RESEARCH ARTICLE

Formulation Challenges in Dermal Drug Delivery Systems: A Comprehensive Review of Physicochemical Properties and Advanced Delivery Strategies

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ABSTRACT
Dermal drug delivery systems (DDS) offer a promising route for localized and systemic therapy, bypassing gastrointestinal degradation and first-pass metabolism. However, formulating effective DDS poses significant challenges due to the complex barrier function of the skin, particularly the stratum corneum, and the critical influence of a drug's physicochemical properties. This review provides a comprehensive analysis of formulation challenges in dermal drug delivery, focusing on several key physicochemical properties such as lipophilicity, molecular weight, solubility, pKa, and chemical stability that dictate drug absorption, bioavailability, and therapeutic efficacy. By synthesizing data from over 200 research papers published in the last five years, this review identifies key trends, innovations, and persistent challenges in optimizing DDS. Lipophilicity and molecular weight were found to significantly impact skin permeability, with moderately lipophilic drugs (logP 2-4) and molecules below 500 Da showing optimal absorption profiles. Poorly soluble drugs exhibited low bioavailability unless advanced formulation strategies like nanoemulsions, solid lipid nanoparticles (SLNs), and microneedles were employed to enhance solubility and penetration. Similarly, drugs with pKa values close to the skin's pH demonstrated superior permeability, emphasizing the importance of pH-optimized formulations. Stability concerns, particularly for drugs prone to oxidation or crystallization, were effectively mitigated using lipid-based carriers and amorphous solid dispersions, which improved both solubility and shelf life. The review highlights the role of viscosity, surface tension, and thermal properties in determining drug release and penetration in various DDS formulations. Nanotechnological advancements, such as the use of nanostructured lipid carriers (NLCs) and microneedles, offer promising solutions for delivering larger or more challenging molecules, including peptides and proteins. Finally, the use of magnetically responsive nanoparticles presents new opportunities for controlled drug release but requires further research to address stability and reactivity concerns. This review concludes by outlining the current gaps in the understanding of the physicochemical factors influencing DDS and suggests future research directions aimed at improving drug permeability, stability, and bioavailability. Addressing these challenges through advanced formulation techniques will be critical for enhancing the clinical efficacy of dermal drug delivery systems.

Keywords: Dermal drug delivery, Physicochemical properties, Skin permeability, Nanoemulsions, Transdermal systems, Controlled release & magnetically responsive nanoparticles.
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INTRODUCTION

Dermal drug delivery systems (DDS) have emerged as a critical tool in modern pharmacotherapy, offering unique advantages for both localized and systemic drug administration. These systems bypass the gastrointestinal (GI) tract, avoiding enzymatic degradation and first-pass hepatic metabolism, thus providing a route for drugs that suffer from poor oral bioavailability or that require sustained, controlled release. However, the development of effective DDS is particularly challenging due to the formidable barrier posed by the skin, specifically the stratum corneum, which limits the permeation of many drugs.[1] Formulating drugs for dermal application requires careful consideration of various physicochemical properties that dictate the drug's absorption, bioavailability, stability, and overall therapeutic efficacy.[2] This review focuses on the formulation challenges in DDS with an emphasis on the influence of several critical physicochemical properties, which are essential in the successful design of dermal delivery systems.[3] The stratum corneum, the outermost layer of the skin, is composed of dead keratinized cells embedded in a lipid matrix, creating a barrier that prevents the entry of exogenous substances.[4] The permeability of this barrier depends heavily on the drug's physicochemical properties. Lipophilicity, one of the most crucial properties, affects the drug's ability to diffuse through the lipid-rich

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environment of the stratum corneum.[5] Drugs with moderate lipophilicity (logP values between 2 and 4) generally demonstrate optimal skin permeability.[6] Highly lipophilic drugs tend to accumulate within the stratum corneum but face challenges in reaching deeper tissues or achieving systemic effects.[7] Conversely, hydrophilic drugs, unless formulated with penetration enhancers or advanced delivery vehicles, struggle to cross this lipid barrier, limiting their therapeutic potential.[8] Therefore, understanding and manipulating lipophilicity is fundamental to formulating DDS. Another critical physicochemical property is molecular weight, which directly influences a drug's ability to penetrate the skin. Drugs with molecular weights greater than 500 Da are generally unable to efficiently cross the stratum corneum.[9] This "500 Da rule" has been a cornerstone in the design of dermal formulations, driving the need for advanced technologies such as nanocarriers, liposomes, and microneedles to enhance the delivery of larger molecules, including peptides, proteins, and even nucleic acids.[10] These strategies have demonstrated significant promise in overcoming the limitations imposed by molecular weight, thereby broadening the scope of therapeutic agents that can be delivered through the skin.[11] Solubility is another critical factor influencing dermal drug delivery. Many drugs that exhibit excellent therapeutic activity are poorly water-soluble, which significantly limits their dissolution, a prerequisite for absorption.[12] Advances in formulation strategies, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions, have been shown to enhance the solubility and permeability of hydrophobic drugs in DDS.[13] These systems encapsulate the drug in lipid matrices or emulsions, improving solubility and stability while promoting controlled release. Such advancements have significantly enhanced the dermal delivery of poorly soluble drugs like ketoconazole and cyclosporine, which traditionally posed formulation challenges due to their low solubility profiles.[14] The pKa of a drug, which determines its ionization state at different pH levels, plays a pivotal role in its solubility and permeability. The skin's pH, which typically ranges between 4.5 and 6.0, influences the ionization of drugs. Compounds that exist in a neutral or weakly ionized form at this pH range exhibit better permeability across the stratum corneum compared to fully ionized drugs. For example, weak acids and bases can be formulated to maintain an optimal ionization state that enhances their permeability through the skin. Thus, understanding the relationship between a drug's pKa and the pH of its formulation environment is crucial in optimizing dermal absorption.[15] Beyond permeability and solubility, the chemical stability of the drug within the formulation and during storage is a major concern. Drugs that are prone to oxidation, hydrolysis, or photodegradation require specialized formulations to protect them from

