CSPS | jpps Journal of Pharmacy and Pharmaceutical Sciences

TYPE Original Research
PUBLISHED 13 November 2026
DOI 10.3389/jpps.2026.17227

Check for updates

OPEN ACCESS

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RECEIVED 25 June 2026
REVISED 27 August 2026
ACCEPTED 27 October 2026
PUBLISHED 13 November 2026

CITATION
Elshamy A, Osama H, Lavasanifar A, Sanaee F, Hu J, Chu Y, Chen L and Mahmoud SH (2026) Development and stability evaluation of extemporaneously compounded nimodipine oral suspension.
J. Pharm. Pharm. Sci. 29:17227.
doi: 10.3389/jpps.2026.17227

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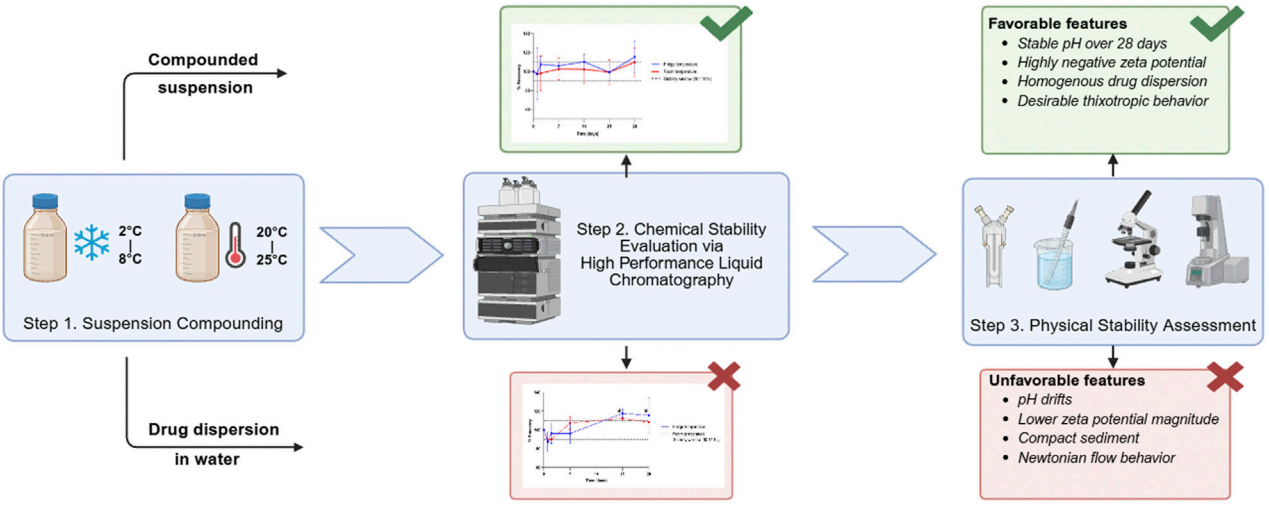
Development and stability evaluation of extemporaneously compounded nimodipine oral suspension

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Background: Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating neurological emergency often complicated by delayed cerebral ischemia. While nimodipine remains the only approved pharmacological intervention proven to improve clinical outcomes in this population, significant pharmacokinetic variability and administration challenges in dysphagic patients severely compromise its consistent clinical efficacy.
Purpose: To formulate an extemporaneously compounded nimodipine oral suspension and to systematically evaluate its physicochemical stability and feeding tube compatibility.
Methods: A compounded nimodipine suspension was prepared in 1:1 ORA-Plus® and ORA-Sweet® vehicles and stored under refrigerated and room temperature conditions for 28 days. Chemical stability was quantified via high-performance liquid chromatography (HPLC). Physical stability was evaluated by measuring pH, particle size, sedimentation volume, zeta potential, and viscosity. Administration feasibility was tested using standard enteral feeding tubes.
Results: The compounded formulation maintained chemical stability (90%–110% recovery) for 3 weeks refrigerated and 4 weeks at room temperature. Compared to the crude dispersion prepared by crushing tablets in water, the compounded suspension demonstrated a more negative baseline zeta potential (–21.43 $\pm$ 1.89 mV vs. –8.42 $\pm$ 2.28 mV, $p < 0.001$) and higher sedimentation volume (0.99 $\pm$ 0.01 vs. 0.26 $\pm$ 0.04, $p < 0.001$), confirming enhanced homogeneity and dispersibility. Rheological analysis confirmed a shear-thinning profile ideal for enteral delivery. Furthermore, feeding tube administration yielded >98% drug recovery without occlusion.
Conclusion: The compounded nimodipine suspension in this study provides a feasible alternative for enteral nimodipine administration. Future studies are needed to evaluate the formulation's bioavailability.

KEYWORDS
aneurysmal subarachnoid hemorrhage, extemporaneous oral suspension, HPLC, nimodipine, stability



GRAPHICAL ABSTRACT
Comparative workflow evaluating the chemical and physical stability of the novel compounded nimodipine suspension versus a crude aqueous tablet dispersion stored under refrigerated and room temperature conditions over 28 days. The structured compounded suspension demonstrated superior chemical stability within the 90–110% recovery window via HPLC, alongside favorable physical characteristics including stable pH, high negative zeta potential, homogeneous dispersion, and thixotropic flow behavior. In contrast, the aqueous dispersion exhibited erratic drug recovery, pH drifts, compact sedimentation, and undesirable Newtonian flow. Created in BioRender. Elshamy, A. (2026) https://BioRender.com/q3gx9qy.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a critical neurological emergency, accounting for approximately 5% of all strokes. It occurs when a cerebral aneurysm ruptures, leading to the accumulation of blood within the subarachnoid space. Despite its relatively low incidence, aSAH carries a disproportionately high mortality rate of 30%–50%. This high mortality is frequently driven not by the initial rupture, but by secondary complications such as vasospasm and delayed cerebral ischemia (DCI). Furthermore, a significant majority of survivors suffer from long-term neurological deficits, contributing to a substantial socioeconomic burden [1–7]. To mitigate these risks, clinical guidelines mandate the prophylactic administration of nimodipine (60 mg orally every 4 h for 21 days post-ictus). Notably, nimodipine remains the only approved pharmacological intervention proven to improve clinical outcomes in this patient population [4, 5].

Nimodipine, a 1, 4-dihydropyridine calcium channel blocker, exerts its action through inhibiting L-type voltage gated calcium channels found in the cerebral blood vessels smooth muscles, hindering the calcium ions influx leading to vasodilation [8–12]. Although the exact neuroprotective mechanism of nimodipine is not fully known to date, nimodipine is suggested to have neuroprotective pathways through endogenous fibrinolytic activity, attenuation of cortical spreading depolarization and anti-inflammatory properties [4, 5, 12–14].

The clinical utility of nimodipine is frequently complicated by significant pharmacokinetic (PK) variability. Research has demonstrated that this erratic PK behavior leads to inconsistent patient outcomes, making it difficult to establish a definitive correlation between drug exposure and therapeutic success [15–19]. While patient-specific covariates, such as age, sex, race, and genetic predisposition, contribute to this variability, drug formulation and administration techniques are increasingly recognized as pivotal factors potentially impacting clinical efficacy [12]. This is particularly problematic in regions with limited formulation options. For instance, in Canada, nimodipine is primarily available only as tablets (Nimotop®, Laboratoire X.O), whereas other markets, such as the USA, utilize soft gelatin capsules and oral solutions. Therefore, clinicians are left with few alternatives for patients who cannot swallow, particularly in countries where manufactured oral solutions of nimodipine are not available commercially [12, 20].

In clinical practice, tablets are frequently crushed in water and administered via feeding tubes for unconscious or dysphagic patients. However, evidence suggests this practice is suboptimal; studies indicate that crushed tablet administration may be associated with a higher prevalence of moderate-to-severe vasospasm and DCI [20–22]. In addition, the manufacturer recommends against crushing nimodipine tablets [23]. Consequently, there is a need for alternative formulations or novel delivery methods to ensure safe and equitable nimodipine administration in countries where oral tablets are the only available option.

The aim of this study was to develop and evaluate the stability of an extemporaneously prepared nimodipine suspension. This approach may serve as a suitable substitute for nimodipine tablets in patients who are unable to ingest the entire tablet, overcoming problems associated with the administration of crushed nimodipine tablet dispersion in water. Also, it can be a potential step towards standardizing the institutional practices and reducing the number of factors accounting for pharmacotherapy variability in aSAH patients.

Materials and methods

Chemicals and reagents

Nimodipine (purity 99.3% ± 0.6%), nifedipine (purity ≥98%) used as the internal standard (IS), HPLC-grade water, acetonitrile and methanol were purchased from Sigma-Aldrich (Oakville, ON, Canada). ORA-Sweet® (Lot: 3090492), ORA-Plus® (Lot: 3492961) and Nimotop® 30 mg tablets (Lot: B0269, Bayer Inc.) were purchased from McKesson Canada (Saint-Laurent, QC, Canada). Sodium hydroxide (NaOH, purity ≥98%) was purchased from Sigma-Aldrich (Oakville, ON, Canada), while hydrochloric acid (HCl) and 30% hydrogen peroxide were purchased from Thermo Fisher Scientific (Mississauga, ON, Canada).

Compounding of nimodipine suspension

Nimotop® 30 mg tablets were crushed in porcelain mortar providing a rough surface for better comminution. ORA-Plus® was added gradually to wet the powder in the mortar. The resulting suspension was transferred to 250 mL amber glass bottles to prevent any photodegradation. The rest of the ORA-Plus® volume was used to wash the mortar walls and transfer the contents to the amber bottles. Equivalent volume of ORA-Sweet® was added to the bottle to set the final concentration of the bottle to be 6 mg/mL. Table 1 outlines the composition of used vehicles [24, 25]. The reason behind choosing this concentration was to facilitate dose calculation as the 30 mg and 60 mg dose will correspond to 5 and 10 mL, respectively. Nimodipine suspension underwent chemical and physical characterization using the scheme illustrated in (Figure 1).

TABLE 1 Composition of ORA-Plus and ORA-Sweet vehicles.

