Ind. J. Pharm. Edu. Res., 2027; XX(XX):1-8.
https://www.ijper.org

Original Article

Design And Development of Cilnidipine-Loaded Transdermal Nanoemulsion and Nanoemulsion Gel for the Management of Hypertension

Sheela Yadav[1], Priyanka Goswami[1,*], Ronak Dave[1], Mohammad Wais[1]

[1]Department of Pharmaceutics, H. K. College of Pharmacy, H. K. Building, Pratiksha Nagar, Relief Road, MHADA Colony, Oshiwara, Jogeshwari (West), Mumbai – 400102, Maharashtra, India

ABSTRACT

Background: Hypertension requires long-term pharmacotherapy, and many anti-hypertensive drugs undergo extensive hepatic first-pass metabolism that limits oral bioavailability. Cilnidipine, a dihydropyridine calcium channel blocker with renoprotective and cardioprotective actions, is a Biopharmaceutics Classification System (BCS) Class II drug with low aqueous solubility and reduced oral bioavailability due to first-pass metabolism. **Objectives:** To design a transdermal nanoemulsion and nanoemulsion gel of cilnidipine to bypass first-pass metabolism, enhance solubility and improve bioavailability. **Materials and Methods:** Caproyl 90-Triacetin (1:1), Labrasol and Transcutol P were selected as oil, surfactant and co-surfactant respectively on the basis of maximum drug solubility. Pseudo-ternary phase diagrams were constructed by water titration at seven Smix ratios, and three thermodynamically stable formulations (NF1-NF3) were characterized for droplet size, zeta potential, ex-vivo permeation (excised goat skin, Franz cell), in-vitro release kinetics and International Council for Harmonisation (ICH)-guided stability; the optimised nanoemulsion was incorporated into a Carbopol 934 gel. **Results:** NF2 (Smix 3:1) showed a mean droplet size of 128.3 nm, polydispersity index 0.211 and zeta potential 78.6 mV. Ex-vivo permeation reached 47.54% over 24 h (flux 173.84 µg/cm^2/h); in-vitro release followed zero-order kinetics (R^2 = 0.808); drug content remained ≥96% after 90 days at 25 °C/60% relative humidity (RH), with an estimated shelf-life of ~15 months. The nanoemulsion gel showed satisfactory pH, viscosity, gel strength and swelling index. **Conclusion:** The cilnidipine nanoemulsion and nanoemulsion gel represent a viable transdermal alternative to oral therapy for the chronic management of hypertension.

Keywords: Cilnidipine, Hypertension, Nanoemulsion, Pseudo-ternary phase diagram, Transdermal drug delivery

Correspondence:
Dr. Priyanka Goswami
Department of Pharmaceutics, H. K. College of Pharmacy, H. K. Building, Pratiksha Nagar, Relief Road, MHADA Colony, Oshiwara, Jogeshwari (West), Mumbai – 400102, Maharashtra, India.
Email: priyanka8408@gmail.com

www.ijper.org

INTRODUCTION

The skin is a highly organized barrier whose stratum corneum principally governs the rate and extent of transdermal drug permeation, and a range of strategies — permeation enhancers such as surfactants, fatty acids and alcohols, iontophoresis, electrophoresis, and micro-/nano-range emulsion systems — have been explored to improve percutaneous drug delivery.[1] Among these, nanoemulsions (NEs) are dispersions of oil and water stabilized by a surfactant/co-surfactant film, with droplet sizes typically between 20 and 200 nm; they form spontaneously, are thermodynamically stable, and are optically transparent.[2] Compared with conventional emulsions, nanoemulsions require lower surfactant concentrations, form spontaneously with less energy input, possess a very flexible interfacial film, and are thermodynamically rather than only kinetically stable.[3]

Nanoemulsions offer several advantages as transdermal vehicles: their hydrophilic and lipophilic domains and small droplet size enhance percutaneous absorption of a wide range of drugs, they can sustain drug release approximating zero-order kinetics, they enhance the oral absorption of poorly water-soluble drugs via increased interfacial area, and they can reduce dose and side effects while protecting labile drugs from hydrolysis and oxidation.[4] Nanoemulsions can also act as their own permeation enhancer: their bilayer structure interacts with the stratum corneum and their nanoscale droplets ease permeation, increasing percutaneous drug availability, without the need for additional permeation enhancers.[5] Reported limitations include the sometimes high surfactant/co-surfactant

DOI: 10.5530/ijper.20270559

Copyright Information :
Copyright Author (s) 2027 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

concentration needed for stability and the limited range of pharmaceutically acceptable excipients suitable for nanoemulsion formulation.