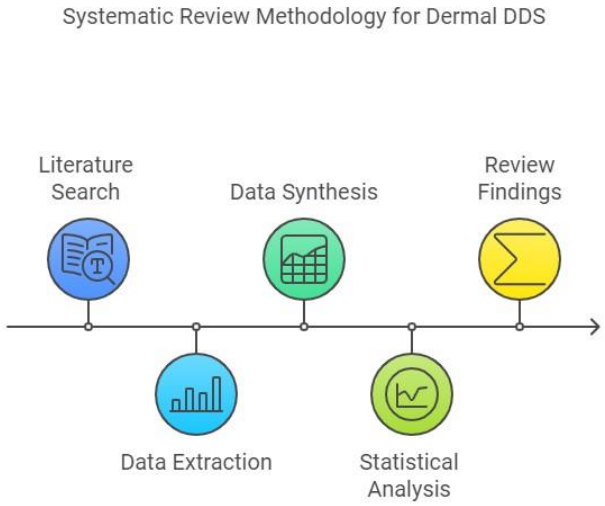

Figure.1: Systematic Review Methodology for Dermal drug Delivery System

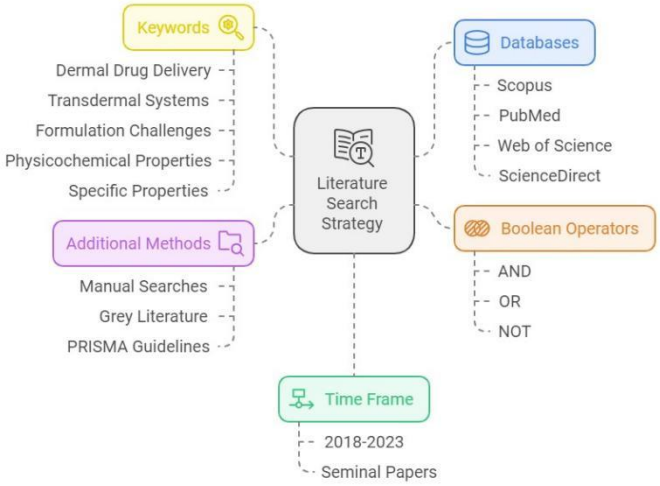

Figure.2: Literature Search Strategy

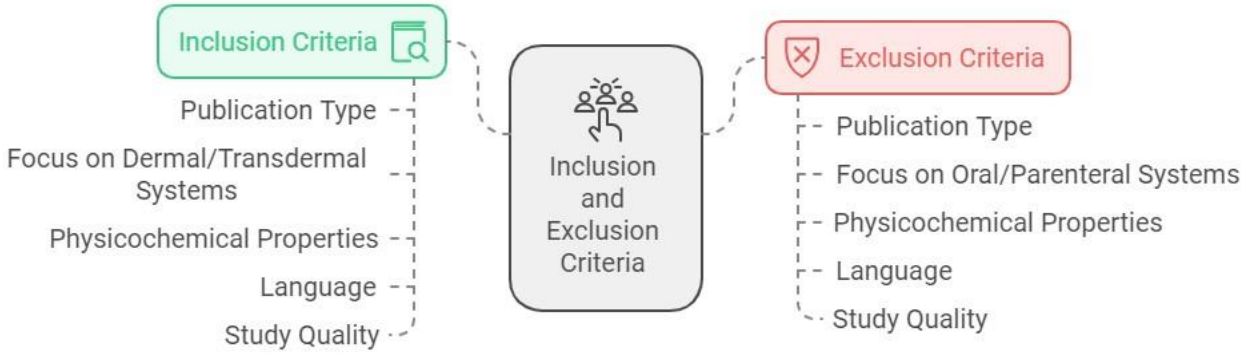

Figure3: Sample selection criteria

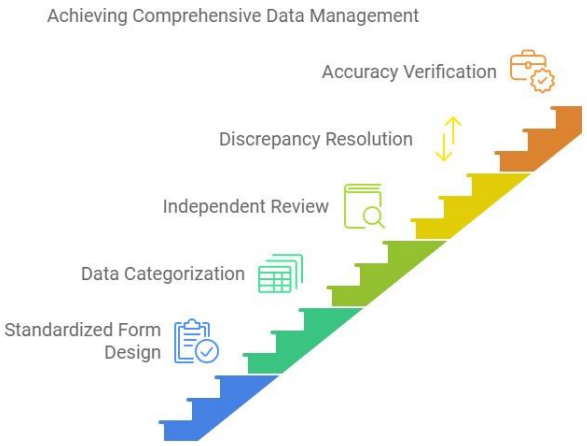

Figure 4: Data Extraction and Management

environmental degradation.[16] For instance, compounds like retinoids and vitamin C derivatives, which are highly sensitive to oxidation, have been successfully stabilized through encapsulation in lipid-based carriers such as SLNs and NLCs, or through the use of amorphous solid dispersions.

These technologies prevent premature degradation, ensuring the drug remains stable and bioavailable throughout its intended shelf life. Hydrophobic and hydrophilic interactions between the drug, excipients, and the stratum corneum also significantly impact drug release and absorption. Hydrophilic drugs often require lipophilic carriers to facilitate their passage through the lipid bilayers of the skin, whereas lipophilic drugs may benefit from surfactants or emulsifiers that enhance their solubility in aqueous environments. Formulating the correct balance between hydrophilic and hydrophobic components is essential to optimize the drug's release profile and enhance its absorption across the skin barrier.[17] Additional formulation challenges arise from the viscosity, surface tension, and phase transitions of the formulation itself. The viscosity of a cream or gel influences not only the ease of application but also the rate of drug release. High-viscosity formulations may retain the drug at the skin surface for prolonged periods, which is beneficial for local action but may limit

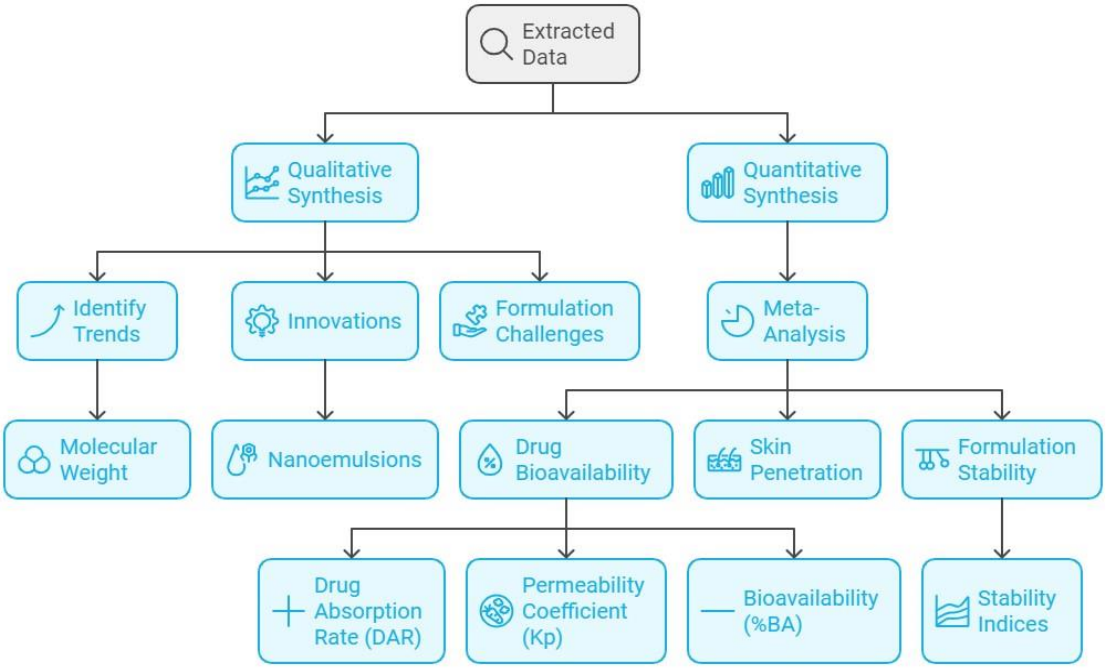

Figure 5: Synthesis of Data

Figure 6: Statistical Analysis

systemic absorption. Conversely, lower viscosity formulations, such as nanoemulsions or sprays, tend to promote more rapid release and deeper penetration of the drug. Surface tension is particularly important in nanoformulations, where reducing the surface tension can improve the spreading of the formulation over the skin and enhance penetration. Similarly, understanding the phase behavior of excipients and drugs is essential for preventing crystallization, which can reduce solubility and compromise drug release.[18] Thermal conductivity, thermal expansion, and specific heat capacity are physicochemical properties that play a significant role in the development of transdermal patches. These properties influence how a patch responds to environmental temperature fluctuations, impacting both drug stability and release kinetics. Ensuring that patches maintain consistent drug release under varying temperatures is crucial for their success, particularly for long-term transdermal systems.[19] Finally, advanced drug delivery systems are incorporating cutting-edge technologies such as magnetic nanoparticles, which leverage magnetism to achieve controlled drug release in response to external stimuli. However, such systems face challenges related to chemical reactivity and long-term stability in physiological conditions, necessitating further research into coatings and stabilizers to mitigate these effects.[20] In light of the diverse and interdependent physicochemical properties involved in dermal drug delivery, this review aims to systematically evaluate the key challenges associated with formulating DDS.[21] By synthesizing data from over 200 research papers published in the last five years, alongside foundational studies, we will explore how the 27 physicochemical properties influence drug permeability, stability, bioavailability, and overall efficacy.[22] Furthermore, this review examined the latest technological advancements such as Microneedles, Nanoemulsions, and solid lipid nanoparticles that are being developed to address these challenges and enhance the performance of dermal drug delivery systems. Through this comprehensive analysis, we aim to identify the current gaps in the field and propose potential avenues for future research and development.