ORA-Plus	ORA-Sweet
Appearance: White aqueous-based viscous liquid	Appearance: Translucent yellow syrup
Composition: • Purified water • Buffer: citric acid, sodium phosphate and trisodium phosphate • Preservatives: methylparaben and potassium sorbate • Suspending agents: MCC, CMC sodium, xanthan gum and carrageenan • Anti-foam agents: dimethicone	Composition: • Sweetener: Sucrose • Glycerin and sorbitol • Buffer: citric acid and sodium phosphate • Preservatives: methylparaben and potassium sorbate • Citrus-berry flavor
Its main purpose is to serve as a suspending vehicle	Its main purpose is to serve as a flavoring agent

CMC, Carboxymethylcellulose; MCC, Microcrystalline cellulose.

Chemical stability evaluation

Instrument

The experiment was conducted using high-performance liquid chromatography coupled to ultraviolet detector (HPLC-UV) (Shimadzu, Kyoto, Japan). This device is comprised of LC-20 AT pumps for solvent delivery, SIL-20A autosampler and coupled to a UV-VIS detector (SPD-10A VP). Reverse-phase separation was performed through a Supelco Discovery® C18 column of dimensions (250 × 4.6 mm, 5 µm) (Sigma-Aldrich, Oakville, ON, Canada). A Discovery® C18 Supelguard™ guard column (20 × 4 mm, 5 µm) purchased from Sigma-Aldrich was used (Oakville, ON, Canada). Data acquisition and chromatographic integration were carried out via LabSolutions Lite® software version 5.93 (Shimadzu, Kyoto, Japan).

Chromatographic conditions

The HPLC-UV analysis method was adapted from Chang et al [26]. The mobile phase (MP) composition was methanol-acetonitrile-water (35:38:27, v/v). The MP flow rate was set to 1 mL/min with a total run time of 10 min and an injection volume of 40 µL. We tested two IS: caffeine and nifedipine; nifedipine showed more consistent results and peak resolution. The detector's wavelength was set at 236 nm. The autosampler and column temperatures were set at ambient conditions.

Stock and working solutions

Stock solutions of nimodipine and nifedipine (IS) were prepared at a concentration of 1 mg/mL by dissolving the required mass of each powder in methanol. Given the light sensitivity of nimodipine and nifedipine, these procedures were conducted under dim light conditions. The IS working solution was subsequently prepared by diluting the stock with methanol to reach a final concentration of 300 µg/mL. All stock solutions were stored in amber vials or wrapped in aluminum foil and refrigerated at (2–8 °C) for a maximum of 2 weeks; however, IS working solutions were prepared freshly for each analysis to ensure stability.

Calibration levels and quality control samples

A seven-point calibration curve was constructed by diluting nimodipine stock to concentrations of 10, 25, 40, 50, 65, 80 and 100 µg/mL using methanol. The quality control (QC) samples were prepared alongside in concentrations of 10, 20, 45 and 90 µg/mL representing the lowest limit of quantification (LLOQ), low-concentration quality control (LQC), medium-concentration quality control (MQC), and high-concentration quality control (HQC), respectively. The four QC levels were used for validating our method. The QC levels were prepared using nimodipine stock and completing the volume to 100 µL using ORA-Sweet® and ORA-Plus® in ratio 1:1. The volume was made up to 1 mL using methanol. Eventually, the calibration and QC levels were spiked with 50 µL of the IS working solution (300 µg/mL).

Sample preparation

Working solutions of the compounded suspension were prepared at a concentration of 1 mg/mL. This was achieved through adding 200 µL of the compounded suspension bottle content to 1 mL methanol. Further dilution was done using

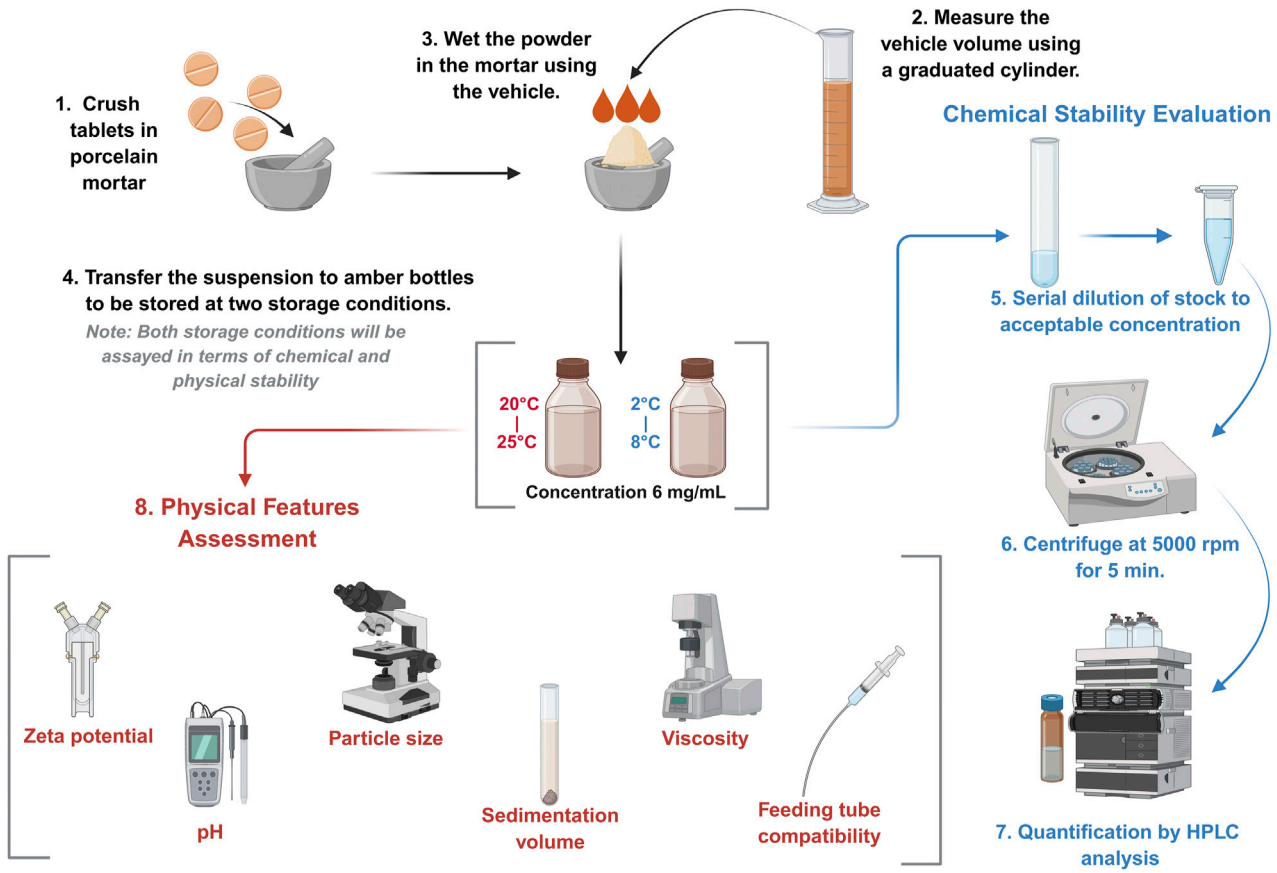


FIGURE 1
Schematic workflow for the development and evaluation of an extemporaneous nimodipine oral suspension. Nimodipine tablets were crushed in a mortar and suspended in ORA-Plus® and ORA-Sweet® vehicles, followed by packaging in amber bottles and assignment to defined storage conditions. Blue arrows indicate the chemical stability assessment pathway, encompassing sample dilution to the appropriate calibration range, centrifugation, and quantification via HPLC. Red arrows track the evaluation of the suspension's physical stability parameters. Abbreviations: HPLC, high-performance liquid chromatography. Created in BioRender. Elshamy, A. (2026) https://BioRender.com/0v5n6nf.

methanol to reach 90 µg/mL. All samples were spiked with 50 µL of the IS working solution (300 µg/mL). Subsequently, this spiked mixture was vortexed for 10 s and then centrifuged at 5,000 rpm for 5 min using an Eppendorf 5424 Microcentrifuge (Eppendorf, Hamburg, Germany). Aliquots of 320 µL of the supernatant were taken into HPLC amber glass vials with glass inserts and 40 µL were injected for analysis. The whole procedure was completed under dim light conditions.

Method validation

Method validation was carried out based on the European Medicines Agency (EMA) Guidelines 2011 [27]. The validation procedure encompassed linearity, selectivity, sensitivity, accuracy and precision.

Linearity

A seven-point calibration curve was constructed using the earlier mentioned concentrations in which the concentrations were plotted on the X-axis and peak area ratio (Nimodipine/IS) on the Y-axis. Linear regression analysis was used to generate the regression equation, slope, intercept and coefficient of determination (r^2).

Selectivity and sensitivity

Selectivity was affirmed by the absence of any interfering peaks when blank samples were injected. Sensitivity was dependent on the LLOQ level to be quantified with adequate precision and accuracy.

Precision and accuracy

Five replicates of each QC level were prepared as mentioned in the QC samples preparation (section *Calibration levels and quality control samples*). The analysis was performed as three independent batches over three consecutive days to evaluate intra-day and inter-day performance of the method. QC samples' concentrations were back calculated using a freshly prepared calibration curve for each day. Precision was reported as coefficient of variation (CV%), while accuracy was computed as the observed concentration/nominal concentration, expressed as percentage error.

Forced degradation assessment

To evaluate the analytical specificity of the HPLC method and confirm that the detected peaks corresponded solely to nimodipine, forced degradation studies were conducted under various stress conditions commonly seen in literature [28–30]. A qualitative

assessment of the nimodipine peak morphology, specifically monitoring peak height reduction, broadening, or splitting, was utilized to verify that the method could successfully resolve nimodipine from its degradation products.

Alkali treatment

Aliquots of 1 mL of freshly prepared nimodipine stock (1 mg/mL) were incubated with 3 mL of 1 N NaOH for 1h at 60 °C, 1h at 80 °C and 2h at 80 °C each condition independently. Temperature was maintained using Fisher Water Bath (Fisherbrand™, Thermo Fisher Scientific, Waltham, MA, USA). After the designated time, the solutions were neutralized to pH close to 7 using 1 N HCl. The pH was measured using Fisherbrand™ accumet™ AB150 Benchtop pH Meter (Thermo Fisher Scientific, Mississauga, ON, Canada). Following this step, the neutralized mixtures were transferred to 10 mL volumetric flasks, and the volume was made up to the mark using methanol. Subsequently, further dilutions of the incubated mixtures to reach a final drug concentration of 90 µg/mL. Aliquots of 320 µL were transferred to amber glass vials for HPLC analysis. This step was repeated three times (n = 3) for each incubation condition.

