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Next-Generation Topical Delivery for Infantile Dermatitis: Exploring the Therapeutic Potential of Solid Lipid Nanoparticles

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ABSTRACT
Background. Infantile dermatitis, most commonly atopic in origin, affects an estimated 15–20% of children worldwide and imposes a substantial burden on quality of life and household finances. The infant skin barrier is structurally and functionally immature: the stratum corneum is roughly 30% thinner than in adults, transepidermal water loss is higher, and the body-surface-area-to-mass ratio is approximately 2.5–3 times greater. These features raise the risk of systemic exposure from topical therapy precisely in the population least able to tolerate it, and they constrain the safe use of the current standard of care.
Scope. This narrative review examines solid lipid nanoparticles (SLNs) and their second-generation counterparts, nanostructured lipid carriers (NLCs), as a topical delivery platform for infantile dermatitis. It covers carrier architecture and composition, production and characterization methodology, mechanisms of cutaneous delivery, the published formulation evidence for dermatitis-relevant actives, and the safety, regulatory and manufacturing considerations governing translation.
Key findings. SLNs deliver drug to the skin through three interacting mechanisms: formation of an occlusive lipid film that reduces transepidermal water loss and hydrates the stratum corneum, size-dependent surface contact and follicular deposition, and sustained release from a solid lipid matrix. Across the formulations reviewed — fluticasone propionate, tacrolimus, ebastine, etofenamate, ibuprofen, curcumin, resveratrol, quercetin and leflunomide — encapsulation consistently improved physical and photochemical stability and moderated the release profile relative to free drug. Where studies progressed to animal disease models, comparable or superior anti-inflammatory efficacy was achieved at substantially reduced doses, including an 8- to 16-fold dose reduction for etofenamate and ibuprofen.
Conclusion. The mechanistic case for SLN-based topical therapy in infantile dermatitis is coherent and is supported by consistent adult and adult-animal data. It is not, however, supported by pediatric evidence. No permeation study identified used infant or neonatal skin, no in vivo study used a neonatal or juvenile animal model, no clinical trial of an SLN formulation for infantile dermatitis was identified, and no regulatory authority has approved such a product. Until pediatric-specific pharmacokinetic, irritation and safety data are generated, SLN delivery for infantile dermatitis should be regarded as a mechanistically promising but clinically unproven strategy.
Keywords: solid lipid nanoparticles; nanostructured lipid carriers; infantile atopic dermatitis; topical drug delivery; pediatric formulation; skin barrier

1. INTRODUCTION

1.1 Disease burden and epidemiology

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that often travels alongside asthma, allergic rhinitis and food allergy [1]. It is common - an estimated 15–20% of children and 1–3% of adults are affected worldwide - and its burden reaches beyond the skin itself: pruritus disrupts sleep in nearly all patients, and families absorb the cost in physician visits, medication and missed school or work [1].

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Reported cumulative incidence ranges from 11% to 21% depending on age group and region [2]. In a clinicoepidemiological study from northern India, infants with AD had a mean onset of 4.2 months and a disease duration of 3.3 months, against a 4.1-year mean onset and 1.9-year duration in older children, with urban children over-represented [3]. A hospital-based study from the same region found AD to be the single commonest skin condition among pediatric dermatology attendees (29.9% of cases; male-to-female ratio 2.25:1; mean onset 4.5 months), with infants presenting mainly as facial, acute eczema and older children showing more chronic, variable disease; symptoms worsened in winter for 62% of patients [4]. A much lower prevalence, 0.42%, was reported among dermatology outpatients in eastern India [5] - a spread that reflects how much regional methodology, not just regional biology, shapes these numbers.

Only three drug classes carry FDA approval for topical AD therapy: corticosteroids, two calcineurin inhibitors, and one phosphodiesterase-4 (PDE4) inhibitor. Because AD is usually lifelong, the treatment needs to be both effective and tolerable long-term. Topical corticosteroids (TCS) remain first-line, but sustained use brings real risks - thinning skin, telangiectasia, striae, and occasionally enough systemic absorption to affect the hypothalamic-pituitary-adrenal axis [6–7] - and these risks are not abstract to caregivers: steroid apprehension is well documented and it undermines adherence [8]. Topical calcineurin inhibitors (pimecrolimus, tacrolimus) have been marketed since 2000; a 2006 boxed warning over a theoretical malignancy risk has not been borne out by later research [9]. Crisaborole, the PDE4 inhibitor, was approved in 2016 and has shown an encouraging early safety record.

1.2 Infant skin physiology relative to adult skin

Infant skin is not simply a smaller version of adult skin - it differs across structural, biochemical and functional parameters, several of which bear directly on how a topical formulation behaves once applied. The stratum corneum and overall epidermis are thinner, corneocytes are smaller, natural moisturizing factor and water-holding capacity are reduced, and transepidermal water loss is elevated at birth and falls only gradually thereafter. Melanocytes and Langerhans cells remain functionally immature, and surface pH runs higher. Together, these features leave a barrier that is more permeable, more easily irritated and less able to hold water than its adult counterpart (Table 1).

Table 1. Structural and functional characteristics of healthy infant skin compared with adult skin.

Parameter	Healthy infant skin compared with adult skin
Epidermal cell size	Smaller corneocytes and keratinocytes [10]
Epidermal surface	Denser network of surface microrelief [10]
Epidermal thickness	Stratum corneum approximately 30% thinner; overall epidermis approximately 20% thinner [10]
Dermal organization	More uniform dermal papillae; extensive but less organized vascular network; lower density of collagen fibre bundles [10–12]
Natural moisturizing factor (NMF)	Lower [13]
Melanin	Lower [14]
Water content	Lower at birth, rising gradually over the first year [10]
Cell turnover	Higher [10]
Hydration and water-holding capacity	Lower hydration at birth, peaking between 3–12 months; water-holding capacity remains lower [10,13]
Immunological barrier	Epidermal Langerhans cells not yet fully matured [14]
Skin pH	Higher [10]
Photoprotection	Melanocytes not yet fully matured [14]
Sebaceous activity	Higher at birth, dropping sharply within the first few days [15]
Transepidermal water loss (TEWL)	Higher at birth, decreasing gradually over the first few years [14]

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1.3 Current standard of care and its limitations in infants

Topical corticosteroids (TCS) remain the anti-inflammatory cornerstone of AD treatment, particularly for flares, once basic skin care and moisturizing alone prove insufficient. Repeated courses of low- to mid-potency TCS applied until clearance are supported by RCT evidence extending to five years in children and one year in adults [16], and a proactive strategy - twice-weekly application to stabilized skin to pre-empt flares - has outperformed reactive treatment alone in a year-long pediatric RCT [17–18]. The British National Formulary sorts TCS into four potency tiers [19], and judicious use of low- to mid-potency agents carries an acceptable long-term safety profile. Higher-potency formulations used over extended periods, however, can cause striae, atrophy, telangiectasia, burning and acneiform eruptions, and rare systemic effects such as HPA-axis suppression occur more often in children, whose body-surface-to-mass ratio runs roughly 2.5 to 3 times that of adults [20]. Twice-weekly proactive dosing has not itself been linked to atrophy [17], though no consensus exists on how much TCS to apply per use.