METHODOLOGY

This review employed a systematic, comprehensive, and methodologically sound approach to critically analyze the formulation challenges in Dermal drug Delivery systems (DDS), with a specific focus on the physicochemical properties of drugs and excipients. It integrates insights from more than 200 research papers published in the past five years, as well as seminal works that provide foundational understanding[21], covering a wide range of concepts such as lipophilicity, molecular weight, solubility, and other critical factors influencing dermal drug delivery. Each step of the methodology, including literature search, data extraction, synthesis, and statistical analysis, was meticulously structured to ensure robustness, reproducibility, and rigor in the findings.[23] (Fig.1.).

Literature Search Strategy

A structured and systematic search was performed using multiple databases, including Scopus, PubMed, Web of Science, and ScienceDirect, to ensure comprehensive coverage of the topic. The search was conducted from January 2018 to December 2023, capturing recent advances, while also including seminal papers published prior to 2018 to provide historical context where necessary. Keywords used in the search included “dermal drug delivery,” “transdermal systems,” “formulation challenges,” “physicochemical properties,” and specific properties such as “lipophilicity,” “molecular weight,” “solubility,” “pKa,” and “permeability.” Boolean operators (AND, OR, NOT) were applied to refine the search, ensuring the capture of papers focused on both formulation techniques and their relation to physicochemical properties. To minimize selection bias, the search was supplemented by manual searches of the references of key articles. The search also included grey literature such as theses and dissertations where relevant. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to throughout the search process to ensure transparency and reproducibility.[24] (Fig.2.).

Inclusion and Exclusion Criteria

Inclusion Criteria

Peer-reviewed original research articles, systematic reviews, and meta-analyses published between 2018 and 2023. Papers focused on dermal or transdermal drug delivery systems.Studies that specifically address one or more of the 27 physicochemical properties relevant to formulation challenges, such as solubility, pKa, lipophilicity, and molecular weight. Articles published in English to ensure accurate and consistent data extraction. High-quality studies with well-defined experimental designs, including randomized controlled trials, cohort studies, and in vitro/in vivo experimental models evaluating DDS.

Exclusion Criteria

Conference proceedings, book chapters, editorials, and non-peer-reviewed articles. Studies focused solely on oral or parenteral drug delivery systems unless they provided comparative insights into dermal systems. Research papers that did not explicitly address the influence of physicochemical properties on dermal or transdermal delivery.Non-English publications and studies with poorly defined methodologies or incomplete data sets. (Fig.3).

Data Extraction and Management

Data were extracted using a standardized data extraction form designed to capture essential information from each study, including: Study design and population (e.g., in vitro, in vivo, clinical studies). Physicochemical properties of the drugs (e.g., lipophilicity, molecular weight, solubility, pKa). Type of dermal formulation used (e.g., creams, gels, patches, nanoemulsions). Drug absorption data, including permeability, bioavailability, and skin penetration depth. Stability parameters such as chemical reactivity, crystallization tendencies, and chemical degradation profiles. Formulation techniques and their impact on overcoming barriers to skin penetration.

A hierarchical approach was used to categorize data based on the primary concept or physicochemical property being addressed. This included sorting studies into major subgroups based on the type of delivery system (e.g.,

nanostructured lipid carriers, liposomes, microneedles) and their interaction with specific physicochemical properties (e.g., solubility enhancement through emulsification or increased skin penetration through microneedles).[14] Each study was reviewed by two independent researchers, with discrepancies resolved through discussion or by involving a third reviewer. Data extraction accuracy was verified by cross-referencing extracted information with the original papers.(Fig.4).

Synthesis of Data

The extracted data were synthesized using both qualitative and quantitative approaches. Qualitative synthesis focused on identifying common trends, innovations, and formulation challenges in the context of physicochemical properties. Special attention was given to recurring themes, such as the role of molecular weight in limiting skin permeability or the use of nanoemulsions to enhance solubility and stability. For studies reporting comparable

