



NANOCARRIER-BASED NANOGEL FOR SELECTIVE EPIDERMAL TARGETING AND REDUCED TRANSDERMAL PERMEATION: FORMULATION PRINCIPLES, EVIDENCE, AND DEVELOPMENT STRATEGIES

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ABSTRACT :

Topical corticosteroid therapy is intended to deliver an effective drug concentration to diseased skin while limiting unnecessary exposure of deeper tissues and systemic circulation. Clobetasol propionate (CP), a very potent topical glucocorticoid, illustrates this challenge: its strong anti-inflammatory activity is accompanied by risks associated with excessive dose, prolonged use, inappropriate application, and unintended absorption. Nanocarrier-based nanogels combine a nanoscale drug-delivery system with a semisolid vehicle and may help control drug release, increase residence at the application site, and influence distribution across individual skin layers. However, improved skin penetration is not synonymous with epidermal targeting. A system designed for epidermal delivery should demonstrate increased drug retention in the intended epidermal compartment alongside controlled or reduced passage into the receptor phase and deeper tissues. This narrative review discusses the skin-barrier basis of epidermal targeting, the rationale for combining nanocarriers with hydrogels, and the relevance of lipid nanoparticles, polymeric nanoparticles, nanocapsules, nanoemulsions, and nanogel platforms to topical CP delivery. Published CP research shows that carrier composition and surface properties can markedly alter drug distribution; some systems have increased epidermal deposition, while others have enhanced overall permeation. The review proposes a development and evaluation framework for a CP 0.05% nanocarrier-based nanogel using hydroxypropyl methylcellulose (HPMC K100), polyvinyl alcohol (PVA), Polysorbate 80, and a Carbopol 934 gel base with triethanolamine, disodium EDTA, and methylparaben, where appropriate to the final formulation. Critical quality attributes, in-vitro release, ex-vivo skin-layer retention, transdermal permeation, rheology, stability, and safety are considered. The evidence supports the feasibility of investigating nanocarrier-based nanogels for localized delivery, but selective epidermal targeting and reduced transdermal permeation must be established experimentally rather than inferred from particle size or release data alone.

Keywords: clobetasol propionate; nanogel; nanocarrier; epidermal targeting; topical drug delivery; skin retention; transdermal permeation; hydrogel.

1. Introduction

The skin is both a protective organ and a therapeutic target. Topical delivery can place a medicine directly at a cutaneous site, potentially reducing the dose required at the target and avoiding some limitations associated with oral or parenteral administration. Nevertheless, topical treatment is not automatically local. A drug may remain on the surface, partition into the stratum corneum, reach viable epidermis, diffuse into the dermis, or cross the skin and enter systemic circulation. The relative amounts in these compartments determine whether a formulation achieves the desired local exposure or produces unwanted distribution.