Topical calcineurin inhibitors (TCIs) - tacrolimus and pimecrolimus - have been approved for AD since 2002, with RCT support for twice-daily intermittent use from three months of age and follow-up extending to five years [21]. A meta-analysis of 25 RCTs found 0.1% tacrolimus comparable to mid-potency hydrocortisone butyrate 0.1%, while 0.03% tacrolimus underperformed that comparator but beat low-potency hydrocortisone acetate 1% [22]. Approved ages differ by product (pimecrolimus 1% and tacrolimus 0.03% from age 2; tacrolimus 0.1% from age 16), and proactive tacrolimus use has shown year-long effectiveness and safety in both children and adults. The most common adverse effect, a transient burning sensation, resolves within a week in roughly 80% of patients; TCIs do not raise bacterial infection risk, though herpes simplex risk is modestly elevated [23]. The 2006 malignancy boxed warning has not been substantiated by long-term controlled trials or registry data, including the largest and longest pediatric pimecrolimus study to date [24].

Emollients sit at the centre of AD management because xerosis and barrier impairment define the disease. Regular moisturizer use repairs barrier structure, cuts transepidermal water loss and restores the lipid barrier's water-handling capacity [25], with RCT evidence for both short- and long-term steroid-sparing effects and flare prevention [26]. No trial has fixed an optimal dose, but guidance generally calls for at least twice-daily application - roughly 250 g weekly in adults [27] - applied within three minutes of bathing and continued even once AD has cleared. Newer prescription emollient devices have shown no clear advantage over over-the-counter moisturizers in head-to-head trials [28]. Some ingredients carry their own anti-inflammatory activity: an aloe vera-olive oil cream matched 0.1% betamethasone for chronic sulfur-mustard-exposure lesions over six weeks [29], virgin coconut oil showed moderate activity in a rat ear-oedema model [30], and shea butter's triterpene esters have shown anti-inflammatory and antitumor effects in vivo and in vitro [31]. In practice, the most reliable way to limit steroid exposure combines consistent baseline emollient care with early anti-inflammatory treatment to head off flares before they escalate [32].

Why this matters more in infants. Four constraints converge in this population: a proportionally larger body surface area relative to mass raises the risk of meaningful systemic corticosteroid absorption; extended or improper potent-steroid use can atrophy skin that is already thinner; sustained anti-inflammatory therapy needs a level of clinical oversight that is not always available; and frequent reapplication, compounded by caregiver anxiety over steroid side effects, undermines adherence. A delivery system that concentrates drug at the application site, sustains local availability and limits the fraction reaching systemic circulation would address all four at once.

1.4 Rationale for lipid nanoparticle-based delivery

Skin is the body's primary barrier against chemical, mechanical, physical and microbial insult, yet it remains vulnerable to rashes, infection, burns, wounds and tumours [33–39]. Topical delivery treats disease directly at the site and can limit systemic exposure, but its effectiveness hinges on the vehicle's ability to actually get drug into the skin. Conventional creams, gels, ointments, pastes and oils are widely used but limited by poor penetration, local irritation and weak drug retention, which has pushed nanotechnology-based delivery - designed to improve penetration, stability and controlled release - to the forefront of skin-disorder therapeutics [40–41].

Among the lipid-based nanosystems explored for topical use - liposomes, ethosomes, transferosomes, SLNs, NLCs, cubosomes and monoolein dispersions - biocompatibility and lipid composition allow efficient loading of lipophilic drugs, controlled release, improved bioavailability and fewer adverse effects [42–43]. Their compositional resemblance to native stratum corneum lipids promotes skin interaction, hydration and potentially deeper penetration.

SLNs and NLCs stand out for dermal use because of their solid lipid matrix and controlled-release capacity: SLNs are built mainly from solid lipids, while NLCs blend solid and liquid lipids to create structural imperfections that raise drug-loading capacity. Both are typically made from biocompatible, GRAS lipids, and both can protect drugs from degradation while improving skin adhesion and penetration. Their small size also produces an occlusive film that lowers transepidermal water loss and raises stratum corneum hydration - potentially enhancing permeation

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while independently treating barrier-compromised skin. In an infant with dermatitis, where the barrier is already impaired and the safety margin is narrow, that combination is not incidental - it targets the specific pharmacological problem this population presents.

1.5 Objective and scope

This review builds the case for, and weighs the evidence gaps against, SLN-based topical therapy in infantile dermatitis, moving through carrier architecture and production (Section 3), the mechanisms of cutaneous delivery and their relevance to an immature barrier (Section 4), the published formulation evidence for dermatitis-relevant actives (Section 5), and the toxicological, regulatory and manufacturing picture (Section 6). Throughout, it draws a clear line between what has been shown in adults and adult animal models and what has been shown in infants, since that boundary - not any mechanistic doubt - is the main obstacle to clinical translation.

2. MATERIALS AND METHODS

Literature was retrieved from PubMed, Scopus, ScienceDirect and Google Scholar, with targeted searches of ClinicalTrials.gov, Google Patents and WIPO PATENTSCOPE for trial and intellectual-property status, and of the FDA, EMA and ICH repositories for regulatory guidance. The search covered January 2000 to the date of submission, prioritizing work from the preceding seven years while retaining older sources that describe foundational methodology still in use.

Search terms combined four clusters: carrier terms ("solid lipid nanoparticles", "SLN", "nanostructured lipid carriers", "NLC", "lipid nanoparticles"); route terms ("topical", "dermal", "transdermal", "skin permeation", "follicular delivery"); disease terms ("atopic dermatitis", "eczema", "allergic contact dermatitis", "infantile dermatitis", "pediatric dermatology"); and active-agent terms ("corticosteroid", "tacrolimus", "pimecrolimus", "antihistamine", "curcumin", "quercetin"). Reference lists of retrieved reviews were hand-searched for additional primary studies.

