Review Article

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Recent Advances in Transdermal Delivery: Correlating Characteristics of Nanoparticles with Permeability in Lipid-based Drug Delivery Systems

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ABSTRACT

Transdermal drug delivery provides a noninvasive alternative to oral administration, though its efficacy is limited by the stratum corneum barrier. Lipid-based drug delivery systems are increasingly used to address this challenge. This review evaluates the relationship between the physicochemical characteristics of lipid-based particles and their resulting transdermal permeability. A structured literature search of ScienceDirect, PubMed, and Google Scholar (2015-2025) was conducted to identify original research articles reporting quantitative *in vivo* and *ex vivo* skin permeability data. The study analyzed nanoemulsions, solid lipid nanoparticles and nanostructured lipid carriers (NLC) based on particle size, polydispersity index (PDI), and zeta potential. Smaller particle size (<150 nm), low PDI, and stable zeta potential (≥ |20| mV) were observed to correlate with increased flux and permeability coefficients. Among the systems reviewed, NLCs frequently demonstrated superior permeability characteristics attributed to a flexible matrix that enhances drug loading and interactions with skin lipids. Optimizing these physicochemical parameters appears essential for achieving superior permeability in lipid-based transdermal systems, offering potential benefits for clinical pharmacy practice and drug bioavailability.

Keywords: Drug delivery system; Lipid carriers; Particle characteristics; Permeability; Transdermal delivery.

1. INTRODUCTION

Drug delivery systems (DDS) are a modern pharmaceutical approach that enable drugs to reach their target location more efficiently through controlled release, increased stability, and optimised distribution, thereby improving bioavailability and reducing side effects compared to conventional methods (Malamatari, 2023). Modern DDS encompasses various strategies, such as nanoparticles, lipid-based carriers, controlled-release formulations, and targeted delivery systems developed to overcome formulation challenges, such as low drug solubility, first-pass metabolism, plasma concentration fluctuations, and the need for repeated dosing (Ainurofiq *et al.* 2023; Chen *et al.* 2024). Among these technologies, lipid-based DDS has gained significant attention in transdermal formulation development because lipid-based nanocarriers such as nanoemulsions, Solid Lipid Nanoparticles (SLN), and Nanostructured Lipid Carriers (NLC) exhibit good biocompatibility, encapsulation capacity for both hydrophilic and lipophilic drugs, and high formulation flexibility (Antonara *et al.* 2025).

Permeability is the ability of a substance to pass through a biological membrane, such as the skin, either passively or with the help of an enhancer. In the context of transdermal preparations, permeability is a key factor that determines how effectively a drug can penetrate the stratum corneum (SC), which is the main barrier of the skin. The higher the permeability of a formulation, the greater the amount of drug that can reach the systemic circulation in a stable and controlled manner (Ainurofiq, *et al.* 2025a). Lipid-based formulations have become one of the most strategic approaches in modern drug delivery systems, especially for molecules that are difficult to dissolve in water and have limited permeability. In general, these formulations consist of drug dispersions in a lipid matrix composed of triglycerides, fatty acids, phospholipids, surfactants, and co-surfactants that are rationally selected to improve drug solubility, stability, and bioavailability. These specific lipid compositions are engineered to interact directly with skin lipids by increasing the fluidity of the lipid layer and creating an occlusive effect that enhances hydration. This interaction effectively bridges the gap between formulation composition and permeability mechanisms, allowing particles to adapt to narrow gaps in the stratum corneum. Particle characteristics such as size, lipid composition, and surface properties are important determinants of the success of lipid-based formulations in transdermal drug delivery (Antonara *et al.* 2025).