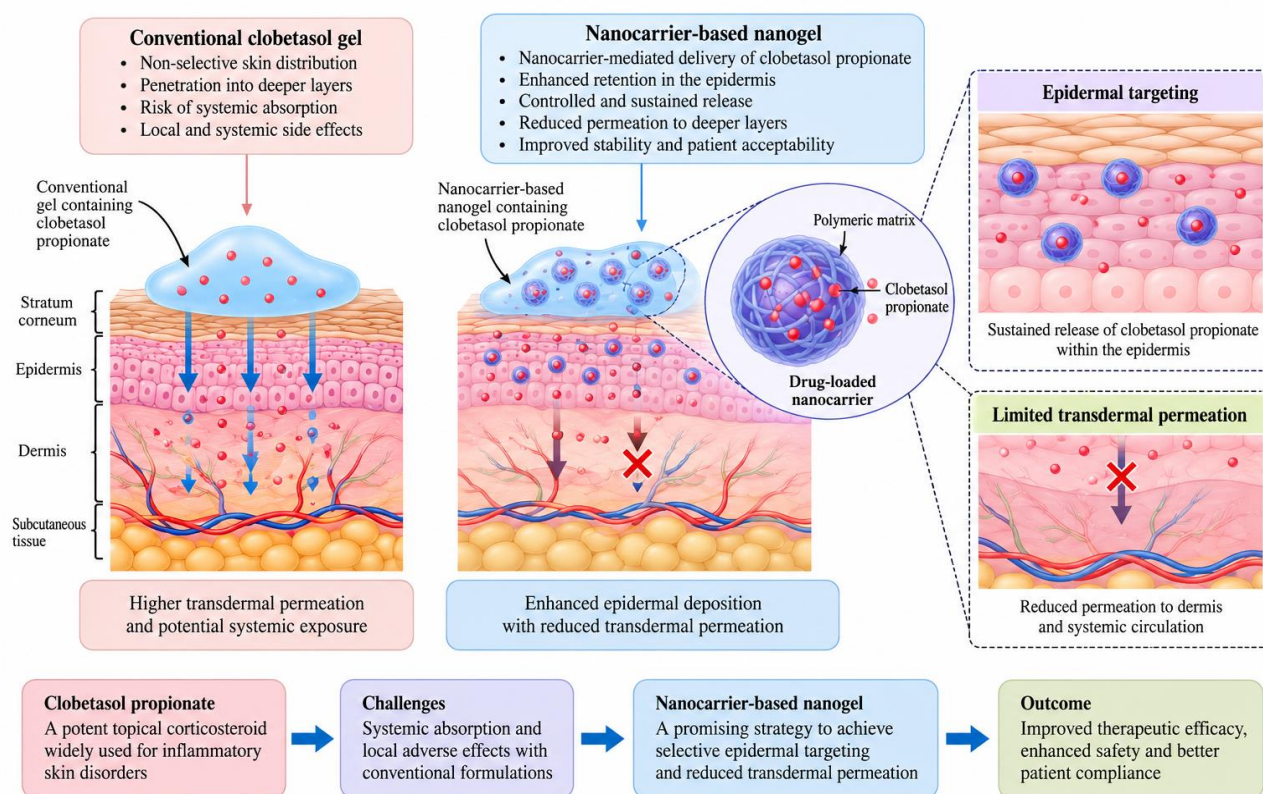
The stratum corneum is the principal barrier to most exogenous compounds. It consists of corneocytes embedded in an intercellular lipid matrix and behaves as a heterogeneous barrier whose permeability varies with hydration, anatomical site, disease state, age, and integrity. A formulation can alter this barrier through hydration, occlusion, lipid interactions, solvent effects, and carrier-skin interactions. Such effects may increase delivery, but they may also increase irritation or systemic exposure. Therefore, the objective of a topical formulation must be defined before selecting a carrier: maximal

transdermal flux is appropriate for some systemic delivery products, whereas localized dermatological therapy may prioritize drug retention in a specific skin layer and minimize passage beyond it.

Clobetasol propionate (CP) is a potent synthetic corticosteroid used in selected inflammatory dermatoses. Its pharmacological strength makes local delivery attractive but also makes dose control and appropriate duration important. Reports on CP nanocarriers have examined lipid nanoparticles, polymeric particles, nanocapsules, nanoemulsions, and gel-based systems. The published evidence is informative but not uniform: some carriers increase epidermal deposition, whereas other formulations increase total skin permeation or flux. This difference reinforces the need to distinguish epidermal targeting from general permeation enhancement [1–4].

A nanocarrier-based nanogel combines two design levels. The nanocarrier can influence drug solubilization, protection, release, and interaction with the skin barrier; the gel vehicle can improve spreadability, residence time, dose handling, and user acceptability. The combined platform may be especially useful when a hydrophobic drug must be distributed uniformly in a topical product. Yet the final performance depends on carrier type, particle size distribution, drug loading, surface chemistry, gel microstructure, rheology, and the balance between drug release and skin partitioning.

This review synthesizes the rationale and available evidence for a nanocarrier-based nanogel intended to support selective epidermal delivery of CP while limiting transdermal escape. It focuses on formulation science, relevant published CP delivery systems, analytical evaluation, and a practical evidence-generating framework. It does not report original experimental results. The formulation components discussed are development considerations and should not be interpreted as a validated or optimized composition without supporting data.



2. Review approach and scope

This article is a narrative review informed by literature on clobetasol propionate topical delivery, nanocarriers for epidermal targeting, nanogels and nano-enabled semisolid formulations, and methods for measuring drug distribution in skin. Relevant publications were identified through targeted searches of PubMed-indexed records, publisher pages, and review literature. Priority was given to studies that directly investigated CP, reported skin-layer distribution or transdermal permeation, or described contemporary formulation and evaluation strategies. The discussion is selective rather than a systematic review: no formal protocol, duplicate screening, or quantitative meta-analysis was performed.

The evidence is interpreted according to the intended product objective. In-vitro release results are considered evidence of release behaviour under the test conditions, not proof of epidermal targeting. Ex-vivo skin studies are considered necessary to quantify drug distribution across skin compartments. In-vivo efficacy and safety claims require suitable studies and cannot be established from physicochemical characterization alone.