A study was carried forward for the Section 5 evidence base if it described an SLN or NLC system loaded with a drug relevant to inflammatory skin disease - corticosteroids, calcineurin inhibitors, antihistamines, NSAIDs or plant-derived anti-inflammatory actives - and reported at least basic physicochemical characterization alongside a permeation, release or efficacy endpoint. Studies confined to non-inflammatory indications (isolated antifungal or oncology applications, for instance) were excluded unless they offered a directly useful methodological comparison, and only English-language publications were included. This is a narrative rather than a systematic review: no formal risk-of-bias assessment or quantitative synthesis was undertaken, and the search was not registered.

3. RESULTS AND DISCUSSION

This section presents and discusses the findings drawn from the literature review, moving through carrier technology and composition, mechanisms of cutaneous delivery, the formulation evidence base, and the safety, regulatory and translational picture.

Solid lipid nanoparticles are colloidal drug carriers built from a lipid matrix that stays solid at both room and body temperature, dispersed in an aqueous medium and stabilized by one or more surfactants. First introduced in the early 1990s as an alternative to liposomes, polymeric nanoparticles and conventional emulsions, SLNs occupy a submicron size range generally cited as roughly 50–1000 nm [44]. The matrix draws on physiological, biodegradable, biocompatible lipids that accommodate lipophilic and, to a lesser extent, hydrophilic actives - a property well suited to the anti-inflammatory and antipruritic agents relevant to infantile dermatitis [44]. This section covers the structural classification of lipid nanoparticles, their building blocks, the main production routes and the physicochemical parameters used to characterize them.

3.1 Definition and structural concept

Structurally, an SLN can be pictured as an oil-in-water nanoemulsion in which the dispersed lipid droplet has been replaced by a solid lipid core - the solid state at physiological temperature being what separates SLNs from nanoemulsions, whose dispersed phase stays liquid. That rigidity governs how drug is retained and released: depending on lipid composition, drug-lipid interactions and processing conditions, the drug may dissolve within the matrix or sit closer to the particle surface, and these structural choices in turn set drug loading, entrapment efficiency, particle size, release kinetics and physical stability 44.

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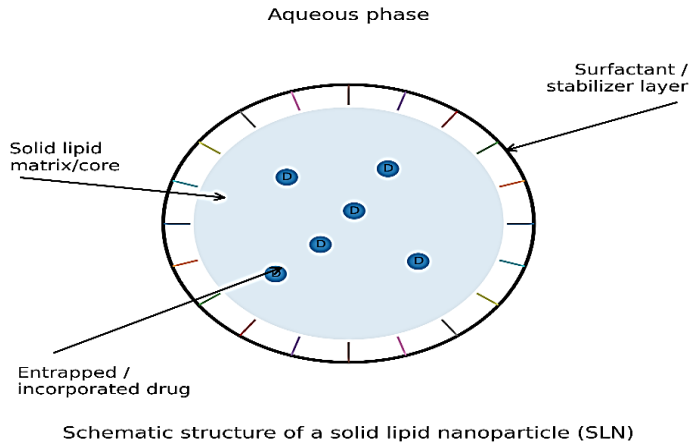

Figure 1. Schematic structure of a solid lipid nanoparticle (SLN).

3.2 First-generation SLN versus second-generation NLC

SLNs are conventionally treated as the first generation of solid lipid carrier systems at the nanometre scale [45]. Relative to earlier colloidal systems, they offer controlled or sustained release, protect chemically unstable molecules such as retinoids and peptides from degradation, rely on relatively low-cost and pharmaceutically acceptable excipients, and work across oral, parenteral, ocular, pulmonary and dermal routes [45]. The same highly ordered crystalline lattice that gives them this stability, though, brings two well-known limitations: drug loading is often low, and drug can be expelled during storage as the matrix shifts from the less-ordered α form toward the tightly packed, thermodynamically stable β form generated during cooling and crystallization [44,46].

Nanostructured lipid carriers were developed as the second generation specifically to address these gaps [44–45]. The NLC matrix blends a solid lipid with a liquid lipid (oil) at a ratio that keeps the mixture solid at room and body temperature; the liquid lipid disrupts the regular crystal lattice, opening structural irregularities that accommodate more drug and amorphous clusters. NLCs generally achieve higher loading, less storage-related drug expulsion, and better long-term physical stability than conventional SLNs as a result [44,47], and fall into three recognised subtypes: imperfect-type, where a moderate amount of liquid lipid creates lattice defects while the particle largely retains its solid character; amorphous-type, where the lipid blend is chosen to solidify without crystallizing and so avoid the polymorphic shifts that expel drug; and multiple-type (oil-in-solid-lipid-in-water), where small oil compartments dispersed through the solid matrix - analogous to a w/o/w emulsion - allow higher loading of very lipophilic actives while the surrounding shell still confers controlled release.

For topical delivery, the choice between SLN and NLC comes down to the drug's physicochemical properties and the required loading capacity, release profile and stability, with NLCs generally favoured where higher loading and reduced storage expulsion matter most [44–45,47].

3.3 Composition

Solid lipids form the structural backbone and are typically drawn from four categories: fatty acids (stearic, palmitic acid); mono-, di- and triglycerides and complex glyceride mixtures (glyceryl monostearate, glyceryl behenate/Compritol® 888 ATO, glyceryl palmitostearate/Precirol® ATO 5, tripalmitin, trilaurin); waxes (cetyl palmitate, beeswax); and steroids (cholesterol) [44,48]. Chain length, branching and lipid purity influence matrix crystallinity, which in turn affects loading, entrapment efficiency and the likelihood of a polymorphic shift during storage.

Liquid lipids for NLC formulation - commonly medium-chain triglycerides, oleic acid, isopropyl myristate, or vegetable oils such as almond, sunflower or coconut oil - are blended with the solid lipid to disrupt its crystalline structure, opening space for more drug while the matrix stays solid at room and physiological temperature [44–45].

Surfactants and stabilizers adsorb at the lipid-water interface during production, lowering interfacial tension and stabilizing the particles electrostatically and/or sterically. Non-ionic surfactants are generally preferred for their lower irritancy - a consideration that matters more for an infant-facing product. Poloxamer 188, a triblock PEO-PPO-PEO copolymer, is widely used for steric stabilization [49], while polysorbates (Tween 20/80) and sorbitan esters (Span series) are chosen by hydrophilic-lipophilic balance [48,50]. PEGylated stabilizers such as macrogol-15-hydroxystearate add steric stabilization, and phospholipids like soy or egg lecithin can serve as co-surfactants that improve biological-membrane compatibility [48]. Ionic surfactants (sodium cholate, sodium deoxycholate, sodium dodecyl sulfate) improve emulsification and modulate surface charge but carry a higher

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irritation risk, so surfactant choice should track both the administration route and the formulation's specific requirements [48,50].