By manipulating lipid composition, transdermal formulations can be strategically designed to modulate the structure of the SC, which serves as the principal barrier of the skin. The SC consists of highly ordered lipid bilayers composed primarily of ceramides, cholesterol, and free fatty acids, forming a tightly packed matrix that restricts drug diffusion. Incorporation of specific lipid components such as phospholipids, surfactants, or edge activators into carrier systems can fluidize or disrupt this ordered lipid arrangement, thereby reducing barrier resistance and facilitating drug transport. This structural modulation directly influences membrane permeability, defined as the ability of a substance to pass through a biological membrane either passively or with the assistance of penetration enhancers. Under steady-state conditions, transdermal transport is commonly described by Fick's first law of diffusion, where flux is proportional to the concentration gradient across the membrane ($J = -D\, dC/dx$). The permeability coefficient (Kp) integrates the diffusion coefficient, partition behavior, and membrane thickness, thus providing a quantitative representation of overall barrier passage. Lipid-based carriers enhance Kp by increasing lipid fluidity, altering lipid packing, and in some cases creating transient diffusion pathways within the SC. Therefore, successful transdermal system design requires careful optimization of both drug physicochemical properties and carrier composition, alongside appropriate penetration-enhancing strategies, to achieve effective and controlled permeation (Akbari *et al.* 2022; Imran *et al.* 2020; Lunter *et al.* 2024)

This literature review focuses on various advanced lipid-based drug delivery systems, also known as lipid nanosystems, designed for transdermal applications. These systems are being investigated for their ability to overcome the limitations of conventional drugs, particularly those with poor solubility, by improving their pharmacokinetic profile and stability (Buya *et al.* 2021; Rehman *et al.* 2024). Lipid nanosystem formulations discussed in this review include SLN, NLC and nanoemulsions.

Solid lipid nanoparticles represent the first generation of lipid nanocarriers (Duan *et al.* 2020). It consists of a solid lipid core stabilized by surfactants. They combine the benefits of colloidal nanocarriers with the occlusive properties of solid lipids. Upon application to skin, SLN can form a thin occlusive film that increases SC hydration and provides controlled drug release. Typical SLN formulations used transdermally have particle sizes between 100-300 nm and carry negative surface charge to the order of -15 to -30 mV due to the lipid constituents and stabilizers (Mohammadi-Samani *et al.* 2018). Subsequently, nanostructured lipid carriers were developed as the second generation of lipid nanocarriers to overcome the drug loading and crystallinity limitations of SLNs (Viegas *et al.* 2023). The NLC is formulated with a mixture of solid and liquid lipids that produce a matrix that is not completely regular or heterogeneous (Chauhan *et al.* 2020; Rehman *et al.* 2024) structure. It allows for a significant increase in drug loading capacity and improves the physical stability of the formulation. The NLC is recognized as a robust and promising system (Beloqui *et al.* 2016; Viegas *et al.* 2023). Distinct from solid lipid carriers, nanoemulsions are submicron colloidal dispersions of oil and water stabilized by surfactants, typically forming oil-in-water droplets in the 20-200 nm range (Rehman *et al.* 2024). Their tiny droplet size and high surfactant content provide a large interfacial area, enhancing drug solubilization and fluidizing the stratum corneum lipids to improve skin permeation. In practice, optimized transdermal nanoemulsions have been reported with diameters on the order of 100-200 nm, low polydispersity, and significant surface charge. Nanoemulsions generally have very small droplet sizes and play an important role in improving drug solubility (Rehman *et al.* 2024).

There are variations in permeability performance arising from differences in the structure and composition of each lipid-based system. Therefore, understanding how the physicochemical properties of the particles influence permeability outcomes is essential for formulation optimization. Key particle characteristics that substantially affect these outcomes include PS, PDI, and zeta potential (ZP) (Ainurofiq *et al.* 2025b). These parameters collectively reflect the dispersibility, stability, and uniformity of the system, which ultimately determine the ability of the particles to permeate through the skin. The values of these parameters are strongly influenced by the physicochemical properties of the drug, the polymer/lipid matrix, and the type of vehicle used (Ainurofiq *et al.* 2014; Antonara *et al.* 2025).

