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Skin Models for Nanoemulgel Permeation: An Overview of Current Practices

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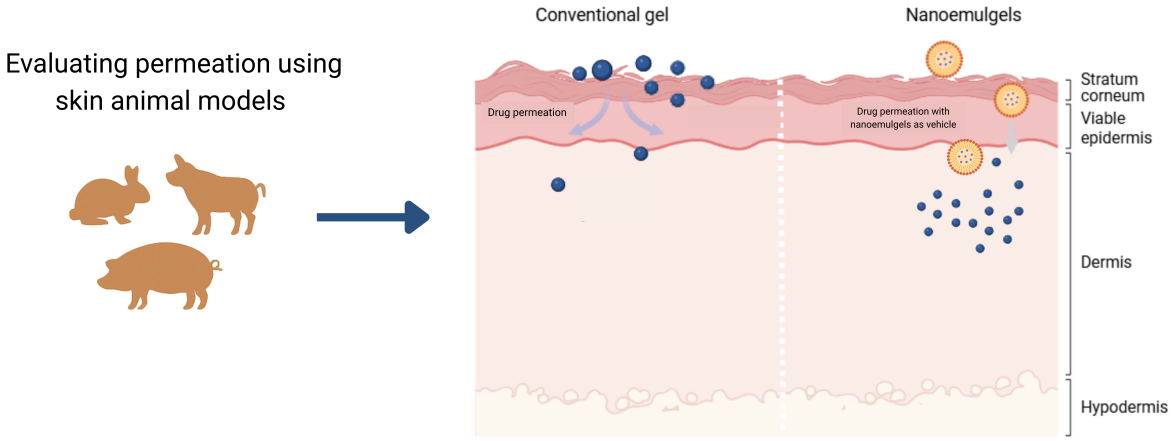
Graphical Abstract



Abstract

Transdermal drug delivery systems are gaining increasing interest due to their ability to bypass first-pass metabolism in the liver and provide better patient compliance while delivering drugs through a controlled-release mechanism. The outermost layer of human skin, known as the stratum corneum, creates a barrier to drug absorption that has proven challenging for water-soluble drugs and large molecules, including natural product compounds. The combination of nanoemulsion characteristics with hydrogel properties in nanoemulgels formulations serves as a novel method to enhance transdermal drug delivery. This review aims to evaluate the permeation efficacy of nanoemulgel systems in animal skin models. To do that, it evaluates nineteen studies examining how different skin structures affect drug permeation outcomes. Nanoemulgels formulations demonstrated superior results compared to traditional gels when combined with penetration enhancers such as clove oil or eucalyptus oil, according to the reviewed studies. These findings highlight the significance of model selection in permeation studies and demonstrate that nanoemulgels are promising vehicles for transdermal drug delivery. Animal skin permeation test results exhibit a similar pattern to those obtained from in vivo studies. However, differences in human skin make these results inapplicable to humans, requiring a thorough examination of differences.

Keywords: Skin, nanoemulgel, permeation, transdermal, ex vivo

Purpose, Rationale, and Limitations

Transdermal delivery of drugs continues to be a technical challenge, especially for poorly soluble drugs to penetrate the skin barrier [1,2]. Maintaining zero-order release kinetics, in which the drug is released at a constant rate independent of concentration, is essential for achieving consistent therapeutic dose levels and for minimizing side effects. Nevertheless, the protein concentration necessary to achieve suf-

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ficient shelf life for traditional transdermal delivery system preparations may exceed that required for pharmacological activity [1]. Nanoemulgel formulations are investigated to enhance transdermal drug permeation, addressing a market need.

In this review, the author summarizes the potential efficiency of nanoemulgel systems for the improvement of transdermal drug permeation, using selected studies involving different classes of active and skin models. The review provides a comprehensive perspective on optimizing formulation variables for extended therapeutic applications by summarizing evidence from various studies. One major limitation is that the study designs and drugs are diverse, which may lead to results that might not be comparable. Further studies will have to focus on these challenges to improve the relevance for human skin.