3.4 Production methods

SLNs and NLCs can be manufactured by high-energy (mechanical) and low-energy (emulsification- or solvent-based) techniques. The four methods most widely reported for dermatological development are compared in Table 2 [51–53].

Table 2. Comparison of the principal production methods used for SLNs/NLCs.

Method	Principle	Advantages	Limitations
Hot high-pressure homogenization (HPH)	Drug-loaded lipid melt is pre-emulsified, then forced through a narrow homogenizing gap (100-2000 bar); recrystallizes on cooling	Solvent-free; fast; scalable to pilot/industrial batches; narrow, reproducible size distribution	Thermal/shear stress unsuitable for heat-labile actives; possible drug loss to the aqueous phase; aggregation on cooling/storage
Microemulsion dilution	A warm, transparent O/W microemulsion is diluted into excess cold water (2-3 degC); particles precipitate instantly	Low mechanical energy; no specialized equipment; mild conditions suit labile drugs	High surfactant load; dilute product needs downstream concentration; batch reproducibility and scale-up are hard
Solvent emulsification-diffusion/evaporation	Lipid dissolved in a partly water-miscible solvent, emulsified into aqueous surfactant, then solvent removed	Room-temperature process; suits thermolabile and peptide actives	Residual solvent is a regulatory concern, especially for infant products; lower loading; slower processing
Ultrasonication/high-shear homogenization	Lipid melt dispersed by rotor-stator mixing, then probe-sonicated before cooling	Simple, low-cost, accessible bench-scale equipment	Broad size distribution; possible metal contamination from probe erosion; poor reproducibility

Beyond these, emerging techniques - microfluidic mixing, phase-inversion temperature processing, membrane-contactor methods and supercritical-fluid production - offer finer control over particle characteristics and can cut or eliminate organic solvent use, though their suitability still depends on formulation, process requirements, scalability and the drug involved [51]. For a pediatric topical formulation, method choice should weigh residual solvents, reproducibility, scalability and API stability, with solvent limits and excipient burden carrying extra weight relative to an adult product.

3.5 Characterization parameters

A consistent panel of characterization parameters is essential for formulation optimization and batch-to-batch reproducibility. Table 3 summarizes the parameters commonly reported in the SLN/NLC literature, the techniques used to determine them, and the typical ranges reported for dermal formulations [54–55].

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Table 3. Core physicochemical characterization parameters for SLNs/NLCs.

Parameter	Technique	What it shows	Typical dermal range
Particle size and PDI	Dynamic light scattering	Mean hydrodynamic diameter and size homogeneity; influences skin deposition and follicular access	~70-300 nm; PDI < 0.3 generally acceptable
Zeta potential	Electrophoretic light scattering	Net surface charge and indicator of colloidal stability (sterically stabilized systems can remain stable at lower absolute values)	Typically -10 to -45 mV, lipid/surfactant-dependent
Entrapment efficiency (%EE)	Ultracentrifugation/ultrafiltration + UV or HPLC assay of free drug	Proportion of drug entrapped within the particles	~60% to >95%, depending on drug lipophilicity and lipid crystallinity
Crystallinity/polymorphism	Differential scanning calorimetry (DSC)	Thermal behaviour, degree of crystallinity, polymorphic form, drug-lipid interactions	Melting endotherm often depressed and broadened relative to bulk lipid
Crystal structure	X-ray diffraction (XRD/PXRD)	Lattice structure; attenuated drug peaks can indicate amorphization	Attenuation/disappearance of sharp drug diffraction peaks
Morphology	TEM/SEM/AFM	Particle shape and surface texture; complements DLS sizing	Predominantly spherical to near-spherical, smooth-surfaced

Particle size and PDI shape drug release, skin deposition and follicular localization: smaller, more homogeneous nanoparticles achieve closer surface contact and may favour follicular deposition, though formulation and skin condition both modulate the effect [56]. Zeta potential indicates colloidal stability, but its reading depends on whether stabilization is mainly electrostatic or steric [49]. DSC and XRD/PXRD are complementary solid-state techniques - the former tracking thermal behaviour and crystallinity, the latter crystal structure and polymorphic state [48] - and together with morphological data they give a coherent picture of a formulation's physicochemical properties and stability [48–49].

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4. MECHANISMS OF CUTANEOUS DELIVERY AND SUITABILITY FOR INFANT SKIN

A topical formulation's clinical performance depends heavily on how the delivery system moves drug across the stratum corneum while controlling its distribution over time and depth. SLNs have drawn interest here [50,57] because they promote dermal and transdermal penetration, act as a drug reservoir, maintain skin hydration and protect labile actives from degradation [58–59] - properties that, in infantile dermatitis, map directly onto the therapeutic problem rather than being merely convenient. This section covers how nanoparticles interact with skin, the specific mechanisms by which SLNs improve delivery, and why those mechanisms matter for an immature barrier.

4.1 Skin penetration pathways for nanoparticles

The stratum corneum is the skin's principal barrier: corneocytes embedded in a continuous lipid matrix present substantial resistance to macromolecules and particulate carriers seeking deeper access [60]. Nanoparticles cross this barrier via one of three routes - intercellular, transcellular or follicular (appendageal) - with the intercellular route generally dominant since tight junctions between corneocytes restrict most transcellular movement [61–62]. The relative contribution of each pathway shifts with the nanoparticle's physicochemical properties, its vehicle, skin condition, application site and local barrier integrity [63].

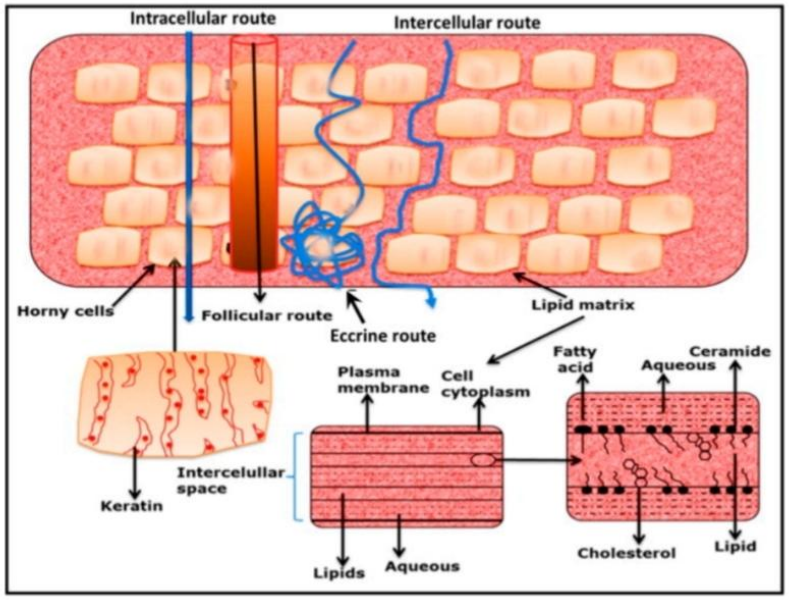

Figure 2. Routes of drug penetration through the skin, showing the intracellular, intercellular, follicular and eccrine (transappendageal) pathways across the horny cell layer and lipid matrix.