3. Epidermal targeting: concept and biological basis

3.1 Skin compartments and target definition

For a topical anti-inflammatory drug, the desired target may include the viable epidermis and, depending on the condition and mechanism, portions of the superficial dermis. The stratum corneum can act as a reservoir, but accumulation in this outermost layer does not necessarily mean that an adequate amount reaches viable target tissue. Conversely, high receptor-phase recovery in a diffusion experiment indicates passage through the skin and may be undesirable for a product intended to act locally. A rigorous targeting claim should therefore specify the intended compartment and quantify drug in at least the stratum corneum, viable epidermis, dermis, and receptor fluid where technically feasible.

The term ‘selective epidermal targeting’ should be used operationally. A suitable formulation should produce greater drug deposition in the intended epidermal layer than a relevant comparator, without a proportional increase in dermal or receptor-phase exposure. Useful measures include the amount of drug per unit skin area in each compartment, the fraction of recovered drug in the epidermis, epidermis-to-dermis ratios, receptor-phase cumulative permeation, steady-state flux where applicable, and total mass balance. A high epidermal concentration alone can be misleading if extraction recovery differs between formulations or if large amounts of drug remain unaccounted for.

3.2 Why nanocarriers may influence skin distribution

Nanocarriers can change the apparent solubility of poorly water-soluble compounds, protect a drug from degradation, modify release rate, and alter contact between the formulation and the skin surface. Depending on composition, particles may remain largely at the surface, accumulate in follicular structures, interact with the stratum corneum, or release drug that subsequently partitions into skin. The intact-particle pathway and the released-drug pathway should not be assumed to be equivalent. For many systems, the carrier may function primarily as a reservoir that controls drug availability rather than as a particle that travels intact into viable tissue.

Carrier properties are interdependent. Particle size and polydispersity affect physical uniformity; surface charge and surface chemistry affect colloidal stability and interaction with biological interfaces; lipid composition and crystallinity influence drug accommodation and leakage; polymer composition influences swelling, degradation, and release; and surfactant concentration can influence both dispersion stability and skin-barrier perturbation. These properties must be considered together rather than optimized in isolation.

3.3 Reduced transdermal permeation is a separate design endpoint

The phrase ‘reduced transdermal permeation’ refers to limiting drug passage across the skin into the receptor compartment, not simply slowing in-vitro release from the dosage form. A formulation can show sustained release while still producing substantial cumulative permeation over a long interval. Likewise, a carrier that improves epidermal deposition may also increase dermal retention. The intended balance should be measured directly. In CP studies, polymeric nanocarriers have been reported to sustain release and reduce transdermal permeability relative to free drug under specific experimental conditions, while other nanocarrier systems have produced increased epidermal delivery or higher permeation than a marketed comparator [1,2]. These findings are not contradictory; they reflect different carrier designs, comparators, skin models, and experimental conditions.

4. Clobetasol propionate and the need for localized delivery

CP is a potent glucocorticoid that suppresses inflammatory processes through glucocorticoid-receptor-mediated regulation of inflammatory gene expression and related cellular responses. Its clinical utility in inflammatory dermatoses must be balanced against local and systemic risks associated with excessive exposure. Potential adverse outcomes of topical corticosteroid misuse or prolonged use can include skin atrophy, striae, telangiectasia, pigmentary changes, secondary infection, and systemic glucocorticoid effects in susceptible circumstances. Risk depends on potency, treated surface area, duration, occlusion, skin integrity, age, and the specific product. Formulation development should not be presented as eliminating these risks unless supported by adequate comparative safety evidence.

CP has limited aqueous solubility and is commonly formulated in semisolid products that use excipients to aid dispersion, solubilization, and application. A nanocarrier can provide a microenvironment for the drug and potentially reduce crystallization or improve distribution within the vehicle. However, encapsulation efficiency, drug loading, and apparent solubility are not interchangeable. A formulation may entrap a high proportion of the added drug but carry relatively little drug per unit carrier mass; another may load more drug but release it too rapidly or show instability during storage.

The most relevant clinical-pharmaceutical objective is not to maximize the amount of CP crossing the skin. It is to establish a reproducible local exposure profile consistent with the therapeutic target, while avoiding unnecessary systemic exposure. A lower nominal drug dose might be advantageous if comparable local efficacy can be demonstrated, but dose reduction cannot be inferred from a laboratory release profile or from epidermal retention alone. Such a claim would require appropriately designed comparative pharmacodynamic, efficacy, and safety studies.