Introduction

The epidermis is a highly specialized, protective shield that minimizes water loss and protects against the environment. The outermost skin layer, stratum corneum (SC), is formed by dehydrated keratinized cells that are packed in a lipid matrix containing large amounts of ceramides, cholesterol, and free fatty acids [3]. Transdermal drug delivery involves delivering a drug through the skin into the systemic circulation, which could have the advantage of bypassing first-pass metabolism and providing a sustained release effect. Transcutaneous delivery generally refers to the transport of drugs across all skin strata, with deep tissue or systemic circulation being the desired target. Topically administered drugs are intended for local action in skin targets without systemic absorption. These are a few of the many advantages of long-term drug delivery and improving patient compliance. However, the skin barrier function is still an obstacle to the successful transdermal transport.

Researchers have developed multiple approaches to increase percutaneous, the passage of a substance through the layers of the skin, typically reaching the dermis or systemic circulation through both passive and active procedures [4, 5]. Animal skin is frequently used as an alternative to predict in vitro percutaneous absorption with ethical considerations, while taking into account the considerable variability in human skin samples caused by changes in age, race, and anatomical donor site [6]. To overcome this, a variety of advanced formulation strategies have been developed. These include vesicular systems (e.g., liposomes, ethosomes, transfersomes), particulate carriers (e.g., solid lipid nanoparticles, nanostructured lipid carriers), dendrimers, and polymeric nanoparticles. Comparative analyses of the properties of animal skin and human skin, including their thickness, lipid composition, hair follicle density, and enzymatic activity, have been conducted to evaluate the appropriateness of animal models in transdermal drug delivery studies [6]. Research has shown that there is considerable intra-individual and inter-individual variability in animal models. In addition, the permeability parameters of animal skin models and human skin have been investigated. The use of cultured human skin models has become an alternative to overcome the limitations associated with animal skin [1, 6, 7].

The stratum corneum consists of layers of desiccated, keratinized cells and an intercellular matrix, mainly comprising ceramides, cholesterol, and free fatty acids [8]. This distinctive structure inhibits the effective penetration of medication molecules into the skin, particularly of hydrophilic and large-sized molecules. Many drug delivery technologies, such as liposomes, ethosomes, transfersomes, solid lipid nanoparticles, dendrimers, and polymer-based nanoparticles, have been developed to improve bioavailability and extend the range of medications that can be administered via the transdermal route [1].

In addition, nanoemulgel has appeared as a transdermal administration method designed to improve drug permeation through the skin [8]. The combination of nanoemulsion and gel to create nanoemulgel provides such benefits as increased drug loading capacity, improved penetration and diffusion, and reduced skin irritation when compared to other nanocarrier systems [1, 9, 10, 11]. Due to ethical and practical constraints in using human skin in preclinical studies, animal skin models such as those derived from rats, rabbits, and pigs are frequently utilized. These models are selected based on anatomical and physiological similarities to human skin. However, differences in stratum corneum thickness, follicle density, and lipid composition can influence drug permeation

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outcomes. This review focuses on the use of various skin models in evaluating in vitro/ex vivo nanoemulgel formulations for transdermal drug delivery. It synthesizes existing literature on formulation performance and examines the relevance of each skin model to predict drug permeation in human applications.

Summary of Relevant Literature

A comprehensive literature review identified 179 potentially relevant papers. The preliminary evaluation of the articles led to the exclusion of 88 articles that were neither original research nor unique entries. The publications were further evaluated based on their titles and abstracts for each inclusion criterion, resulting in the exclusion of 36 articles. We subsequently examined the whole texts of the remaining 55 papers, resulting in the exclusion of 27 articles due to inaccessibility of the full text and failure to meet the inclusion criteria. Nineteen articles were subsequently subject to data extraction. The summary of these articles is listed in Table SI, in the supporting file.