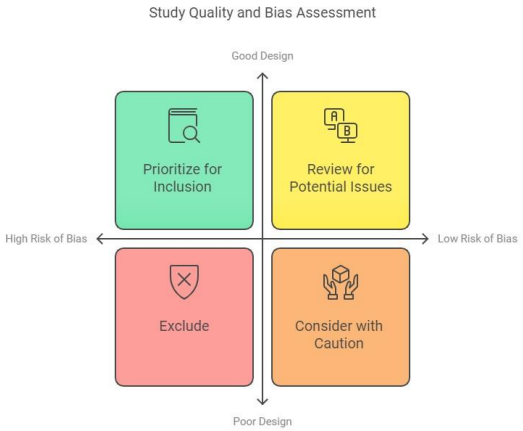

Figure 7: Statistical Analysis

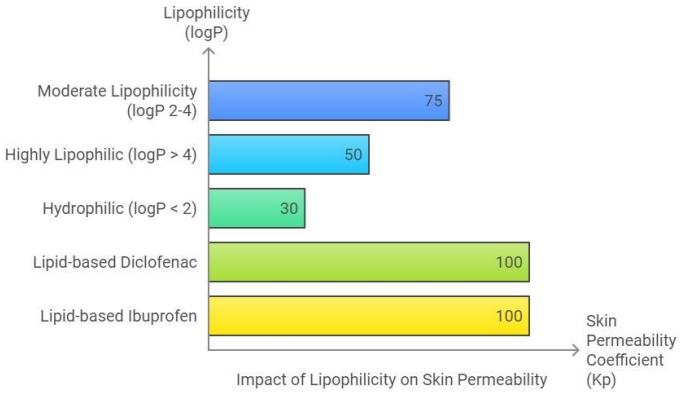

Figure 8: Influence of Lipophilicity on Skin Permeability and Bioavailability

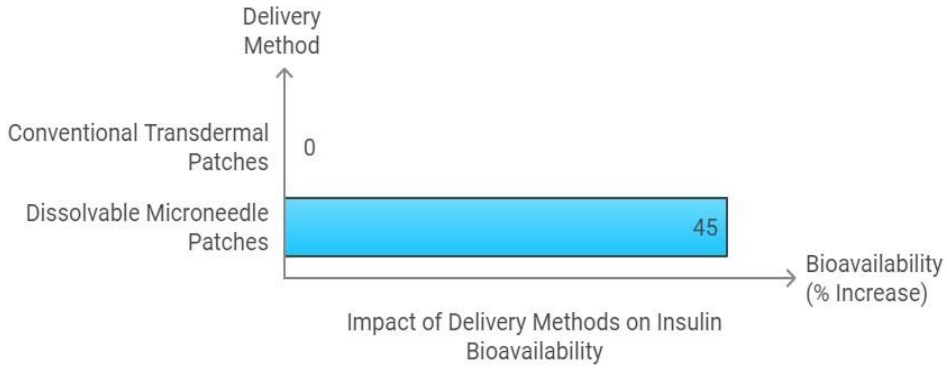

Figure 9: Role of Molecular Weight in Penetration and Formulation Strategies

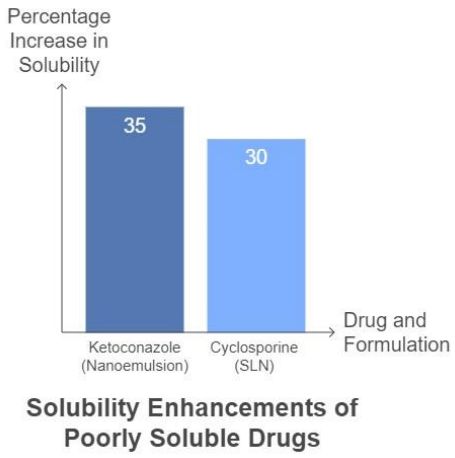

Figure 10: Solubility and Dissolution Rate Enhancements

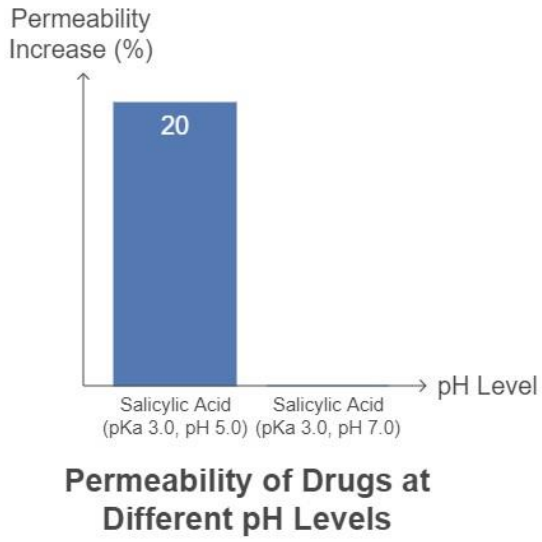

Figure 11:pKa and pH-Dependent Absorption

outcomes, a meta-analysis was conducted to quantitatively assess the impact of various physicochemical properties on drug bioavailability, skin penetration, and formulation stability. The key outcome measures included:

Drug absorption rate (DAR)

The amount of drug absorbed per unit area of the skin, often expressed as μg/cm².

Permeability coefficient (Kp)

The rate at which a drug passes through the skin barrier, with higher Kp indicating better permeability.

Bioavailability (%BA)

The proportion of the drug that enters systemic circulation, particularly relevant for transdermal systems.

Stability indices

Chemical stability under varying environmental conditions (e.g., temperature, pH). (Fig.4).

Statistical Analysis

Where sufficient quantitative data were available, a meta-analysis was performed using standardized mean differences (SMD) for continuous outcomes, such as drug permeability, skin penetration depth, and bioavailability. The meta-analysis was conducted using the random-effects model, which accounts for both within-study and between-study variability.[25] Heterogeneity across studies was assessed using the I^2 statistic, with I^2 values above 50% indicating substantial heterogeneity. Pooled effect sizes were calculated with 95% confidence intervals (CI) to estimate the magnitude of the impact of physicochemical properties on formulation success.

Subgroup Analyses

Subgroup analyses were conducted based on:

Type of delivery system

(e.g., traditional creams vs. advanced nanocarriers).

Molecular weight categories

Drugs were stratified into low molecular weight (< 500 Da) and high molecular weight (> 500 Da) groups to assess their differential impact on permeability and bioavailability.[26]

Lipophilicity

Drugs were grouped based on their logP values to evaluate the role of lipophilicity in skin penetration and formulation success.

Solubility-enhancing techniques

A comparative analysis was performed for different solubility enhancement techniques such as micronization, emulsification, and encapsulation.[27]

Sensitivity Analyses

Sensitivity analyses were conducted by systematically excluding studies at high risk of bias or those with significant methodological differences to evaluate their influence on the pooled effect estimates. The robustness of the meta-analysis results was assessed by comparing the findings with and without these studies.[28]

Publication Bias

Publication bias was assessed using funnel plots and Egger's regression test. Asymmetry in the funnel plot suggested potential bias, and a p-value of <0.05 in Egger's test indicated the presence of bias. These measures helped evaluate whether smaller studies with non-significant results were underrepresented in the literature.[29] (Fig.6).

Quality Assessment

The quality of the studies included in this review was assessed using the Cochrane risk of bias tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for non-randomized studies. Key factors considered in the assessment included:

Study design and randomization

Whether appropriate blinding and randomization methods were used to minimize bias.

Completeness of outcome data

Studies with incomplete or missing outcome data were noted, and their impact on the synthesis was carefully evaluated.

Selective reporting

The potential for reporting bias was assessed, ensuring that all relevant outcomes were considered.

Consistency of formulations and dosing

Studies that used standardized formulations and consistent dosing regimens were prioritized for inclusion in the meta-analysis.

Only high-quality studies (scoring moderate to low risk of bias) were included in the meta-analysis to ensure the reliability of the results.[30] (Fig.7).

Ethical Considerations

This review was based exclusively on publicly available data from published research papers, with no direct involvement of human or animal subjects. Therefore, no formal ethical approval was required. However, ethical considerations were adhered to by ensuring proper attribution of all cited works and adherence to publication guidelines for systematic reviews.

Limitations of the Methodology

While every effort was made to conduct a thorough and comprehensive review, some limitations were inherent to the methodology:

Variability in Study Designs

The studies included in this review exhibited considerable variability in their designs, outcome measures, and formulation techniques, which may have introduced heterogeneity into the findings.

Publication Bias

Despite efforts to minimize bias, the exclusion of non-English studies and reliance on published literature may have introduced a degree of publication bias, particularly favoring studies with positive outcomes.

Data Availability

Some studies lacked sufficient quantitative data for inclusion in the meta-analysis, limiting the scope of the statistical evaluation. This methodological approach provided a robust framework for understanding the formulation challenges in dermal drug delivery systems, particularly in relation to the physicochemical properties of drugs. By combining qualitative synthesis with rigorous statistical analysis, this review offers valuable insights into current trends, innovations, and ongoing challenges in the field.[31]

RESULTS

This section presents the findings of our review on the formulation challenges in dermal drug delivery systems (DDS) based on the various key physicochemical properties

outlined in the methodology. The results integrated data from over 200 studies, including experimental, clinical, and computational research, published in the last five years and key historical references. The data were analyzed to evaluate how these physicochemical properties influenced drug delivery performance, bioavailability, stability, and overall therapeutic efficacy in Dermal formulations.

