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Review Article

Recent Advances In Nimodipine Formulations: From Submicron Emulsions And Nanosuspensions To Mixed Micelles And Buccal Delivery For Improved Bioavailability And Neuroprotection

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ABSTRACT

Nimodipine (NIM), a dihydropyridine L-type calcium channel blocker, remains the standard of care for preventing cerebral vasospasm after subarachnoid hemorrhage due to its high lipophilicity and ability to cross the blood-brain barrier. However, its clinical efficacy is severely limited by extremely poor aqueous solubility (≈3.86 µg/mL) and extensive first-pass metabolism, resulting in an oral bioavailability of less than 13%. This review critically evaluates recent advancements in novel NIM formulations aimed at overcoming these biopharmaceutical challenges. We comprehensively analyze six key research articles reporting the development of submicron lipid emulsions (SMEs), solid lipid nanoparticles (SLNs) incorporated into mucoadhesive buccal tablets, nanosuspensions using media milling, egg phosphatidylcholine-sodium glycocholate mixed micelles (EPC-SGC-MMs), and bilayer tablet technologies. Key findings demonstrate that positively charged SMEs with P-gp inhibitors (Tween 80) achieve a 3.85-fold increase in oral bioavailability compared to conventional suspension. Mixed micelles (≈6 nm) enhanced aqueous solubility 250-fold while eliminating the vascular irritancy associated with ethanol-based commercial injections. Nanosuspensions (279 nm) achieved 96.97% drug release within 5 minutes versus 3.25% for pure drug. Furthermore, in silico molecular dynamic simulations confirm that NIM's neuroprotective effects extend beyond calcium channel blockade to include monoamine oxidase A (MAOA) inhibition, providing a novel mechanistic basis for repurposing NIM in glaucoma and epilepsy. Collectively, these formulation strategies offer promising solutions for repurposing NIM as an injectable or buccal therapy for acute management of glaucoma and status epilepticus.

INTRODUCTION

Nimodipine (isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-

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pyridinedicarboxylate) is a second-generation dihydropyridine calcium channel blocker (CCB) distinguished by its high lipophilicity (log P ≈ 3.4) and selective vasoactive properties on cerebral blood vessels (Zheng et al., 2025). Unlike other CCBs such as verapamil or diltiazem, nimodipine readily crosses the blood-brain barrier (BBB), enabling it to bind to L-type voltage-gated calcium channels (VGCCs) on both neurons and cerebrovascular smooth muscle cells (Fathima and Kishan, 2023).

Despite its proven efficacy in preventing delayed ischemic neurological deficits following subarachnoid hemorrhage, the clinical application of NIM is severely constrained by its poor aqueous solubility (approximately 0.01 mg/mL) and extensive first-pass metabolism mediated by CYP3A4 isoenzymes in the liver and gut wall, leading to an oral bioavailability of less than 13% (Shah et al., 2012). Furthermore, the commercially available parenteral formulation contains high concentrations of ethanol (23.7% v/v) and polyethylene glycol 400 (17% v/v), which cause significant local vascular irritation, phlebitis, and patient discomfort (Song et al., 2013).

Emerging evidence suggests that calcium dysregulation is a common pathological denominator in both glaucoma and epilepsy. In glaucoma, calcium overload through L-type channels triggers excitotoxicity and apoptosis of retinal ganglion cells (RGCs). In epilepsy, sustained calcium influx perpetuates neuronal hyperexcitability and seizure generation (Zheng et al., 2025). Given its ability to inhibit L-type VGCCs and its brain-enrichment characteristics, NIM represents an ideal candidate for repurposing in these neurodegenerative conditions.

This review consolidates findings from six recent research articles to:

1. evaluate novel formulation strategies for improving NIM solubility and bioavailability, including submicron lipid emulsions (SMEs), solid lipid nanoparticles (SLNs) in buccal tablets, nanosuspensions, and mixed micelles.
2. assess the physicochemical, pharmacokinetic, and safety profiles of these advanced formulations
3. explore the emerging mechanistic understanding of NIM as a monoamine oxidase A (MAOA) inhibitor.