Discussion

Skin Model in Permeation Studies

A summary of the comparison of skin types with permeation results on nanoemulgel formulations is provided in the table (Table 1). The permeation test utilized three types of skin from the study articles: rat skin, porcine skin, and rabbit skin. A comparative histological analysis by Todo et al. (2017) supports the strategic selection of skin models in transdermal drug research. As summarized in Table 1, porcine skin shows the closest resemblance to human skin in terms of dermal structure, stratum corneum thickness (~21–26 µm), and lipid composition, making it the most predictive model for human permeability. In contrast, rat skin, with its thin barrier and dense hair follicles, exhibits up to 50-fold higher permeability than human skin, often overestimating absorption. Rabbit skin shares a similar thickness with human skin but has a different lipid profile, potentially limiting polar compound diffusion [6]. These structural differences account for the varied permeation outcomes observed in nanoemulgel studies and underscore the importance of model selection in predicting clinical relevance.

Table 1. Characteristics, Advantages, and Limitations of Commonly Used Animal Skin Models in Permeation Studies

Skin Model	Stratum corneum Thickness (µm)	Hair Follicle Density (/cm²)	Advantages	Limitation
Human	16.8-18.2	~6	Reference standard	Ethical and logistical limitations; variability among donors
Rat	45945	~8000	Easily available; high permeability; suitable for initial screening	Overestimates permeation; structurally less like human skin
Rabbit	20	~80	Moderate permeability; similar thickness to human skin; accessible model	Variable barrier function: lipid profile differs from humans
Porcine (ear)	21-26	~20	Closest model to human skin; structurally and histologically analogous	Slightly thicker SC: availability may vary; higher cost than rodent models

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Rat Skin

Rat skin is frequently used in permeation studies because of its availability, thickness, and high density of hair follicles. Rat skin measures 10-15 μm in thickness and consists of three main components: stratum corneum, epidermis, and dermis. Rat skin has greater permeability than human skin, and this facilitates the examination of active component absorption [4]. Although the kinematic parameters of permeation into rat skin may reflect those of human skin, there are notable structural differences, including a thinner epidermis and stratum corneum as well as a more densely populated array of hair follicles and sweat glands. A divergence may result in discrepancies in the penetration profile of a chemical between rat and human epidermis [4, 6]. Research indicates that reduced thickness of the stratum corneum in mice, relative to human skin, facilitates elevated flux values as demonstrated in a study examining the abdominal and dorsal skin of mice, where the dorsal region possesses a greater density of hair follicles compared to the abdominal skin [31].

The permeation test results indicated a high flux value, and this is consistent with in vivo test outcomes demonstrating the intended therapeutic efficacy. Razzaq et al. (2021) find that using rat abdomen skin for ex vivo permeation testing produces a significant drug flux, which is subsequently validated by antidiabetic action in mice used for an in vivo experiment [12]. Morteza-Semnani et al. (2022) conducted a study that uses rodent abdominal skin because the obtained permeability and flux values are relatively high and exhibit a strong correlation with in vivo data. This result suggests that the analgesic efficacy of sodium diclofenac is significantly enhanced by its permeation through the epidermis layers [13]. Rat skin can provide valuable information regarding the in vivo activity of transdermal formulations; however, the experimental results may be restricted by the substantial physiological disparities between rat and human skin, particularly in terms of permeability and inflammatory responses [32]. Even if the ex vivo permeation results through rat skin were effective, the interpretation had to take these aspects into account once high flow factors were achieved and aligned with in vivo flows. Additional research is required to identify voids and improve models of human medication tuning.

Rabbit Skin

Rabbit skin is generally more permeable than human skin and similar to rat skin, but the differences in percutaneous absorption between rabbits and humans are inconsistent. Compared to the dorsal skin of rats (8000/cm^2) and other rodents, rabbit ear skin has a significantly reduced hair follicle density (80/cm^2). A number of molecules, including lidocaine, triptorelin, and thiocolchicoside, also demonstrate comparable permeability in rabbit ear skin. The epidermis of rabbit skin is denser, and the stratum corneum is thinner than that of human skin. However, differences in the lipid composition of rabbit stratum corneum compared to pig stratum corneum suggest the potential for a significantly higher concentration of nonpolar lipids.

