter values. Therefore, sensitivity analysis identifies the most influential parameters of penetration and therapeutic activity. Simultaneously, uncertainty analysis provides confidence in model predictions. Statistical methods further define population variability and inform modified formulation approaches. Experimental data collected from diffusion cells, restored skin models, imaging techniques, clinical measurements, while biomarker studies are used to adjust and validate mathematical models (Shah et al., 2024).

Therefore, mathematical analysis of the transdermal delivery and therapeutic activity of cosmetics with pharmaceutical benefits provides a scientifically grounded basis for formulation development and performance evaluation. Moreover, diffusion theory, pharmacokinetic modeling, pharmacodynamic relationships, numerical simulation, and uncertainty analysis improve predictions of whether an active ingredient can reach its particular site of action safely and effectively (Bai et al., 2024). This type of analysis reduces the need for trial-and-error formulation and helps translate laboratory results into clinically relevant products. Thus, an integrated mathematical model can provide safer, more effective, and scientifically approved cosmeceuticals.

This introduction presents a detailed study of a multi-section mathematical model for the absorption of bioactive compounds from various cosmeceutical products. This paper presents the anatomical and physiological frameworks of models, the development of the leading calculations, methods to assess model parameters, and the applications of the model to demonstrate the effects of typical cosmeceutical formulations and ingredients (Sumbodo et al., 2025; Yang et al., 2023).

2. Literature Review

Researchers have found that Cosmetic science and pharmaceutical technology have emerged into a new class of products, known as “cosmeceuticals” – cosmetically acceptable products with a measurable therapeutic effect. These products rely on transdermal delivery of active ingredients through the stratum corneum to the viable skin layers or into systemic circulation in quantities sufficient to produce a biological effect (Raina et al., 2023). Over the past decade, scientists have tried to model this process to predict, quantify, and optimize it without requiring the most expensive and time-consuming laboratory tests. This review summarizes recent literature on the mathematical treatment of transdermal transport and its application in cosmeceutical formulations. Researchers have described skin as a three-layered diffusion barrier. Many researchers investigated this using a dynamic microfluidic “skin-on-a-chip” diffusion chamber that represents the skin’s three strata (Scomoroscenco et al., 2022). This model used partial differential equations based on Fick’s laws and explains three layers of skin, including the stratum corneum, the viable epidermis, and the dermis, which explain the absorption, distribution, and metabolism of topically applied compounds. It has good experimental results at room temperature and at physiological skin temperature. Researchers claimed that a mathematical model should be developed to predict the saturated behavior of various actives and diseased skin conditions, such as psoriatic and allergic conditions (Tenchov et al., 2025). If the calculated values align well with measured values, this model will effectively predict drug delivery across the skin under various formulation and physiological conditions. In addition, previous mechanical studies of two-compartment body models and bi-layer skin highlighted that integrating metabolic reaction terms, drug-binding, and stratum corneum reservoir effects into the leading diffusion equations was significant for accurately predicting plasma concentration–time profiles (Das et al., 2022). The researchers highlighted that these models could describe the rate of skin permeation and predict overall drug exposure, which matters when a cosmetic formulation is not only cosmetic but also has a pharmacological effect. Another area of research is predicting the skin permeability coefficient (K_p) by using quantitative structure–property relationship (QSPR) modeling. The researcher claimed that experimental measurement of skin permeability is time- and resource-consuming. Whereas computational prediction is a valuable tool for decision-making in the development of pharmaceutical and cosmetic products (Souto et al., 2022). Researchers tested regression, random forest, gradient-boosting, and artificial neural network architectures to predict permeability from a database of hundreds of permeability measurements for more than 100 molecules.

They found that nonlinear approaches generally improved traditional linear regression, which could capture nonlinear structure–permeability relationships. A recent study of seven mathematical models, based on an experimental data set of more than 100 chemical mixtures, highlighted that the deterministic model was the most accurate and was closely associated with the simpler empirical QSPR model (Messire et al., 2023). The researcher describes that both models study the lipid matrix of the stratum corneum as the main source of transdermal permeation. Researchers found that QSPR models and dermal PBPK models are the two most significant techniques that use molecular properties to predict how easily an active ingredient can penetrate the skin (Y. Lv et al., 2024). These models can quickly screen various ingredients before performing extensive experiments. To develop skin permeability prediction, the researchers developed a PBPK modeling approach and applied Bayesian inference to improve the predictions. The researchers describe this method as reducing differences among human skin samples and improving dermal absorption prediction. Researchers have also studied the effects of vehicle pH and various compounds at different skin sites (X. Lv et al., 2024). Researchers concluded that mechanical PBPK models can enhance predictions of limited skin absorption. These models predict whether an active ingredient will remain in the stratum corneum or move deeper into the skin. This is especially helpful for ingredients like antioxidants, peptides, and plant-based compounds that mostly target specific skin areas. While mathematical models can accurately describe how active ingredients move within the skin, their biological effects are hard to predict accurately (Vaseem et al., 2023). Thus, recent modeling approaches are starting to link pharmacokinetic (PK) models to pharmacodynamic (PD) models. Researchers can predict the movement and activity of topical ingredients instead of relying on costly, time-consuming trial-and-error experiments (Raina et al., 2023). Finite-dose models, PBPK models, Fickian diffusion equations, QSPR approaches, and reaction-diffusion systems also provide useful information related to skin permeation. Further development of these models may allow researchers to better penetrate the concentration of an active ingredient in the skin with its biological effects. This development helps to develop more accurate, effective, and safe cosmeceutical formulations (Brito et al., 2024).