Acid treatment

Acid treatment followed the same procedure of alkali degradation. Initially, incubating 1 mL aliquots of nimodipine stock solutions with 3 mL of 1 N HCl at 80 °C for 6h. Based on nimodipine's physicochemical features, nimodipine is known to be susceptible to both acid and basic/caustic degradation, caustic degradation is much faster and easier. On the contrary, acid hydrolysis necessitates higher temperatures for longer incubation duration. This explains the chosen parameters for each stress condition [23, 30]. Similarly, after the designated time, the incubated mixture was neutralized using 1 N NaOH to a pH close to 7. Thereafter, this mixture was transferred to 10 mL volumetric flasks that were topped to the mark using methanol. Finally, aliquots of 320 µL were pipetted into amber glass vials for HPLC analysis. This condition was tested in triplicate as well.

Oxidative degradation

Oxidation is a very common degradation pathway converting the dihydropyridine ring in nimodipine's chemical structure to its pyridine analogue [31, 32]. Drug oxidation was forced by using hydrogen peroxide as an oxidizing agent. Hydrogen peroxide 30% was diluted by 10 folds using distilled water. Secondly, aliquots of 1 mL of freshly prepared nimodipine stock were incubated with 9 mL 3% hydrogen peroxide in glass tubes wrapped in foil for 15 and 30 min. After which, the mixture was diluted using methanol to reach final drug concentration of 90 µg/mL. Ultimately, aliquots of 320 µL were taken into amber glass vials for HPLC analysis. Triplicates were performed for each incubation time.

Chemical stability of the compounded suspension

To assess the stability of the compounded suspension, the study was conducted at two different storage conditions: room temperature (20–25 °C, RT) and fridge temperature (2–8 °C, FT). Five independent amber bottles were prepared, as described in Section *Compounding of nimodipine suspension*, for each storage condition (n = 10 bottles total) and diluted for chemical stability evaluation. For each bottle, a triplicate analysis was used to assess stability at pre-set time points: baseline (zero time), day 1, day 2 and then weekly intervals on days 7, 14, 21 and 28. Bottles were swirled for 2 min before sample withdrawal to ensure uniformity and homogenous distribution of the suspended particles. A calibration curve was prepared freshly on each day to generate a regression equation for back calculating the sample concentrations. The results were expressed as percentage recovery relative to the zero time of each bottle. The suspension was deemed chemically stable if the mean percentage recovery was between 90% and 110% in accordance with the Stability and Compatibility Study Guidelines for the American Journal of Health-System Pharmacy (AJHP) [33].

Control preparation and chemical stability

Control was prepared as the comparator by dispersing crushed tablets in distilled water following the same procedure in Section *Compounding of nimodipine suspension*, with the only difference of replacing the suspending vehicle (ORA-Plus®/ORA-Sweet® 1:1) with distilled water. This simulates the process nimodipine tablets undergo in hospitalized aSAH patients who are unable to swallow whole tablets [22]. Three independent amber bottles were prepared for each storage condition (n = 6 bottles total). Mirroring what we did in (section *Chemical stability of the compounded suspension*), a triplicate was used to test stability at the following time points: baseline (zero time), day 1, day 2 and weekly intervals on days 7, 21 and 28.

Physical stability evaluation

To investigate physical stability, three batches of compounded suspension were prepared for each storage condition. These were compared against a control group consisting of three batches of crude nimodipine tablet dispersion in water, per storage condition. Samples were assessed in terms of pH, zeta potential (ZP), sedimentation volume, particle size via microscopy and viscosity. These physical attributes were measured at baseline (zero time) and at weekly intervals on days 7, 21 and 28.

pH measurement

The pH measurement was carried out using Fisherbrand™ accumet™ AB150 Benchtop pH Meter (Fisherbrand™, Thermo Fisher Scientific, Waltham, MA, USA). For each bottle, aliquots of 3 mL were taken into a Falcon tube, and the pH electrode was submerged until a stable reading was obtained. The reading was recorded and the electrode was rinsed with water to avoid any cross-contamination. Each bottle was assayed in triplicate.

Zeta potential

ZP was measured using Malvern Zetasizer Ultra (Malvern Panalytical Ltd., Worcestershire, UK) for all 12 bottles. Aliquots of 100 µL were taken from each bottle and diluted by adding 1 mL of

deionized water in Eppendorf tubes (1.7 mL). The mixtures were vortexed for 10 s and transferred into the Folded Capillary Cell (DTS1070) using a syringe. The experiment was conducted in quintuplicate (n = 5) for each bottle. As a result, 15 readings were procured per storage condition for each suspending vehicle type at each time point. Software used for data acquisition was ZS Explorer 2.1.0.15 (Malvern Panalytical Ltd., Worcestershire, UK).

Sedimentation volume

A total of 12 transparent graduated cylinders were labelled corresponding to the 12 bottles; split into halves per storage condition (RT or FT) and suspension type (compounded or crude tablet dispersion in water). At baseline (zero time), a 5 mL aliquot was transferred to the indicated cylinder. The cylinders were homogenized by inversion and then stored undisturbed at the designated storage temperature. Sedimentation volume (F) was defined as the ratio of the ultimate volume of the sediment (V_u) to the original volume of the suspension (V_0). The suspension was visually checked for changes using transparent graduated cylinders.

Particle size measurement

A 100 µL aliquot was pipetted out from each bottle and diluted with 10 mL of distilled water in glass test tubes. Next, the tubes were inverted for mixing and 2-3 drops were taken onto a glass slide. Particles were visualized using Zeiss Axio Observer A1 light microscope (Zeiss, Toronto, ON, Canada). For each bottle, one representative snapshot was captured at each time point. Particle size annotations were executed using Fiji/ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Viscosity

Viscosity was assayed exclusively for the compounded suspension. The flow behavior of the formulation was characterized using a rotational rheometer (DHR-3, TA Instruments, USA) equipped with a 40 mm cone-plate geometry [34]. Apparent viscosity was measured over a shear rate range of 0.1–1000 s^{-1}. Rheological measurements were conducted on freshly prepared samples (zero time) and after 28 days of storage. Samples were stored either at RT or FT, and measurements were performed at the corresponding temperatures using the rheometer's temperature control system. All tests were carried out in triplicate (n = 3), and the graphs were plotted using OriginPro version 2018C software (OriginLab Corporation, Northampton, MA, USA).

Feeding tube compatibility

Feeding tube compatibility was evaluated using two commonly utilized types of feeding tubes: Salem Sump™ polyvinyl chloride (PVC) tubes (14 FR 48 IN) with ENFit connection (Cardinal Health Canada Inc., Calgary, AB, Canada) and Corflo Nasogastric/Nasointestinal Tube ENFit and STYLET (12 FR) (Canadian Hospital Specialties Limited, Oakville, ON, Canada). Additional accessories comprised the ENFit NeoMed 60 mL ORAL/ENTERAL Syringes and the Kangaroo™ Y-site Extensions with ENFit connection (Specialty Food Shop, Toronto, ON, Canada).

Feeding tube occlusion

Primarily, a new set of Nimotop® 30 mg tablets were crushed in a porcelain mortar followed by adding an equivalent volume of ORA-Plus®/ORA-Sweet® to reach a final concentration of 6 mg/mL. Afterwards, the mortar was tilted gently for an even suspension and 10 mL were withdrawn by the ENFit syringe. The syringe was locked with the tip of the Y-site extension inserted at the proximal end of the feeding tube, while the distal end of the tube was placed in a collecting beaker. After pushing the syringe content into the feeding tube line, the line was flushed twice with 10 mL of tap water. This procedure was carried out 6 times for each line simulating the number of nimodipine doses administered per day. Two lines from each feeding tube type were evaluated for their patency after a six-replicate cycle of suspension administration and flushing.

Feeding tube adsorption

Aiming to reach a target concentration of 6 mg/mL, Nimotop® 30 mg tablets were crushed in a porcelain mortar and suspended in 1:1 ratio of ORA-Plus® and ORA-Sweet® mixture. For the baseline, a 2 mL aliquot was taken directly from the mortar after proper mixing using the pestle. To maintain matrix consistency with the injected samples, baseline was diluted with 4 mL of tap water. For the experimental evaluation, a volume of 10 mL (equivalent to a dose of 60 mg) was drawn in the ENFit syringe and injected through the feeding tube with the distal end of the feeding tube placed in a Falcon tube. Then, the feeding tube was flushed using 10 mL tap water on two cycles. Subsequently, air was drawn into the syringe and injected into the tube to ensure no remnants of the suspension and water were entrapped. Further dilutions were conducted to reach a final concentration of 90 µg/mL, and each sample was spiked with 50 µL of 300 µg/mL of the IS working solution. Then, all samples were vortexed for 10 s followed by centrifugation at 5000 rpm for 5 min. Eventually, a volume of 320 µL of the supernatant were taken into HPLC vials for quantification. For the adsorption experiment, two lines per feeding tube type were evaluated with each assayed in triplicate. Results were expressed as mean percentage recovery relative to baseline.

Statistical analysis

For chemical stability, data were analyzed using a two-way mixed-design ANOVA, with storage conditions as the between-subjects factor and time (days) as the within-subjects factor. Normality was assessed visually via Quantile-Quantile (Q-Q) plots and histograms, while homogeneity of variances was confirmed using Levene's test. To account for potential violations of sphericity, p-values for main effects and interactions were reported using the Greenhouse-Geisser (G-G) correction. Post-hoc pairwise comparisons between specific time points and baseline (day 0) were performed using Fisher's Least Significant Difference (LSD), contingent upon a statistically significant F-test

($p < 0.05$). For physical stability, normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed data were reported as median with interquartile range (IQR) and analyzed using the Wilcoxon rank-sum test. All statistical tests were two-tailed with significance set at $p < 0.05$. Analyses were performed using Stata software version 18.0 (StataCorp, College Station, TX, USA).

Results

Chemical stability evaluation

Method validation

Linearity

The calibration curves were found to be consistently linear with ($r^2 \geq 0.99$) over the tested concentrations range (10–100 µg/mL).