5. Nanocarrier platforms relevant to epidermal delivery

5.1 Nanostructured lipid carriers and solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) use solid lipids or mixtures of solid and liquid lipids to accommodate drug

molecules. NLCs are designed to reduce the highly ordered packing associated with some solid lipid matrices, potentially providing more space for drug incorporation and influencing release. Their lipidic composition can also contribute to occlusion and skin hydration. For topical products, the practical advantages include compatibility with semisolid vehicles and the possibility of sustained release.

A CP-loaded NLC study by Silva and colleagues evaluated epidermal targeting using skin-layer separation. Both coated and uncoated NLC formulations produced markedly greater epidermal CP amounts than a commercial formulation under the reported conditions, while the uncoated system did not show the same dermal retention pattern as the coated system [1]. The study is important because it assessed drug in defined skin compartments rather than relying only on total permeation. It also illustrates that surface modification can change distribution, and that ‘more skin delivery’ must be qualified by where the drug is recovered.

NLCs do not inherently guarantee reduced transdermal permeation. A separate CP NLC-gel study reported sustained in-vitro release and higher permeation-related parameters than a marketed formulation [3]. Such findings may be useful when enhanced delivery through the skin is the goal, but they cannot by themselves support a claim of reduced transdermal escape. Lipid type, drug partitioning, surfactant system, gel composition, and test conditions need to be matched to the intended endpoint.

5.2 Polymeric nanoparticles and nanocapsules

Polymeric nanospheres, nanocapsules, and lipid-core nanocapsules can provide different drug-distribution profiles. Nanospheres generally distribute drug throughout a polymer matrix, whereas nanocapsules contain a core surrounded by a shell. The relative contribution of diffusion, matrix relaxation, polymer degradation, and drug partitioning varies with polymer chemistry and formulation. Surface properties may also influence interaction with follicular openings and the stratum corneum.

Research comparing polymeric nanocarriers for topical CP has examined the balance between interfollicular permeation and follicular uptake. In that work, the tested carriers showed sustained release, and skin permeation experiments using heat-separated human epidermis indicated reduced transdermal permeability relative to free drug under the study conditions [2]. Follicular uptake varied by carrier type and application conditions. These observations support a central design principle: carrier selection should be linked to a defined distribution objective, and a carrier’s effect should be assessed in the actual final dosage form.

5.3 Nanoemulsions and nanoemulgels

Nanoemulsions are dispersions of oil and water stabilized by surfactants, often with small droplet sizes. They can improve apparent solubilization of lipophilic drugs and may enhance delivery through interactions among oil phase, surfactant, and skin lipids. Incorporation into a gel can improve viscosity, reduce runoff, and facilitate application. Yet surfactants and cosolvents may also increase barrier disruption or irritancy, so formulation benefits must be balanced against tolerability.

A quality-by-design study of a CP-17 nanoemulgel used a structured experimental design to investigate formulation factors and evaluated droplet size, release, rheology, ex-vivo permeation and retention, and in-vivo outcomes [4]. The reported formulation showed enhanced permeation and skin retention relative to its comparator. This is evidence that optimization can improve several quality attributes simultaneously, but the reported increase in permeation means it should not be interpreted as direct proof that all nanoemulgels reduce transdermal flux.

5.4 Nanogels and nanocarrier-in-gel systems

The term ‘nanogel’ is used inconsistently in the literature. It can refer to nanoscale, crosslinked hydrogel particles or to a conventional semisolid gel containing dispersed nanocarriers. These are not identical architectures. A formulation consisting of nanoparticles dispersed in a Carbopol gel is more precisely described as a nanocarrier-loaded gel or nanoparticle-based nanogel unless the gel network itself exists at the nanoscale. The manuscript and product specification should define the architecture explicitly to avoid ambiguity.

A nanocarrier-loaded gel can combine the carrier’s drug-release properties with the gel’s residence time and handling characteristics. The gel may reduce runoff, enable more uniform dose application, and protect the dispersion from rapid separation. Conversely, the polymer network can alter particle mobility, drug diffusion, water activity, and release kinetics. High viscosity is not automatically desirable: a very viscous system may be difficult to spread, whereas a low-viscosity system may run off or provide inconsistent dosing.

A 2022 review of novel dermal delivery systems for CP describes a range of carrier classes and emphasizes the need to evaluate delivery, stability, and safety together [5]. The present review narrows the focus to a design question: how should a CP nanocarrier-loaded gel be evaluated if the primary objective is epidermal retention with limited transdermal permeation? The answer depends on layer-resolved skin analysis and comparative endpoints, not on the label ‘nano’ or ‘gel’.