Via the **intercellular route**, drug molecules and small particles travel through the lipid-rich spaces between corneocytes, favouring small, lipophilic molecules that partition readily into that environment; the **transcellular route** requires passage through the corneocytes themselves and is considerably more resistant owing to their structural rigidity [62–63]. Most nanoparticle systems applied to skin accumulate in the outer stratum corneum rather than reaching transdermal depths, so it is prudent to assume intact particles do not generally penetrate far beyond the superficial layers [64]. Hair follicles interrupt the stratum corneum at intervals, creating shunt pathways - the **follicular route** - that let nanoparticles bypass sections of the intact barrier and accumulate in the follicular infundibulum [65]. This matters for pediatric use specifically: infant skin carries a higher density of hair follicles per unit area than adult skin, so follicular deposition likely contributes proportionally more to overall nanoparticle delivery in this age group [66].

4.2 SLN-specific mechanisms of skin delivery

An SLN's performance as a topical vehicle depends on several interacting variables - particle size, lipid matrix type and crystalline structure, surfactant composition, drug distribution within the particle, formulation viscosity and the physiological state of the application site - which together shape three principal delivery mechanisms [58]. On application, SLNs deposit on the skin surface and form a largely continuous **lipid film**, with the degree of occlusion depending on particle size, lipid concentration, dose and crystallinity [67–68]. By cutting transepidermal water loss, this film hydrates the outer stratum corneum, which loosens its lipids and widens intercorneocyte spaces, in turn helping the entrapped drug partition into the outer skin layers. The occlusive effect is therefore not

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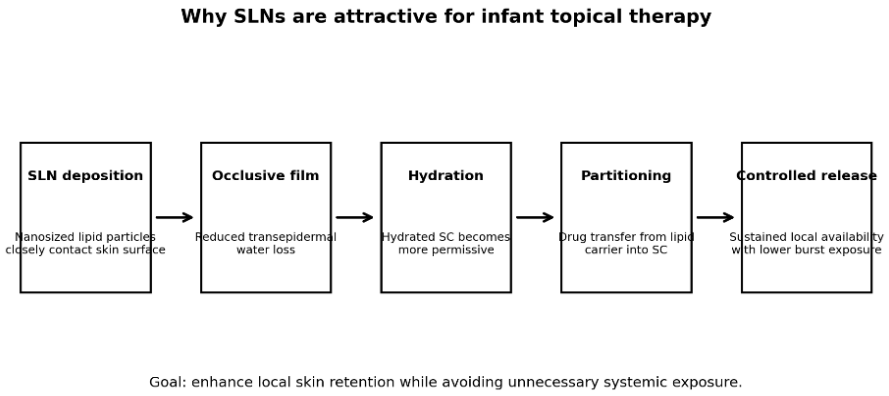
a cosmetic by-product but an active contributor to delivery [68] - and, in dermatitis, a therapeutic effect in its own right, since barrier hydration is itself a treatment goal.

Particle size gives SLNs a large surface-area-to-volume ratio and closer, more even contact with the irregular skin surface; smaller particles generally form better films and stronger occlusion, though smaller does not automatically mean deeper penetration. The available evidence indicates SLNs largely stay at the skin surface and accumulate in follicles, with deeper penetration depending heavily on formulation design [56,64]. Finally, the solid lipid matrix acts as a **reservoir for sustained release**, retaining drug at the application site and releasing it gradually rather than in a burst - avoiding sharp systemic peaks and extending the local therapeutic effect [58], a behaviour of particular value in infants, where confining exposure to the treated area is a primary safety objective [69].

Figure 3. Proposed sequence linking SLN surface deposition, occlusion, hydration, drug partitioning and controlled local release in topical therapy for infant skin.



4.3 Relevance of these mechanisms to infant skin

As Section 1.2 outlined, infant skin differs structurally and functionally from adult skin: the stratum corneum is present from birth but continues maturing over the first few years, during which barrier and water-retention functions stay weaker than in adults [69]. Infants also carry a substantially larger body surface area relative to body weight, exposing proportionally more of the body to any applied agent [70–71] - a combination that leaves infant skin more permeable and more prone to irritation and injury, and more so still with preterm birth, low birth weight or pre-existing dermatitis [71].

This heightened permeability forces a balancing act: enough active agent reaching the affected skin against minimal systemic absorption. Conventional formulations, especially over large or damaged areas, carry a real risk of clinically significant systemic drug levels [20]. SLNs' occlusive, slow-release behaviour addresses this directly, maintaining local drug availability while limiting the systemic fraction [58–59] - the core argument for treating SLNs as a next-generation delivery platform here. It remains, though, a hypothesis grounded in mechanism rather than an established finding: dedicated pediatric pharmacokinetic and safety data are limited, and further work is needed before these benefits can be confirmed clinically [69].

A second advantage is biocompatibility - the lipid excipients used are typically physiological or biodegradable, and skin generally tolerates them well [59] - though biocompatibility is not set by the lipid core alone. Excipient purity, surfactant and preservative choice, particle size and shape, and applied dose all influence irritation potential, and these considerations carry extra weight for infant products, where careful excipient selection and formal irritation testing are mandatory development steps rather than optional ones [48].

4.4 Comparison with other nanocarriers used in dermatitis

SLNs are one of several nanocarrier classes under investigation for topical treatment of inflammatory and infectious skin disease. Liposomes and niosomes are vesicular carriers that can accommodate both hydrophilic and lipophilic drugs [72–73], while polymeric nanoparticles rely on natural or synthetic polymers for controlled release and surface functionality [74]. Table 4 reflects general trends from the literature rather than a strict ranking, since performance varies considerably with formulation and manufacturing method.

Table 4. Qualitative comparison of major nanocarrier classes relevant to topical dermatitis delivery.