The objective of this review is to critically evaluate how the key physicochemical characteristics of lipid-based delivery systems, including SLN, NLC, and lipid emulsions affect transdermal permeability. This review integrates mechanistic evidence, experimental data, and comparative formulation findings to clarify how particle size, dispersity, and surface charge regulate interactions with the stratum corneum and shape permeation outcomes. The integrated analysis aims to establish a coherent framework describing the permeability behavior of different lipid-based carriers and to identify particle attributes that consistently enhance transdermal drug delivery performance.

2. METHODOLOGY OF LITERATURE REVIEW

This study was conducted as a structured literature review to evaluate lipid-based nanosystems in enhancing skin permeability for transdermal drug delivery.A comprehensive search was performed in ScienceDirect, PubMed, and Google Scholar for articles published between January 2015 and March 2025 using

combinations of keywords with Boolean operators ("AND," "OR," "NOT"), including ("solid lipid nanoparticles" OR "SLN" OR "nanostructured lipid carriers" OR "NLC" OR "nanoemulsion") AND ("transdermal delivery" OR "skin permeability"). Studies were included if they were original experimental research investigating SLN, NLC, or nanoemulsion systems for dermal or transdermal delivery and reported physicochemical characteristics such as particle size, PDI, and ZP, together with quantitative permeability outcomes obtained from *in vitro, ex vivo,* or *in vivo* models. Extracted permeability parameters included steady-state flux (Jss), permeability coefficient (Kp), enhancement ratio (ER), and cumulative drug permeation (Q). Studies were excluded if they were review articles, conference abstracts, or non-peer-reviewed publications, focused on non-lipid nanocarriers or did not provide measurable permeability data. Duplicate records were identified and removed manually. The selection process consisted of title and abstract screening, followed by full-text eligibility assessment and structured data extraction using a predefined format to ensure consistency. Information regarding formulation composition, lipid-based type, skin model (human, animal, or synthetic membrane), and experimental conditions was also recorded. Due to heterogeneity in formulation variables, skin models, permeability testing methods, and reporting units across studies, findings were analyzed descriptively and comparatively rather than through quantitative pooling. A formal risk-of-bias assessment was not performed, which represents a methodological limitation and should be considered when interpreting comparative performance across nanosystems.

3. DISCUSSION

3.1 Nanoemulsion Transdermal

Nanoemulsions are drug delivery systems composed of two immiscible phases oil and water, stabilized by surfactants and cosurfactants (Al-Mumtahanah *et al.* 2024). In transdermal delivery, absorption effectiveness is highly dependent on the system's ability to interact with and penetrate the stratum corneum. Therefore, PS, PDI, and ZP values are not sufficient as characterization results alone, but need to be reviewed in relation to system stability and their implications for enhancing drug permeation (Bamisaye *et al.* 2023). With this approach, characterization data can be further analyzed to determine the extent to which differences in physicochemical parameters contribute to variations in permeation performance (Table 1).

Table 1. Physicochemical characteristics and permeability of nanoemulsion-based transdermal drug delivery systems

Characteristics			Permeability	Source
PS (nm)	ZP (mV)	PDI		
112 ± 2.3	+26 ± 1.1	0.15 ± 0.02	• Jss: 138.82 ± 8.40 µg/cm^2·h • ER: 8.23-fold compared with the drug suspension • Q24h: 77.96 ± 3.5 %/cm^2 • Drug deposition in the skin: 10.98%	(Altamimi *et al.* 2021)
175.5 ± 1.56	-21.5 ± 0.12	0.192 ± 0.06	• Q24: 58.63% • ER: 2.12 • Jss: 16.85 µg/cm^2·h	(Akhter *et al.* 2024)
95.86 ± 4.90	+24.31 ± 4.81	0.252	• Jss: 250.7 ± 91.0 µg/cm^2·h • ER: 3.59 • Kp: 5.179 ± 0.4104 × 10^{-3} cm/h • Q24h: 5.98 mg/cm^2 • Q48h: 12.21 mg/cm^2	(Shakeel *et al.* 2021)
186.60 ± 2.84	−13.90 ± 0.99	0.19 ± 0.025	• Q24h: 1237.11 ± 44.33 µg/cm^2 • Jss: 47.53 ± 4.98 µg/cm^2·h • Kp: 19.01 ± 2.96 × 10^{-3} cm/h • ER: 7.43	(Musallam *et al.* 2025)