6. Formulation design considerations for a CP 0.05% nanocarrier-based nanogel

6.1 Define the formulation architecture before optimization

A development plan should first state whether the nanosystem is a lipid carrier, polymeric particle, nanocapsule, or nanoemulsion, and whether it is subsequently dispersed into a macroscopic gel. The nanocarrier composition and preparation process must be described separately from the gel-base composition. Without this distinction, the term nanogel can obscure the mechanism responsible for drug release and skin distribution.

For the formulation context considered here, CP at 0.05% is the target drug concentration. HPMC K100 and PVA may be considered as polymeric materials in the dispersion or carrier-related phase, while Polysorbate 80 may function as a surfactant depending on the chosen architecture. A Carbopol

934 gel base with triethanolamine for neutralization, disodium EDTA as a chelating agent, and methylparaben as a preservative may be considered for the final semisolid. These are candidate formulation components, not a validated recipe. Their actual functions, concentrations, compatibility, and inclusion should be justified by the selected nanocarrier design and preliminary compatibility testing.

The formulation should avoid redundant or incompatible polymers and surfactants. HPMC, PVA, and Carbopol can each influence viscosity or film formation, but their combined use may create an overly viscous, difficult-to-spread product or change release behaviour. Polysorbate 80 may stabilize dispersions but can also influence drug partitioning and skin-barrier behaviour. Triethanolamine quantity should be adjusted to achieve the intended pH and gel formation rather than fixed without measurement. EDTA and methylparaben should be evaluated for compatibility, preservative effectiveness, and regulatory suitability.

6.2 Critical quality attributes

A target product profile should identify critical quality attributes (CQAs) before batch optimization. Relevant CQAs include appearance and homogeneity, drug content and content uniformity, particle size, polydispersity index, zeta potential where meaningful, encapsulation efficiency, drug loading, pH, viscosity and rheology, spreadability, extrudability if packaged in a tube, in-vitro release, skin-layer deposition, receptor-phase permeation, microbial quality, and stability. The most important attributes are those that can affect safety, efficacy, reproducibility, and product usability.

Particle size should be reported with the measurement method, dispersion medium, dilution conditions, temperature, and number of independent batches. A single average value is insufficient; the distribution and polydispersity should also be considered. Zeta potential can provide information about electrostatic stability but should not be treated as a universal stability predictor, especially in systems stabilized sterically by non-ionic surfactants. Morphology assessed by microscopy should complement, not replace, particle-size measurements.

Drug entrapment efficiency can be calculated as the percentage of total drug associated with the carrier after separating free drug using a validated method. The separation technique must be shown not to disrupt the carrier or allow drug redistribution during processing. Drug loading should be reported separately, typically as the amount of drug associated with the carrier relative to carrier mass or total formulation mass, with the calculation clearly defined. Assay validation should establish specificity, linearity, accuracy, precision, and a suitable quantification limit for the intended matrix.

6.3 Gel-base optimization and usability

The gel base should be optimized after confirming that the nanocarrier dispersion remains physically and chemically stable in the selected polymer matrix. Important tests include pH, viscosity across relevant shear rates, thixotropic recovery, spreadability, and homogeneity. A single viscosity reading may not adequately characterize a shear-thinning gel. If the product is intended for repeated use, dose uniformity after dispensing and redispersion or mixing requirements should also be considered.

The pH should be compatible with skin application and the stability of CP and excipients. The target pH must be justified by formulation data rather than by assuming a single universal skin pH. The preservative system requires suitable microbial limits and, where applicable, preservative efficacy testing. Packaging should minimize contamination, water loss, and exposure to light or oxygen where these are relevant to product stability.

6.4 Quality-by-design approach

A quality-by-design strategy can help separate high-impact variables from lower-impact variables. Candidate material attributes include polymer grade, lipid or oil composition, surfactant concentration, and drug-to-carrier ratio. Candidate process parameters include mixing speed, homogenization or sonication energy, temperature, order of addition, cooling rate, and equilibration time. Responses should include both formulation CQAs and the biological performance endpoints that reflect the target product profile.

A factorial or response-surface design may be used to investigate interactions among a manageable number of factors. Optimization should not rely exclusively on particle size or entrapment efficiency. For this product concept, a multi-response decision should consider physical stability, reproducible drug content, acceptable rheology, controlled release, increased epidermal retention, and reduced receptor-phase permeation. The best batch is the one that balances these outcomes while remaining manufacturable and tolerable, not necessarily the batch with the smallest particles.

7. Evaluation strategy: from dispersion characterization to skin targeting

7.1 Physicochemical characterization

Initial characterization should establish whether the carrier is reproducible and whether the drug remains appropriately associated with the formulation. Particle size and polydispersity can be measured by dynamic light scattering, while zeta potential can be assessed by electrophoretic mobility where appropriate. Transmission electron microscopy, scanning electron microscopy, or atomic force microscopy may provide complementary morphological information, although sample preparation can alter structures and should be described. Differential scanning calorimetry or X-ray diffraction may be useful when the carrier's solid state and drug crystallinity are central to performance.