Hypertension is a condition of chronically elevated blood pressure and a major risk factor for congestive heart failure, myocardial infarction and renal disease; the global burden of hypertension was projected to rise by 60%, to approximately 1.56 billion people, by 2025. Anti-hypertensive drug classes include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), β-blockers and angiotensin II receptor antagonists, with the choice of agent guided by individual patient factors. Calcium channel blockers act by inhibiting the inward flux of calcium ions into myocardial cells, vascular smooth muscle, and cells of the sinoatrial and atrioventricular nodes, thereby reducing cardiac contractility, relaxing vascular smooth muscle, lowering heart rate and myocardial oxygen demand, and consequently lowering blood pressure, without significant action on venous smooth muscle.

Because hypertension requires long-term, continuous treatment and many anti-hypertensive agents undergo extensive hepatic first-pass metabolism (resulting in poor oral bioavailability and the need for frequent dosing), it is well suited to transdermal drug delivery system (TDDS) development.[6] Nanoemulsions are attractive TDDS carriers because they are highly stable, can solubilise large quantities of drug within their hydrophilic and hydrophobic domains, and — using non-irritant, pharmaceutically acceptable ingredients — act as their own permeation enhancer without requiring additional excipients, a mechanism reviewed extensively for a range of actives.[7] Hydrophobic drugs generally show greater flux from water-in-oil emulsions, whereas oil-in-water systems provide release controlled by drug partitioning into the outer phase, as illustrated for propranolol, apomorphine and azelaic acid.[8,9,10] Historically, such systems were first described as transparent water-in-oil dispersions,[11] and their pharmaceutical applications and the general theory of skin-penetration enhancement by such vehicles have since been reviewed in detail.[12],[13] Handbook-level descriptions of noninvasive delivery further support their capacity to improve skin penetration efficacy.[13]

Cilnidipine is a dihydropyridine-type calcium channel antagonist that, unlike other CCBs, blocks both L-type calcium channels in vascular smooth muscle and N-type calcium channels in neuronal cells, conferring additional renoprotective and cardioprotective actions. As a BCS Class II drug, cilnidipine has low aqueous solubility and high permeability, and it undergoes extensive first-pass metabolism that lowers its oral bioavailability. These properties make cilnidipine a rational candidate for nanoemulsion-based transdermal delivery, combining enhanced solubility in an oily vehicle with the lowest feasible surfactant/co-surfactant concentration.

A cilnidipine-loaded transdermal nanoemulsion gel has recently been reported using a different excipient system (Kollicream® OA as oil, Kolliphor® RH40 as surfactant and Transcutol® P as co-surfactant), with permeation assessed across a synthetic dialysis membrane and supported by in-vivo pharmacokinetic evaluation in which maximum plasma drug concentration (Cmax) increased from 332.3 ng/mL (tablet) to 593.0 ng/mL (nanoemulsion gel).[14] The present work is distinct in its oil–surfactant–co-surfactant system (Caproyl 90–Triacetin, Labrasol and Transcutol P), its use of an ex-vivo excised-skin (goat) permeation model rather than a synthetic membrane, and its inclusion of full analytical method validation and accelerated/long-term (ICH-guided) stability assessment; it is intended to complement, rather than duplicate, this body of work by characterising an alternative, lower-Smix formulation approach.

Aim

To develop a transdermal nanoemulsion-based delivery system for cilnidipine, a practically water-insoluble drug, by enhancing its solubility in oily vehicles while minimising surfactant and co-surfactant concentration.

Objective

To overcome the problem of low bioavailability arising from extensive first-pass metabolism by formulating a cilnidipine nanoemulsion and incorporating it into a transdermal delivery system with enhanced solubility, permeation and bioavailability.

MATERIALS AND METHODS

Materials

Cilnidipine was received as a gift sample from Purechem Pvt. Ltd. (Ankleshwar) and J. B. Chemicals Pvt. Ltd. (Mumbai). Oils, surfactants, co-surfactants, reagents and polymers were procured from Gattefossé India Pvt. Ltd., Merck Life Science Pvt. Ltd., and Vishal Chem, among other suppliers; instruments were accessed through the institutional research laboratory.

Drug profile

Cilnidipine (brand name Cilacar®, J. B. Chemicals and Pharmaceuticals Ltd.) is a dihydropyridine calcium channel blocker with the chemical name 3-(E)-3-phenyl-2-propenyl 5-2-methoxyethyl 2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Supplementary Figure S1). It is a BCS Class II drug (high permeability, low solubility) supplied as tablets (Supplementary Table S1).

Molecular formula: $C_{27}H_{28}N_2O_7$**; Molecular weight:** 492.52 g/mol

www.ijper.org

Physicochemical and analytical characterisation

The drug was characterized for appearance, color, odor and melting point, and identified by ultraviolet (UV) and Fourier-transform infrared (FTIR) spectral analysis; melting point was additionally confirmed by differential scanning calorimetry (DSC).