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Nanocarrier	Stability	Drug-loading capacity	Skin irritation potential	Relative cost
SLNs	Generally good; polymorphic transition possible	Good for lipophilic actives; matrix-dependent	Low with well-tolerated lipids; excipient choice still matters	Moderate
Liposomes	Lower; prone to oxidation, hydrolysis, leakage, vesicle fusion	Both hydrophilic and lipophilic drugs; retention design-dependent	Usually biocompatible; composition-dependent	Moderate to high
Niosomes	Often more storage-stable than liposomes	Hydrophilic and lipophilic drugs	Surfactant-dependent; excess surfactant may irritate	Low to moderate
Polymeric NPs	Often good; polymer- and process-dependent	Flexible; drug encapsulated or surface-associated	Depends on polymer chemistry and degradation products	Moderate to high

Compared with liposomes, SLNs have a solid, rigid matrix and do not depend on an intact phospholipid bilayer surviving storage, though liposomes retain a genuine edge in carrying aqueous- and lipid-soluble drugs in separate compartments [73]. Niosomes swap phospholipids for non-ionic surfactants, giving good storage stability, simpler preparation and lower cost, though surfactant choice still governs both performance and tolerability [75–76]. Polymeric nanoparticles offer real flexibility for controlled release and surface engineering, but their safety hinges on polymer chemistry, degradation by-products and residual processing materials, so toxicity or tissue-accumulation concerns must be judged formulation by formulation [74] - a formulation-specific uncertainty that is itself a disadvantage for an infant-facing product relative to a carrier built from physiological lipids.

4.5 Drug loading and interim synthesis

SLNs suit the poorly water-soluble actives relevant to dermatitis particularly well: lipophilic corticosteroids partition readily into the hydrophobic core [77], and calcineurin inhibitors (tacrolimus, pimecrolimus) and natural anti-inflammatory compounds (curcumin, quercetin) are similarly good candidates, though whether loading actually improves their anti-inflammatory efficiency at the target site remains an active research question [77]. Successful loading depends on more than drug-lipid affinity - what matters practically is how much drug stays in the particle, the physical state it adopts, its compatibility with other components, its release kinetics and its eventual skin penetration [44]. A highly crystalline matrix tends to expel drug over time, while a less ordered one accommodates a larger payload, which is the mechanistic basis for the NLC modification described in Section 3.2; DSC, XRD, drug-content analysis and in vitro release/permeation testing are the standard ways to confirm a formulation behaves as intended [48].

Taken as a whole, the case for SLNs in infantile dermatitis does not rest on nanoparticles crossing the skin barrier wholesale - it rests on their being engineered to interact with that barrier in a controlled, predictable way. Nanoscale size raises surface contact with the stratum corneum, the lipid matrix forms an occlusive film, the resulting hydration promotes drug partitioning into the superficial skin, and the solid matrix governs release rate. For infants, that combination could support effective local therapy while reducing the need for high concentrations of freely available drug [58] - but because infant skin behaves unpredictably with respect to permeability and clearance, any candidate formulation still needs formal evaluation for irritation, sensitization, local retention, permeation and systemic exposure, particularly where the barrier is already inflamed [69]. SLNs remain a mechanistically sound platform for next-generation topical treatment here, especially for lipophilic drugs where the goal is sustained local presence with limited systemic exposure - but these are potential benefits awaiting pediatric-specific validation, not demonstrated clinical superiority.

5. EVIDENCE BASE: REPORTED SLN AND NLC FORMULATIONS FOR DERMATITIS-RELEVANT ACTIVES

5.1 Formulations across drug classes

Among corticosteroid systems, fluticasone propionate has been formulated as a semi-solid NLC using a quality-by-design approach, treating particle size and release rate as the critical attributes [78]. The optimized formulation reached ~188 nm (PDI ~0.23) and released only about 11% of loaded drug over 24 hours - the slowest release

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among the semi-solid NLCs tested, favouring once- or twice-daily dosing - and, unusually for this pool, was carried through to a rat model of chronic atopic dermatitis across skin-bleaching, paw-oedema, transepidermal-water-loss and histopathology endpoints, outperforming the conventional comparator on both efficacy and safety [78].

Tacrolimus poses a different problem: as a BCS class II molecule with low aqueous solubility and a molecular weight above 800 Da, it penetrates intact stratum corneum poorly, and the marketed ointment is widely reported to leave a greasy, tacky film - a compliance issue that matters more with an infant or toddler likely to rub the treated site [79]. Chitosan-decorated tacrolimus SLNs prepared by solvent evaporation gave particles of 439-669 nm with 69-84% entrapment efficiency; zeta potential for the uncoated particles ran -26 to -15 mV but reversed to positive after chitosan coating, which the authors tie to better electrostatic interaction with the negatively charged skin surface and improved retention over inflamed sites [79].

For allergic contact dermatitis, where oral antihistamines are conventionally paired with topical steroids despite the atrophy risk, ebastine-loaded SLNs (Compritol® 888 ATO/Tween 80, optimized by central composite design) produced ~155 nm particles with zeta potential near -16 mV and entrapment above 78% [80]. Embedded in a chitosan hydrogel - chitosan chosen partly for its own mild anti-inflammatory contribution - the system sustained release to 24 hours, somewhat slower in the hydrogel (~74%) than as a plain dispersion (~83%), and is one of the few studies here with a genuine disease-model endpoint: tested against picryl chloride-induced allergic contact dermatitis in BALB/c mouse ears over 15 days, ear swelling, mast cell counts and histopathology all showed symptom relief relative to untreated controls [80].

NSAID-loaded SLNs offer a useful reference point beyond dermatitis-specific actives. Etofenamate and ibuprofen were encapsulated in Compritol-based SLNs by fusion-emulsification, reaching entrapment efficiencies above 90%, particle sizes below 250 nm and twelve months of physical stability with scalable production [81]. Franz diffusion cell studies on human skin showed higher permeation than marketed comparator gels, and a rat paw-oedema model found SLN hydrogels containing roughly 8-fold less etofenamate and 16-fold less ibuprofen produced comparable anti-inflammatory effects to the commercial formulations, with no epidermal histological changes [81] - arguably the single most persuasive in vivo evidence here that SLN encapsulation lowers the effective dose and, by extension, systemic exposure.