Drug content should be quantified using a validated chromatographic or spectrophotometric method with adequate specificity. Chromatographic analysis is preferable where excipients, degradation products, or matrix interference could compromise selectivity. Entrapment efficiency should be determined using a validated free-drug separation method and reported with replicate measurements and variability. Results should be presented as mean and standard deviation with the number of independent batches or replicates stated clearly.

7.2 *In-vitro drug release*

In-vitro release testing can compare the rate and extent of CP release from the nanocarrier dispersion, the nanocarrier-loaded gel, a suitable drug-containing gel without nanocarriers, and a relevant marketed comparator. The apparatus, membrane, receptor medium, temperature, agitation, sampling schedule, replacement volume, and sink conditions should be justified. The membrane should not become the rate-limiting step, and recovery studies should establish that CP is not lost through adsorption or precipitation.

Release profiles can be explored using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models when the data and assumptions support their use. Model fit should not be interpreted as definitive proof of a single physical mechanism. Model comparison should consider the fitting range, residuals, parameter plausibility, and whether the assumptions of each model apply. Most importantly, sustained in-vitro release does not demonstrate epidermal targeting or reduced transdermal permeation; it is one part of a broader performance assessment.

7.3 *Ex-vivo skin permeation and retention*

Ex-vivo skin testing is central to the claim of selective epidermal targeting. Franz diffusion cells are commonly used to measure permeation through a defined skin area under controlled temperature and receptor conditions. The skin source, anatomical site, thickness, integrity test, storage history, exposed area, applied dose, receptor medium, and sampling schedule should be reported. Human skin is highly relevant where ethically and practically available; porcine skin is often used as a surrogate, but differences between species and anatomical sites should be acknowledged.

At the end of the experiment, the skin should be processed to distinguish surface residue, stratum corneum, viable epidermis, and dermis where feasible. Surface washing and tape stripping must be standardized. Epidermis–dermis separation can be performed using a validated technique appropriate to the skin source. Drug extraction from each compartment should be validated for recovery and precision. Receptor fluid should be analyzed at each sampling point, and cumulative permeation should be corrected for the drug removed during prior sampling.

A minimum comparative design should include the nanocarrier-loaded nanogel, a matched gel containing unencapsulated CP, and a relevant marketed comparator. A blank carrier gel can help identify matrix-related effects. The drug dose per unit area and application conditions should be matched, and skin donors or tissue replicates should be handled as independent biological sources where applicable. The study should include enough independent samples to estimate variability; sample size should be justified by the expected effect and study design.

The key outputs should include: (i) CP recovered from the epidermis per unit area; (ii) CP recovered from the dermis per unit area; (iii) cumulative amount in receptor fluid per unit area; (iv) steady-state flux and lag time when the profile supports their calculation; (v) epidermis-to-dermis distribution; and (vi) total recovery or mass balance. A formulation may be considered promising for epidermal targeting if it increases epidermal deposition while maintaining or reducing dermal and receptor-phase exposure relative to the comparator. Predefined acceptance criteria should be set before the study.

7.4 *Skin integrity, irritation, and safety*

Barrier integrity should be assessed before permeation testing and, where possible, after exposure to the formulation. Electrical resistance, transepidermal water loss, or another validated integrity method may be appropriate depending on the model. A formulation that increases epidermal deposition by damaging the barrier is not necessarily an acceptable product. Irritation and sensitization risks should be assessed using suitable validated approaches and ethical requirements. In-vivo studies, if required, should be designed only after adequate in-vitro and ex-vivo characterization and should follow applicable institutional and regulatory standards.

For CP-containing products, local tolerability is particularly important because the active ingredient is a potent corticosteroid. A nanocarrier formulation should not be described as safer than a conventional product unless comparative data support that conclusion. Claims of reduced systemic exposure require appropriate pharmacokinetic or validated surrogate evidence, not simply lower receptor-fluid recovery in a single ex-vivo experiment.

8. What the current evidence supports—and what it does not

Published studies establish that nanocarrier composition can influence CP release, follicular uptake, epidermal retention, dermal distribution, and transdermal passage. The CP-loaded NLC study by Silva et al. is directly relevant because it measured drug in separate skin layers and reported greater epidermal deposition than a commercial comparator under the tested conditions [1]. A study of polymeric carriers reported sustained release and reduced transdermal permeability relative to free drug, with carrier-dependent follicular uptake [2]. These findings support the scientific rationale for studying carrier systems when the goal is localized delivery.