Table:1 Overview of Nimodipine and Its Research Significance

S. No.	Parameter	Details
1	Drug	Nimodipine
2	Chemical nature	Second-generation dihydropyridine calcium channel blocker with high lipid solubility
3	Lipophilicity	High lipophilicity (log P ~3.4), enabling efficient membrane permeability
4	Mechanism of action	Blocks L-type voltage-gated calcium channels in neurons and vascular smooth muscle
5	Blood-brain barrier penetration	Easily crosses the blood-brain barrier (BBB), resulting in higher brain concentrations compared to other calcium channel blockers
6	Comparison with other CCBs	Shows better CNS selectivity than drugs like verapamil and diltiazem
7	Clinical use	Primarily used to prevent neurological complications after subarachnoid hemorrhage
8	Solubility limitation	Poor aqueous solubility (~0.01 mg/mL), limiting formulation and drug delivery
9	Bioavailability issue	Low oral bioavailability (<15%) due to extensive first-pass metabolism

10	Metabolism	Mainly metabolized by CYP3A4 enzymes in liver and intestine
11	Limitations of injectable form	Conventional injectable formulations contain high concentrations of ethanol and polyethylene glycol (PEG), leading to irritation and vascular complications
12	Safety concerns	May cause phlebitis, vascular irritation, and discomfort during administration
13	Role in glaucoma	Reduces calcium overload, thereby protecting retinal ganglion cells from degeneration
14	Role in epilepsy	Controls excessive calcium influx, reducing neuronal hyperexcitability
15	Pathological relevance	Calcium dysregulation is a common factor in both glaucoma and epilepsy
16	Therapeutic potential	Suitable for repurposing in neurodegenerative and neurological disorders
17	Advanced formulations	Includes nanoemulsions, solid lipid nanoparticles, nanosuspensions, and micelles
18	Aim of research	To improve solubility, bioavailability, and safety of Nimodipine formulations
19	Emerging mechanism	Shows potential inhibition of monoamine oxidase A (MAOA)
20	Future perspective	Development of safer and more effective injectable systems for CNS targeting

2. Physicochemical and Biopharmaceutical Challenges of Nimodipine

Nimodipine is classified as a BCS Class II drug (low solubility, high permeability). Its solubility in water is only 3.86 µg/mL, while in 0.1N HCl it is 0.0598 mg/mL, increasing in alkaline media (pH 6.8 phosphate buffer: 0.6597 mg/mL) (Mohanakrishnan et al., 2023). The drug exhibits pH-dependent solubility, with enhanced dissolution in the presence of alkalizing agents.

Table 2: Solubility Profile of Nimodipine in Different Media Data source: Mohanakrishnan et al. (2023)

S. No.	Medium	Solubility (mg/mL)	Observation
1	Distilled Water	0.00386	Very poor
2	0.1 N HCl	0.0598	Poor (acidic pH)
3	0.001 N HCl	0.219	Slightly better
4	pH 4.5 Acetate Buffer	0.0598	Poor
5	pH 6.8 Phosphate Buffer	0.6597	Moderate (alkaline pH)
6	pH 7.5 Phosphate Buffer	1.12	Improved

7	pH 2.1 Simulated Gastric Fluid	0.818	Moderate
8	pH 5 Simulated Intestinal Fluid	0.8498	Moderate

Data source: Mohanakrishnan et al. (2023)

The major limitation for oral administration is the extensive first-pass metabolism by CYP3A4, which reduces systemic bioavailability to approximately 13%. Additionally, NIM is a substrate for P-glycoprotein (P-gp) efflux transporters expressed in enterocytes, which actively pump the drug back into the intestinal lumen, further reducing absorption (Fathima and Kishan, 2023).

For intravenous administration, the primary challenge is the requirement for organic cosolvents (ethanol and PEG 400) to maintain the drug in solution. Upon dilution with infusion fluids (saline, glucose), these cosolvents become diluted below their effective concentration, leading to drug crystallization and precipitation, which poses serious safety risks including embolism and phlebitis (Song et al., 2013).

Therefore, the ideal NIM formulation must achieve: (1) enhanced aqueous solubility without toxic solvents; (2) reduced P-gp efflux; (3) lymphatic transport to bypass hepatic first-pass metabolism; and (4) physical compatibility with intravenous infusion fluids.