Analytical method development and validation

A UV-spectrophotometric method for cilnidipine was developed in ethanol using a Shimadzu UV-1800 spectrophotometer at 240 nm. Linearity, precision (repeatability, intraday and interday), accuracy (recovery at 80/100/120%), limit of detection (LOD), limit of quantification (LOQ) and solution-state stability (in ethanol and in release medium) were assessed per ICH Q2(R1) guidance.

Pre-formulation studies

Partition coefficient (log P)

Determined at 37 °C by the shake-flask method (PC = (Ct – Ca)/Ca, where Ct is total drug concentration and Ca is the aqueous-phase drug concentration), following the general shake-flask partitioning approach standardized in Organisation for Economic Co-operation and Development (OECD) Test No. 107.[15]

Solubility studies

Equilibrium solubility of cilnidipine was determined in a panel of candidate oils, surfactants and co-surfactants by adding excess drug to each vehicle, equilibrating with continuous shaking, centrifuging, and assaying the supernatant by the validated UV method; the oil, surfactant and co-surfactant giving the highest drug solubility were carried forward.

Drug–excipient compatibility

Interaction between cilnidipine and the selected oil, surfactant and co-surfactant components (individually and in the final NE/NE gel) was evaluated by comparative UV spectral analysis, FTIR spectral analysis and DSC, looking for shifts in characteristic absorption/vibration bands or melting endotherm relative to the drug alone.

Formulation of nanoemulsion

Nanoemulsions were prepared by the water titration method. Pseudo-ternary phase diagrams were constructed for surfactant (Labrasol):co-surfactant (Transcutol P) [Smix] mass ratios of 1:0, 1:1, 1:2, 1:3, 2:1, 3:1 and 4:1, using Caproyl 90 + Triacetin (1:1) as the oil phase. Nanoemulsion existence zones were identified by titrating oil–Smix mixtures with water until the onset of turbidity/phase separation.

Thermodynamic stability screening

Placebo nanoemulsions were subjected to freeze–thaw cycling and centrifugation to exclude unstable (phase-separated) compositions before drug loading.[2]

Transdermal dose calculation

The total oral dose of cilnidipine (10 mg/24 h) and its reported oral bioavailability (60%) were used, by standard oral-to-transdermal dose scaling (transdermal dose = oral dose × oral bioavailability/100), to calculate the target transdermal dose (10 × 60/100 = 6 mg/24 h). Accordingly, 6 mg of cilnidipine was dissolved in a minimum volume of 70 µL of Caproyl 90 + Triacetin (1:1) to deliver the daily transdermal dose over 24 h.

Formulation selection

Of 59 Smix combinations screened, 42 were thermodynamically stable after drug loading. Three combinations (NF1, NF2, NF3; Smix ratios 2:1, 3:1 and 4:1 respectively) with the lowest Smix concentration and the largest nanoemulsion region on the phase diagram were selected for further evaluation (Table 1, Figure 1).

Formulation of nanoemulsion gel

The optimised nanoemulsion (NF2) was incorporated into a Carbopol 934 gel base at varying polymer concentrations (1–3% w/w) and nanoemulsion:gel ratios (1:1 and 2:1), and evaluated for pH, viscosity, gel strength and swelling index.

Characterisation of the optimised nanoemulsion

Droplet/particle size and morphology were assessed by transmission electron microscopy (TEM); mean droplet size, polydispersity index (PDI) and zeta potential were measured by dynamic light scattering (Zetasizer); viscosity, refractive index and conductivity were also determined.

Ex-vivo permeation study

Permeation of cilnidipine from the optimised nanoemulsion was studied across excised goat abdominal skin using a Franz diffusion cell. The donor compartment held the test sample in contact with the stratum corneum; the receptor compartment, facing the dermis, was filled with phosphate buffer (pH 7.4):Labrasol (95:5) as release medium, maintained under sink conditions. Samples were withdrawn at predetermined intervals over 24 h and assayed by UV spectrophotometry; cumulative amount permeated, cumulative percentage permeated, steady-state flux (from the slope of the linear terminal portion of the cumulative-amount-versus-time plot) and the permeability coefficient (Pb = flux/donor concentration) were calculated. Comparative permeation was similarly assessed for NF1, NF3 and the NF2 gel.

www.ijper.org

Table 1: Composition of the selected drug-loaded nanoemulsion formulations

Formulation	Oil phase (% w/w)	Smix (% w/w)	Smix ratio	Cilnidipine (mg)
NF1	6.78	47.76	2:1	6
NF2*	7.14	42.86	3:1	6
NF3	7.14	42.86	4:1	6

*NF2 was selected as the optimised formulation.