Other CP nanoformulations demonstrate that nanotechnology can also enhance overall permeation. The NLC-based gel work reported improved permeation-related parameters compared with a marketed formulation [3], while a more recent quality-by-design nanoemulgel study reported increases in both ex-vivo permeation and skin retention [4]. Such outcomes may be desirable for some topical targets but demonstrate why the term ‘nanocarrier’ cannot be used as a proxy for reduced transdermal permeation. The direction of the effect depends on the full formulation and the experimental context. The broader literature review on novel dermal delivery cargos for CP summarizes multiple carrier classes and identifies formulation, stability, and safety issues relevant to translation [5]. Reviews of topical nanotechnology in psoriasis likewise describe diverse approaches and emphasize the complexity of achieving adequate local delivery in diseased skin [6]. A 2025 report on a CP-containing nanolipid carrier gel further illustrates the continuing interest in combining lipid carriers with a topical gel vehicle, although its dual-active formulation and disease context differ from the single-drug formulation considered here [7].

The current evidence does not establish that a specific combination of HPMC K100, PVA, Polysorbate 80, Carbopol 934, triethanolamine, EDTA, and methylparaben will selectively retain CP in the epidermis. Nor does it prove that a CP 0.05% nanocarrier-based nanogel will reduce systemic exposure,

prevent adverse effects, or outperform marketed formulations. These are hypotheses to test. The principal evidence gap is the lack of formulation-specific, layer-resolved ex-vivo data for the proposed composition, accompanied by validated analytical recovery and a matched comparator.

The article's central proposition is therefore developmental rather than confirmatory: a nanocarrier-loaded gel may be engineered for localized epidermal delivery, but the target profile must be demonstrated through a combination of formulation characterization, in-vitro release, skin-layer retention, receptor-phase permeation, safety evaluation, and stability assessment. A manuscript reporting original research should present the actual experimental methods and results; a review article should synthesize published findings and clearly label proposed work as future investigation.

9. Recommended development workflow

A staged workflow can reduce the risk of optimizing a formulation for the wrong endpoint.

1. Define the target product profile: specify the intended skin compartment, comparator, desired application properties, dosing assumptions, and the requirement to limit receptor-phase passage.
2. Select and justify one nanocarrier architecture. Avoid combining unrelated carrier approaches before establishing why each component is needed.
3. Conduct drug–excipient compatibility and preliminary solubility studies. Confirm that the analytical method can distinguish CP from excipients and potential degradants.
4. Optimize the nanocarrier dispersion using a structured experimental design. Measure size distribution, stability, drug loading, entrapment efficiency, and release behaviour.
5. Incorporate the selected dispersion into the gel base and re-evaluate particle attributes, drug content, pH, rheology, spreadability, homogeneity, and physical stability.
6. Conduct comparative in-vitro release testing using matched drug doses and justified sink conditions.
7. Perform ex-vivo permeation and layer-retention studies with a matched unencapsulated-drug gel and a relevant marketed product. Quantify epidermis, dermis, and receptor-phase drug separately.
8. Assess skin integrity, irritation potential, microbial quality, and accelerated/long-term stability according to the intended development stage.
9. Only after adequate performance and safety evidence, consider in-vivo efficacy or pharmacokinetic evaluation under an approved protocol.

This sequence prevents a common development error: choosing a batch solely because it has small particles or high encapsulation efficiency, then discovering that it releases the drug too quickly, is difficult to spread, or produces greater transdermal flux than intended.

10. Stability, scale-up, and translational challenges

Physical stability challenges include particle aggregation, changes in size distribution, sedimentation or creaming in fluid dispersions, gel syneresis, phase separation, and changes in viscosity. Chemical stability challenges include CP degradation, oxidation of susceptible excipients, and changes associated with light, temperature, or pH. Drug leakage from a carrier during storage can change the fraction of free drug and therefore alter release and skin distribution even if total assay remains acceptable.

Stability testing should include a suitable range of temperatures and conditions based on the product and packaging. Samples should be assessed at predefined intervals for appearance, pH, viscosity, particle size, polydispersity, assay, degradation products where relevant, release performance, and microbial quality. Accelerated testing can support early formulation comparison but does not replace long-term stability data. The final container–closure system should be included because packaging can influence water loss, drug adsorption, light exposure, and contamination risk.