Selectivity and sensitivity

There were no interfering peaks with nimodipine and the IS peaks eluting at 6.3 min and 4.5 min, respectively. Furthermore, there was not any carryover observed in the MP injections when they were injected after the highest level of calibration multiple times. The chromatograms of the blank vehicle (ORA-Plus®/ORA-Sweet® 1:1), calibration level and both analytes in a sample are demonstrated in (Figure 2). The LLOQ detected with acceptable precision and accuracy was 10 µg/mL.

Precision and accuracy

The intra-day and inter-day performance of our method were assessed by quintuplicate injections (n = 5) of the four QC levels as three independent batches over three consecutive days. As illustrated in (Table 2), the intra-day CV% and percentage error were below 15% for the LLOQ and the other QC levels, whereas the inter-day CV% and percentage error were below 20% for the LLOQ and below 15% for the rest of the QC levels, aligning with the cutoff values established by the EMA guidelines [27].

Forced degradation assessment

Forced degradation studies were conducted to verify that the analytical method selectively detected intact nimodipine rather than its breakdown products. Under alkaline treatment (1 N NaOH), a distinct degradant peak emerged between 4 and 5 min, accompanied by significant morphological alterations to the nimodipine peak (splitting and tailing), after one hour at 60 °C, with harsher conditions drastically reducing the overall response intensity. Acidic treatment (1 N HCl at 80 °C) similarly distorted the nimodipine peak and produced a degradant peak near 5 min. Notably, the alterations were more pronounced under alkaline rather than acidic conditions, which aligns with established literature regarding nimodipine's susceptibility profile [23, 30]. Finally, oxidative stress rapidly induced peak deformities despite shorter incubation periods, presenting a distinct broad peak after 3 min and halving nimodipine's absorbance when the exposure time was doubled.

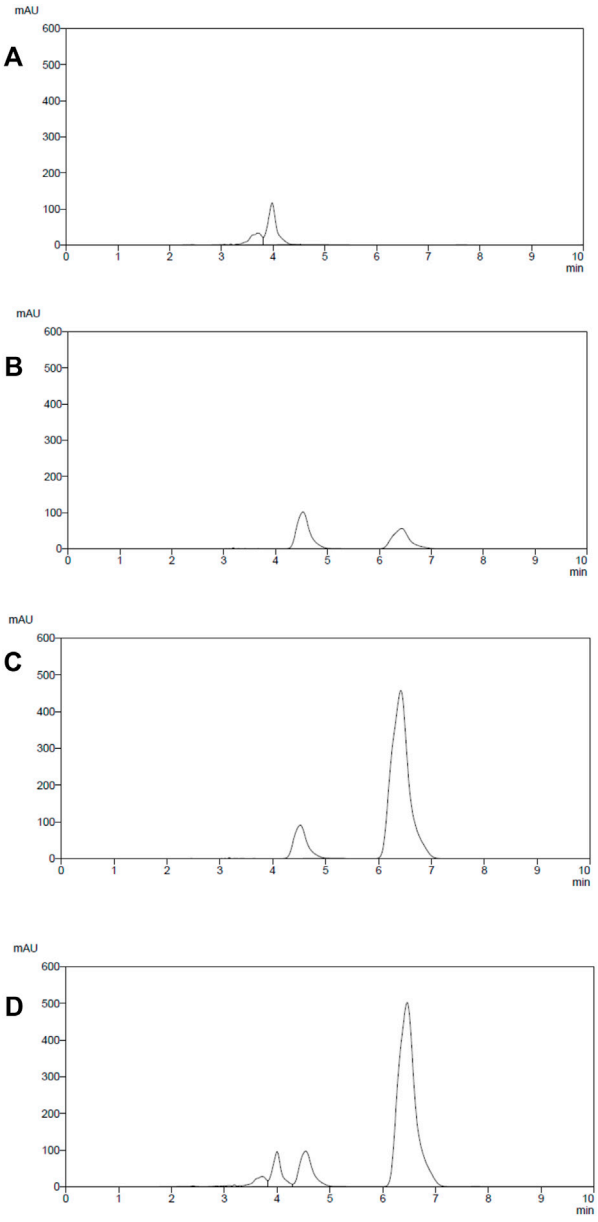


FIGURE 2
Chromatograms of **(A)** Blank vehicle without drug; **(B)** Calibration level of nifedipine (300 µg/mL, 4.5 min) and nimodipine (10 µg/mL, 6.3 min); **(C)** Calibration level of nifedipine (300 µg/mL, 4.5 min) and nimodipine (80 µg/mL, 6.3 min); **(D)** Crushed tablet suspended in ORA-Plus/ORA-Sweet having the formula excipients (3–4 min), nifedipine (300 µg/mL, 4.5 min) and nimodipine (90 µg/mL, 6.3 min).

Chemical stability of the compounded suspension

Nimodipine compounded suspension chemical stability was evaluated across five independent batches per storage condition (n = 10 bottles total). Three replicates per bottle were analyzed at each time point. Baseline concentrations were (5419.84 ± 653.09 µg/mL) and (5846.19 ± 549.97 µg/mL) for the suspension stored at FT and RT, respectively. The percentage recovery results are summarized in Table 3 and (Figure 3). Regarding the FT condition, average recovery percentage was

TABLE 2 Inter- and intra-day precision and accuracy for nimodipine HPLC assay utilized in the study.

Validation parameter	QC concentration (μg/mL)	Measured concentration (μg/mL) (Mean ± SD)	Precision CV%	Accuracy-error percentage (%)
Intra-day (n = 5)	10 (LLOQ)	8.67 ± 0.30	3.43%	13.26%
	20 (LQC)	18.68 ± 2.44	13.05%	6.61%
	45 (MQC)	46.90 ± 2.84	6.06%	4.22%
	90 (HQC)	88.07 ± 9.68	10.99%	2.14%
Inter-day (n = 15)	10 (LLOQ)	11.61 ± 2.03	17.46%	16.07%
	20 (LQC)	21.64 ± 1.45	6.70%	8.22%
	45 (MQC)	45.58 ± 5.57	12.21%	1.29%
	90 (HQC)	99.32 ± 14.10	14.19%	10.36%

CV%, Coefficient of variation; HPLC, high-performance liquid chromatography; HQC, high-concentration quality control; LLOQ, lowest limit of quantification; LQC, low-concentration quality control; MQC, medium-concentration quality control; QC, quality control; SD, standard deviation.

TABLE 3 Chemical stability of nimodipine compounded suspension and control prepared by dispersing crushed tablets in water over 28 days at two different storage conditions.

	Fridge temperature (FT)		Room temperature (RT)	
Day	ORA-Plus/ORA-Sweet (1:1)[a]	Crude tablet dispersion in water[b]	ORA-Plus/ORA-Sweet (1:1)[a]	Crude tablet dispersion in water[b]
0 (Baseline)	100% (5419.84 ± 653.09 μg/mL)[c]	100% (4277.68 ± 544.67 μg/mL)[c]	100% (5846.19 ± 549.97 μg/mL)[c]	100% (5559.87 ± 220.13 μg/mL)[c]
1	97.42% ± 27.25	87.53% ± 10.22	98.20% ± 18.67	89.08% ± 2.09
2	107.51% ± 8.28	96.34% ± 10.83	97.78% ± 18.18	89.95% ± 5.05
7	106.05% ± 3.33	96.30% ± 11.41[d]	102.64% ± 11.41	107.43% ± 7.05[d]
14	110.18% ± 7.97	-	102.33% ± 14.87	-
21	99.14% ± 8.50	117.63% ± 4.51[d,*]	99.38% ± 12.95	112.24% ± 1.34[d]
28	115.36% ± 16.46	115.61% ± 18.81[d,*]	109.75% ± 15.20	108.22% ± 6.94[d]

FT, fridge temperature (2–8 °C); RT, room temperature (20–25 °C).
[a]n = 5 independent batches; triplicate measurements per batch.
[b]n = 3 independent batches; triplicate measurements per batch.
[c]Baseline concentrations are presented as (mean ± standard deviation) and considered as 100% recovery; All other days are presented as % recovery ± standard deviation.
[d]Baseline concentrations for these days were different since they were assayed by preparing new batches where the baseline concentrations were (4455.35 ± 300.17 μg/mL) and (5013.13 ± 328.34 μg/mL) for the FT and RT, respectively.
*Indicates significant difference ($p < 0.05$) compared to the day 0 baseline.

within the acceptable range (90–110%) for the suspension at FT for 3 weeks. The RT samples were within the acceptable stability limits for the entire study duration. Two-way mixed-design ANOVA showed no significant differences either for storage condition ($p = 0.56$) or time ($p = 0.13$). Besides, the storage-time interaction was insignificant ($p = 0.72$).

Chemical stability of the crude tablet dispersion

The chemical stability of the crude drug dispersion in water was evaluated across three independent batches per storage condition (n = 6 total bottles), with triplicate analyses performed for each bottle at every time point. Mean baseline concentrations were 4277.68 ± 544.67 μg/mL for FT and 5559.87 ± 220.13 μg/mL for RT storage. The control tablet dispersion failed to meet the established chemical stability criteria, as drug recovery fell below the 90% threshold within 24 h under both conditions (87.53% at FT and 89.08% at RT). At subsequent time points, the percentage recovery exhibited high variability and failed to consistently remain within the acceptable target range. Although two-way mixed-design ANOVA showed no significant differences for main effect of storage conditions ($p = 0.75$) and the storage-time interaction ($p = 0.38$), the effect of time was significant ($p = 0.0099$). Subsequently, post-hoc Fisher's LSD for multiple comparisons against baseline was conducted. Fisher's LSD revealed significant deviations from baseline on day 21 ($p = 0.016$) and on day 28 ($p = 0.03$) for the crude tablet dispersion in water stored at FT. Alongside, with the percentage recovery range (90–110%), the drug dispersion in water at both storage conditions demonstrated fluctuations, advocating its poor stability relative to the compounded suspension. The recovery results are summarized in Table 3 and (Figure 3).