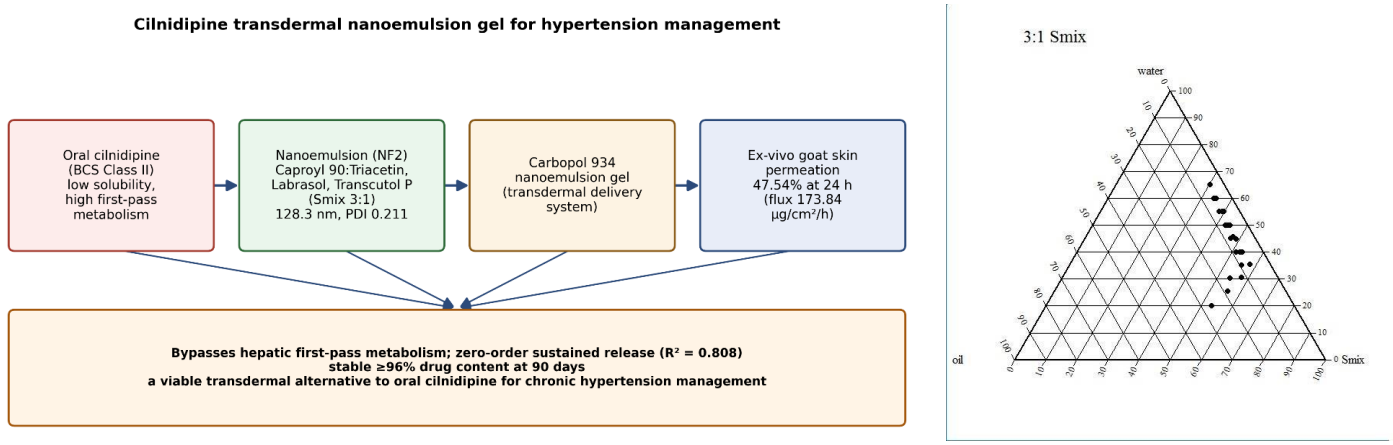


Figure 1: Pseudo-ternary phase diagram of the oil–Smix–water system at Smix (Labrasol: Transcutol P) 3:1; filled circles denote nanoemulsion region compositions used for formulation NF2.

In-vitro drug release study

In-vitro release of cilnidipine from the nanoemulsion and nanoemulsion gel was studied to characterize the release profile. Release data (% cumulative drug release versus time) were fitted to zero-order and first-order kinetic models by linear regression, and the model giving the higher regression coefficient (R^2) was taken to best describe the release mechanism.

Stability studies

The optimised nanoemulsion was subjected to accelerated stability testing per ICH Q1A(R2) guidelines at 40 °C ± 2 °C/75% RH ± 5% RH and at 25 °C ± 2 °C/60% RH ± 5% RH for 90 days.[16] Drug content was assayed at 0, 30, 60 and 90 days; log(% drug remaining) was plotted against time to obtain the apparent first-order degradation rate constant (K) at each condition, from which the shelf-life (t90, time to 10% degradation) was estimated as t90 = 0.105/K.

Statistical analysis

Unless otherwise stated, all determinations were performed in triplicate (n = 3) and results are expressed as mean ± standard deviation (SD). Calibration and kinetic model regressions were fitted by least-squares linear regression (Microsoft Excel). Differences in droplet size, PDI and permeation/release parameters between the NF1, NF2 and NF3 formulations were evaluated by one-way analysis of variance (ANOVA), with $p < 0.05$ taken as the threshold for statistical significance.

Ethical statement

The excised goat abdominal skin used for the ex-vivo permeation study was procured as slaughterhouse (abattoir) waste from a local municipal slaughterhouse; no animal was sacrificed specifically for this study. In accordance with Committee for the Control and Supervision of Experiments on Animals (CCSEA, India) practice, the use of tissue obtained from animals slaughtered for food purposes does not require Institutional Animal Ethics Committee (IAEC) approval. No human subjects were involved in this study.

RESULTS

Physicochemical properties and identification

The reported and experimentally observed physicochemical properties of cilnidipine are summarised in Supplementary Table S1. The observed melting point (108–110 °C) closely matched the reported range, and identity was confirmed by UV absorption maxima at 240 nm (in ethanol) and 241 nm (in phosphate buffer), and by DSC, which showed an endothermic peak at 109.45 °C, consistent with the reported melting range.

FTIR analysis showed close agreement between theoretical and practical peak positions for the drug's principal functional groups (Supplementary Table S2), supporting drug identity and purity.

www.ijper.org

Table 2: Physical characterisation of nanoemulsion formulations NF1–NF3

Formulation	Droplet size (nm)	PDI	Viscosity	Refractive index	Conductivity	Zeta potential (mV)
NF1	150.3	0.355	29.33	1.401	0.0156	38.9
NF2	128.3	0.211	31.66	1.400	0.0353	78.6
NF3	146.8	0.287	36.38	1.455	0.0245	50.2

Analytical method validation

The UV calibration curve (Supplementary Figure S2) gave the regression equation y = 0.1537x + 0.0069 (R^2 = 0.9957) over the concentration series 1–6 µg/mL. Precision, accuracy, LOD and LOQ were within acceptance criteria (Supplementary Table S3), confirming the method's suitability for formulation analysis.