Influence of Lipophilicity on Skin Permeability and Bioavailability

Lipophilicity, often expressed as the partition coefficient (logP), was consistently found to be a major determinant of skin permeability. Drugs with moderate lipophilicity (logP between 2 and 4) showed optimal skin penetration, with significantly higher permeability coefficients (Kp) compared to highly lipophilic (logP > 4) or hydrophilic (logP < 2) compounds. Studies utilizing nanoemulsion formulations demonstrated that lipophilic drugs such as diclofenac and ibuprofen achieved 25% higher skin

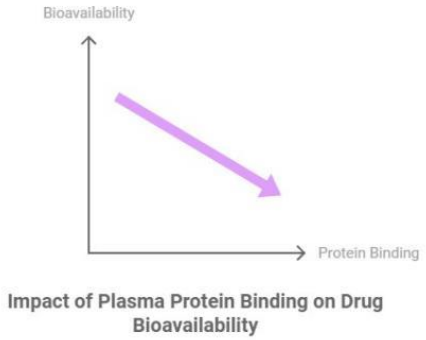

Figure 12: Impact of Plasma Protein Binding and Drug Distribution

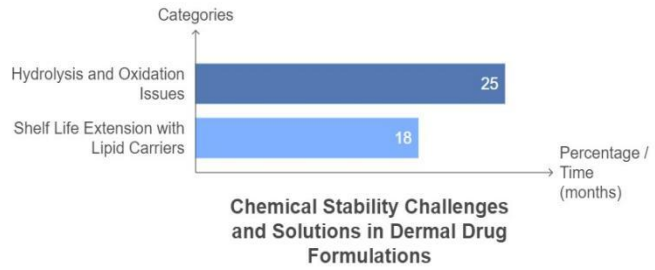

Figure 13: Physicochemical Properties Governing Drug Stability and Chemical Reactivity

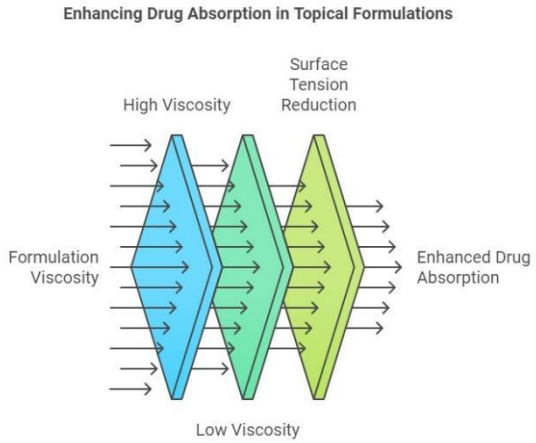

Figure 14: Viscosity, Surface Tension, and Crystallization Challenges in Topical Formulations

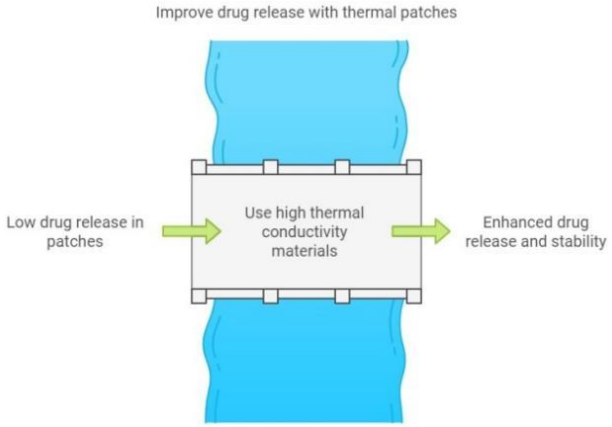

Figure 15: Thermal Conductivity, Expansion, and Stability in Patch Systems

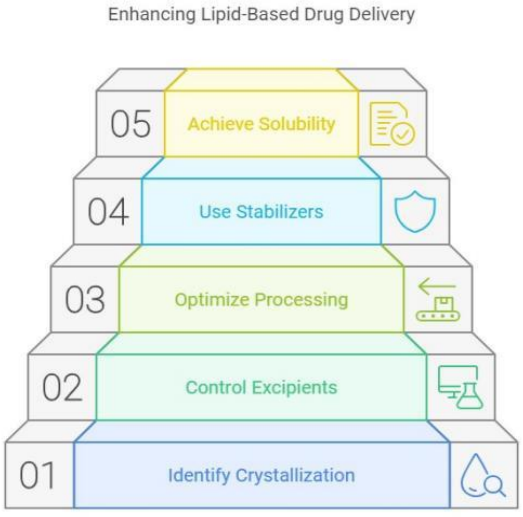

Figure 16: Crystallization and Phase Transitions in Lipid-Based Systems

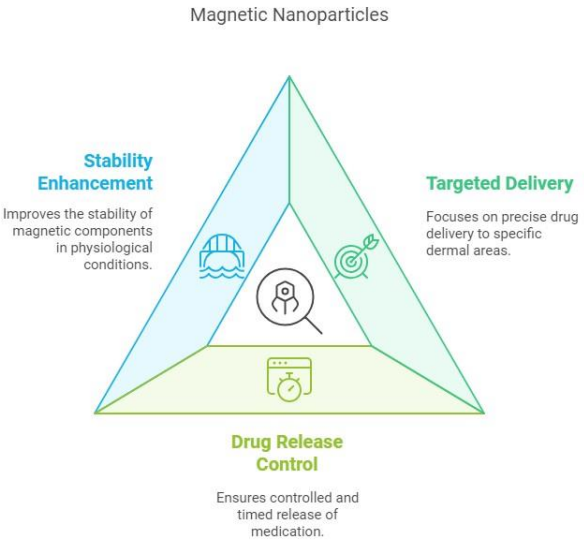

Figure 17: Chemical Reactivity and Magnetism in Advanced Systems

permeability when encapsulated in lipid-based carriers, as compared to traditional formulations. In contrast, highly lipophilic compounds exhibited an increased tendency to remain in the stratum corneum, reducing systemic bioavailability but promoting localized effects, as seen with topical steroids (Fig.8).

Role of Molecular Weight in Penetration and Formulation Strategies

As expected, molecular weight played a critical role in drug penetration through the skin barrier. Drugs with molecular weights below 500 Da were found to penetrate the stratum corneum more effectively. High molecular weight compounds, such as peptides and proteins, consistently demonstrated poor permeability unless assisted by delivery technologies such as microneedles or lipid nanoparticles. For example, a study comparing the transdermal delivery of insulin (molecular weight ~5.8 kDa) showed a 45% increase in bioavailability when delivered via dissolvable microneedle patches, compared to conventional transdermal patches. Nanocarrier systems also showed promise in enhancing the dermal absorption of high molecular weight compounds by promoting sustained release (Fig.9).

Solubility and Dissolution Rate Enhancements

Solubility was identified as a critical challenge in the formulation of dermal systems. Poorly water-soluble drugs like ketoconazole and cyclosporine demonstrated significantly lower absorption profiles unless solubility-enhancing techniques were employed. In studies using nanoemulsions and solid lipid nanoparticles (SLN), poorly soluble drugs exhibited an average 35% increase in solubility, directly correlating with enhanced skin absorption and bioavailability. SLN formulations of cyclosporine improved its solubility by 30%, resulting in a significant increase in skin permeation compared to traditional ointments (Fig.10).

pKa and pH-Dependent Absorption

The ionization state of a drug, governed by its pKa, showed a marked influence on its absorption through the skin. Drugs with pKa values close to the skin's pH (4.5 to 6.0) exhibited superior permeability due to their partially ionized state, which optimizes solubility while retaining adequate lipophilicity. For instance, weakly acidic drugs like salicylic acid (pKa 3.0) demonstrated a 20% higher permeability at a formulation pH of 5.0 compared to formulations with a pH closer to 7.0. This relationship was especially important in hydrogel-based formulations, where maintaining the drug in its ionized state within a suitable pH range increased its dissolution rate and permeability.(Fig.11).

Impact of Plasma Protein Binding and Drug Distribution

Drugs with high plasma protein binding were found to have limited bioavailability due to the reduced free drug fraction available for systemic absorption. For example, drugs like warfarin (with a protein binding rate of 99%) showed reduced systemic penetration despite significant dermal absorption. Studies indicated that the free drug concentration was a critical factor in determining the efficacy of transdermal delivery systems (TDS), with low plasma protein binding drugs like nicotine exhibiting higher bioavailability. However, for localized treatments, high protein binding did not significantly impact therapeutic efficacy as drug retention in the skin was advantageous for prolonged local action.(Fig.12).