Abbrev: Jss, steady-state flux; ER, enhancement ratio; Kp, permeability coefficient; Q24h, cumulative permeation at 24 hour; Q48h, cumulative permeation at 48 hour

In the study by Altamimi *et al.* (2021), a cationic luteolin-loaded nanoemulsion exhibited a PS of 112 ± 2.3 nm, a PDI of 0.15, and a positive ZP of +26 mV. Meanwhile, Akhter *et al.* (2024) formulated a

nanoemulsion gel containing *Cucumis melo* var. *agrestis* extract with a droplet size of 175.5 ± 1.56 nm, a PDI of 0.192, and a negative ZP (−21.5 mV). Shakeel *et al.* (2021) also reported excellent characteristics for their optimized formulation, NEO-NE4, which had a droplet size of 95.86 ± 4.90 nm, a PDI of 0.252, and a ZP of −24.31 ± 4.81 mV. In another study, Musallam *et al.* (2025) developed a nanoemulsion–foam hybrid system containing terbinafine hydrochloride, characterized by a particle size of 186.60 ± 2.84 nm, a ZP of −13.90 ± 0.99 mV, and a PDI of 0.19 ± 0.025. These values collectively indicate homogeneous and stable dispersions, which are essential for enhancing drug release and transdermal permeation. The consistency of these physicochemical parameters reflects favorable uniformity and stability, serving as critical indicators of successful nanoemulsion design for transdermal drug delivery.

The enhancement of skin permeation by nanoemulsions is attributed to several synergistic mechanisms. First, the nanoscale droplet size facilitates penetration through intercellular lipid pathways in the SC. Smaller droplets provide a greater surface area, resulting in an increased concentration gradient between the formulation and the skin, thereby promoting deeper drug diffusion. Second, surfactants and cosurfactants interact with skin lipids, temporarily disrupting lamellar lipid organization and reducing diffusional resistance, which enhances permeability. However, it is crucial to note that the high surfactant concentrations often required to stabilize nanoemulsions can compromise skin barrier integrity and lead to local irritation or cytotoxicity. Consequently, while surfactant-mediated lipid fluidization is a primary driver of flux, formulation optimization must carefully balance permeability enhancement with dermatological safety, ensuring that surfactant levels remain within non-irritating limits. Third, the surface charge of the droplets (zeta potential) also contributes to permeation behavior. Positively charged formulations, such as CNE4 (Altamimi *et al.* 2021), demonstrate substantial permeation enhancement due to electrostatic attraction between cationic droplets and the negatively charged skin surface. This results in high flux (138.82 ± 8.4 μg/cm^2·h) and Kp (2.31 × 10^{-2} cm/h), significantly exceeding those of anionic formulations or drug suspensions. However, despite their superior permeation performance, cationic nanoemulsions present potential safety concerns. Strong electrostatic interactions with skin lipids may cause excessive disruption of the SC barrier, potentially increasing transepidermal water loss, irritation, and cytotoxicity, particularly with repeated or long-term application. Conversely, moderately negative formulations such as CME-NEG (Akhter *et al.* 2024) achieved a 2.12-fold improvement in permeation compared to conventional gel, primarily through enhanced skin hydration and gradual diffusion enabled by lipid fluidization. Similarly, Shakeel *et al.* (2021) showed that although NEO-NE4 possessed a negative ZP, its small droplet size, low viscosity, and surfactant-mediated lipid modulation resulted in high permeation (flux 0.2507 ± 0.0910 mg/cm^2·h) and a 3.59-fold enhancement compared to pure NEO oil. The nanoemulsion–foam hybrid developed by (Musallam *et al.* 2025) yielded the highest permeation values, with a permeated amount of 1237.11 ± 44.33 μg/cm^2, a flux of 47.53 ± 4.98 μg/cm^2·h, and a 7.43-fold enhancement relative to control foam. This demonstrates that permeation enhancement is also influenced by formulation architecture, where the foam-hybrid structure promotes greater drug release and skin contact.

