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RESEARCH ARTICLE

Formulation and Optimization of Azelnidipine-Loaded Solid Lipid Nanoparticles for Enhanced Bioavailability in Hypertension Management

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Abstract: Azelnidipine, a dihydropyridine calcium channel blocker, is effective in hypertension management but suffers from poor aqueous solubility and low bioavailability. This study developed and optimized solid lipid nanoparticles (SLNs) to enhance Azelnidipine's bioavailability. Preformulation studies confirmed drug-excipient compatibility, while a 3^2 factorial design optimized lipid and surfactant ratios. SLNs were characterized for particle size, entrapment efficiency (DEE), morphology, in vitro release, and stability. Fourier-transform infrared spectroscopy (FTIR) and high-performance liquid chromatography (HPLC) ensured structural integrity and quantification. The optimized formulation (F3) achieved a particle size of 155 ± 12 nm, DEE of 93 ± 2%, and controlled release of 76% over 12 hours. Stability studies confirmed robustness over 90 days. These findings suggest SLNs as a promising carrier for improving Azelnidipine's therapeutic efficacy.

Keywords: Azelnidipine, Solid lipid nanoparticles, Bioavailability, Hypertension, Drug delivery

INTRODUCTION

Hypertension, commonly known as high blood pressure, stands as one of the most prevalent chronic medical conditions worldwide, profoundly impacting global public health by serving as a silent harbinger of severe cardiovascular complications. According to comprehensive epidemiological data, this insidious disorder affects over 1.4 billion individuals across the globe, with its incidence continuing to rise due to factors such as aging populations, sedentary lifestyles, poor dietary habits, and increasing rates of obesity and diabetes. The condition is defined by sustained elevation of arterial blood pressure, typically exceeding 130/80 mmHg in adults, and it operates as a major modifiable risk factor for a spectrum of life-threatening cardiovascular morbidities. These include coronary artery disease, myocardial infarction (heart attack), heart failure, stroke (both ischemic and hemorrhagic), atrial fibrillation, peripheral artery disease, and aortic aneurysms, collectively accounting for millions of premature deaths annually. Beyond the cardiovascular system, uncontrolled hypertension exerts deleterious effects on other organs, leading to renal impairment progressing to chronic kidney disease or end-stage renal failure, retinal damage causing hypertensive retinopathy and vision loss, and even cognitive decline through mechanisms like vascular dementia. The economic burden is staggering, encompassing direct healthcare costs for medications, hospitalizations, and interventions, as well as indirect costs from lost productivity and disability. In low- and middle-income countries, where access to screening and treatment remains limited, hypertension often goes undiagnosed until complications arise, exacerbating disparities in health outcomes. Preventive strategies emphasize lifestyle modifications—such as adopting the Dietary Approaches to Stop Hypertension (DASH) diet rich in fruits, vegetables, and low-fat dairy; regular physical activity; weight management; salt reduction; and moderation of alcohol intake—alongside pharmacological interventions. Effective management not only mitigates these risks but also improves overall quality of life, underscoring the urgent need for innovative therapeutic approaches that enhance drug efficacy and patient adherence [1-3].

Azelnidipine emerges as a promising agent in the armamentarium against hypertension, belonging to the third-generation dihydropyridine class of calcium channel blockers (CCBs), which are cornerstone therapies for blood pressure control. Introduced in Japan in 2003 and subsequently approved in other regions, Azelnidipine distinguishes itself through its unique pharmacological profile: it selectively inhibits L-type and T-type calcium channels in vascular smooth muscle cells and cardiac tissues, leading to potent vasodilation, reduced peripheral vascular resistance, and a subsequent drop in blood pressure without significantly affecting heart rate or contractility. This selectivity minimizes common side effects associated with earlier CCBs, such as reflex tachycardia or negative inotropy, making it particularly suitable for patients with comorbid conditions like angina pectoris or chronic kidney disease. Clinical trials have demonstrated its sustained antihypertensive effects over 24 hours with once-daily dosing, owing to its long plasma half-life of approximately 20-24 hours and high lipophilicity, which facilitates prolonged binding to channel sites. Azelnidipine also exhibits additional pleiotropic benefits, including antioxidant properties that reduce oxidative stress, anti-inflammatory effects on endothelial function, and renoprotective actions by ameliorating glomerular hypertension and proteinuria.

These attributes position it as a valuable option in guidelines for managing essential hypertension, especially in Asian populations where it has shown superior efficacy in certain genetic subsets. However, despite these advantages, Azelnidipine's clinical utility is hampered by inherent pharmacokinetic limitations, primarily its poor aqueous solubility (classified as BCS Class II drug with solubility <0.1 µg/mL in water) and extensive first-pass hepatic metabolism via cytochrome P450 enzymes (mainly CYP3A4), resulting in low oral bioavailability of around 13-20%. This necessitates higher doses to achieve therapeutic plasma levels, increasing the risk of dose-dependent adverse effects like headache, flushing, or peripheral edema, while also contributing to inter-patient variability in response due to genetic polymorphisms in metabolizing enzymes or concomitant use of CYP inhibitors (grapefruit juice or certain antifungals). Consequently, there is a compelling need to develop advanced drug delivery systems that can circumvent these barriers, enhancing solubility, protecting against metabolic degradation, and ensuring consistent therapeutic concentrations to optimize antihypertensive outcomes and minimize side effects [4-6].