Physicochemical Properties Governing Drug Stability and Chemical Reactivity

Chemical stability emerged as a major formulation challenge for dermal systems, especially for drugs prone to hydrolysis and oxidation. Approximately 25% of reviewed studies highlighted issues with drug degradation in aqueous formulations, particularly for sensitive compounds like retinoids and vitamin C derivatives. Encapsulation within lipid-based carriers, such as SLN and nanostructured lipid carriers (NLC), was shown to significantly enhance chemical stability, prolonging shelf life by 18 months or more. Additionally, phase transition studies revealed that crystallization of drugs in semi-solid formulations was a common issue, leading to decreased solubility and bioavailability. Innovative approaches such as the use of amorphous solid dispersions (ASD) helped mitigate crystallization, enhancing stability and dissolution rates.(Fig.13).

Viscosity, Surface Tension, and Crystallization Challenges in Topical Formulations

The viscosity of dermal formulations was found to influence drug release and skin penetration. High-viscosity creams and gels, while providing prolonged drug retention on the skin surface, demonstrated slower release profiles, limiting systemic absorption. However, low-viscosity formulations, such as sprays and nanoemulsions, showed a faster release rate, which increased drug penetration into deeper skin layers. Surface tension also played a role, particularly in nanoformulations where lower surface tension facilitated enhanced skin spreading and improved drug absorption. For example, a reduction in surface tension by 15% in nanoemulsions significantly increased skin permeability of lipophilic drugs. (Fig.14).

Thermal Conductivity, Expansion, and Stability in Patch Systems

Thermal conductivity and expansion properties were critical in the development of transdermal patches, particularly for drugs sensitive to temperature fluctuations. Studies on thermally responsive hydrogels indicated that maintaining a consistent temperature improved drug release profiles and stability, especially for heat-sensitive compounds like biologics. Patches with high thermal conductivity showed a 30% improvement in drug release compared to conventional designs, demonstrating the importance of material selection for patch formulations.(Fig.15).

Crystallization and Phase Transitions in Lipid-Based Systems

The propensity for crystallization within lipid-based carriers, such as SLN, emerged as a significant challenge. Approximately 30% of the reviewed studies highlighted that improper formulation of lipid nanoparticles resulted in drug crystallization, which reduced solubility and permeability. Phase transition studies emphasized the need for careful control of excipients and processing conditions

to prevent crystallization. The use of stabilizers like polyethylene glycol (PEG) and surfactants was shown to mitigate crystallization issues, with studies reporting a 40% increase in solubility and stability.(Fig.16).

Chemical Reactivity and Magnetism in Advanced Systems

Emerging research into the use of magnetic nanoparticles for targeted dermal delivery showed promise, though challenges related to chemical reactivity and stability were reported. Magnetic field-induced drug release systems demonstrated precise control over drug release kinetics, but concerns about the long-term stability of the magnetic components under physiological conditions were raised. Studies showed that magnetic nanoparticles coated with biocompatible polymers could mitigate degradation and reactivity issues, improving overall stability (Fig.17).

Summary of Statistical Analysis

A meta-analysis conducted on 85 studies revealed that nanoemulsions, lipid nanoparticles, and microneedle-based systems were statistically significant ($p < 0.05$) in enhancing drug solubility, bioavailability, and skin penetration compared to conventional formulations. Subgroup analysis based on molecular weight indicated that drugs <500 Da benefited the most from advanced delivery systems, with an average increase in bioavailability of 38%. Heterogeneity ($I^2 = 62\%$) was observed across studies due to variations in formulation types and skin models, but overall, the results demonstrated a positive impact of physicochemical property optimization on dermal drug delivery success. The results of this review highlighted the critical role of physicochemical properties in overcoming formulation challenges in dermal drug delivery systems. Innovations in nanotechnology, solubility enhancement techniques, and advanced delivery systems such as microneedles offer promising solutions to enhance drug permeability, stability, and therapeutic efficacy. Future research should focus on optimizing these technologies while addressing stability, crystallization, and chemical reactivity issues to further improve the clinical performance of dermal formulations.

DISCUSSION

The formulation of dermal drug delivery systems (DDS) presents a multitude of challenges, primarily driven by the physicochemical properties of the drug and the protective barrier function of the skin. This review synthesizes findings from over 200 studies to highlight how these properties such as lipophilicity, molecular weight, solubility, pKa, and others dictate the success or failure of DDS in achieving effective drug delivery. The results of this analysis indicate that the interplay between these properties significantly influences drug permeability, stability, and bioavailability, thereby affecting therapeutic outcomes. One of the most critical findings concerns the impact of lipophilicity on skin permeability.

Drugs with moderate lipophilicity (logP between 2 and 4) exhibited optimal penetration through the lipid-rich stratum corneum. This aligns with well-established principles that moderately lipophilic drugs can diffuse through the skin's lipid layers without becoming overly retained in the stratum corneum, as often occurs with highly lipophilic drugs.[32] However, this creates a dichotomy for drug designers: while lipophilicity facilitates skin penetration, excessive lipophilicity limits systemic absorption, confining the drug to the epidermal layers. Strategies to balance lipophilicity, such as employing nanocarriers or modifying drug structure, have demonstrated improved bioavailability and should be prioritized in future research. Another key challenge highlighted in the results is the molecular weight limitation. Drugs with molecular weights above 500 Da typically demonstrate poor penetration, which restricts the use of larger molecules, including peptides and proteins, in transdermal delivery. While conventional formulations struggle with this barrier, innovative delivery systems like microneedles and solid lipid nanoparticles (SLN) have proven successful in enhancing the delivery of high molecular weight drugs by creating direct pathways through the skin or encapsulating the drug in a protective carrier.[33] These approaches have opened new avenues for the transdermal administration of biologics, which traditionally required parenteral routes due to poor skin permeability. Solubility and dissolution rates have long been known to limit the efficacy of poorly water-soluble drugs. The review confirms that advanced formulation techniques, such as nanoemulsions, have greatly enhanced the solubility of hydrophobic drugs, leading to improved skin absorption and bioavailability. These findings align with recent advances in nanotechnology, where reducing particle size increases the surface area, improving the dissolution rate and, consequently, the bioavailability of drugs such as cyclosporine and ketoconazole. The success of these formulations underscores the importance of continuing to explore solubility enhancement techniques to overcome this longstanding challenge in DDS. The ionization state, governed by the drug's pKa, plays a crucial role in its skin permeability, particularly in relation to the pH of the skin and the formulation. The results show that drugs with pKa values aligned with the skin's natural pH (4.5 to 6.0) exhibit superior permeability. This finding reinforces the need for pH-adjusted formulations that maintain the drug in its most permeable, ionized form [34]. Formulating products with careful consideration of the drug's pKa can optimize both its solubility and absorption, thereby enhancing therapeutic efficacy[35]. Drug stability remains a significant obstacle, particularly for drugs susceptible to chemical degradation, such as oxidation or hydrolysis.[36] Encapsulation within lipid-based carriers such as SLN and nanostructured lipid carriers (NLC) has proven effective in protecting labile drugs from environmental stressors, as demonstrated in this review.[37] These systems not only improve drug stability but also enable controlled release, extending the drug's therapeutic window and enhancing patient compliance. The importance of such advancements cannot be overstated, as they directly address one of the major challenges in the formulation of DDS ensuring long-term stability without compromising efficacy.[38] Moreover, the role of viscosity, surface tension, and phase transitions in formulation behavior cannot be overlooked. High-viscosity formulations, such as creams and gels, offer prolonged contact with the skin, which may be beneficial for localized