Meanwhile, the epidermis of rabbit ear skin in vivo is significantly thinner than that of porcine ear skin [6, 31]. The hair follicle density, though significantly less than in other furry rodents, is still higher than in pigs or humans, whose densities are 29, 30, and 6 hairs per cm², respectively [6]. A study reported that methotrexate in nanoemulgels formulation shows flux values of 14.9 ± 1.98 μg/cm²·h and 15.8 ± 1.78 μg/cm²·h, indicating increased percutaneous absorption that may contribute to a prolonged biological half-life (from 4 to 10 hours) [30]. However, the relationship between drug half-life and flux must be interpreted cautiously. The longer half-life observed may not solely reflect skin retention but could also involve systemic pharmacokinetics [30].

Porcine Skin

Porcine skin, especially from the ear (21–26 μm SC thickness; ~20 follicles/cm²), is histologically closest to human skin in terms of lipid composition, stratum corneum structure, and dermal collagen arrangement [31]. The thickness of the living epidermis and the arrangement of collagen fibers in the dermis are analogous to those found in human skin. Porcine skin, obtained from the abdominal area, particularly in the form of dermatomal (standardized) or full-thickness, as well as isolated porcine epidermis, is commonly used for evaluating the penetration of transdermal drug delivery systems [22]. Nanoemulgel formulations have

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demonstrated high flux values in porcine models, highlighting their utility for preclinical screening. Porcine skin is preferred for its physiological similarity, including ceramide-rich membranes and skin pH, which support reliable prediction of human transdermal absorption. In one study, andrographolide nanoemulgels showed significant drug penetration (65.87–21.11 µg) through the stratum corneum and high retention (403.67–784.79 µg) in the dermal and epidermal layers [27]. Another study found that the transdermal flux (Jss) of ketoconazole was 1.819 µg/cm²·h in nanoemulgel, five times higher than in conventional gel (0.371 µg/cm²h). The permeability coefficient (Kp) of nanoemulgel was 0.047×10^{-3} cm/h, compared to 0.4×10^{-2} cm/h in the gel [23]. These findings reinforce the applicability of porcine skin in evaluating nanoemulgel formulations and their enhanced permeation potential [23]. Laboratory studies have shown that similar substances can access the epidermis of mice, rabbits, and pigs. The extent of the similarity depends on the experimental parameters, the chemical family of the tested compounds [6], and the active principle. Therefore, the selection of an adequate animal skin model needs to be carefully considered to match the aims of the study and the characteristics of the tested active compounds.

Transdermal Permeation Study Methods

Various methods are utilized to assess the permeability of active agents, including transdermal measurements. The Franz diffusion cell is the most common method used for monitoring the transport of active compounds from the donor, which simulates the topical formulation, to the acceptor or receptor, thereby replicating a systemic circulation [4, 6]. Experimental conditions, including temperature, receptor media, and study duration, significantly influence permeation results. The suitability of receptor media that replicate a physiological environment and preserve the integrity of skin samples during the study is crucial for producing reliable permeation data. Experimental parameters (such as temperature, receptor media, or study time) can have a strong impact on the detection of permeation results. The selection of receptor media that imitate an in vivo environment while protecting the skin pieces from being affected throughout the experiments is important for generating reliable skin permeation data.

The integrity and permeability of skin membranes are substantially affected by the length of a permeation study involving skin samples. Prolonged exposure of skin samples to specified experimental housing conditions, such as particular measurements and regulated temperature and humidity (control), may result in a gradual reduction in skin barrier properties over time. The stratum corneum acts as the main barrier in transdermal drug delivery, where significant changes in the structure and function take place during the drug permeation test. It becomes more hydrophobic and more closely packed than the standard lamellar [32]. This organization is altered by experimental conditions applied to skin samples, resulting in a limited ability to restrict the penetration of active principles [33]. The hydration status of skin samples can be changed and may affect the partitioning and diffusion of active compounds through the skin barrier. A skin integrity assessment during in vitro permeation studies is critical to obtain reliable & reproducible data. In addition, the experimental time duration should be minimized to the time required to obtain meaningful permeation data. In permeation studies, the timing of skin tests is critical to assess the freshness of the skin membrane and its permeation characteristics. Understanding this relationship is essential for improving drug delivery systems and obtaining reproducible experimental results [34].