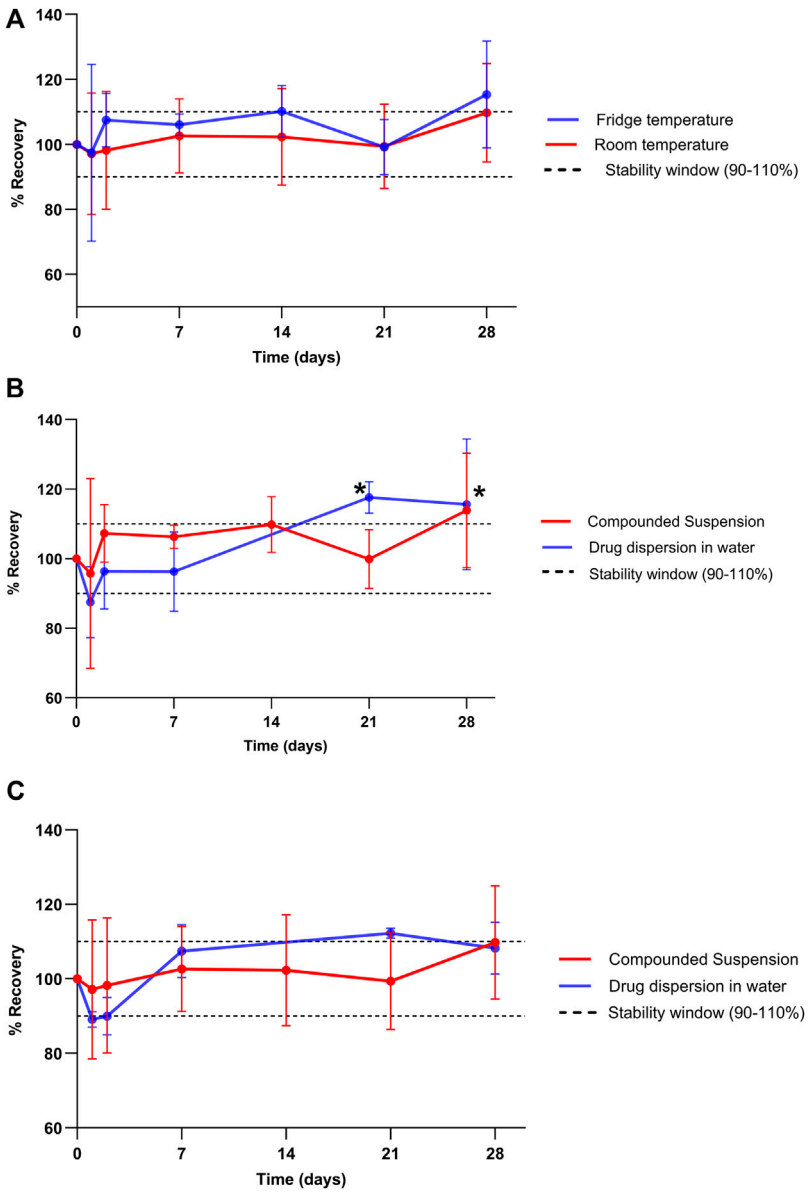


FIGURE 3
Chemical stability of nimodipine compounded suspension and control prepared by dispersing crushed tablets in water across a 28-day study duration. **(A)** Chemical stability of the compounded suspension in two different storage conditions; **(B)** Chemical stability of the compounded suspension (red) against the drug dispersion in water (blue) when preserved in the fridge for 28 days; **(C)** Chemical stability of the compounded suspension (red) against the drug dispersion in water suspension (blue) when kept at room temperature for 28 days. * Indicates significant difference ($p < 0.05$) compared to the day 0 baseline.

Physical stability evaluation

pH measurement

The pH of the compounded suspension was stable throughout the 28 days of the study at both storage conditions. There was a significant difference in the baseline pH when comparing the compounded suspension (4.34 ± 0.04) to the drug dispersion in water (6.08 ± 0.70), $p < 0.001$. Similarly, this significant difference was maintained on day 28 where the pH was (4.29 ± 0.02 vs. 6.47 ± 0.38, $p < 0.001$) at FT and (4.32 ± 0.03 vs. 6.76 ± 0.06, $p < 0.001$) at RT (Table 4). Furthermore, the pH showed no significant changes in the compounded suspension over time at both storage conditions; however, the pH of the drug dispersion in water significantly increased over time (5.42 ± 0.14 vs. 6.47 ± 0.38, $p < 0.001$) when stored at FT at baseline and on day 28, respectively. This highlighted the instability of crude nimodipine tablet dispersion in water.

Zeta potential

ZP was evaluated as a key indicator of particle dispersibility and formulation homogeneity. Throughout the 28-day study duration, the compounded suspension exhibited a significantly more negative ZP compared to the

TABLE 4 Summary of the physical attributes' measurements for nimodipine compounded suspension and control prepared by dispersing crushed tablets in water.

Physical attribute	Time point	Compounded suspension (FT)	Crude tablet dispersion in water (FT)	*p*-value	Compounded suspension (RT)	Crude tablet dispersion in water (RT)	*p*-value
Zeta Potential (ZP; mV)[a]	**Baseline**	−20.26 ± 1.77	−10.1 ± 1.22	**0.0012**	−22.60 ± 1.31	−6.75 ± 1.77	**0.0002**
	Day 7	−20.07 ± 0.86	−9.046 ± 1.80	**0.0007**	−21.59 ± 1.81	−12.48 ± 0.75	**0.0013**
	Day 21	−20.33 ± 0.11	−8.17 ± 0.58	**<0.001**	−21.62 ± 0.37	−7.22 ± 4.78	**0.0065**
	Day 28	−21.27 ± 0.73	−8.89 ± 1.45	**0.0002**	−20.84 ± 0.97	−8.33 ± 4.58	**0.0098**
pH[b]	**Baseline**	4.37 ± 0.05	5.42 ± 0.14	**<0.001**	4.32 ± 0.03	6.75 ± 0.11	**<0.001**
	Day 7	4.3 ± 0.03	5.21 ± 0.05	**<0.001**	4.33 ± 0.03	6.81 ± 0.06	**<0.001**
	Day 21	4.28 ± 0.03	5.68 ± 0.23	**< 0.001**	4.28 ± 0.02	6.70 ± 0.11	**<0.001**
	Day 28	4.29 ± 0.02	6.47 ± 0.38	**<0.001**	4.32 ± 0.03	6.76 ± 0.06	**< 0.001**
Sedimentation volume[c]	**Baseline**	0.99 ± 0.01	0.23 ± 0.04	**< 0.001**	1.00 ± 0.00	0.29 ± 0.01	**<0.001**
	Day 7	0.96 ± 0.03	0.23 ± 0.04	**< 0.001**	0.97 ± 0.01	0.29 ± 0.01	**<0.001**
	Day 21	0.88 ± 0.16	0.23 ± 0.04	**0.0023**	0.95 ± 0.01	0.29 ± 0.01	**<0.001**
	Day 28	0.87 ± 0.16	0.23 ± 0.04	**0.0028**	0.92 ± 0.02	0.29 ± 0.01	**<0.001**
Particle size (μm^2)[d]	**Baseline**	1841.01 (1614.49)	1279.67 (938.89)	0.143	1996.01 (2019.85)	1429.69 (1050.16)	0.161
	Day 7	2040.71 (1547.92)	1519.11 (1055.13)	0.07	1663.17 (1005.45)	1365.11 (1293.58)	0.467
	Day 21	1321.40 (1275.69)	1278.68 (1295.57)	0.706	1647.28 (1571.77)	1889.2 (1637.34)	0.458
	Day 28	1553.88 (1632.37)	1399.89 (1411.81)	0.519	1347.23 (1365.11)	1607.53 (2213.59)	0.446

FT, fridge temperature (2–8 °C); RT, room temperature (20–25 °C); mV, millivolts; ZP, zeta potential. Boldface p-values represent statistical significance.
[a]n = 3 independent batches represented as mean ± standard deviation; quintuplicate measurements per batch.
[b]n = 3 independent batches represented as mean ± standard deviation; triplicate measurements per batch.
[c]n = 3 independent batches represented as mean ± standard deviation; single reading per batch.
[d]Values represent the median (interquartile range) of all particles identified in one representative microscopic field.

drug dispersion in water (Table 4). This strongly negative charge indicates enhanced electrostatic repulsion between suspended particles, facilitating uniform distribution and ensuring consistent dosing upon shaking. At baseline, the mean ZP of the compounded suspension was significantly more negative than that of the drug dispersion in water (−21.43 ± 1.89 mV vs. −8.42 ± 2.28 mV, $p < 0.001$). This robust electrostatic stability was maintained through day 28, with the compounded formulation recording ZP values of −21.27 ± 0.73 mV under refrigeration (FT) and −20.84 ± 0.97 mV at room temperature (RT). Both end-of-study values remained significantly more negative than their respective control counterparts (−8.89 ± 1.45 mV, $p < 0.001$; and −8.33 ± 4.58 mV, $p = 0.0098$). Furthermore, longitudinal analysis revealed no significant fluctuations in ZP over time for either preparation ($p > 0.05$).

Sedimentation volume

Throughout the 28-day study, F values were consistently higher for the compounded suspension compared to the crude tablet dispersion in water (Table 4). At baseline, the mean F of the compounded formulation was significantly greater than that of the control tablet dispersion in water (0.99 ± 0.01 vs. 0.26 ± 0.04, $p < 0.001$). This difference was maintained on day 28 under both refrigerated (FT: 0.87 ± 0.16 vs. 0.23 ± 0.04, $p = 0.0028$) and room temperature conditions (RT: 0.92 ± 0.02 vs. 0.29 ± 0.01, $p < 0.001$). Notably, the F values for the tablet dispersion in water remained completely static across all four time points regardless of storage condition, reflecting the rapid formation of a compact, deflocculated sediment. In contrast, longitudinal analysis of the compounded suspension revealed no significant changes in F over time under FT. While the RT samples exhibited a minor statistical reduction from baseline (1.00 ± 0.00) to day 28 (0.92 ± 0.02, $p = 0.0023$), this slight decrease did not compromise the overall uniform dispersion of the formulation. These sedimentation profiles strongly corroborate the zeta potential findings, further affirming the superior homogeneity and dispersion capabilities of the compounded suspension. Furthermore, routine visual inspection of the graduated cylinders confirmed the absence of discoloration, hard caking, or rapid settling in the compounded formulation throughout the study duration.