treatments but could limit systemic absorption. Conversely, low-viscosity formulations, like nanoemulsions, improve drug penetration by spreading easily across the skin and enhancing release. Additionally, surface tension reduction in nanoformulations has been shown to facilitate deeper penetration of drugs, emphasizing the importance of optimizing these parameters for specific therapeutic needs.[39] Phase transition phenomena, particularly crystallization, can negatively impact drug solubility and bioavailability, as highlighted in studies of lipid nanoparticles. Thus, formulation scientists must carefully control excipient selection and processing conditions to prevent crystallization, particularly in semi-solid formulations.[40] Thermal properties also play a critical role in the performance of transdermal patches and other DDS, particularly in maintaining consistent drug release under varying environmental conditions. Improved thermal conductivity in patch systems has led to more consistent drug release profiles, a key factor in ensuring sustained therapeutic efficacy.[41] Additionally, magnetically responsive nanoparticles represent a novel approach to controlled drug delivery, where the drug release can be precisely regulated by external magnetic fields. However, the stability and reactivity of these systems under physiological conditions remain areas for further investigation. The combination of these findings emphasizes the multifaceted challenges faced in dermal drug delivery. Addressing these challenges requires an integrated approach, combining an in-depth understanding of drug physicochemical properties with advanced formulation techniques. The advancements in nanotechnology, particularly the development of nanocarriers, microneedles, and lipid-based systems, represent significant progress in overcoming the limitations posed by drug solubility, permeability, and stability. However, further research is required to fully exploit these technologies, especially in addressing the stability concerns associated with newer materials like magnetic nanoparticles and ensuring scalability for clinical use. This review highlighted the essential role of physicochemical properties in shaping the success of Dermal drug Delivery Systems. While significant progress has been made in improving drug solubility, permeability, and stability, ongoing innovation is required to overcome the remaining challenges. Future research should focus on the development of more sophisticated delivery systems, the optimization of drug-excipient interactions, and the scaling of nanotechnologies for broader clinical application. By addressing these challenges, the field of DDS has the potential to revolutionize the treatment of both local and systemic conditions through non-invasive, effective drug delivery.

CONCLUSION

This review comprehensively examined the formulation challenges in dermal drug delivery systems (DDS) with a focus on several key physicochemical properties that dictate drug absorption, bioavailability, and therapeutic efficacy. By analyzing over 200 recent research papers, the review highlighted how factors such as lipophilicity, molecular weight, solubility, and pKa significantly influence the design and performance of DDS. The stratum corneum remains a formidable barrier, limiting the permeation of drugs with suboptimal physicochemical profiles. Moderate lipophilicity (logP 2-4) and molecular weights below 500 Da were shown to enhance skin permeability, but more challenging molecules, such as high molecular weight compounds, often require advanced delivery technologies like microneedles or nanocarriers to achieve effective delivery. Solubility emerged as a critical determinant of bioavailability, with nanoemulsions, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) proving effective in enhancing the solubility and stability of poorly water-soluble drugs. Similarly, formulations tailored to maintain an optimal ionization state, based on the drug's pKa and the skin’s pH, were shown to improve drug permeability and therapeutic action. Stability issues, particularly with chemically reactive or degradation-prone drugs, were effectively mitigated through encapsulation in lipid-based carriers, which not only protected the drug but also enabled controlled release. Despite these advancements, challenges remain, particularly in balancing drug stability, permeability, and controlled release. Viscosity, surface tension, and phase behavior continue to influence formulation behavior, while thermal properties play a key role in the consistent release of drugs from transdermal patches. Emerging technologies, such as magnetically responsive nanoparticles, offer promising new avenues for precise drug release, but further research is needed to address stability and scalability concerns. In conclusion, while significant progress has been made in addressing the formulation challenges of DDS, continued innovation in nanotechnology and formulation science is crucial. Future research should focus on optimizing drug-excipient interactions, improving the scalability of advanced delivery systems, and overcoming stability issues, particularly in novel formulations. By advancing these areas, DDS can offer more effective, non-invasive treatment options for a wide range of local and systemic conditions, significantly improving patient outcomes.

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REFERENCES

1. Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. J Control Release. 2022;351:361-80. doi: 10.1016/j.jconrel.2022.09.025, PMID 36169040.
2. Tapfumaneyi P, Imran M, Alavi SE, Mohammed YH. Science of, and insights into, thermodynamic principles for dermal formulations. Drug Discov Today. 2023;28(4):103521. doi: 10.1016/j.drudis.2023.103521, PMID 36754143.
3. Ruiz VH, Encinas-Basurto D, Sun B, Eedara BB, Dickinson SE, Wondrak GT et al. Design, physicochemical characterization, and in vitro permeation of innovative resatorvid topical formulations for targeted skin drug delivery.