The plant-derived literature is smaller but growing. Curcumin and resveratrol, esterified with oleic acid and co-formulated with linolenic acid in an SLN system, showed no meaningful cytotoxicity in keratinocyte (NCTC 2544) or monocyte (THP-1) lines and suppressed IL-6 in the keratinocyte line - a cytokine directly implicated in dermatitis inflammation [82]. Quercetin has drawn more attention: an early solvent-free solid lipid nanosystem built on glyceryl dibehenate stayed physically stable for eight weeks refrigerated [83], and a more recent formulation embedding quercetin-loaded lipid nanoparticles in a Carbopol hydrogel validated a stability-indicating HPLC-PDA assay and confirmed retained antioxidant activity through accelerated and long-term storage [84]. A related but non-SLN vesicular quercetin system tested on TPA-inflamed mouse dorsal skin found 5% PEG gave the greatest reduction in oedema and leukocyte infiltration among the ratios tested [85] - outside the strict SLN/NLC definition used elsewhere here, but useful supporting evidence for quercetin's topical anti-inflammatory activity once nanoencapsulated. Finally, leflunomide-loaded SLNs, developed for psoriasis rather than dermatitis, add further weight: prepared by microemulsion, the ellipsoidal particles (~273 nm, ~65% entrapment, >93% drug content) showed significantly improved photostability ($p < 0.001$) and better in vitro anti-inflammatory activity than free drug [86].

Across drug classes, a consistent picture holds: SLN/NLC encapsulation tends to improve stability and moderate the release profile relative to free drug, and in the studies that reached in vivo testing, this translated into comparable or better efficacy at meaningfully lower doses.

5.2 Permeation, in vivo evidence and the pediatric gap

Sustained rather than burst release is a recurring theme - most strikingly the fluticasone NLC's 11% release at 24 hours [78], with the ebastine and etofenamate/ibuprofen systems showing a comparable if less pronounced pattern [80–81] - and this favours less frequent dosing and lower cumulative skin exposure, a real consideration for infants whose barrier is still maturing. None of the permeation or retention data reviewed, however, was generated on infant or neonatal skin: every ex vivo and in vitro permeation study identified used adult human, porcine or synthetic membrane models, so extrapolating to an infant's thinner, more permeable stratum corneum remains an assumption rather than a finding - and since infant skin is more permeable, the likely direction of error is not a conservative one.

In vivo evidence is more substantial than a first pass through the abstracts suggests: three studies went beyond physicochemical characterization to a genuine disease or inflammation model - the fluticasone NLC in a rat chronic-AD model [78], the ebastine SLN hydrogel in a mouse allergic-contact-dermatitis model [80], and the etofenamate/ibuprofen SLN hydrogel in a rat paw-oedema model, which additionally showed meaningful dose-sparing [81]. The curcumin/resveratrol work stops at the cellular level [82], and the TPA-induced mouse model used

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for the vesicular quercetin system sits outside the strict SLN definition [85]. Even on this stronger base, one gap holds across every study: not one tested a dermatitis formulation in a neonatal or juvenile animal model, let alone in infants - every in vivo data point traces back to adult humans or adult rodents. That gap, stated plainly rather than glossed over, is the largest single obstacle between the mechanistic case built in Section 4 and actual clinical use in infantile dermatitis.

5.3 Stability

Long-term stability was reported inconsistently across the pool, but the available results are encouraging: the etofenamate/ibuprofen SLNs held stable for twelve months [81], the quercetin solid lipid nanosystem for eight weeks refrigerated [83], and the leflunomide system showed a statistically significant photostability gain over free drug [86]. Where NLCs rather than conventional SLNs were used, studies did not report the drug-expulsion problems that affect first-generation SLNs on storage - consistent with the mechanistic rationale for NLC development given in Section 3.2.

5.4 Consolidated summary of reviewed formulations

Table 5. Summary of SLN and NLC formulations reported for dermatitis-relevant active pharmaceutical ingredients.

API	Carrier system	Particle size	Entrapment efficiency	Key finding	Ref.
Fluticasone propionate	QbD-optimized semi-solid NLC	~188 nm (PDI 0.229)	Not reported	Superior efficacy/safety vs. conventional formulation in rat chronic AD model	[78]
Tacrolimus	Chitosan-coated SLN gel	439-669 nm	68.95-83.68%	Chitosan coating reverses zeta potential to positive; improved retention at inflamed sites	[79]
Ebastine	SLN (Compritol/Tween 80) in chitosan hydrogel	155.2 +/- 1.5 nm	>78%	In vivo efficacy in mouse ACD model over 15 days; sustained 24 h release	[80]
Etofenamate and ibuprofen	SLN (Compritol/Tween 80)	<250 nm	>90%	8-16-fold dose reduction with comparable efficacy in rat paw oedema model; 12-month stability	[81]
Curcumin + resveratrol	SLN (oleic acid-esterified, with linolenic acid)	Not reported	Not reported	No cytotoxicity in skin cell lines; IL-6 suppression	[82]
Quercetin	Solvent-free solid lipid nanosystem (glyceryl dibehenate)	Not reported	Not reported	8-week refrigerated stability; optimized topical delivery of a poorly soluble flavonoid	[83]
Quercetin	Lipid nanoparticle-Carbopol hydrogel	~104 nm (PDI 0.12)	Not reported	Validated stability-indicating HPLC-PDA assay; >90% retention and preserved antioxidant/anti-inflammatory activity after 180-day storage	[84]
Leflunomide	SLN (microemulsion) in hydrogel	273.1 nm	65.25 +/- 0.95%	Improved photostability ($p < 0.001$) and in vitro anti-inflammatory activity vs. free drug	[86]
Quercetin (vesicular, non-SLN)	PEG-containing phospholipid vesicles	Varies with PEG%	Not reported	Greatest oedema and leukocyte reduction at 5% PEG in TPA-induced mouse model	[85]

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6. SAFETY, REGULATORY STATUS AND TRANSLATIONAL OUTLOOK

6.1 Toxicological and biocompatibility profile

Most reports on cutaneous SLNs describe formulations built from glyceryl monostearate, stearic acid, Precirol® ATO 5, Compritol® 888 ATO, and mono-, di- and triglycerides, stabilized with Poloxamer 188 or 407, Tween 80, or lecithin [87–88]. Because these materials resemble native skin lipids and sebum, SLNs are generally considered low-irritancy and well tolerated, particularly against polymeric or strongly surfactant-based alternatives [88]. Laboratory data offer qualified support: exposure of cultured HaCaT and NCTC 2544 keratinocytes and dermal fibroblasts to empty or drug-loaded SLNs did not reduce viability relative to controls, and topical application in animals produced no overt toxicity [88–89]. But a recent assessment of SLNs/NLCs for atopic dermatitis notes that long-term or continuous treatment, and nanoparticle accumulation or re-entry, have not been studied, despite reports that glyceryl monostearate can alter dermal fibroblast behaviour [88], and that nanoparticles have been found to persist in hair follicles for days after application [88] - both concerns that carry extra weight in children, whose follicular permeability is greater and whose smaller body size raises the systemic consequence of any absorbed dose.