Overall, the mechanisms underlying transdermal permeation enhancement in nanoemulsion systems are governed not only by droplet size reduction and surfactant effects but also by the physicochemical properties of the lipid matrix and the electrostatic interactions between droplets and the skin surface. The reviewed data show a consistent correlation between particle characteristics and permeability outcomes. Formulations with smaller particle sizes (<120 nm) and low PDI (<0.25) tend to exhibit higher flux, Kp, and ER. Additionally, ZP values greater than 20 mV contribute to system stability by preventing aggregation, thereby preserving particle size during permeation and ultimately increasing drug deposition within the skin.

Before extending the comparison to other lipid-based systems, it is important to acknowledge that cumulative permeation values (Q) reported across the reviewed nanoemulsion, SLN, and NLC studies are expressed in heterogeneous units, including percentage (%), absolute mass per unit area (μg/cm^2 or mg/cm^2), and occasionally as time-dependent ranges. Because these studies differ in drug loading, donor concentration, membrane type, diffusion area, and experimental duration, Q values cannot be directly compared across formulations. Percentage-based Q reflects relative permeation with respect to the applied dose, whereas mass-per-area units represent absolute permeated amounts that are highly dependent on formulation strength and testing conditions. Therefore, in the present comparative analysis, greater emphasis is placed on Jss, Kp, and ER, as these parameters more consistently reflect intrinsic permeation performance under steady-state diffusion conditions. This methodological heterogeneity should be considered when interpreting cross-system comparisons among nanoemulsion, SLN, and NLC formulations.

3.2 Solid Lipid Nanoparticle

The permeability data summarized in Table 2 reveal pronounced differences among SLN formulations, indicating that transdermal performance is governed not solely by PS and surface charge, but critically by lipid matrix composition and surfactant selection. A comparative analysis demonstrates that similar nanoscale characteristics do not necessarily yield equivalent permeability outcomes, highlighting the importance of formulation design.

Table 2. Physicochemical characteristics and permeability of solid lipid nanoparticle-based transdermal drug delivery systems

Characteristics			Permeability	Source
PS (nm)	ZP (mV)	PDI		
111–490 (F4: 111)	-30 ± 2.4	0.214–0.387 (F4: 0.296)	• Jss: 49.62 ± 0.68 μg/cm²·h • Kp: (9.90 ± 0.10) × 10^{-2} cm/h • Q12h: 75% of the administered drug	(El-Telbany *et al.* 2021a)
205	-16.6	0.127	• Jss: 615 μg/cm² (with argan oil) dan 417 μg/cm² (without argan oil)	(Khan *et al.* 2022)
237.0 ± 21.3	−20.6 ± 1.0	0.285 ± 0.015	• Jss: 8.832 ± 1.045 μg/cm²·h • Kp: (2.983 ± 0.782) × 10^{-2} cm/h • ER: 1.10 (compared with the conventional gel)	(Krishnatreyya *et al.* 2019)
95.57 ± 6.3	−31.8 ± 3.15	0.283	• Egg membrane flux: 54.354 ± 1.43 μg cm^{-2} h^{-1} • Rat skin flux: 193.454 ± 4.324 μg cm^{-2} h^{-1} • Marketed formulation (rat skin): 116.345 ± 2.238 μg·cm^{-2}·h^{-1}	(Aland *et al.* 2019)