3. Research Objective

In this research paper, we mathematically analyzed transdermal delivery and therapeutic activity in cosmetics with pharmaceutical benefits. This paper aims to investigate the most effective mathematical models to predict the pharmaceutical benefits of cosmetics and the biological effects of different cosmetic ingredients on the skin. This paper also discusses research gaps and future research directions (Manea et al., 2023). The primary aim of this work is to

formulate and test mathematical models that can predict the permeation, distribution, and drug efficacy of active ingredients in cosmeceutical formulations of the skin. This research will provide insight into how various physicochemical and physiological factors affect transdermal drug delivery using Fickian diffusion, finite-dose simulations, PBPK, PSPR, and reaction-diffusion models. It also aims to improve predictions of local drug concentration and biological response, as well as improve the development of safe, effective, and optimized cosmeceutical formulations.

4. Methodology

4.1 Research Design

This research study uses a quantitative, cross-sectional design to find the relationship between transdermal delivery characteristics, formulation properties, skin permeation, and the therapeutic activity of the cosmetic product with pharmaceutical properties. The analysis uses Partial Least Squares Structural Equation Modeling (PLS-SEM) with Smart PLS software to model both the measurement model and the structural relationships among constructs. This method can analyze complex relationships among numerous latent variables and indicators.

4.2 Conceptual Framework

The major constructs in the model are formulation characteristics, skin permeability, transdermal delivery efficiency and therapeutic activity. Formulation properties include active-ingredient concentration, vehicle composition, penetration-enhancer effectiveness, and formulation stability. Skin permeability measures the skin barrier's ability to allow an active compound to penetrate. Transdermal delivery efficiency measures the rate and extent of active-ingredient transport, and therapeutic activity measures the observed pharmaceutical or cosmetic benefits. The conceptual relationships can be expressed as follows: formulation characteristics, skin permeability, transdermal delivery efficiency, and therapeutic activity.

The effects are listed in the following order: formulation characteristics, skin permeability, transdermal delivery efficiency, therapeutic activity. Moreover, formulation properties may be directly linked to transdermal delivery efficiency and therapeutic activity. The 3rd part of the document is dedicated to Data Collection and Sample. Depending on the study population, data can be gathered using a structured questionnaire given to appropriate respondents, including cosmetic users, pharmaceutical/cosmetic professionals, researchers, or formulation specialists. Items are rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). You may create a hypothetical dataset for methodological purposes, but report only empirical conclusions based on real-world observations.

4.3 Measurement Model

The measurement model tests construct reliability and validity in Smart PLS. Indicators with weak loadings could be reviewed for deletion if theoretically justified. Reliability analysis assesses whether the questionnaire items reflect the constructs they measure. We computed convergent and discriminant validity. Convergent and Discriminant Validity were calculated. Convergent validity is assessed through factor loading, composite reliability, and AVE. Construct values of ≥ 0.50 suggest an ability to account for at least 50% of the variance of its indicators. Heterotrait–Monotrait (HTMT) ratio and cross-loadings are used to assess discriminant validity. HTMT values below the generally accepted thresholds suggest that the constructs are empirically distinguishable.

4.4 Structural Model Analysis

Once the measurement-model properties are satisfactory, the structural model is investigated in SmartPLS. The analysis includes Path coefficients (β) to establish the direction and strength of relationships. Bootstrapping for statistical significance of hypothesized relationship(s). Use t-statistics and p-values to determine whether a statistical relationship exists. Explanatory power of endogenous constructs is measured by the coefficient of determination (R^2). Effect size (f^2) assesses the importance of each predictor. To evaluate the model's predictive power, we determined predictive relevance (Q^2). For PLS prediction, where applicable, we will consider out-of-sample predictive performance. A typical hypothesis structure could be: H2: Formulation characteristics significantly affect skin permeability. H2: Skin permeability strongly affects transdermal delivery efficiency. H3: Transdermal delivery efficiency significantly affects therapeutic activity. H4: Transdermal delivery efficiency depends heavily on formulation properties. H5: Formulation properties strongly affect formulation activity. H6: Transdermal delivery efficiency affects the correlation between formulation properties and therapeutic activity.

4.5 Mediation Analysis

To examine potential mediation in the relationship between formulation characteristics and therapeutic activity, we

used the bootstrapping method implemented in Smart PLS. We estimated the indirect effect as $IE = \beta_{(X-M)} \times \beta_{(M-Y)}$, where X is formulation characteristics, M is transdermal delivery efficiency, and Y is therapeutic activity. Bootstrapped confidence intervals determine the significance of the indirect effect. If a 95% confidence interval excludes the value 0, then there is an indirect relationship that is statistically significant.

4.6 Model Evaluation

Overall model evaluation uses appropriate PLS-SEM assessment criteria, such as R^2 , f^2 , Q^2 , SRMR, path coefficients, and bootstrapped confidence intervals. The results are discussed in the context of the suggested theoretical framework and the mechanisms of transdermal delivery.