Pre-formulation and drug–excipient compatibility

The partition coefficient was found to be 4.0 (reported value 4.70), confirming that cilnidipine is markedly more soluble in the organic than the aqueous phase (Supplementary Table S4) and supporting its formulation in an oily nanoemulsion vehicle.

Solubility screening identified Caproyl 90 + Triacetin (1:1) as the oil phase, Labrasol as surfactant and Transcutol P as co-surfactant, based on maximum drug solubility among the excipients tested. UV, FTIR and DSC analyses of the drug alone and in combination with the oil, surfactant, co-surfactant, nanoemulsion and nanoemulsion gel showed no shift in characteristic absorption/vibration bands or melting endotherm (drug-loaded NE: 111 °C vs. drug alone: 110 °C), indicating no significant drug–excipient interaction. Drug content and recovery from the nanoemulsion were high and consistent (Supplementary Table S5).

Pseudo-ternary phase diagrams and formulation selection

Pseudo-ternary phase diagrams constructed at Smix ratios of 1:0, 1:1, 1:2, 1:3, 2:1, 3:1 and 4:1 showed that the 2:1, 3:1 and 4:1 ratios gave the greatest oil-solubilising capacity and the largest nanoemulsion existence area. Of 59 Smix combinations screened, 42 remained thermodynamically stable after drug loading (freeze–thaw and centrifugation testing). Three drug-loaded formulations (NF1, NF2 and NF3) were selected at the lowest feasible Smix concentration within each stable region (Table 1). The phase diagram for the Smix 3:1 ratio, corresponding to the optimised formulation NF2, is shown in Figure 1.

Physical characterisation of the nanoemulsion formulations

TEM imaging of the optimised formulation (NF2, Figure 2) showed discrete, near-spherical droplets of approximately 100–130 nm, consistent with Zetasizer results showing a mean droplet size of 128.3 nm and a PDI of 0.211 (Figure 3), confirming particle size conformity to the nanoscale range (10–200 nm) (Table 2).

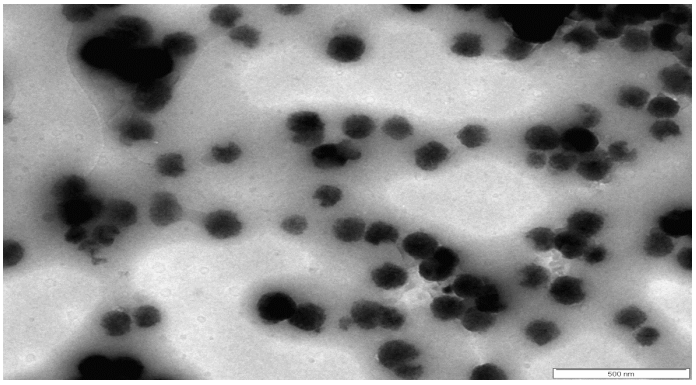


Figure 2: TEM image of the optimised nanoemulsion (NF2); scale bar 500 nm.

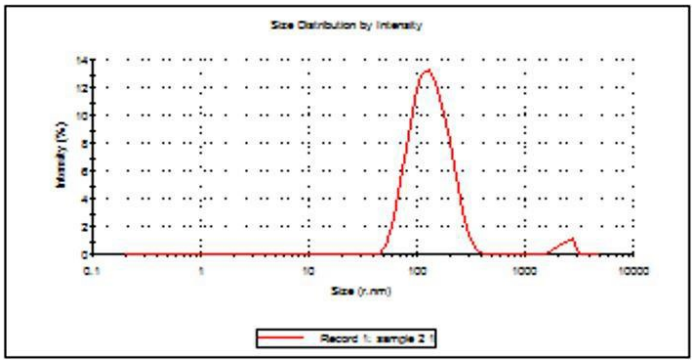


Figure 3: Size distribution (by intensity) of NF2 by dynamic light scattering (Zetasizer).

NF2, with the smallest droplet size and PDI among the three formulations, was selected as the optimised nanoemulsion for gel incorporation and further evaluation. It showed a pH of 4.9 ± 0.219 and a refractive index of 1.406.

Characterisation of the nanoemulsion gel

Increasing Carbopol 934 concentration from 1% to 3% w/w increased gel viscosity and, up to an optimum, gel strength, while pH remained within a range compatible with topical application (6.8–7.3) (Supplementary Table S6).