Particle size measurement

Microscopic evaluation revealed that the suspended particles were coarse (>1 μm) and exhibited an irregular morphology with jagged borders (Figure 4). Consequently, particle dimensions

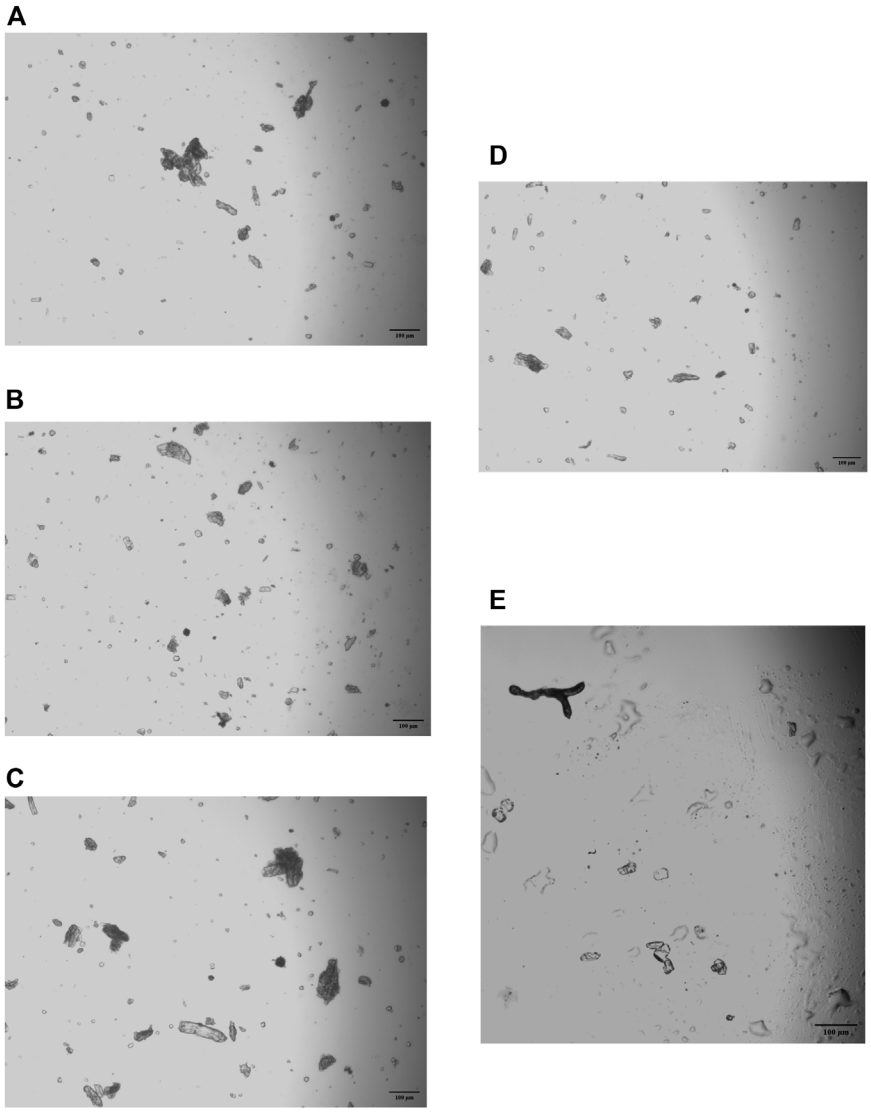


FIGURE 4
Microscopy results at baseline for **(A)** Compounded suspension stored in the fridge; **(B)** Compounded suspension kept at room temperature; **(C)** Crude tablet dispersion in water and stored in the fridge; **(D)** Crude tablet dispersion in water and kept at room temperature; **(E)** Blank vehicle (no drug tablet in it).

were quantified by two-dimensional surface area (μm^2) using Fiji/ImageJ software. Weekly investigations revealed no significant differences in particle area between the compounded suspension and nimodipine dispersion in water (Table 4). At baseline, the median (IQR) particle area for suspensions designated for FT storage was 1814.01 [1614.49] μm^2 for the compounded formulation compared to 1279.67 [938.89] μm^2 for the crude tablet dispersion in water (p = 0.143). Similarly, no significant difference was observed between the suspensions designated for RT storage (compounded suspension vs. crude tablet dispersion in water: 1996.00 [2019.85] μm^2 vs. 1429.69 [1050.16] μm^2, p = 0.161). Furthermore, longitudinal analysis demonstrated no significant changes in particle area reflecting no aggregation over the study duration for either preparation.

Viscosity

Compounded suspension exhibited pronounced shear-thinning behavior, with apparent viscosity decreasing continuously as shear rate increased, indicating a non-Newtonian flow characteristic. Compared with freshly prepared samples (baseline), suspensions stored for 28 days showed higher apparent viscosities, particularly in the low-shear region (<10 s^{-1}) plotted in (Figure 5), suggesting the development of a more structured network, likely arising from enhanced particle-particle interactions during storage. At the same storage time, samples stored at FT consistently displayed higher viscosities than those stored at RT (Figure 5), which can be attributed to reduced molecular mobility and enhanced intermolecular interactions at lower temperature, leading to a more persistent microstructure due to the presence of viscosity inducing agents in the vehicle used. From low to high shear rates, the apparent viscosity

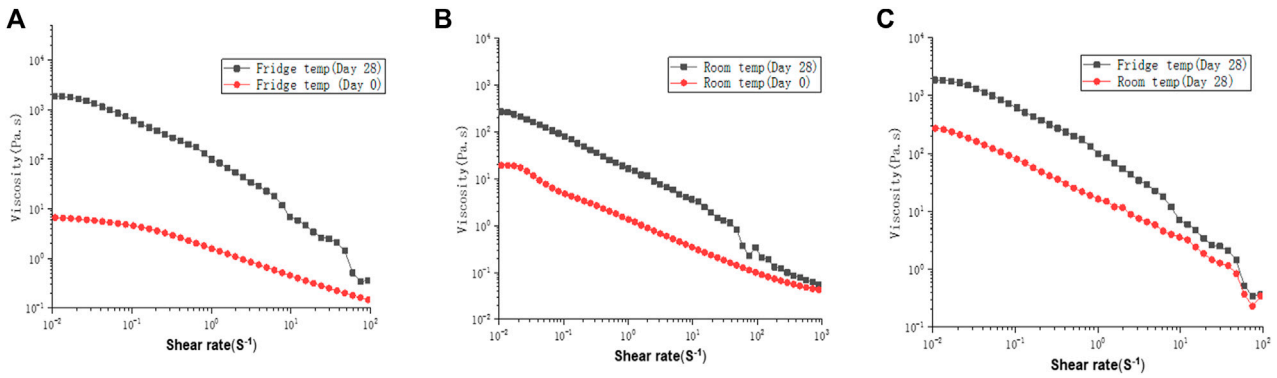


FIGURE 5
This figure demonstrates the shear-thinning behavior exhibited by the compounded suspension over shear rate range of (0.1–1000 s^{-1}); **(A)** Comparison between the flow properties at baseline and on day 28 for the compounded suspension stored in the fridge; **(B)** Comparison between the flow properties at baseline and on day 28 for the compounded suspension kept at room temperature; **(C)** Comparison between the flow properties on day 28 for the compounded suspension at different storage conditions.

ranged between (19-0.04 Pa. s) and (270-0.06 Pa. s) at baseline and day 28 for the RT storage condition. Regarding the FT preserved suspensions, they demonstrated apparent viscosities of (7-0.07 Pa. s) and (1860-0.09 Pa. s) at baseline and day 28, respectively. Notably, the viscosity differences diminished at high shear rates, implying that the structured network could be readily disrupted under applied shear.

Feeding tube compatibility

Feeding tube occlusion

Both Salem Sump™ and Corflo feeding tubes maintained full patency. No occlusions were detected following the six-replicate cycle of medication administration and flushing. Regarding the flushing protocol, the second 10 mL was clearer than the first 10 mL suggesting that the first 10 mL cleared majority of the residue, while the second 10 mL ensured lumen cleanliness.

Feeding tube adsorption

Both tubes showed excellent compatibility with our suspension delivery yielding acceptable recovery percentages. The Corflo Nasogastric/Nasointestinal ENFit tubes demonstrated an average recovery of (101.95 ± 13.27%; n = 2 lines; triplicate measurements per line), while the Salem Sump™ PVC ENFit tubes recorded an average recovery of (98.26 ± 5.87%; n = 2 lines; triplicate measurements per line). Based on these results, our suspension could be effectively delivered through both types of enteral tubes without any major loss and/or tube adsorption observed.

Discussion

The limited availability of enteral nimodipine dosage forms in Canada poses significant administration challenges for unconscious, dysphagic and ventilated patients [22]. Although the manufacturer advises against crushing nimodipine tablets due to compromised bioavailability [23], this practice remains the only option for enteral administration via feeding tubes in this patient population. However, dispersing crushed nimodipine tablets in water and feeding tube administration has been associated with potentially poorer clinical outcomes, including increased rates of vasospasm and DCI [15, 16, 18, 21, 22]. Furthermore, while an intravenous (IV) formulation is available in Europe, Australia, and China, its clinical utility is hindered by the high ethanol content (~23.7% v/v). This can cause vascular irritation, phlebitis, and injection-site reactions, alongside an inherent risk of hypotensive crises, which ultimately led to its discontinuation in North America [35–37]. Additionally, the IV route has demonstrated equivalence to the oral route [37], aligning with findings from Soppi *et al.* [38] and Kronvall *et al.* who reported no significant differences in clinical outcomes between parenteral and enteral administration [39]. Soppi *et al.* compared Nimotop® IV infusion to enteral administration of tablets (two 30 mg Nimotop® tablets), crushed in 1% hypromellose for unconscious or ventilated patients [38]. Similarly, Kronvall *et al.* compared Nimotop® whole tablets or crushed tablets suspended in water to Nimotop® IV infusion [39]. Given the need for a safe, effective, and convenient enteral option, this study aimed to formulate an extemporaneous oral nimodipine suspension and systematically evaluate its stability.