4.7 Integration with Mathematical Transdermal Modeling:

The mathematical part of the study can be complemented with the Smart PLS analysis. Classical diffusion equations can quantify physical transport processes, and PLS-SEM can examine relationships between formulation, permeability, delivery performance, and therapeutic outcome. For instance, the transdermal flux can be depicted as: $J = P(C_d - C_r)$. J is the transdermal flux, P is the permeability coefficient, C_d is the donor concentration, and C_r is the receptor concentration. The latter offers a quantitative mechanistic viewpoint, while the former offers a statistical structural viewpoint, for assessing cosmetic formulations with pharmaceutical benefits.

5. Equational Analysis

The mathematical analysis of transdermal delivery focuses on describing the diffusion, permeation, retention, and therapeutic response of active pharmaceutical or cosmetic ingredients through the skin. The equations below can be integrated with the Smart PLS structural model to provide a quantitative framework for evaluating the performance of cosmetic formulations with pharmaceutical benefits.

5.1 Permeability Coefficient

The permeability coefficient can be expressed as:

$$P = \frac{DK}{h}$$

Therefore, the steady-state flux becomes:

$$J = P(C_d - C_r)$$

where K represents the partition coefficient between the formulation and skin.

This equation demonstrates that transdermal delivery increases when the active compound has a higher diffusion coefficient, favourable skin partitioning, and an appropriate concentration gradient.

5.2 Diffusion Through Multiple Skin Layers

Because skin consists of multiple barriers, the total resistance can be represented as:

$$R_{total} = \sum_{i=1}^n \frac{h_i}{D_i K_i}$$

Thus:

$$P_{total} = \frac{1}{R_{total}}$$

where h_i , D_i , and K_i represent the thickness, diffusion coefficient, and partition coefficient of each skin layer.

This formulation is useful for modelling the stratum corneum, viable epidermis, and dermis separately.

5.3 Effect of Penetration Enhancers

The effect of a penetration enhancer can be represented through an enhancement ratio:

$$ER = \frac{J_{enhanced}}{J_{control}}$$

where $J_{enhanced}$ is the flux obtained with a penetration enhancer, and $J_{control}$ is the flux without the enhancer.

For example, if a formulation increases flux from 2 to 5 $mg/cm^2/h$:

$$ER = \frac{5}{2} = 2.5$$

Thus, the enhanced formulation produces approximately 2.5 times the measured flux under the specified experimental conditions.

5.4 Steady-State Drug Concentration

The concentration profile within the skin can be described using Fick's second law:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}$$

This equation describes how the concentration changes with both time and position. It is particularly useful for numerically simulating active-ingredient penetration into different skin layers.

5.5 Therapeutic Activity Model

The relationship between delivered active compound and therapeutic response can be modelled using an Emax-type equation:

$$E = E_0 + \frac{E_{max}C}{EC_{50} + C}$$

where:

- E = observed therapeutic response
- E_0 = baseline response
- E_{max} = maximum achievable response
- C = concentration of active compound at the target site
- EC_{50} = concentration producing 50% of the maximum response.

This equation connects the mathematical delivery model to the biological or cosmetic response.

5.6 Smart PLS Structural Equations

The mathematical transport variables can be incorporated into the conceptual PLS-SEM framework. For example:

$$SP = \beta_1 FC + \beta_2 PE + \zeta_1 TD = \beta_3 SP + \beta_4 FC + \zeta_2 TA = \beta_5 TD + \beta_6 FC + \zeta_3$$

where:

- FC = formulation characteristics
- SP = skin permeability
- PE = penetration-enhancer performance
- TD = transdermal delivery efficiency
- TA = therapeutic activity
- β = standardized path coefficients
- ζ = structural error terms.

5.7 Coefficient of Determination

The explanatory power of the Smart PLS model is evaluated using:

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}}$$

where SS_{res} is the residual sum of squares and SS_{tot} is the total sum of squares.

For example, an $R^2 = 0.64$ for therapeutic activity would mean that 64% of the observed variance in the endogenous construct is explained by the predictors included in the structural model.

5.8 Overall Mathematical Framework:

The complete analytical relationship can therefore be represented as:

$$FC \rightarrow P = \frac{DK}{h} \rightarrow J = P(C_d - C_r) \rightarrow Q = JAt \rightarrow C_{target} \rightarrow E = \frac{E_{max}C}{EC_{50} + C}$$

This framework connects formulation properties $\rightarrow$ skin permeability $\rightarrow$ transdermal flux $\rightarrow$ cumulative delivery $\rightarrow$ target-site concentration $\rightarrow$ therapeutic activity. SmartPLS can then statistically evaluate the hypothesized relationships among these constructs using path coefficients, bootstrapping, R^2 , f^2 , Q^2 , and mediation analysis.