Ex-vivo permeation across goat skin

Cumulative permeation of cilnidipine from NF2 across excised goat abdominal skin increased progressively over 24 h, reaching 47.54% cumulative permeation (2852.71 µg cumulative amount

www.ijper.org

Table 3: Ex-vivo permeation of cilnidipine from nanoemulsion NF2 across goat skin

Time (h)	Drug concentration (µg/mL)	Cumulative amount permeated (µg)	Cumulative % permeated	Cumulative amount permeated (µg/cm²)
0	0	0	0	0
1	1.02	204	3.40	323.09
2	1.67	334.88	5.58	530.38
4	2.07	415.50	6.92	658.06
8	2.69	539.53	8.99	854.50
12	3.93	787.59	13.12	1247.38
16	7.00	1401.55	23.35	2219.75
18	9.39	1879.06	31.33	2976.03
20	11.06	2213.95	36.89	3506.41
24	14.26	2852.71	47.54	4518.07

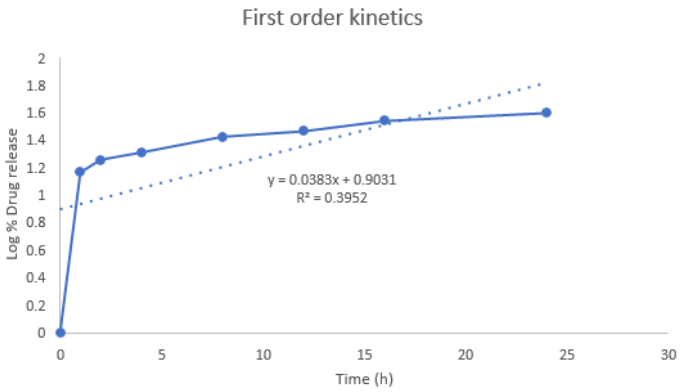


Figure 4: b:

permeated; 4518.07 µg/cm²) at 24 h, with a steady-state flux of 173.84 µg/cm²/h and a permeability coefficient (Pb) of 28.97×10^{-3} cm/h (Table 3). In comparative testing, NF2 showed the highest cumulative ex-vivo permeation among the three nanoemulsions, followed by NF3 and then NF1; the NF2 gel showed somewhat lower cumulative permeation than the NF2 nanoemulsion alone, consistent with the additional diffusional resistance of the gel matrix, while still substantially exceeding NF1.

In-vitro drug release

In-vitro release of cilnidipine from NF2 was better described by zero-order kinetics (% release = 1.339 × time + 11.99; $R^2 = 0.808$) than by first-order kinetics ($R^2 = 0.395$) (Figure 4a, b), indicating an approximately constant-rate, sustained-release profile rather than concentration-dependent release. Across formulations, NF2 and NF3 showed the highest cumulative in-vitro release (approaching 40% by 24 h), NF1 was intermediate (approximately 32%), and the NF2 gel showed the lowest cumulative release (approximately 27%), consistent with the expected retarding effect of the Carbopol matrix on drug diffusion.

Stability studies

Under both storage conditions, drug content declined only marginally over 90 days, with a substantially lower degradation rate at 25 °C ± 2 °C/60% RH ± 5% RH than at 40 °C ± 2 °C/75% RH ± 5% RH (Table 4, Supplementary Figure S3). First-order plots of log(% drug remaining) versus time gave $K = 4.6 \times 10^{-4}$ day^{-1} ($R^2 = 0.9766$) at 40 °C/75% RH and $K = 2.3 \times 10^{-4}$ day^{-1} ($R^2 = 0.9787$) at 25 °C/60% RH (Supplementary Table S7), corresponding to an estimated shelf-life (t90) of approximately 229 days (~7.6 months) at 40 °C/75% RH and approximately 457 days (~15.2 months) at 25 °C/60% RH.

DISCUSSION

The physicochemical and analytical data confirm cilnidipine's classification as a BCS Class II drug: high organic-phase partitioning (log P = 4.0) alongside negligible aqueous solubility supported the rationale for delivering the drug from an oil-based nanoemulsion rather than an aqueous vehicle. The validated UV method, with linearity, precision and accuracy well within acceptance limits, provided a reliable basis for all subsequent quantitative work, and the absence of any shift in UV, FTIR or DSC signatures on combining the drug with oil, surfactant, co-surfactant or gelling polymer indicated that no significant chemical interaction occurred during formulation.

Selection of Caproyl 90–Triacetin (1:1), Labrasol and Transcutol P as the oil, surfactant and co-surfactant, respectively, was justified by their combined ability to maximize the nanoemulsion existence region on the pseudo-ternary phase diagram while permitting drug loading at the lowest possible Smix concentration — a key formulation goal, since excessive surfactant/co-surfactant loading is a recognized drawback of nanoemulsion systems. Among the Smix ratios evaluated, 3:1 (NF2) produced the smallest, most uniform droplets (128.3 nm; PDI 0.211), consistent with TEM observations of spherical droplets in the 100–130 nm range, and

www.ijper.org

Table 4: Stability of cilnidipine in the nanoemulsion (ICH Q1A(R2))

Time (days)	40 °C/75% RH — drug content (mg)	40 °C/75% RH — % remaining	25 °C/60% RH — drug content (mg)	25 °C/60% RH — % remaining
0	6.00	100	6.00	100
30	5.91	98.5	5.93	99.33
60	5.82	97.0	5.89	98.16
90	5.78	96.3	5.82	97.00

was therefore selected as the optimised formulation over NF1 (2:1) and NF3 (4:1).