Abbrev: Jss, steady-state flux; ER, enhancement ratio; Kp, permeability coefficient; Q12h, cumulative permeation at 12 hour

The optimized SLN reported by (El-Telbany *et al.* 2021) (111 nm; −30 ± 2.4 mV; PDI 0.296) achieved a steady-state flux of 49.62 ± 0.68 μg/cm^2·h and Kp of (9.90 ± 0.10) × 10^{-2} cm/h, with approximately 75% cumulative permeation within 12 h. While the reduced particle size enhances interfacial contact with the stratum corneum, the relatively high magnitude of ZP primarily ensures colloidal stability rather than directly driving permeation. The enhanced flux is plausibly linked to the structural characteristics of the solid lipid matrix and its ability to regulate drug release. A partially imperfect or less crystalline lipid core facilitates controlled drug diffusion toward the nanoparticle surface, maintaining a favorable thermodynamic activity gradient at the skin interface. Additionally, the surfactant system used in SLN stabilization may contribute to transient lipid fluidization in the SC, thereby reducing diffusional resistance.

In contrast, the SLN formulation described by Krishnatreyya *et al.* (2019) (237.0 ± 21.3 nm; −20.6 ± 1.0 mV; PDI 0.285 ± 0.015) exhibited a substantially lower steady-state flux of 8.832 ± 1.045 μg/cm^2·h and Kp of (2.983 ± 0.782) × 10^{-2} cm/h, despite maintaining acceptable nanoparticle homogeneity. The larger PS likely reduced effective contact area and limited access to intercellular lipid pathways. However, the modest ER (1.10) suggests that compositional factors were equally influential. A more crystalline lipid matrix can restrict drug mobility within the solid core, reducing the fraction of drug available for immediate partitioning into the skin. Furthermore, surfactant characteristics, particularly hydrophilic-lipophilic balance and interfacial activity, may influence both nanoparticle stabilization and the extent of barrier perturbation. If the surfactant exhibits limited lipid-disordering capacity, permeation enhancement may remain modest despite nanoscale dimensions.

A more pronounced permeation profile was observed in the SLN gel reported by Aland *et al.* (2019) (95.57 ± 6.3 nm; −31.8 ± 3.15 mV; PDI 0.283), which achieved a rat skin flux of 193.454 ± 4.324 μg/cm^2·h, substantially exceeding that of the marketed formulation (116.345 ± 2.238 μg/cm^2·h). Beyond its smaller PS and strong electrostatic stabilization, the enhanced performance likely reflects optimized lipid-surfactant interactions that promote efficient drug release and skin penetration. Structural imperfections within the lipid matrix may have facilitated drug diffusion from the solid core, while the surfactant system may have enhanced interfacial contact and localized lipid reorganization within the SC.

The SLN hydrogel system reported by Khan *et al.* (2022) further underscores the decisive role of formulation composition. Despite a relatively larger PS (205 nm) and moderate ZP (-16.6 mV), the system achieved reported steady-state flux values of 615 μg/cm^2 (with argan oil) and 417 μg/cm^2 (without argan oil). The marked increase in permeation in the presence of argan oil indicates that lipid excipients and permeation enhancers can compensate for less optimal nanoparticle dimensions. The unsaturated fatty acids present in argan oil likely increased stratum corneum lipid fluidity, thereby amplifying drug diffusion independent of PS reduction.

Taken together, these findings demonstrate that differences in SLN permeability performance arise from a coordinated interplay among particle size, surface charge magnitude, lipid crystallinity, and surfactant

characteristics. While nanoscale dimensions and adequate electrostatic stabilization contribute to dispersion stability and skin contact, the internal organization of the lipid matrix and the lipid-modulating capacity of surfactants ultimately determine drug release behavior and barrier interaction. Therefore, the observed variability among SLN formulations should be interpreted within a compositional framework, where lipid selection and surfactant optimization are central determinants of transdermal efficacy rather than secondary formulation parameters.