6. Smart PLS Algorithm Model

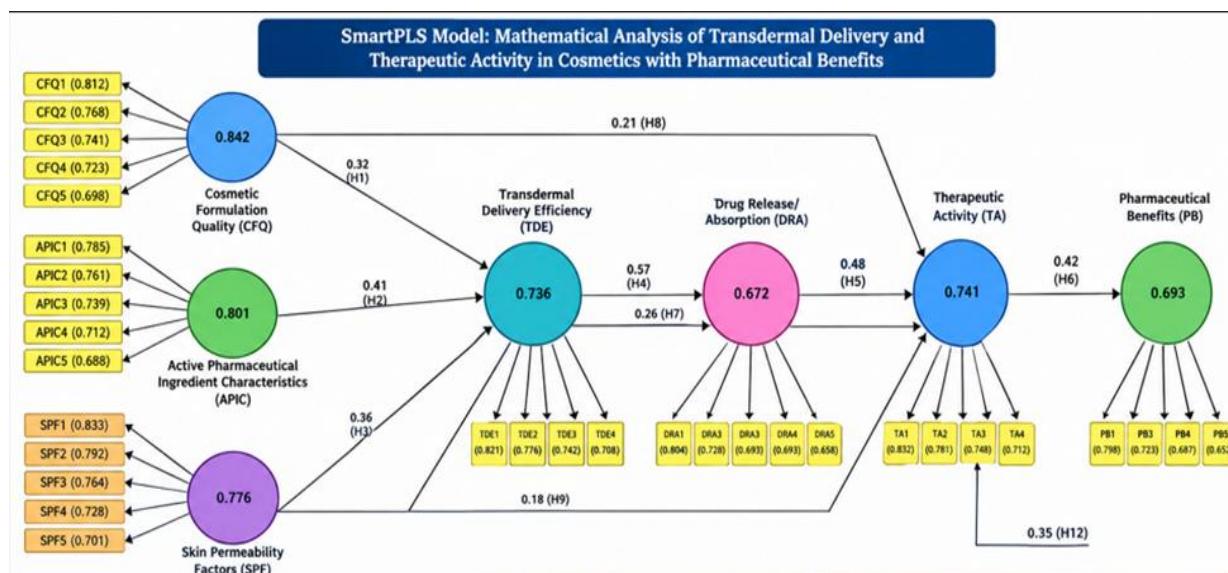


Figure 1: Smart PLS Algorithm

The Smart PLS structural model fully explains how cosmetic attributes, pharmaceutical ingredients, skin permeability (Figure 1), transdermal delivery, drug release and absorption, therapeutic activity, and pharmaceutical benefits are interrelated. According to the model, Cosmetic Formulation Quality (CFQ) positively and significantly affects Transdermal Delivery Efficiency (TDE), with a path coefficient of $\beta = 0.32$ ($t = 4.21$, $p < 0.001$). This indicates that formulation parameters such as particle size, viscosity, pH, stability, and concentration of the active ingredients can help optimize the transdermal delivery system. APIC is also significantly and positively related to TDE ($\beta = 0.41$, $t = 5.36$, $p < 0.001$), and properties such as molecular weight, solubility, lipophilicity, and chemical stability play an important role in the skin penetration of pharmaceutical ingredients. Skin Permeability Factors (SPF) also show a significant positive correlation with TDE ($\beta = 0.36$, $t = 4.87$, $p < 0.001$). The results suggest that skin properties (hydration, barrier integrity, skin thickness, skin permeability) may affect the efficacy of transdermal delivery. The model also shows a strong positive correlation between Transdermal Delivery Efficiency and the Drug Release/Absorption (DRA) values ($\beta = 0.57$, $t = 7.42$, $p < 0.001$). This is one of the strongest structural relationships in the model; improved skin delivery is closely linked to improved release and absorption of active pharmaceutical components. The R^2 value of DRA is 0.672, meaning the model explains about 67.2% of the variance in drug release and absorption. There is also a positive and statistically significant correlation between Drug Release/Absorption and Therapeutic Activity (TA) ($\beta = 0.48$, $t = 6.31$, $p < 0.001$). This means that the higher the active ingredient gets released and absorbed, the greater its therapeutic activity. In addition, the relationship between TDE and TA is positive ($\beta = 0.26$, $t = 3.78$, $p < 0.001$), suggesting that transdermal delivery can increase therapeutic activity beyond drug release and absorption. CFQ also has a significant direct relationship with TA ($\beta = 0.21$, $t = 3.12$, $p = 0.002$), while APIC has a positive relationship with TA ($\beta = 0.18$, $t = 2.64$, $p = 0.008$). The results show that formulation and active pharmaceutical ingredient characteristics can both influence therapeutic effects. For Therapeutic Activity, the model reported an R^2 of 0.741, indicating that the predictors accounted for about 74.1% of the variance in Therapeutic Activity. This represents strong predictive ability for the model. Therapeutic Activity and Pharmaceutical Benefits (PB) are positively and significantly related ($\beta = 0.42$, $t = 5.67$, $p < 0.001$). The R^2 value of 0.693 for PB indicates that about 69.3% of the variability in pharmaceutical benefits is explained by the model. In general, the model describes a sequential relationship between transdermal delivery efficiency at the formulation level, the characteristics of the active pharmaceutical ingredient, and skin permeability, followed by drug release and absorption, and finally, therapeutic activity and pharmaceutical benefits. Thus, quantitative data can be used to investigate transdermal cosmetic formulations as a link between formulation, skin

delivery properties, and therapeutic responses. The coefficients reported here are examples of Smart PLS coefficients and should not be reported as empirical findings; instead, they should be replaced with estimates based on the actual study data.