The reason behind choosing suspension as our dosage form is because tablet is the only dosage form available in Canada [22]. Also, nimodipine's high lipophilicity renders it practically insoluble in water [23] and formulating it as a solution using high organic solvent already exists in the USA market (Nymalize®, Azurity Pharmaceuticals, Inc.). The high polyethylene glycol (PEG) 400 content in these solution forms has cathartic-like effect that causes side effects such as diarrhea [22, 40, 41]. McElhiney *et al.* tried compounding nimodipine as oil-based suspension, but it did not work either due to stability issues, or adverse effects such as diarrhea [42].

Although ORA-Plus® and ORA-Sweet® are standard vehicles for extemporaneous compounding in hospital settings, to our knowledge, there is no report of their use in making compounded nimodipine suspensions. Vehicle choice plays a critical role in gastrointestinal (GI) tolerance, particularly during

intensive 21-day treatment courses. Hyperosmolar liquid vehicles, including vehicle systems containing high concentrations of sorbitol or sugar-based syrups like Ora-Sweet, have been identified as potential osmotic cathartics capable of inducing diarrhea in enterally fed patients [43]. However, in our formulation, Ora-Sweet is blended in a 1:1 ratio with Ora-Plus, a vehicle characterized by a low osmolality (157 mOsm/kg) [24]. This equal-part combination substantially dilutes the hyperosmolar burden of the final vehicle system. Under standard clinical dosing (60 mg nimodipine every 4 h, or 60 mL/day of a 6 mg/mL suspension), a patient receives a cumulative volume of only 30 mL/day of Ora-Sweet. Additionally, compounding with sugar-free alternatives such as Ora-Sweet SF, which possesses roughly half the osmolality of standard Ora-Sweet, offers an established strategy to further reduce overall osmolality when combined 1:1 with Ora-Plus [44]. So, we selected this 1:1 vehicle combination to facilitate the seamless translation of our formulation into clinical practice, given the availability of both vehicles and acceptable viscosity of the 1:1 ratio of the two vehicles for administration through feeding tubes. Furthermore, equivalent volumes of ORA-Plus® and ORA-Sweet® have demonstrated established stability for other extemporaneous preparations, including a mycophenolate mofetil suspension [45] and a suspension of nifedipine, a structurally related calcium channel blocker [46]; both remained stable for up to 3 months under refrigerated and room-temperature conditions. These precedents strongly supported the use of this vehicle ratio for compounding nimodipine.

While numerous studies have utilized HPLC for nimodipine assays in various formulations and biological matrices [26, 47, 48], our analytical approach was specifically adapted from Shang *et al.*, who successfully employed HPLC to quantify nimodipine in tablets [26]. This method was validated within our laboratory, demonstrating linearity over a concentration range of 10–100 μg/mL. The assay also exhibited excellent selectivity, with no interfering peaks observed at the retention time of the analyte. Furthermore, the method demonstrated acceptable intra-day and inter-day precision and accuracy adhering to the EMA guidelines acceptance criteria [27]. Forced degradation studies were conducted using stress conditions (acidic, alkaline, and oxidative) to verify that the analytical peak corresponded exclusively to intact nimodipine [28–30].

Our compounded nimodipine suspension maintained chemical stability, defined as retaining 90%–110% of the baseline concentration, for 3 weeks under FT and 4 weeks at RT using a light resistant container for the formulation. We clarify that the one-week shorter stability duration under FT storage conditions was ascribed to a higher rate of solvent evaporation, leading to apparent hyper-concentration, rather than chemical degradation. FT storage environments maintain low relative humidity; combined with repeated opening of the samples for periodic sampling, this promotes gradual water loss, leading to hyper-concentration, agreeing with literature [49, 50].While this study evaluated stability over a one-month duration, this timeframe is clinically sufficient given that the standard treatment course for nimodipine is strictly 21 days. Additionally, based on the standard dosing regimen of 60 mg every 4 h [4, 5], a 250 mL bottle would be depleted in 4 days, which falls well within our proven stability window. In contrast, the dispersion of nimodipine tablets in water fell outside the acceptable 90–110% cutoff, suggesting the inhomogeneity of the tablet dispersion in water. Conversely, our novel suspension recovery was consistently within the acceptable window for 3 weeks for FT storage and 4 weeks for RT storage, highlighting the superior stabilizing properties of ORA-Plus® and ORA-Sweet® vehicles in maintaining a homogenous suspension. Clinically, the flavoring agents in ORA-Sweet® offer a significant palatability advantage over a simple crude tablet dispersion in water, and the availability of ORA-Sweet SF® provides an equivalent option for diabetic patients [25]. Altogether, these findings work together justifying why the compounded suspension is deemed a convenient and feasible clinical alternative to the current practice of dispersing the drug in water.

The compounded suspension maintained physical stability throughout the four-week study, exhibiting no changes in color or odor. It retained its yellowish tinge with faint berry odor characteristic of the ORA-Sweet® vehicle [25]. Additionally, the compounded suspension maintained a highly stable mean pH of 4.34 ± 0.04 from baseline to the final day of the study, regardless of storage conditions. This stability is attributed to the buffering system (citric acid/sodium phosphate) present in the suspending agents, which maintains the pH within a narrow range of 4–4.5 [24, 25]. In contrast, the pH of the crude tablet dispersion in water fluctuated significantly over a wider range (5.42–6.47, $p < 0.001$). This was evident in the pH trajectory for the tablet dispersion in water under FT storage (Table 4). Unlike our novel suspension, the crude tablet dispersion lacks any buffering capacity, rendering this system liable for pH drifts. Under FT storage, the initial lower pH was most likely due to the high solubility of carbon dioxide gas at cold temperatures. Periodic opening of the bottles for sampling promoted degassing of carbon dioxide, alongside the temperature-mediated dissolution of the tablet excipients and accumulation of the excipients by day 28, led to an upward pH shift [51, 52]. These changes showcase the necessity of having a buffered structured vehicle for extemporaneous preparations to avoid the inherent instability of the crude dispersions.

Additionally, the compounded suspension demonstrated superior homogeneity and particle distribution. This was supported by a more negative mean ZP of −21.43 ± 1.89 mV, compared to −8.42 ± 2.28 mV for the comparator prepared following dispersion of crushed nimodipine tablets in water ($p < 0.001$). This highly negative ZP, an inherent feature of the formulation that did not require the external addition of electrostatic stabilizers, remained consistent over the four-week duration of the study. Furthermore, the sedimentation volume (F) results indicated that the compounded suspension have a significantly higher mean F value (0.99 ± 0.01) than the crude tablet dispersion in water (0.26 ± 0.04, $p < 0.001$), reflecting the formation of a more flocculated suspension in nimodipine suspension prepared using ORA-Plus®/ORA-Sweet® vehicles. The higher sedimentation volume of this formulation implies better dispersity during storage which is attributed to the presence of flocculating agents in the ORA-Plus® vehicle [24].

Particle size characterization was conducted to monitor physical appearance and assess potential crystal growth or aggregation during storage. While Dynamic Light Scattering (DLS) is the standard method for sub-micron particles with regular or spherical geometry, it was unsuitable for our formulation. As

outlined in ISO 22412:2017, DLS is optimized for sub-micrometer systems where Brownian motion dominates. For particles exceeding 1μm, gravitational sedimentation prevails over thermal diffusion, breaching a core principle of DLS theory [53, 54]. Furthermore, our compounded formulations contain highly irregular, polydisperse particles (Figure 4). In such polydisperse systems, larger coarse particles induce severe intensity bias by masking scattering signals from smaller fragments, leading to artificially elevated polydispersity indices, a phenomenon observed during our preliminary testing. Consequently, optical microscopy paired with ImageJ digital software analysis was utilized as a direct, morphology-based alternative. Particle dimensions were quantified as two-dimensional surface areas, which more accurately represent irregular, non-spherical fragments than hydrodynamic diameter assumptions. A total of approximately 550 individual particles were analyzed across four weekly time points. No statistically significant changes in particle surface area were observed over the 4-week storage period ($p > 0.05$), reflecting the consistent comminution achieved by uniform manual compounding procedures. Nevertheless, we acknowledge that optical microscopy represents a semi-quantitative approach constrained by 2D area projections and lower sampling throughput compared to ensemble methods like laser diffraction. Future evaluations could benefit from advanced 3D automated image analysis or static laser diffraction designed for coarse, polydisperse suspensions.

Nimodipine is known to exist in two polymorphs; modification I is the commercial metastable racemate polymorph, while modification II is the stable conglomerate polymorph [55, 56]. According to Grunenberg *et al.*, both modifications are enantiotropic; capable of undergoing transformations based on temperature [56]. FT storage could lead to supersaturation and polymorphic transitions, secondary to solvent evaporation [49, 55, 56]. Additionally, modification I tends to be seen as coarse chunks that grow into plates. On the other hand, modification II tends to be in the form of more homogenous circular aggregates [55–57]. Based on the coarse irregular particles seen through our microscopy findings (Figure 4) and the precedent description of Grunenberg *et al.* [56] and Cardoso *et al.* [55], it could be tentatively said that the observed particles were in modification I form. However, this needs to be confirmed using specialized techniques such as differential scattering calorimetry, X-ray diffraction and dissolution methods [55–57]. It is not clear however if the bioavailability of nimodipine would change with changing forms. Therefore, it is prudent to evaluate the formulation's bioavailability prior to implementation.

Viscosity was evaluated exclusively for the compounded suspension to characterize its flow behavior. As expected, the suspension demonstrated shear-thinning behavior across a shear rate range of 0.1–1000 s^{-1}, which is attributable to the viscosity inducing agents used in the ORA-Plus® [24]. According to Mezger, shear rates between 10^{-2} s^{-1} and 10^{-1} s^{-1} simulate low-shear conditions where particles undergo sedimentation or levelling. Increasing the shear rate to 10^{1} s^{-1} simulates gentle shaking, while 10^{2} s^{-1} represents vigorous mixing [58]. The National Dysphagia Diet (NDD) utilizes a shear rate of 50 s^{-1} as a benchmark for classifying liquid viscosity [59, 60]. At baseline (shear rate of 47.44 s^{-1}), the apparent viscosity of the compounded suspension was 0.200 Pa. s (200 mPa. s) at FT and 0.143 Pa. s (143 mPa. s) at RT. These values classify the suspension within the "nectar-thick" range. However, by day 28, the apparent viscosities at this same shear rate increased to 1.44 Pa. s (1440 mPa. s) and 1.16 Pa. s (1160 mPa. s) for FT and RT, respectively, shifting the suspension into the "honey-thick" classification. This indicates a time-dependent increase in viscosity, particularly under refrigeration. Ultimately, the high viscosity at low shear rates ($<10^{-1}$ s^{-1}) suggests robust stability against sedimentation at rest, which is consistent with the high F values observed. Conversely, the decreased viscosity at higher shear rates (10^{0}-10^{1} s^{-1}) ensures the suspension remains easy to pour and administer.