3. Advanced Formulation Strategies for Nimodipine

3.1 Submicron Lipid Emulsions (SMEs) with Charge Inducers and P-gp Inhibitors

Fathima and Kishan (2023) developed submicron lipid emulsions (SMEs) of nimodipine using soybean oil, egg lecithin (EPC-80), and varying charge inducers (oleic acid for negative charge; stearylamine for positive charge) with or without Tween 80 as a P-gp inhibitor. Five formulations (F1-F5) were prepared by homogenization followed by ultrasonication, yielding mean particle sizes ranging from 93.1 ± 4.55 nm (negatively charged F1) to 136.8 ± 11.76 nm (control F5). Zeta potentials ranged from -26.5 ± 1.02 mV (negative) to +46.3 ± 1.89 mV (positive).

The entrapment efficiency was remarkably high across all formulations (99.50-99.95%), indicating near-complete drug incorporation into the lipid core.

In vitro release studies in 0.1N HCl and pH 6.8 phosphate buffer showed cumulative release below 82% over 24 hours, with negatively charged formulations (F1, F3) releasing slightly faster than positively charged ones (F2, F4). This was attributed to the rigidifying effect of cholesterol and charge inducers on the interfacial membrane, which retards drug diffusion.

The most significant finding was the oral bioavailability study in male Wistar rats. Positively charged SME containing stearylamine and Tween 80 (F4) achieved a relative bioavailability

3.85 times higher than the nimodipine suspension (F6). The Cmax of F4 was 10.214 ± 1.136 µg/mL compared to 9.144 ± 0.797 µg/mL for the

commercial injection, with AUC(0-∞) values of 461.91 and 427.85 $\mu g \cdot mL^{-1} \cdot min^{-1}$, respectively. The enhanced bioavailability was attributed to three synergistic mechanisms: (1) increased uptake of positively charged globules by negatively charged enterocytes; (2) P-gp inhibition by Tween 80; and (3) lymphatic transport of the lipid carrier, bypassing hepatic first-pass metabolism.

3.2 Solid Lipid Nanoparticles (SLNs) and Mucoadhesive Buccal Tablets

Neelakandan et al. (2023) formulated nimodipine-loaded solid lipid nanoparticles (SLNs) using palmitic acid or stearic acid as the lipid matrix and Tween 80 as a surfactant via high-shear homogenization and ultrasonication. The optimized SLN formulation (P2) using palmitic acid (100 mg) and 20% Tween 80 exhibited a particle size of 131.4 ± 33.23 nm, PDI of 0.170, zeta potential of -13.5 ± 8.05 mV, entrapment efficiency of 96.9%, and in vitro drug release of 89.4% over 6 hours.

FTIR spectroscopy confirmed no chemical interaction between nimodipine and the lipid excipients. DSC and XRD studies revealed that the drug changed from a crystalline to an amorphous form within the SLNs, which is favorable for enhanced dissolution.

These SLNs were subsequently incorporated into mucoadhesive buccal tablets using various ratios of Carbopol 934, HPMC K4M, and HEC. The optimized buccal tablet (NT3) containing 60 mg Carbopol and 25 mg HPMC K4M showed 89.08% drug release at 8 hours, surface pH of 6.1 (within salivary pH range), mucoadhesive strength of 29.5 g, and ex vivo mucoadhesive time exceeding 8 hours. The buccal route offers the advantage of direct absorption into the systemic circulation via the internal jugular vein, completely bypassing first-pass metabolism and P-gp efflux in the gut.

3.3 Nanosuspension Using Media Milling

Shah et al. (2012) employed a media milling technique to prepare nimodipine nanosuspensions. Using zirconium oxide beads (0.1 mm and 0.5 mm in a 50:50 ratio) and a 2% w/v drug concentration, they achieved a mean particle size of 279 nm (batch NM39). The optimized formulation used a drug-to-stabilizer ratio of 1:1.5 and a stabilizer-to-stabilizer ratio (HPC:PVP K-30) of 0.75:0.25.

The most impressive result was the dissolution profile: the optimized nanosuspension released 96.97% of nimodipine within 5 minutes in pH 4.5 acetate buffer, compared to only 3.25% for the pure drug. DSC thermograms confirmed that the crystallinity of the drug was maintained after nanosizing (no amorphous conversion), indicating that the enhanced dissolution was solely due to increased surface area and reduced diffusion layer thickness according to the Nernst-Brunner-Noyes-Whitney equation.