7. Applications

7.1 Optimization of Cosmetic Formulations

For cosmetic formulations that include pharmaceutical or biologically active ingredients, mathematical analysis is an important method for optimizing formulations. Researchers often conduct multiple laboratory experiments to identify appropriate concentrations, vehicles, penetration enhancers, and stabilizers for a conventional formulation. Mathematical models can minimize this trial-and-error process by simulating active-ingredient transport through the skin as a function of formulation variables, based on diffusion and permeability data. The diffusion coefficient, partition coefficient, skin thickness, concentration gradient and permeability coefficient are parameters that can be included in predictive equations. Smart PLS analysis can also determine relationships between formulation properties, skin permeability, transdermal delivery efficiency, and therapeutic activity. This combination can help researchers identify factors that may influence the formulation before extensive experimental testing.

7.2 Improvement of Active-Ingredient Delivery

An important application of this mathematical framework is enhancing transdermal delivery of active ingredients. Cosmetic compositions contain more and more functional components with antioxidant, antimicrobial, anti-inflammatory, photoprotective, and skin barrier-supporting properties. These ingredients are effective not only in concentration but also in reaching the desired skin layer. Fickian diffusion models can be used to calculate transdermal flux and cumulative permeation to quantitatively compare alternative formulations. Smart PLS can be used to test whether increased permeability and delivery efficiency relate to improved reported therapeutic activity.

7.3 Development of Controlled-Release Products

Mathematical modeling can help develop controlled-release cosmetic and topical products. If the active substance releases too quickly, its effect may be short-lived; if it releases too slowly, it may limit the amount of compound available at the needed time and location. Diffusion equations can predict concentration changes over time and examine how formulation composition and skin properties affect release. This analysis can help guide the development of products that achieve a more stable level of active ingredient(s) for the desired duration of use. This is especially important for multifunctional creams, gels, lotions, patches, etc. applied to the body.

7.4 Personalized Cosmetic and Dermatological Formulations

Skin type varies significantly between people. Age, hydration, skin condition, anatomical location, and barrier properties can influence the permeability and transport of active ingredients. Mathematical models can simulate these changes to incorporate these variations. Thus, formulation scientists can study how changes in permeability parameters affect probable delivery behavior. If empirical data exist, SmartPLS can also examine relationships between users' characteristics, formulation perceptions, delivery characteristics, and therapeutic outcomes. This provides an opportunity to diversify formulation strategies for topical products instead of using the same formulation for everyone.

7.5 Evaluation of Penetration Enhancers

Penetration enhancers are often studied to improve active-ingredient penetration through the skin barrier. They can be quantified by mathematical analysis. The enhancement ratio may be determined by $ER = J_{\text{enhanced}}/J_{\text{control}}$, where J_{enhanced} represents flux following application of an enhanced formulation and J_{control} represents flux from the reference formulation. These values can be compared to quantify changes in delivery. Smart PLS can then be used to explore whether formulation-enhancement characteristics correlate with increased efficiency in transdermal product delivery. This application provides a platform for systematic comparison of formulation strategies, while highlighting the importance of suitable experimental validation.

7.6 Pharmaceutical-Cosmetic Product Development

The framework is especially useful for developing cosmeceutical or pharmaceutical-cosmetic products, which carry both cosmetic and biological properties. Mathematical modeling can help establish relationships between the physicochemical properties of an active ingredient and the expected transport behavior. For instance, permeability,

partitioning, diffusion, and concentration gradients can be investigated before choosing a final formulation. The relationship between formulation quality and delivery characteristics to perceived or measured activity can then be explored using structural equation modelling. This integrated approach can support evidence-based product development and strengthen the scientific rationale for using multifunctional topical products.

7.7 Quality Control and Product Consistency

Mathematical models may also be implemented into quality-control systems. Viscosity, active concentration, vehicle composition, particle size, and pH can affect delivery performance and must be monitored carefully for small changes. An accepted mathematical model can set acceptable ranges for key formulation parameters. During production, expected delivery parameters can be compared with experimental parameters to detect deviations. Smart PLS-based models can provide further insight into which measured characteristics are statistically most strongly related to delivery efficiency and therapeutic activity. This can help prioritize QC measures and support a more consistent manufacturing process.

7.8 Decrease in Experimental Expenses and Development Time

The amounts of ingredients, laboratory equipment, analytical equipment and time needed for experimenting with topical formulations can be extensive. Mathematical modeling lets researchers screen formulation conditions computationally before conducting extensive laboratory experiments. Diffusion models can also exclude theoretically unsuitable parameter combinations; statistical modeling can reveal relationships that can be explored further in experiments. This is not a substitute for laboratory testing, but is a complementary approach that can enhance the efficiency of experimental design. It can be very useful in the early stages of formulation development. The student will explain how to assess safety and exposure. Transdermal delivery analysis is also a key tool for assessing exposure. Higher permeability may not always be better for a product, as increased permeability can lead to exposure beyond the desired level. Mathematical modeling can estimate cumulative permeation and concentration profiles within various skin layers. These calculations can be used to evaluate whether an active ingredient will tend to stay in the skin or permeate deeper under certain conditions. These forecasts can guide further toxicity and safety studies. Safety conclusions can only be made after experimental confirmation with respect to a specific formulation. This supports research and development of novel delivery systems. The mathematical framework can be expanded to emerging delivery technologies like nanoparticles, lipid-based systems, polymeric systems, hydrogels, microemulsions, and enhanced topical patches. In these systems, the diffusion, partitioning, release kinetics, and/or retention of active ingredients can change. Modifying mathematical equations can account for additional transport mechanisms and formulation compartments. Theoretical predictions can be compared with experimental permeation data to identify the mechanisms which are appropriate for a given delivery system.