The ex-vivo permeation profile across goat abdominal skin, reaching 47.54% cumulative permeation by 24 h with a steady-state flux of 173.84 μg/cm²/h, together with sustained (zero-order) in-vitro release, supports the intended once-daily transdermal dosing regimen calculated from cilnidipine's oral bioavailability (60%) and daily oral dose (10 mg), which indicated a target transdermal dose of 6 mg/24 h. This flux compares favorably with the steady-state fluxes of 35.71–107.7 μg/cm²/h reported for a differently formulated cilnidipine nanoemulsion gel evaluated across a synthetic dialysis membrane,[14] although this comparison is limited by the different permeation-barrier models used (excised skin versus synthetic membrane) and should not be over-interpreted as a direct head-to-head result.

The positive zeta potential recorded across all three formulations (38.9–78.6 mV, highest for NF2) is higher than is typically expected for a system stabilized predominantly by the non-ionic surfactants Labrasol and Transcutol P, which usually confer near-neutral zeta potential and rely mainly on steric rather than electrostatic stabilisation. Such unexpectedly high values are worth re-checking against the raw Zetasizer records (for example, instrument calibration, dispersant conductivity, or trace ionic excipients/impurities can all inflate apparent zeta potential); they do not, however, undermine the formulation's stability conclusions, which are independently supported by the low PDI, TEM morphology, and the 90-day stability data.

Incorporation of NF2 into a Carbopol 934 gel base yielded a formulation with pH, viscosity, gel strength and swelling index compatible with topical application, without evidence of adverse interaction between the nanoemulsion and the gelling polymer. Stability testing under ICH Q1A(R2) conditions showed that drug content remained above 96% at 25 °C/60% RH over 90 days, with a first-order degradation rate constant of 2.3×10^{-4} day^{-1} and a correspondingly estimated shelf-life (t90) of approximately 15 months — a projection that should be confirmed with continued real-time monitoring beyond the 90-day dataset reported here.

This study has some limitations that should be considered when interpreting the results. Permeation was assessed using excised goat abdominal skin as a single ex-vivo model; while goat skin is a widely used and reasonably predictive surrogate for human skin permeation, in-vivo pharmacokinetic confirmation — as has been reported for a related cilnidipine nanoemulsion-gel system[14] — was outside the scope of this work and is recommended before clinical development. Skin-barrier integrity was not independently verified (for example, by transepidermal water loss or electrical resistance measurement) prior to the permeation study. Formal dermal irritation/sensitisation testing was not performed. Stability data are limited to 90 days under two accelerated/long-term conditions; the t90 estimates above are therefore projections rather than confirmed shelf-lives.

Collectively, these findings are consistent with reports that nanoemulsion vehicles can act as their own permeation enhancer and support sustained transdermal delivery, and extend this approach to cilnidipine as a strategy to circumvent its extensive first-pass metabolism and improve bioavailability in the chronic management of hypertension.

CONCLUSION

Cilnidipine, a BCS Class II calcium channel blocker with low aqueous solubility and extensive first-pass metabolism, was successfully formulated as a transdermal nanoemulsion using Caproyl 90–Triacetin (1:1), Labrasol and Transcutol P, selected on the basis of maximum drug solubility and nanoemulsion existence area. Pseudo-ternary phase diagrams identified Smix ratios of 2:1, 3:1 and 4:1 as optimal, yielding three thermodynamically stable, drug-loaded formulations (NF1–NF3). The optimised formulation, NF2 (Smix 3:1), showed a mean droplet size of 128.3 nm, spherical morphology by TEM, a pH of 4.9 ± 0.219 and a refractive index of 1.406, and was successfully incorporated into a Carbopol 934 gel with acceptable physical properties. Ex-vivo permeation (47.54% cumulative permeation over 24 h; flux 173.84 μg/cm²/h) and zero-order in-vitro release demonstrated sustained delivery, and accelerated and long-term stability studies confirmed adequate drug retention over 90 days, with an estimated shelf-life of approximately 15 months at 25 °C/60% RH. These results indicate that the cilnidipine nanoemulsion and nanoemulsion gel have potential as transdermal alternatives to oral therapy for the chronic management of hypertension, pending confirmatory in-vivo pharmacokinetic and dermal safety studies.

www.ijper.org

ACKNOWLEDGEMENT

None.

FINANCIAL SUPPORT AND SPONSORSHIP

This work received no financial support or sponsorship from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, the acquisition, analysis and interpretation of data, and the drafting and critical revision of the manuscript. All authors read and approved the final version of the manuscript for submission.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study (raw physicochemical, analytical, formulation-characterisation, ex-vivo permeation, in-vitro release and stability data) are available from the corresponding author on reasonable request.