3.3 Nanostructured Lipid Carriers

Nanostructured lipid carriers are formulated with a combination of solid and liquid lipids (ratio 70:30 to 99:1) that produce a lipid matrix that is not completely regular. This structure can increase drug loading capacity and reduce drug expulsion during storage (Viegas *et al.* 2023). The effectiveness of NLC penetration is greatly influenced by its composition and physicochemical properties (Table 3), such as PS, aggregation level, ZP, hydrophobicity level, lipid solubility in the skin, ability to dissolve skin lipids, and the ability of particles to form an occlusive film layer on the skin surface (Chauhan *et al.* 2020).

The formulation by Espinosa-Olivares *et al.* (2020) has a very small PS (±117 nm) with low PDI and moderate ZP (−15.5 mV), indicating fairly homogeneous dispersion, but this is not fully reflected in its permeability because the resulting Q, flux, and Kp values are still relatively low, suggesting that penetration through the skin has not been optimized despite the favorable size. In contrast, Singh *et al.* (2025) presented a particle size of approximately 162 nm with a ZP of −23 mV and a PDI close to the ideal limit, and actually showed the most superior permeability performance as evidenced by very high flux (452.31 µg/cm^2/h), large Kp, and the highest enhancement ratio of 2.65. This indicates that the specific lipid composition likely facilitated a stronger interaction with SC lipids, allowing it to be the most effective at penetrating the skin layer despite slightly larger particles.

Table 3. Physicochemical characteristics and permeability of nanostructured lipid carrier-based transdermal drug delivery systems

Characteristics			Permeability	Source
PS (nm)	ZP (mV)	PDI		
162.6 ± 4.2 nm	-23.11	0.295 ± 0.012	• Q24h: 31.36% • Jss: 452.31 ± 5.2 µg/cm²·h • Kp: (7.5 ± 0.3) × 10^{-3}cm/h • ER: 2.65	(Singh *et al.* 2025)
118.4 ± 5.94	-29.6 ± 1.26	0.135 ± 0.038	• Q24h: 1250 µg/cm^2 • Jss: 48.37 µg/ cm²·h • ER: 1.64 (relative bioavailability vs. oral)	(Unnisa *et al.* 2023)
117.7-213.9 nm	-4.1 to -15.5 mV	0.20-0.24	• Q: 1.18-1.98 µg/cm² • Jss: 0.92-1.95 µg/cm²·h • Kp: (1.9-4.8) × 10^{-2} cm/h	(Espinosa-Olivares *et al.* 2020)
191 ± 5.20	−10.00 ± 0.30 mV	0.33 ± 0.01	• Jss: 14.09 µg/cm²·h (quercetin) and 3.70 µg/cm²·h (resveratrol) • Kp: 7.21 × 10^{-2} cm/h (quercetin) and 4.69 × 10^{-2} cm/h (resveratrol) • ER: 1.95 (quercetin) and 1.50 (resveratrol)	(Imran *et al.* 2020)

Abbrev: Jss, flux; ER, enhancement ratio; Kp, permeability coefficient; Q24h, cumulative permeation at 24 hour

The formulation by Unnisa *et al.* (2023) exhibits the most stable physical characteristics, with a small particle size (118 nm), very low PDI (0.135), and the most negative ZP (-29.6 mV), representing the most homogeneous and electrostatically stable system. However, despite having a substantial flux of 48.37 µg/cm^2/h and good bioavailability enhancement (1.64 fold), its enhancement ratio is not as high as Singh's formulation, indicating that while the physical stability was maximized, the permeation enhancement was effective but not superior to the Singh formulation. Meanwhile, Imran *et al.* (2020) had the largest particle size (191 nm) and lowest ZP (-10 mV) with the largest PDI, resulting in lower physical stability compared to the other three journals. However, the Kp value was quite large, and the drug flux produced especially for quercetin that is,14.09 µg/cm^2/h was still competitive, with a respectable ER of 1.95. Overall, when evaluating the balance between physical characteristics and permeability performance, the formulation by Singh *et*

al. (2025) demonstrated the highest flux and enhancement ratio among the reviewed studies. Despite not having the smallest particle size or lowest PDI, the combination of stable zeta potential and its specific lipid structure resulted in superior permeability outcomes in this comparison, making it a highly effective candidate for transdermal delivery.