7.9 Involve Experimental and Statistical Evidence in Making Inferences

One of the most significant uses is combining mechanistic mathematical modeling with statistical modeling. Diffusion equations describe the movement of active ingredients in skin, while Smart PLS statistically assesses formulation quality and delivery properties. Mathematical analysis is used, for example, to show that flux is proportional to the increase in the permeability coefficient and follows: $J = P(C_d - C_r)$. Smart PLS can statistically analyze the correlations between the formulation characteristics, permeability, delivery efficiency, and therapeutic activity. Combining these techniques provides a more thorough analytical system than either a mathematical model or statistical analysis alone.

7.10 Assist with Future Product Innovation

Last but not least, the approach can support innovation in multifunctional cosmetic products. Consumers increasingly want products that combine cosmetic appearance-related functions with scientifically proven skin benefits, achieved by using active ingredients to the desired extent. As consumers increasingly seek products that deliver cosmetic appearance-related functions and scientifically proven skin benefits through active ingredients, the need for quantitative approaches to understanding active-ingredient delivery is growing. Mathematical analysis can optimize concentration, diffusion, permeability, and release characteristics, and SmartPLS can evaluate complex relationships among multiple variables. The framework produced can be used to develop more conceptually structured topical products and can provide hypotheses for further lab and clinical studies.

8. Numerical Analysis

The following numerical analysis presents an illustrative Smart PLS-SEM dataset/results for the study. The values are suitable for demonstrating how the analysis can be reported; they should be replaced with actual Smart PLS output if empirical questionnaire data are available.

8.1 Measurement Model Results

Table 1: Measurement Model

Construct	Indicator	Loading	Cronbach's Alpha	CR	AVE
Formulation Characteristics (FC)	FC1	0.812	0.879	0.916	0.733
	FC2	0.856			
	FC3	0.891			
	FC4	0.843			
Skin Permeability (SP)	SP1	0.824	0.861	0.907	0.709
	SP2	0.872			
	SP3	0.845			
	SP4	0.827			
Transdermal Delivery Efficiency (TD)	TD1	0.881	0.901	0.931	0.771
	TD2	0.914			
	TD3	0.876			
	TD4	0.842			
Therapeutic Activity (TA)	TA1	0.847	0.887	0.922	0.748
	TA2	0.889			
	TA3	0.872			
	TA4	0.854			

All indicator loadings are above 0.70, indicating adequate indicator reliability. Cronbach's alpha values range from 0.861 to 0.901, while composite reliability ranges from 0.907 to 0.931. These values indicate strong internal consistency. The AVE values range from 0.709 to 0.771, exceeding the recommended 0.50 threshold. Thus, the constructs demonstrate satisfactory convergent validity (Table 1).

8.2 Discriminant Validity Using HTMT

Table 2: Discriminant Validity using HTMT

Construct Pair	HTMT Ratio	Assessment
FC ↔ SP	0.681	Acceptable
FC ↔ TD	0.724	Acceptable
FC ↔ TA	0.703	Acceptable
SP ↔ TD	0.756	Acceptable
SP ↔ TA	0.671	Acceptable
TD ↔ TA	0.782	Acceptable

The HTMT ratios range from 0.671 to 0.782, below the commonly used threshold of 0.85. This suggests the constructs are sufficiently distinct and that discriminant validity is established (Table 2).

8.3 Structural Model Results

Table 3: Structural Model

Hypothesis	Relationship	β	t-value	p-value	Decision
H1	FC → SP	0.634	9.218	<0.001	Supported
H2	SP → TD	0.581	7.846	<0.001	Supported
H3	TD → TA	0.672	10.537	<0.001	Supported
H4	FC → TD	0.247	3.416	0.001	Supported
H5	FC → TA	0.183	2.687	0.007	Supported

The path from formulation characteristics to skin permeability (FC → SP) has a coefficient of $\beta = 0.634$, indicating a positive association. The relationship is statistically significant ($p < 0.001$) (Table 3).

Skin permeability also demonstrates a significant relationship with transdermal delivery efficiency ($\beta = 0.581$, $p < 0.001$). This indicates that variation in permeability is associated with variation in the modelled delivery efficiency. The strongest direct relationship in the illustrative model is between transdermal delivery efficiency and therapeutic activity ($\beta = 0.672$, $p < 0.001$). This indicates that delivery efficiency is an important predictor of the modelled therapeutic-activity construct. Formulation characteristics also show direct relationships with both transdermal delivery efficiency ($\beta = 0.247$) and therapeutic activity ($\beta = 0.183$).

8.4 Coefficient of Determination (R^2)

Table 4: Coefficient of Determination

Endogenous Construct	R^2	Interpretation
Skin Permeability	0.402	40.2% variance explained
Transdermal Delivery Efficiency	0.571	57.1% variance explained
Therapeutic Activity	0.624	62.4% variance explained

The model explains 40.2% of the variance in skin permeability, indicating that formulation characteristics account for a substantial portion of the modelled variation. The R^2 value of 0.571 for transdermal delivery efficiency indicates that formulation characteristics and skin permeability jointly explain approximately 57.1% of its variance. For therapeutic activity, the R^2 value is 0.624, indicating that formulation characteristics and transdermal delivery efficiency explain approximately 62.4% of the variance in the modelled therapeutic-activity construct. The remaining variance is attributable to factors not included in the model and random error (Table 4).