Impact of Nanoemulgel Formulation on Active Substance Permeation

The evaluation of permeation parameters is crucial to understanding the transdermal delivery of active compounds. Key parameters include permeation flux, delay time, and permeability coefficient, which provide essential information on the amount and rate of drug penetration through the skin [14]. The values are affected by numerous factors, including but not limited to the physicochemical properties of the active substance (e.g., molecular weight, lipophilicity, and degree of ionization), formulation composition (e.g., presence of permeation facilitators), and experimental conditions such as temperature and choice of media receptacles. Advancements in formulation technology, including dosage form technology and modification of excipients within formulations, have

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been developed to overcome the problems associated with skin permeation.

Nanoemulgels—typically with particle sizes ranging from 20–200 nm—are a combination of nanoemulsion and hydrogel, increasing permeability to the stratum corneum and improving targeted delivery of active compounds to the skin. The new integrated three-dimensional structure possesses hydrogel characteristics that ensure practical applications to the sluggish properties of nanoemulsion, which enhance drug penetration through the skin [18]. Recent research shows that nanoemulgel provides a much higher rate of permeation and retention of active substances in the skin than conventional gel formulations [13, 15, 17, 19, 23]. Nanoemulgel formulations have been compared to nanoemulsion formulations, and the results show that the addition of nanoemulsion as a carrier in a gel system not only significantly increases delivery and permeation but also enhances formulation stability. The reduced particle size of nanoemulgel formulations enhances their ability to traverse the skin's structural barriers and facilitates improved localization of the active compound within the epidermal and dermal layers. This increased drug retention primarily refers to the accumulation of the drug in the skin rather than its absorption into systemic circulation. Such localized retention is especially desirable in transdermal drug delivery systems aimed at providing targeted therapeutic effects while minimizing systemic exposure. [25].

The permeation of active compounds into the skin can be enhanced through modifications to both the dosage form and the formulation, including the incorporation of permeability enhancers. Such permeation enhancers as surfactants and penetration promoters increase drug penetration across the skin by modifying the architecture of the stratum corneum, improving drug solubility, or increasing drug partitioning in the stratum corneum [34, 35]. Permeation enhancers, including penetration enhancers or nanocarriers, can be used in nanoemulgel formulations to facilitate transdermal delivery of active principles by modifying the skin barrier and increasing the thermodynamic activity of the drug in the formulation. Ahmad et al. (2023) reveal that skin permeability enhancers like eucalyptus oil and clove oil increase the efficacy of nanoemulgel formulations, which can be attributed to improved skin permeability, easy spreadability, skin hydration, and retention on the skin, resulting in an extended duration of action [16]. Another study by N. Gupta et al. (2024) suggests a glycyrrhizin-based nanoemulgel formulation as a permeability enhancer with a much better profile of skin penetration as opposed to both conventional nanoemulgel and gel formulations [22].

Conclusion

Across the reviewed studies, nanoemulgel consistently showed better performance than traditional gel formulations, especially when combined with penetration enhancers like eucalyptus and clove oil. These enhancers modify the skin barrier to enhance drug delivery. However, caution is necessary when applying results from animal models, particularly rodents, to humans. More research is needed to improve experimental models that consider differences in skin structure and permeability between species for more accurate predictions in transdermal drug development.

Author Contributions: Anni'sya Alfanura was responsible for the conceptualization of the study, conducting the literature survey, drafting the original manuscript, and editing. Farida Hayati and Oktavia Indrati contributed to the refinement of the concept, provided critical input, and participated in reviewing and revising the manuscript. Farida Hayati also served as the corresponding author, overseeing communication with the journal and ensuring the integrity of the submission process. All authors have read and approved the final version of the manuscript."

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solubility of NAP in different surfactants and co-surfactants, and HLB values of selected surfactants; Table S2: summary of regression analysis findings for responses R1, R2 and R3 for quadratic equation fitting and Fig. S1: observation of stress stability studies of different formulations. See DOI: https://doi.org/10.1039/d4pm00059e," RSC Pharm., vol. 1, no. 3, pp. 498–512, 2024, doi: https://doi.org/10.1039/d4pm00059e.

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