3.4 Comparative Analysis and Physicochemical Determinants of Permeability

While nanoemulsions, SLNs, and NLCs utilize distinct structural mechanisms, ranging from surfactant-mediated fluidization to lipid occlusion, a unifying analytical framework reveals that specific physicochemical parameters serve as universal determinants of transdermal success across these systems. Analysis of the pooled data indicates that particle size is the primary predictor of flux, with a critical threshold observed below 200 nm. Formulations within the 95-180 nm range (Shakeel *et al.* 2021; Unnisa *et al.* 2023) consistently exhibited superior flux (>45 $\mu g/cm^2 \cdot h$) and Enhancement ratios (>2.0) compared to larger particles, regardless of the lipid type. This confirms that maximizing the specific surface area for stratum corneum interaction is more critical than the carrier matrix state (solid *vs.* liquid).

Regarding surface charge, a clearer linkage exists between zeta potential magnitude and permeation consistency. Values exceeding |20| mV were essential across all tables to maintain a low PDI (<0.3), which prevents aggregation and ensures uniform drug distribution. Critically, a balance was observed. While cationic formulations (Altamimi *et al.* 2021) achieved high permeation *via* electrostatic attraction to the skin, anionic carriers (El-Telbany *et al.* 2021) relied on occlusion-mediated hydration. The selection between these strategies must weigh the higher permeation of cationic systems against their potential for electrostatic irritation.

However, the interpretation of these results is limited by the lack of standardized comparison criteria across the reviewed studies. The heterogeneity in permeability metrics, where cumulative amounts (Q) are reported variously as percentages (Singh *et al.* 2025) or mass per area (Musallam *et al.* 2025), precludes a direct quantitative ranking of efficacy. Furthermore, the variability in *ex vivo* models introduces biological variance that may affect the translatability of flux values. Consequently, while NLCs generally offered the best balance of loading and flux, future studies must adopt standardized protocols to allow for robust cross-formulation meta-analysis.

4. CONCLUSION

This structured review demonstrates that the transdermal effectiveness of lipid-based nanocarriers is governed not merely by individual parameters like particle size or ZP, but by the integrated interaction between lipid matrix structure, surfactant composition, and thermodynamic activity. Permeation enhancement arises from a synergistic combination of nanoscale surface contact, lipid fluidization, and occlusive effects. Critically, the choice of carrier involves distinct compromises, while nanoemulsions often provide the highest flux due to their fluid phase, they present greater risks of skin irritation. The SLNs offer superior physical stability but are limited by lipid crystallization and lower drug loading, while NLCs effectively bridge these limitations by incorporating liquid lipids to create an imperfect matrix, though their superiority is highly formulation-dependent.

However, the interpretation of these findings is constrained by the heterogeneity of current research, particularly the variability in skin models (*in vivo vs*. *ex vivo*) and inconsistent permeability metrics (Q *vs*. Flux), and diverse experimental methodologies. These limitations restrict direct cross-study comparisons and the establishment of a universal standard. Consequently, future research must prioritize the development of standardized *ex vivo* permeability protocols and a deeper mechanistic understanding of drug-carrier-skin interactions. To facilitate clinical translation and regulatory acceptance, formulation strategies must move beyond permeability enhancement alone to simultaneously optimize safety profiles, long-term stability, and industrial scalability.

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STATEMENT OF ORIGINALITY AND EXCLUSIVE SUBMISSION

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The authors declare that there is no conflict of interest.

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