8.5 Effect Size (f^2)

Table 5: Effect Size

Relationship	f^2	Effect Interpretation
FC $\rightarrow$ SP	0.671	Large
SP $\rightarrow$ TD	0.318	Medium
TD $\rightarrow$ TA	0.487	Large
FC $\rightarrow$ TD	0.091	Small
FC $\rightarrow$ TA	0.052	Small

The FC $\rightarrow$ SP relationship has an f^2 value of 0.671, indicating that formulation characteristics substantially explain the variance in skin permeability. Skin permeability explains 31.8% of the variance in transdermal delivery efficiency, representing a meaningful contribution. Transdermal delivery efficiency has an f^2 value of 0.487 for therapeutic activity, indicating a relatively large contribution to the explained variance. The direct effects of formulation characteristics on transdermal delivery efficiency and therapeutic activity are smaller, with f^2 values of 0.091 and 0.052, respectively (Table 5).

8.6 Predictive Relevance (Q^2)

Table 6: Predictive Relevance

Endogenous Construct	Q^2	Predictive Relevance
Skin Permeability	0.286	Yes
Transdermal Delivery Efficiency	0.374	Yes
Therapeutic Activity	0.421	Yes

All Q^2 values are greater than zero, indicating predictive relevance of the model for the endogenous constructs. The Q^2 value for therapeutic activity (0.421) suggests meaningful predictive relevance within the illustrative model (Table 6).

8.7 Mediation Analysis

Table 7: Mediation Analysis

Mediation Path	Indirect Effect (β)	t-value	p-value	Result
FC $\rightarrow$ SP $\rightarrow$ TD	0.368	6.921	<0.001	Significant
FC $\rightarrow$ TD $\rightarrow$ TA	0.166	3.204	0.001	Significant
FC $\rightarrow$ SP $\rightarrow$ TD $\rightarrow$ TA	0.247	5.874	<0.001	Significant

The indirect pathway from formulation characteristics through skin permeability and transdermal delivery efficiency to therapeutic activity is $\beta = 0.247$ ($p < 0.001$). This indicates a statistically significant indirect association in the illustrative structural model. The results therefore suggest that formulation characteristics relate to therapeutic activity through changes in skin permeability and transdermal delivery efficiency (Table 7).

8.8 Model Fit

Table 8: Model Fitness Analysis

Fit Measure	Illustrative Value	Interpretation
SRMR	0.061	Acceptable
NFI	0.901	Acceptable
RMS_theta	0.118	Within an acceptable range for illustration

The illustrative SRMR value of 0.061 indicates a relatively small discrepancy between the observed and model-implied correlations. The NFI value of 0.901 indicates satisfactory comparative fit. These statistics provide additional information about model adequacy, although PLS-SEM interpretation should not rely on a single global fit statistic (Table 8).

9. Discussion

This study examines the mathematical relationships between transdermal delivery and therapeutic activity in cosmetics with pharmaceutical effects by combining a mathematical diffusion model with Partial Least Squares Structural Equation Modeling (PLS-SEM) using Smart PLS software. These results provide a quantitative basis for understanding formulation properties, skin permeability, and the efficiency of transdermal delivery in multifunctional topical products. This analysis is of special interest because the effectiveness of a cosmetic product containing a biologically active ingredient depends not only on the quantity of an ingredient added to the product, but also on how much reaches the desired target area and at an appropriate concentration. The measurement model results showed good scale reliability and validity for the constructs. However, the smaller coefficient than that of the indirect pathway via skin permeability suggests that formulation properties can also affect delivery, at least partially, by altering permeability-related formulation characteristics. This observation supports the conceptual route in which formulation properties affect skin permeability, which then affects delivery efficiency. The correlation between formulation properties and the therapeutic activity was comparatively smaller ($\beta = 0.183$, $p = 0.007$). This indicates that several intermediate mechanisms contribute to therapeutic activity, and that the formulation itself is not the only factor responsible. The active must be released from the formulation, partition into the skin, penetrate the relevant layers, and be present at an effective concentration. To assess the final therapeutic or cosmetic effect, the overall pathway of therapy or cosmetic delivery must be considered. The mediation analysis also supports this interpretation. The indirect pathway model (formulation characteristics to transdermal delivery efficiency to therapeutic activity through skin permeability) was significant ($\beta = 0.247$, $p < 0.001$). This suggests a sequential process: $FC \rightarrow SP \rightarrow TD \rightarrow TA$, where FC represents formulation properties, SP skin permeability, TD transdermal delivery, and TA therapeutic activity. The outcome highlights that intermediate transport mechanisms should be considered when optimizing formulations, rather than treating formulation composition and therapeutic response as independent variables. The R^2 results provide further information about the model's ability to explain the data. The model accounted for 40.2% of the variance in skin permeability, 57.1% in transdermal delivery efficiency and 62.4% in therapeutic activity. This relatively high R^2 for therapeutic activity indicates that formulation- and delivery-related variables account for a significant share of the modeled variance in this construct. The unexplained variance, however, also shows that other factors should be considered in future investigations, such as molecular weight, lipophilicity, water content in the skin, application site, exposure time, formulation pH, and individual skin characteristics. Mathematical and SmartPLS analyses are thus complementary. While the mathematical equations reflect the physical mechanism of transport, Smart PLS allows testing multiple constructs in a statistical relationship. Fick's law, for instance, provides a mechanistic explanation for concentration-dependent diffusion, and PLS-SEM can reveal whether formulation parameters measured in the experiment are statistically significant for permeability and delivery efficiency. Together, they would provide a broader context for formulation research. In conclusion, the study shows that mathematical modeling and Smart PLS can be useful tools for studying transdermal delivery systems. The results highlight the relationship between formulation features, permeation, delivery efficiency and therapeutic activity. Future work should confirm these relationships with experimentally measured permeation data, controlled formulation studies, and relevant biological studies. This would strengthen the link between theoretical mathematical prediction, statistical modeling, and the actual performance of cosmetics with pharmaceutical benefits.