The decisive limitation is the population studied. Nearly all work on SLN excipient tolerability, pharmaceutical performance and clinical behaviour has been done in adults or adult animals, and adult skin differs from infant skin in two material respects - barrier function and the ratio of skin surface area to body weight, the latter especially consequential since an equivalent applied dose has a much larger systemic effect in a child. None of the studies reviewed accounted for this, none examined SLN biocompatibility in infants or children, and the term “infantile dermatitis” appeared in the title or abstract of none of them. On the available evidence, SLNs have not been adequately characterized for this clinical setting and cannot presently be recommended for use in infants.

6.2 Regulatory considerations

ICH E11(R1), which governs pediatric clinical studies, holds that formulations should be chosen for a child’s physiological needs rather than age alone, accounting for excipient safety, tolerability and the practicability of caregiver dosing [90]. ICH E11A, on pediatric extrapolation, is directly relevant here given that virtually all available SLN safety and efficacy data comes from adult studies [91]. The FDA and EMA both align with ICH guidance and require pediatric formulations to be designed for ease of administration with demonstrably safe excipients [90–92], though regional divergence in requirements can still complicate simultaneous approval across jurisdictions. No SLN-based medicine for infantile dermatitis, atopic or otherwise, appears to have been approved by any major regulator; the only SLN-containing consumer product identified is a Polish moisturizer with no indication for inflammation or infection, and all reviewed AD studies were in vitro, in animals, or in adults. SLNs for cutaneous use in infantile dermatitis should accordingly be regarded as unapproved and unproven.

6.3 Patents, clinical trials and commercialization

A review of Google Patents and WIPO PATENTSCOPE, together with recent patent-focused literature, points to substantial research interest in lipid nanoparticle production and stabilization - patent WO2019055525A1 describes a method for reducing Ostwald ripening [93], and patent reviews identify multiple filings covering dermal, ocular and injectable SLN systems [94–95] - but no patent specifically addressing SLN production for infantile dermatitis was identified. A ClinicalTrials.gov search for SLN trials in pediatric skin conditions returned no relevant entries; the closest match is a terminated early-phase trial of a doxycycline nanoparticle hydrogel for atopic dermatitis (NCT02910011) [96], the only nanoparticle-medicine trial for AD identified in this review. A broader “atopic dermatitis” search returned roughly 76 trials, none concerning infantile dermatitis or lipid nanoparticles [97] - an absence of clinical data worth stating plainly rather than assuming away.

6.4 Manufacturing, scale-up and translational barriers

Laboratory-scale SLN preparation by high-shear homogenization, hot/cold homogenization or ultrasonication does not translate directly to continuous, high-volume production at therapeutic quality and consistency. Scale-up reviews point to high-pressure homogenization and membrane-based methods as the most promising routes, though both need careful optimization of temperature, pressure and flow rate [53,98–99], and solvent removal, where required, adds further process complexity. Continuous manufacturing is generally disfavoured in pharmaceutical production because of batch-qualification difficulty, though it has worked elsewhere - notably for complex lipid nanoparticles in mRNA vaccine delivery - so a comparable approach for SLNs is plausible but would need substantial development work.

A further challenge is the metastability of SLN dispersions: Ostwald ripening, where the lipid shifts from a less to a more stable crystal form with effective dissolution of smaller particles, degrades the system over time [100–101], and particles may also agglomerate, raising mean size and suspension viscosity. Both phenomena matter more, not less, for a product meant for frequent application to a child, which must hold specification across a

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commercially viable shelf life. Cost is the final factor: a formulation with these properties - including any cold-chain requirement - combined with the extra preclinical and clinical work needed for pediatric safety and efficacy, would run considerably more expensive than a conventional cream or gel with the same active, and whether that premium is justified depends on the indication and the size of the advantage SLN delivery actually provides.

6.5 Future perspectives

Several studies have combined lipid nanoparticles with secondary delivery vehicles - SLNs embedded in chitosan hydrogels, Carbopol gels and oleogels [80,102–103] - improving spreadability, application comfort and skin residence time, a meaningful consideration for sensitive, easily irritated pediatric skin where site retention drives therapeutic effect. The hydrogel also appears to benefit the nanoparticles themselves, restricting particle mobility and thereby reducing aggregation and Ostwald ripening. Among the options reviewed, the SLN-hydrogel combination looks the most promising basis for a pediatric product.

Because the reviewed literature does not address SLN use in children, pharmacokinetic, safety and efficacy studies in this population are the clear priority. Given the range of physiology across developmental stages, a single SLN formulation is unlikely to suit the whole pediatric age range - percutaneous permeability, surface area and body weight all vary considerably from neonate to adolescent, each affecting a delivery vehicle's safety and efficacy. A more defensible strategy would stratify by age and optimize composition - lipid selection, particle size, applied quantity - separately for each group rather than applying one formulation across all patients, consistent with ICH E11(R1)'s emphasis on physiological differences in pediatric study design [90–91].

7. CONCLUSION

Solid lipid nanoparticles form a mechanistically coherent, well-tolerated platform with genuine potential as a topical vehicle for infantile dermatitis. The argument holds together internally: infant skin is thinner, more permeable and disproportionately large relative to body mass, which makes systemic absorption the principal safety constraint on topical therapy, and SLNs answer that constraint directly - forming an occlusive film that hydrates an already-compromised barrier, depositing preferentially in the stratum corneum and follicles rather than penetrating transdermally, and releasing drug slowly from a solid matrix. The formulation literature backs these claims: encapsulation consistently improved stability and moderated release, and in the studies that reached animal disease models it matched or beat free-drug efficacy at substantially lower doses.

What the literature does not support is the final step. No study identified tested an SLN or NLC dermatitis formulation on infant or neonatal skin, in a neonatal or juvenile animal model, or in infants themselves; no clinical trial of such a formulation exists; no regulator has approved one; no patent addresses the indication. The biocompatibility data, while reassuring, come entirely from adult cells, adult animals and adult patients, and say nothing about long-term exposure, nanoparticle accumulation, or the consequences of prolonged follicular retention in a population with greater follicular permeability. Translational obstacles compound this gap: scale-up needs process development that has not been undertaken for this application, Ostwald ripening and agglomeration threaten the shelf life a pediatric product would require, and the cost premium over a conventional cream is substantial.

The honest position sits between the two extremes. SLN-based delivery for infantile dermatitis is not an established therapy and should not be described as one, but it is not an unfounded proposition either, since the mechanism is sound and the adult evidence points consistently in its favour. It is a well-supported hypothesis still waiting on the pediatric-specific pharmacokinetic, irritation and safety data that would let it be tested - and generating that data, starting with juvenile animal models and age-stratified formulation optimization, is the necessary next step. Defining precisely which evidence is missing is, in the meantime, the most useful contribution a review like this one can make.

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