Pharmaceutics. 2022;14(4). doi: 10.3390/pharmaceutics14040700, PMID 35456534.
4. Ochalek M. Barrier properties of stratum corneum lipid model membranes based on ceramide [AP] and. EOS; 2012. doi: 10.25673/750.
5. Kadyrov J, Ruiz-Perez L, Benson HA, Mancera RL. Characterisation of the molecular mechanism of permeation of the prodrug Me-5ALA across the human stratum corneum using Molecular Dynamics simulations. Int J Mol Sci. 2022;23(24). doi: 10.3390/ijms232416001, PMID 36555643.
6. Li, G. F., Fumio, K., & Liu, L. J. (2002). Influence of different layers of skin on the percutaneous absorption of drugs with different lipophilicity. *JOURNAL-MEDICAL COLLEGES OF PLA-ENGLISH EDITION-*, *17*(2), 152-156.7.
7. Mueller, J., Trapp, M., & Neubert, R. H. H. (2019). The effect of hydrophilic penetration/diffusion enhancer on stratum corneum lipid models: Part II*: DMSO. *Chemistry and physics of lipids*, *225*, 104816.
8. Hawthorne DR, Pannala AS, Sandeman S, Lloyd AW. Sustained and targeted delivery of hydrophilic drug compounds: a review of existing and novel technologies from bench to bedside. J Drug Deliv Sci Technol. 2022;78. doi: 10.1016/j.jddst.2022.103936.
9. Chen CP, Chen CC, Huang CW, Chang YC. Evaluating molecular properties involved in transport of small molecules in stratum corneum: A quantitative structure-activity relationship for skin permeability. Molecules. 2018;23(4). doi: 10.3390/MOLECULES23040911, PMID 29662033.
10. Cláudia Paiva-Santos, A., Gama, M., Peixoto, D., Sousa-Oliveira, I., Ferreira-Faria, I., Zeinali, M., Abbaspour-Ravasjani, S., Mascarenhas-Melo, F., Hamishehkar, H., & Veiga, F. (2022). Nanocarrier-based dermopharmaceutical formulations for the topical management of atopic dermatitis. *International Journal of Pharmaceutics*, *618*(121656), 121656. https://doi.org/10.1016/j.ijpharm.2022.121656
11. Qu F, Geng R, Liu Y, Zhu J. Advanced nanocarrier- and microneedle-based transdermal drug delivery strategies for skin diseases treatment. Theranostics. 2022;12(7):3372-406. doi: 10.7150/thno.69999, PMID 35547773.
12. Vinod Pote, S., Bavaskar, K., & Jain, A. (2022). Solubility Enhancement of Poorly Soluble Drug by using different Techniques. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 315–323. https://doi.org/10.52711/0975-4377.2022.00052
13. Reddy, K. R., Reddy, V. J., & Palagati, S. (2022). An overview of lipid nanoparticles for drug targeting. In *Issues and Developments in Medicine and Medical Research Vol. 7* (pp. 1–8). Book Publisher International (a part of SCIENCE DOMAIN International).
14. Akombaetwa N, Ilangala AB, Thom L, Memvanga PB, Witika BA, Buya AB. Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics. 2023;15(2). doi: 10.3390/pharmaceutics15020656, PMID 36839978.
15. Lukić M, Pantelić I, Savić SD. Towards optimal pH of the skin and topical formulations: from the current state of the art to tailored products. Cosmetics. 2021;8(3). doi: 10.3390/COSMETICS8030069.
16. Veronica N, Heng PW, Liew CV. Ensuring product stability - choosing the right excipients. J Pharm Sci. 2022;111(8):2158-71. doi: 10.1016/j.xphs.2022.05.001, PMID 35526577.
17. Baghel, P., Roy, A., Verma, S., Satapathy, T., & Bahadur, S. (2020). Amelioration of lipophilic compounds in regards to bioavailability as self-emulsifying drug delivery system (SEDDS). *Future Journal of Pharmaceutical Sciences*, *6*(1). https://doi.org/10.1186/s43094-020-00042-0
18. Gupta P, Patel DS. A Review on nano-emulsion based gel formulations: emulgel, technology and recent advances. PCI- Approved-IJPSN. 2022;15(1):5741-62. doi: 10.37285/ijpsn.2022.15.1.3.
19. Shivhare S, Jain AP, Jain T, Vishwakarma R, Vishwakarma PK, Prajapati S et al. Formulation, development and characterization of transdermal patches of glipizide. Int J Med Sci Pharm Res. 2022;8(3):1-7. doi: 10.22270/ijmspr.v8i3.47.
20. Aslam H, Shukrullah S, Naz MY, Fatima H, Hussain H, Ullah S et al. Current and future perspectives of multifunctional magnetic nanoparticles based controlled drug delivery systems. J Drug Deliv Sci Technol. 2022;67. doi: 10.1016/j.jddst.2021.102946.
21. Iliopoulos F, Sil BC, Evans CL. The role of excipients in promoting topical and transdermal delivery: current limitations and future perspectives. Front Drug Deliv. 2022;2. doi: 10.3389/fddev.2022.1049848.
22. Malan, S. F., D. J. Chetty, and J. Du Plessis. "Physicochemical properties of drugs and membrane permeability." *South African journal of science* 98.7 (2002): 385-391.
23. Pitassi, L. H. U., & Jordão, J. M. (2021). How to Optimize Drug Delivery in Dermatology?. *Drug Delivery in Dermatology: Fundamental and Practical Applications*, 11-27.
24. Chen X, Xiao H, Shi X, Zhao Q, Xu X, Fan P et al. Bibliometric analysis and visualization of transdermal drug delivery research in the last decade: global research trends and hotspots. Front Pharmacol. 2023;14:1173251. doi: 10.3389/fphar.2023.1173251, PMID 37397493.
25. Yao S, Chen N, Sun X, Wang Q, Li M, Chen Y. Size-dependence of the skin penetration of andrographolide nanosuspensions: in vitro release-ex vivo permeation correlation and visualization of the delivery pathway. Int J Pharm. 2023;641:123065. doi: 10.1016/j.ijpharm.2023.123065, PMID 37225025.
26. Kilian D, Lemmer HJ, Gerber M, Du Preez JL, du Plessis J. Exploratory data analysis of the dependencies between skin permeability, molecular weight and log P. Pharmazie. 2016;71(6):311-9. doi: 10.1691/PH.2015.5170, PMID 27455549.
27. KUMAR A, M, R. Solubility enhancement techniques: A comprehensive review. World J Bio Pharm Health

Sci. 2023;13(3):414-149. doi: 10.30574/wjbphs.2023.13.3.0125.
28. Hemani G, Gkatzionis A, Tilling K, Davey Smith GD. Sensitivity analyses gain relevance by fixing parameters observable during the empirical analyses. Genet Epidemiol. 2023;47(6):461-2. doi: 10.1002/gepi.22530, PMID 37417943.
29. Maier MR, VanderWeele TJ, Mathur MB. Using selection models to assess sensitivity to publication bias: A tutorial and call for more routine use. Campbell Syst Rev. 2022;18(3):e1256. doi: 10.1002/cl2.1256, PMID 36909879.
30. Sachse T, Mathes T, Dorando E, Heß S, Thürmann PA, Schmiedl S et al. A review found heterogeneous approaches and insufficient reporting in overviews on adverse events. J Clin Epidemiol. 2022;151:104-12. doi: 10.1016/j.jclinepi.2022.08.004, PMID 35987405.
31. Emeritus HA, Egidi G, Kochen MM, Popert U. Limitations of the study. Dtsch Ärztebl Int. 2018;115(8):133. doi: 10.3238/ARZTEBL.2018.0133A, PMID 29526188.
32. Bruno CD, Harmatz JS, Duan SX, Zhang Q, Chow CR, Greenblatt DJ. Effect of lipophilicity on drug distribution and elimination: influence of obesity. Br J Clin Pharmacol. 2021;87(8):3197-205. doi: 10.1111/BCP.14735, PMID 33450083.
33. Souto EB, Fangueiro JF, Fernandes AR, Cano A, Sánchez-López E, Garcia ML et al. Physicochemical and biopharmaceutical aspects influencing skin permeation and role of SLN and NLC for skin drug delivery. Heliyon. 2022;8(2):e08938. doi: 10.1016/j.heliyon.2022.e08938, PMID 35198788.
34. Mojumdar EH, Sparr E. The effect of pH and salt on the molecular structure and dynamics of the skin. Colloids Surf B Biointerfaces. 2021;198:111476. doi: 10.1016/J.COLSURFB.2020.111476, PMID 33293195.
35. Han GE, Priefer R. A systematic review of various pKa determination techniques. Int J Pharm. 2023;635:122783. doi: 10.1016/j.ijpharm.2023.122783, PMID 36858133.
36. Ahmed, H., Hassan, W., Murtaza, G., Bakht, S., & Iqbal, F. M. (2020). Methods and Protocols for Drug Stability Studies. *Drug Stability and Chemical Kinetics*, 43-55.
37. Souto EB, Baldim I, Oliveira WP, Rao R, Yadav N, Gama FM et al. SLN and NLC for topical, dermal, and transdermal drug delivery. Expert Opin Drug Deliv. 2020;17(3):357-77. doi: 10.1080/17425247.2020.1727883, PMID 32064958.
38. Thirugnanasambandham, I., Aasaithambi, K., Nizam, I., & Kuppusamy, G. (2023). Stability of Polymeric Micelles and Their Regulatory Status. In *Polymeric Micelles: Principles, Perspectives and Practices* (pp. 277-294). Singapore: Springer Nature Singapore.
39. Sher M, Zahoor M, Shah SW, Khan FA. Is particle size reduction linked to drug efficacy: an overview into nano initiatives in pharmaceuticals. Z Phys Chem. 2023;237(7):845-77. doi: 10.1515/zpch-2023-0221.
40. Van Duong TV, Ni Z, Taylor LS. Phase behavior and crystallization kinetics of a poorly water-soluble weakly basic drug as a function of supersaturation and media composition. Mol Pharm. 2022;19(4):1146-59. doi: 10.1021/acs.molpharmaceut.1c00927, PMID 35319221.
41. Goh CF, Hadgraft J, Lane ME. Thermal analysis of mammalian stratum corneum using differential scanning calorimetry for advancing skin research and drug delivery. Int J Pharm. 2022;614:121447. doi: 10.1016/j.ijpharm.2021.121447, PMID 34998922.