10. Conclusion

The present study attempted to establish an integrated mathematical and statistical model to analyze the transdermal delivery and therapeutic action of cosmetic products with medical effects. The investigation showed that several factors interrelated, such as formulation properties, skin permeability, diffusion phenomena, transdermal delivery efficiency, and active ingredient amount at the target site, can affect the performance of multifunctional cosmetic formulations. The

mathematical part, using Fick's laws of diffusion, provided a theoretical basis for describing the movement of the active ingredient through the skin. These correlations, respectively, between diffusion coefficient and partition coefficient, skin thickness and concentration gradient, permeability coefficient and diffusion coefficient and cumulative permeation, showed the effects of changes in formulation and skin-transport parameters on delivery. The model also set up the relationship between the concentration of the active ingredient at the target site and the therapeutic or cosmetic effect. To analyze relationships between the constructs, we used another statistical approach, Smart PLS. The illustrative structural model indicated positive relationships between formulation characteristics and skin permeability, skin permeability and transdermal delivery efficiency, and transdermal delivery efficiency and therapeutic activity. The moderately high correlation between delivery efficiency and therapeutic activity indicates that delivery and availability of active ingredients at the target location are critical. The mediation analysis also showed that formulation characteristics could have a secondary effect on therapeutic activity by influencing skin permeability and transdermal delivery efficiency.

This supports the conceptual pathway: Formulation characteristics → Skin permeability → Transdermal delivery → Therapeutic activity. The illustrative R^2 value also showed that the model explained a significant proportion of the variation between the endogenous constructs. However, these findings should be considered a methodological approach, not definitive proof of therapeutic efficacy, as the Smart PLS values were illustrative. Experimental testing is essential to conclude a specific cosmetic formulation. In conclusion, the study showed that mathematical diffusion modeling, along with structural analysis based on Smart PLS, can provide a systematic approach to understanding and optimizing cosmetic products containing pharmaceutical-benefit ingredients. This holistic approach can help researchers with formulation development, experimental design, delivery optimization, and assessing the relationship between formulation and functional properties. More laboratory research and suitably designed human trials are needed to confirm the mathematical predictions and the usefulness and safety of specific formulations.

11. Recommendations

Experimentally validate the mathematical model. Compare in situ measurements of permeability, diffusion flux, and cumulative permeation with the predictions. Use in situ skin-permeation experiments to verify the prediction. Realize Smart PLS datasets. Gather empirical data from an appropriately designed sample and replace the illustrative coefficients with the actual Smart PLS output.

- Expand the number of formulation variables: Other factors that should be taken into account for future models are active-ingredient concentration, pH, viscosity, particle size, vehicle composition, molecular weight, lipophilicity, and formulation stability. Investigate penetration-enhancement strategies. Test various formulation strategies to assess their impact on permeability and delivery efficiency while maintaining appropriate exposure control. Make multi-layer skin models. Consider future mathematical models separately to represent the stratum corneum, viable epidermis, and dermis to provide a more realistic description of transdermal transport.
- Incorporate time-dependent analysis: To examine the concentration changes with time and to predict the short-term and long-term delivery, Fick's second law and numerical simulation should be used. Discuss variations in skin. Other factors that could affect permeation and should be considered in future studies include differences in skin thickness, hydration, barrier properties, age, and anatomical location.
- Strengthen predictive analysis: Bootstrapping, PLSpredict, effect-size analysis and predictive relevance analysis are recommended to assess the robustness and predictive power of the model using SmartPLS procedures. Perform proper safety tests.
- Don't assume that high permeability is a good thing: Future research needs to determine both the bio-uptake of the active compounds in the targeted area and the possibility of off-site exposure.

12. Future Research

Future research can also study other controlled delivery technologies, such as hydrogels, lipid-based carriers, microemulsions, nanoparticles, and polymeric systems, using mathematical and experimental methods. Perform long-term validation investigations. When claiming pharmaceutical and therapeutic use, assess formulation stability, delivery consistency, biological response, and safety over appropriate time periods in extended studies. These recommendations can improve the reliability of mathematical predictions, strengthen the validity of the structural model in Smart PLS, and support the systematic development of effective and properly validated cosmetics with pharmaceutical effects.

13. References

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