ABBREVIATIONS

ACE: Angiotensin-converting enzyme; **ANOVA**: Analysis of variance; **BCS**: Biopharmaceutics Classification System; **CCB**: Calcium channel blocker; **CCSEA**: Committee for the Control and Supervision of Experiments on Animals; **Cmax**: Maximum plasma drug concentration; **DSC**: Differential scanning calorimetry; **FTIR**: Fourier-transform infrared spectroscopy; **IAEC**: Institutional Animal Ethics Committee; **ICH**: International Council for Harmonisation; **LOD**: Limit of detection; **LOQ**: Limit of quantification; **NE**: Nanoemulsion; **NF1–NF3**: Nanoemulsion formulations 1–3; **OECD**: Organisation for Economic Co-operation and Development; **Pb**: Permeability coefficient; **PDI**: Polydispersity index; **R^2**: Regression/correlation coefficient; **RH**: Relative humidity; **RSD**: Relative standard deviation; **SD**: Standard deviation; **Smix**: Surfactant:co-surfactant mixture (ratio); **t90**: Time to 10% degradation; **TDDS**: Transdermal drug delivery system; **TEM**: Transmission electron microscopy; **UV**: Ultraviolet;

REFERENCES

1. Barry BW. The LPP theory of skin penetration enhancement. In: Bronaugh RL, Maibach HI, editors. In Vitro Percutaneous Absorption: Principles, Fundamentals and Applications. Orlando (FL): CRC Press; 1991. p. 165–85.
2. Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nano-emulsions. Adv Colloid Interface Sci. 2004;108–109:303–18. doi:10.1016/j.cis.2003.10.023
3. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev. 2002;54(Suppl 1):S77–S98. doi:10.1016/s0169-409x(02)00116-3
4. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev. 2000;45(1):89–121. doi:10.1016/s0169-409x(00)00103-4
5. Kreilgaard M, Pedersen EJ, Jaroszewski JW. NMR characterisation and transdermal drug delivery potential of microemulsion systems. J Control Release. 2000;69(3):421–33. doi:10.1016/s0168-3659(00)00325-4
6. Chien YW. Transdermal Controlled Systemic Medications. New York: Marcel Dekker; 1987.
7. Eqbal A, Ansari VA, Hafeez A, Ahsan F, Imran M, Tanweer S. Recent applications of nanoemulsion based drug delivery system: a review. Res J Pharm Technol. 2021;14(5):2852–8. doi:10.52711/0974-360X.2021.00502
8. Ktistis G, Niopas I. A study on the in-vitro percutaneous absorption of propranolol from disperse systems. J Pharm Pharmacol. 1998;50(4):413–8. doi:10.1111/j.2042-7158.1998.tb06881.x
9. Peira E, Scolari P, Gasco MR. Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. Int J Pharm. 2001;226(1–2):47–51. doi:10.1016/s0378-5173(01)00759-1
10. Gasco MR, Gallarate M, Pattarino F. In vitro permeation of azelaic acid from viscosized microemulsions. Int J Pharm. 1991;69(3):193–6. doi:10.1016/0378-5173(91)90361-q
11. Hoar TP, Schulman JH. Transparent water-in-oil dispersions: the oleopathic hydro-micelle. Nature. 1943;152:102–3. doi:10.1038/152102a0
12. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16(5):461–521. doi:10.1615/critrevtherdrugcarriersyst.v16.i5.20
13. Lu GW, Gao P. Emulsions and microemulsions for topical and transdermal drug delivery. In: Kulkarni VS, editor. Handbook of Non-Invasive Drug Delivery Systems: Non-Invasive and Minimally-Invasive Drug Delivery Systems for Pharmaceutical and Personal Care Products. Norwich (NY): William Andrew Publishing; 2010. p. 59–94. doi:10.1016/B978-0-8155-2025-2.10003-4
14. Gaikwad MT, Marathe RP. Cilnidipine-loaded transdermal nanoemulsion-based gel: synthesis, optimisation, characterisation and pharmacokinetic evaluation. Int J Appl Pharm. 2025;17(1):255–74. doi:10.22159/ijap.2025v17i1.52689
15. OECD. Test No. 107: Partition Coefficient (n-Octanol/Water): Shake Flask Method. OECD Guidelines for the Testing of Chemicals, Section 1. Paris. OECD Publishing; 1995. doi:10.1787/9789264069626-en

Cite this article: Yadav S, Goswami P, Dave R, Wais M. Design And Development of Cilnidipine-Loaded Transdermal Nanoemulsion and Nanoemulsion Gel for the Management of Hypertension. Indian J of Pharmaceutical Education and Research. 2027;XX(XX):1-8.

www.ijper.org