3.4 Egg Phosphatidylcholine-Sodium Glycocholate Mixed Micelles (EPC-SGC-MMs)

Song et al. (2013) developed a novel injectable mixed micelle formulation to replace the toxic ethanol-based commercial injection. Using the coprecipitation method, optimized NIM-EPC-SGC-MMs were prepared with an EPC:SGC mass ratio of 1:1, total concentration of 40 mg/mL, NIM concentration of 0.5 mg/mL, and pH 7.4.

The critical micelle concentration (CMC) of the EPC/SGC binary mixture was determined using the pyrene 1:3 ratio method and found to be 0.0095 mg/mL. The mean particle size was

6.099 ± 0.048 nm with a polydispersity index of 0.107, and TEM confirmed spherical morphology. The water solubility of nimodipine was enhanced 250-fold to 0.468 ± 0.009 mg/mL, with solubilizing efficiency of 93.8% and drug loading of 1.17%.

Critically, the mixed micelles showed excellent physical compatibility with sodium chloride injection, glucose injection, and sterile water even after 500-fold dilution, with no drug crystallization observed for up to 10 hours. In contrast, the commercial injection showed crystal formation within 30 minutes after 10-fold dilution. Pharmacokinetic studies in rats showed bioequivalence between the mixed micelles and commercial injection (AUC(0-∞):

461.91 vs. 427.85 $\mu g \cdot mL^{-1} \cdot min^{-1}$; $P > 0.05$). Most importantly, the vascular irritability study in rabbits demonstrated that the mixed micelles caused no histopathological damage (no vasodilation, hemorrhage, or inflammatory cell infiltration), whereas the commercial injection caused severe venous irritation due to ethanol content.

3.5 Bilayer Tablets for Combination Therapy

Mohanakrishnan et al. (2023) developed a bilayer tablet combining nimodipine as an immediate-release (IR) layer for acute blood pressure lowering and metformin as a controlled-release (CR) layer for type 2 diabetes mellitus. The nimodipine IR layer used crospovidone as a superdisintegrant and released the drug within 15 minutes. The metformin CR layer used HPMC K100M, sodium bicarbonate, and Eudragit RSPO, achieving 85.15% drug release over 20 hours. FTIR studies confirmed no drug-excipient interactions. This approach demonstrates the feasibility of fixed-dose combination products containing nimodipine for patients with comorbid hypertension and diabetes.

4. Mechanistic Insights: Molecular Targets Beyond Calcium Channels

Zheng et al. (2025) conducted an in silico target identification and molecular dynamic simulation study to explore novel mechanisms of nimodipine in neurodegenerative diseases. Using network analysis, they identified 33 intersecting drug-disease targets.

Protein-protein interaction (PPI) network analysis combined with GO and KEGG enrichment highlighted 12 key targets: CASP3, TNF, BAX, BCL2, IL1B, GSK3B, IL1A, MAOB, MAOA,BDNF, APP, and GFAP.

Molecular docking revealed binding energies below -6 kcal/mol for MAOA (-7.343 kcal/mol), GSK3B, MAOB, CASP3, BCL2, IL1B, and APP. Molecular dynamics simulation (100 ns) of MAOA-nimodipine complex demonstrated stable binding with an average dynamic binding energy of -52.39 ± 3.05 kcal/mol, which was significantly higher than that of harmine (-26.66± 2.75 kcal/mol), a known MAOA inhibitor.

The dynamic cross-correlation matrix (DCCM) showed that nimodipine induced new negative correlations in residues 100-200 and 300-400 of MAOA, similar to harmine. Importantly, nimodipine interacted with functionally critical MAOA residues (305LYS, 407TYR, 444TYR) during the dynamic simulation, even though these interactions were not observed in static docking. The authors concluded that nimodipine may exert neuroprotective effects in Alzheimer's and Parkinson's diseases by inhibiting MAOA activity and modulating cerebral oxidative stress, in addition to its classical calcium channel blockade.

This novel mechanism has direct implications for glaucoma and epilepsy, where MAOA-induced oxidative stress and neuroinflammation play significant roles. Thus, nimodipine's dual action (L-type calcium channel blockade + MAOA inhibition) makes it uniquely suited for repurposing in these conditions.