Building upon the favorable flow characteristics established in the previous section, we evaluated the practical administration of the compounded suspension through two common feeding tubes: Salem Sump™ polyvinyl chloride (PVC) tubes and Corflo® Nasogastric/Nasointestinal ENFit® tubes. To our knowledge, these represent the standard tubes utilized in the hospitals, and no prior studies have investigated nimodipine administration using these specific models. The compounded nimodipine suspension was administered through two lines of each tube type using a six-replicate cycle of injection followed by flushing. Throughout this procedure, all lines maintained full patency with no observed occlusions. Visually, the second 10 mL water flush was notably clearer than the initial 10 mL flush. Consequently, to ensure complete clearance of the suspension, we recommend a minimum flush volume of 20 mL of tap water following dose administration for either tube type.

Given that the tubes maintained their patency without occlusion, we subsequently evaluated the potential for drug adsorption to the feeding tube walls to verify that the dose was effectively delivered without significant loss. Both tube types yielded an average nimodipine recovery exceeding 98%, confirming that no clinically significant drug adherence occurred. Although, nimodipine is known to adsorb to PVC [35], a primary component of the Salem Sump tubes, no major drug loss was detected in this study. This discrepancy can likely be attributed to formulation differences, as the interactions reported in the literature specifically involved the IV formulation of nimodipine [35]. Furthermore, contact time is a critical variable; an infused IV solution is exposed to PVC tubing for a substantially longer duration than an enteral dose pushed rapidly through a feeding tube. Finally, specific tube manufacturing variations and overall PVC content may also influence the extent of adsorption.

In clinical practice, enteral feeding tubes are frequently used to deliver complex enteral nutrition (EN) formulas alongside pharmacotherapy. These nutritional formulations contain diverse lipids, proteins, carbohydrates, and electrolytes that may physically or chemically interact with suspended drug particles. Although physical compatibility with liquid EN formulas was not directly evaluated in the present study, existing clinical literature provides relevant context regarding nimodipine's interaction with food. According to the reference product monograph, food co-administration alters nimodipine's absorption kinetics by reducing peak plasma concentrations (Cmax) by approximately 40% and doubling time to reach peak plasma concentrations (Tmax), while leaving the total extent of absorption (AUC) largely unaffected [23]. However, these historical data were established using conventional whole tablets rather than compounded oral liquid suspensions. Consequently, how physical mixing with liquid EN formulas within the narrow lumen of a

feeding tube affects particle aggregation, drug solubility, or tube patency requires dedicated investigation.

The reported association between crushed nimodipine tablets and poorer clinical outcomes may, at least in part, stem from physical delivery failure rather than tablet crushing itself. Nimodipine is a highly lipophilic, BCS Class II molecule with minimal aqueous solubility [61]. When tablets are crushed in water at the bedside, the resulting dispersion is an unstable, deflocculated slurry. Lacking suspending agents, viscosity modifiers, or adequate surface charge, the particles undergo rapid, immediate sedimentation, reaching minimum sedimentation volume on the day of preparation, while suffering significant drug loss to mortar, pestle, and syringe surfaces. Furthermore, unstandardized bedside crushing exposes photolabile nimodipine to ambient ICU light during variable preparation delays, promoting photolytic degradation. These physical barriers lead to unpredictable dosing. Because crushed tablets represent the sole starting material in jurisdictions where oral solutions are unmarketed, utilizing a structured vehicle system (1:1 ORA-Plus/ORA-Sweet) directly addresses these delivery failures. The thixotropic network of ORA-Plus maintains homogeneous particle suspension at rest to ensure uniform volumetric dosing, while its higher negative ZP suppresses particle agglomeration and enteral line adhesion. Crucially, standardizing preparation in the pharmacy, clinicians can mitigate the risks associated with prolonged lag times and bright ICU lighting, ensuring the patient receives a potent, non-degraded dose. Although observational clinical data link crushed tablets to adverse outcomes, stabilizing the physicochemical platform is a mandatory prerequisite for achieving reliable therapeutic drug delivery.

Although utilizing pharmaceutical-grade pure nimodipine powder represents a theoretical alternative to avoid tablet crushing, this approach is operationally and clinically unfeasible for hospital compounding. Bulk raw powder is expensive, unavailable through standard hospital supply chains, and presents significant handling challenges. Physically, pure nimodipine is cohesive and electrostatic, requiring pre-formulation additives (such as glidants and flow modifiers) to overcome severe surface adhesion and clumping. Furthermore, bulk weighing introduces substantial risks of dosing errors compared to using pre-formulated commercial tablets and increases light-induced degradation due to a high exposed surface area. Consequently, utilizing commercially available tablets provides a safe, pragmatic, and reproducible starting material for extemporaneous compounding in clinical practice.

ORA-Blend® is a commercial, pre-mixed 1:1 mixture ORA-Sweet® and ORA-Plus®, containing the same preservatives, pH modifiers, suspending agents, and is also marketed in a SF version [62]. Although this vehicle would facilitate extemporaneous compounding by reducing preparation time and volumetric measurement errors, we chose to adopt the equivalent ratios of ORA-Sweet® and ORA-Plus®, mimicking their previous application with another calcium channel blocker, nifedipine [46]. We speculate that our physicochemical findings, thixotropic behavior and feeding tube compatibility can be extrapolated to the ORA-Blend® vehicle without compromising the stability profile of the developed suspension.

This study has limitations. First, the formulation was evaluated strictly *in vitro*. Future *in vivo* safety and pharmacokinetic studies are necessary to determine how gastrointestinal motility, enzymatic activity, and hepatic first-pass metabolism impact the bioavailability of this specific suspension. Another limitation of this study is the absence of a comparator group using the commercially available FDA-approved nimodipine oral solution. Because this formulation is not currently marketed or readily procurable in Canada, its inclusion was not feasible. Consequently, direct benchmarking against an established reference standard with known bioavailability and clinical efficacy data was not performed. Additionally, while drug loss to the enteral feeding tube walls was negligible and tube patency was successfully maintained in our administration model, these findings are derived from a single-dose simulation. Consequently, these results cannot be definitively extrapolated to extended 21-day clinical treatment regimens, where cumulative drug adsorption or gradual lumen occlusion could theoretically occur over repeated dosing cycles. In clinical practice, this risk is largely mitigated by standardized administration protocols that dictate thorough water flushes before and after each dose, as well as institutional schedules for routine tube replacement. Nevertheless, the absence of a continuous 21-day multi-dose simulation remains a study limitation. Extended compatibility and accumulation assessments over the full treatment duration should be incorporated into future prospective and bioavailability investigations. Furthermore, while our vehicle system (1:1 Ora-Plus:Ora-Sweet) was designed to minimize hyperosmolar exposure relative to PEG-400-based commercial solutions, the gastrointestinal tolerability of this formulation was not formally evaluated *in vivo*. Given that nimodipine therapy requires an intensive 21-day administration regimen in critically ill patients, osmotic catharsis and diarrhea remain theoretical risks that could disrupt patient management. *In vitro* osmolality profiles and vehicle dilution strategies cannot definitively establish clinical safety or gut comfort over extended therapy. Consequently, formal clinical evaluations assessing gastrointestinal tolerability across the full 21-day treatment duration represent a necessary next step prior to routine clinical adoption. Finally, a notable limitation of this study is that physical compatibility with commercial enteral nutrition (EN) formulas was not assessed. Because EN formulas contain complex macromolecular matrices that could potentially induce drug precipitation, alter suspension viscosity, or cause physical tube blockage, co-administration compatibility remains to be fully verified. Building upon the baseline stability established in this work, future research should follow a structured progression: first, evaluating *in vitro* physical and chemical compatibility (e.g., precipitation, binding, and flow dynamics) during simulated co-administration with various commercial EN formulas; second, conducting extended multi-dose compatibility evaluations over full treatment durations; and ultimately, executing formal *in vivo* bioavailability and pharmacokinetic studies.

Conclusion

This study successfully addresses a critical gap in the management of unconscious, dysphagic, and ventilated patients

by formulating a physically and chemically stable extemporaneous nimodipine oral suspension. Utilizing a 1:1 vehicle of ORA-Plus® and ORA-Sweet®, the compounded preparation maintained chemical stability for up to 4 weeks at room temperature. Furthermore, it demonstrated superior physical characteristics, including a stable pH, favorable sedimentation volume, and high dispersibility, compared to the standard drug dispersion in water. Its shear-thinning rheological profile aligns with National Dysphagia Diet standards, ensuring ease of administration, and it can be effectively delivered through standard enteral feeding tubes with >98% drug recovery and no observed occlusion. Extended future *in vitro* studies are mandatory to investigate the long-term compatibility between our novel suspension and enteral feeding tubes, alongside potential drug-food interactions. Future *in vivo* studies are essential to evaluate the formulation's safety and bioavailability prior to implementation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AE: Conceptualization, Methodology, Investigation, Formal Analysis, Data curation, Visualization, Writing – original draft, Writing – review and editing. HO: Methodology, Investigation, Writing – review and editing. AL: Data curation, Writing – review and editing. FS: Data curation, Writing – review and editing. JH: Investigation, Writing – review and editing. YC: Investigation, Writing – review and editing. LC: Investigation, Writing – review and editing. SM: Conceptualization, Supervision, Project Administration, Writing – review and editing, Data curation, Funding acquisition. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This research was supported by the Canadian Institutes of Health Research (CIHR) -Funding Reference Number (192195).

Acknowledgments

The authors would like to acknowledge Maged Kharouba (Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta) and Asma Aboelezz (Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta) for their valued assistance in the HPLC training and methodology revision. Additionally, the authors would like to thank Ellen Gunn (Research Assistant) for her assistance with the purchases and administrative tasks.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work, the authors used Google Gemini in order to improve sentence structure. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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