Scale-up can alter mixing and energy input, affecting particle size, drug distribution, and batch-to-batch reproducibility. Sonication or high-shear processing that works in a small batch may not transfer directly to larger volumes. Process parameters should therefore be defined in measurable terms, and critical steps should be monitored. A robust process should tolerate reasonable variation without losing key quality attributes.

Regulatory translation requires a clear description of the nanocarrier architecture, excipient quality, manufacturing controls, analytical methods, microbiological quality, and the relationship between quality attributes and performance. The term ‘nanogel’ should be used consistently, and claims should match the evidence. A formulation is not clinically safer merely because it contains nanomaterials, and the long-term effects of repeated exposure should be considered where relevant.

Reproducibility is a further challenge in skin research. Skin donor variability, anatomical site, tissue storage, barrier integrity, and test-cell conditions can all affect results. Studies should report enough methodological detail for replication and should not compare numerical permeation values across unrelated studies as though they were directly interchangeable. Differences in skin source, dose, receptor medium, sampling period, and assay method can explain apparently inconsistent findings.

11. Limitations of the available evidence

The evidence base includes different carrier architectures, drug concentrations, comparators, skin models, and study endpoints. Some reports prioritize enhanced permeation, whereas others examine epidermal retention or follicular uptake. As a result, the findings cannot be combined into a single quantitative estimate of the effectiveness of nanocarrier-based nanogels for epidermal targeting. This narrative review did not perform a systematic search with duplicate screening or formal risk-of-bias assessment.

A further limitation is that many formulation studies use ex-vivo skin or animal models, which may not fully predict performance in human diseased skin. Barrier disruption in psoriasis or eczema may change drug penetration relative to healthy skin. Carrier stability in the formulation may also differ from its behaviour after application to hydrated or damaged skin. Accordingly, claims should remain limited to the experimental models and conditions studied.

Finally, the proposed CP 0.05% composition has not been validated in this review. Its components are discussed as formulation considerations, not as evidence of an optimized or clinically effective product. No original particle-size values, entrapment efficiencies, release percentages, permeation data, statistical tests, or therapeutic outcomes are presented because such results were not provided.

12. Future perspectives

Future research should move from general permeation enhancement toward measurable, compartment-specific delivery objectives. The most useful studies will compare matched formulations and report drug in the stratum corneum, viable epidermis, dermis, and receptor phase, with validated extraction recovery and complete mass balance. Fluorescent labelling alone is insufficient to prove that the active drug follows the same path as the carrier; where possible, both carrier and drug should be quantified independently.

A second priority is to integrate quality-by-design with biological performance. Formulation variables should be linked to epidermal retention and receptor-phase permeation, rather than only to particle size and in-vitro release. Predictive models may help identify combinations of carrier composition, surfactant concentration, and gel rheology that achieve a target distribution profile. However, such models should be trained and validated with sufficiently diverse experimental data.

A third priority is the use of clinically relevant models and endpoints. Where feasible, human skin from appropriate sources should be included, and disease-relevant barrier conditions should be considered. Follow-up studies should evaluate irritation, repeated-use tolerability, and pharmacodynamic activity at exposures that are relevant to the intended indication. If the objective is to reduce systemic exposure, the development programme should include a suitable assessment of systemic absorption rather than relying solely on in-vitro proxies.

Finally, terminology and reporting should be standardized. Authors should define whether their product is a nanogel or a nanocarrier-loaded hydrogel, provide detailed preparation and characterization methods, report independent batches, and distinguish measured outcomes from proposed mechanisms. Such practices will improve reproducibility and make it easier to compare formulations across laboratories.

13. Conclusion

Nanocarrier-based nanogels offer a rational platform for investigating localized delivery of clobetasol propionate, combining the potential benefits of a nanoscale carrier with the handling and residence characteristics of a topical gel. Published studies demonstrate that carrier composition and surface properties can change epidermal retention, follicular uptake, and transdermal permeation. They also show that nanocarriers may increase overall skin permeation rather than reduce it. Therefore, selective epidermal targeting cannot be inferred from nanoscale particle size, high entrapment efficiency, or sustained in-vitro release alone.

For a CP 0.05% nanocarrier-based nanogel, the key development requirement is a comparative, validated evaluation of drug distribution across skin layers and into receptor fluid, supported by physicochemical characterization, rheology, stability, and safety testing. The proposed HPMC K100/PVA/Polysorbate 80 carrier-related system and Carbopol 934 gel base may be explored as formulation candidates, but their compatibility and performance must be demonstrated experimentally. A successful product would be one that reproducibly increases drug availability in the intended epidermal compartment while controlling deeper permeation and maintaining acceptable quality and tolerability. This remains a testable formulation objective, not an established outcome.

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