5. Implications for Glaucoma and Epilepsy Management

5.1 Glaucoma

Glaucoma is characterized by progressive loss of retinal ganglion cells (RGCs) due to elevated intraocular pressure (IOP), excitotoxicity, and calcium overload. Nimodipine's ability to block L-type calcium channels on RGCs can directly reduce calcium-mediated apoptosis. Additionally, its vasodilatory effect on ocular vessels improves blood flow to the optic nerve head, which is often compromised in normal-tension glaucoma. The novel MAOA inhibition mechanism further reduces oxidative stress in the retina. An injectable formulation (either intravitreal or intravenous) would be ideal for acute glaucoma episodes or as a neuroprotective adjunct to IOP-lowering surgery.

5.2 Epilepsy

In epilepsy, excessive glutamate release during seizures activates VGCCs, leading to sustained calcium influx that perpetuates neuronal firing. Nimodipine's anticonvulsant activity has been demonstrated in multiple animal models, including ischemia-induced, pentylenetetrazol-induced, and bicuculline-induced seizures. The ability to rapidly achieve therapeutic CNS concentrations via intravenous administration is critical for status epilepticus. The mixed micelle formulation (Song et al., 2013) offers a safe, non-irritating injectable option for this indication.

6. Comparative Evaluation of Formulation Strategies

Table:3 Comparative Summary of Nimodipine Formulations

Formulation Type	Key Advantage	Bioavailability	Safety Profile
SMEs (F4)	3.85× higher oral absorption	3.85-fold vs. suspension	No irritation
SLN Buccal Tablet (NT3)	Bypasses liver metabolism	Not quantified	No mucosal irritation
Nanosuspension (NM39)	97% drug release in 5 minutes	Not reported	Maintains drug stability
Mixed Micelles	250× more soluble; no alcohol	Equal to IV injection	No vein damage

Bilayer Tablet	Combines two drugs in one tablet	Not reported	No drug-excipient issues

3. Future Perspectives and Conclusion

The six research articles reviewed here demonstrate that nimodipine's poor solubility and low bioavailability can be successfully overcome using modern formulation technologies. Positively charged SMEs with P-gp inhibitors offer a practical oral delivery system with nearly 4-fold higher bioavailability. Mixed micelles provide a safe, ethanol-free intravenous formulation that eliminates phlebitis and crystallization upon dilution.

Nanosuspensions achieve nearly immediate dissolution, ideal for rapid onset. Buccal SLN tablets bypass hepatic metabolism entirely. For the specific goal of repurposing nimodipine injection for acute management of glaucoma and epilepsy, the mixed micelle formulation (Song et al., 2013) appears most promising due to its:

- excellent safety profile (no vascular irritation)
- physical compatibility with infusion fluids
- bioequivalence to commercial injection
- simple, scalable preparation method. Future studies should evaluate this formulation in animal models of acute glaucoma (optic nerve crush, acute IOP elevation) and status epilepticus, along with neuroprotection assays using RGC cultures and neuronal cell lines.

CONCLUSION:

Advanced formulation technologies have successfully addressed the biopharmaceutical limitations of nimodipine. The mixed micelle formulation, in particular, offers a safe, effective, and scalable injectable product with potential for repurposing in glaucoma and epilepsy.

Table:4 Conclusion of the Review

Aspect	Conclusion Summary
Overall Finding	Advanced formulation technologies have successfully overcome nimodipine's poor solubility and low bioavailability.
Submicron Lipid Emulsions (SMEs)	Positively charged SMEs with P-gp inhibitor (Tween 80) provide a practical oral delivery system with nearly 4-fold higher bioavailability (3.85× vs. suspension).
Mixed Micelles (EPC-SGC-MMs)	Offer a safe, ethanol-free intravenous formulation that eliminates phlebitis, prevents crystallization upon dilution, and is bioequivalent to commercial injection.
Nanosuspensions	Achieve nearly immediate dissolution (96.97% in 5 minutes), ideal for rapid onset of action.

Buccal SLN Tablets	Bypass hepatic first-pass metabolism entirely via absorption through the buccal mucosa.
Bilayer Tablets	Demonstrate feasibility of fixed-dose combination products (nimodipine + metformin) for comorbid conditions.

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