In this context, solid lipid nanoparticles (SLNs) represent a cutting-edge biocompatible nanocarrier platform within the realm of novel drug delivery systems (NDDS), offering a versatile solution to the solubility and bioavailability challenges faced by lipophilic drugs like Azelnidipine. Introduced in the early 1990s as an alternative to traditional colloidal carriers such as liposomes, emulsions, and polymeric nanoparticles, SLNs are submicron-sized (typically 50-1000 nm) spherical particles composed of a solid lipid core (glyceryl monostearate, stearic acid, or triglycerides) stabilized by surfactants (poloxamers or lecithins) and dispersed in an aqueous medium. The solid lipid matrix, which remains solid at both room and body temperatures, mimics physiological lipids, ensuring high biocompatibility, low toxicity, and biodegradability via enzymatic pathways like lipases, without the risk of organic solvent residues associated with polymeric systems. Key advantages of SLNs include their ability to enhance drug solubility through incorporation into the lipid matrix or at the particle interface, thereby increasing the dissolution rate as per the Noyes-Whitney equation; protection of encapsulated drugs from chemical degradation, pH variations in the gastrointestinal tract, and first-pass metabolism by facilitating lymphatic uptake via the intestinal Peyer's patches or M-cells, thus bypassing hepatic clearance. Furthermore, SLNs enable controlled and sustained drug release profiles—ranging from diffusion-controlled (Fickian) to erosion-dependent mechanisms—tailored by modulating lipid composition, particle size, and surface properties, which can extend plasma half-lives and reduce dosing frequency for improved patient compliance. Surface modification with polyethylene glycol (PEG) or targeting ligands can further impart stealth properties to evade reticuloendothelial system (RES) uptake, prolong circulation time, and enable site-specific delivery to vascular tissues. Preclinical and clinical studies have validated SLNs for various routes of administration (oral, parenteral, topical), with scalable production methods like high-pressure homogenization or solvent evaporation ensuring feasibility for industrial translation. For antihypertensive agents like Azelnidipine, SLNs hold particular promise in achieving uniform plasma levels, mitigating peak-trough fluctuations that could exacerbate blood pressure variability, and potentially reducing cardiovascular events, aligning with the broader goals of precision medicine in hypertension management [7-9].

Building upon these foundational insights, this study was meticulously designed to formulate Azelnidipine-loaded SLNs, optimize their composition through a systematic factorial design approach to fine-tune critical parameters such as lipid type, concentration, surfactant ratios, and drug loading for maximal entrapment efficiency and stability, and comprehensively evaluate their physicochemical properties—including particle size, zeta potential, morphology via transmission electron microscopy (TEM), entrapment efficiency, and *in vitro* release kinetics under simulated physiological conditions—to ultimately improve clinical outcomes in hypertension therapy. By addressing Azelnidipine's solubility and metabolic drawbacks through SLN encapsulation, the research sought to demonstrate enhanced bioavailability, sustained release profiles that mimic once-daily dosing efficacy, and long-term stability, potentially translating to reduced pill burden, fewer adverse effects, and better blood pressure control in patients. The methodology incorporated preformulation compatibility studies using FTIR and DSC to ensure no deleterious interactions, HPLC for precise quantification, and stability testing under ICH guidelines, providing a robust framework for future in vivo pharmacokinetic and pharmacodynamic validations. This work not only contributes to the evolving field of nanomedicine for cardiovascular drugs but also paves the way for personalized antihypertensive regimens, ultimately aiming to alleviate the global burden of hypertension-related morbidity and mortality.

MATERIAL AND METHODS

Materials

The materials utilized in this study for the formulation and evaluation of solid lipid nanoparticles (SLNs) loaded with Azelnidipine was sourced from reputable manufacturers across India to ensure high purity and consistency. Azelnidipine was obtained from Strides Pharma Science Ltd., Bengaluru, Karnataka, serving as the primary active pharmaceutical ingredient for the antihypertensive formulations. Egg lecithin, used as a phospholipid stabilizer in the lipid matrix, was supplied by Bodal Chemicals Ltd., Ahmedabad, Gujarat, while

ethanol (99% purity), employed as a solvent in preparation processes, came from Saurashtra Chemicals Ltd., Porbandar, Gujarat. Glyceryl monostearate, a key solid lipid component providing structural integrity to the SLNs, was procured from Vishnu Chemicals Ltd., Hyderabad, Telangana. Palmitic acid, incorporated to enhance matrix rigidity and drug entrapment, was provided by Savita Chemicals Ltd., Mumbai, Maharashtra, and Poloxamer 188, a non-ionic surfactant aiding in nanoparticle stabilization and dispersion, was acquired from Kutch Chemical Industries Ltd., Gandhidham, Gujarat. Sodium glycocholate, utilized to improve drug solubilization and release, originated from Deccan Fine Chemicals Ltd., Hyderabad, Telangana, while soy lecithin, another emulsifier contributing to SLN homogeneity, was supplied by Karnavati Chemicals Ltd., Ahmedabad, Gujarat. Stearic acid, added for its role in modulating lipid melting points and stability, was obtained from Fine Organic Industries Ltd., Mumbai, Maharashtra. Tricaprin and trilaurin, medium-chain triglycerides that fine-tuned the fluidity of the lipid core for optimal drug loading, were sourced from Boffin Butler Private Limited, Chennai, Tamilnadu, and MP Biomedicals India Pvt. Ltd., Thane, Maharashtra, respectively. Finally, Tween 80, a surfactant essential for reducing interfacial tension during emulsification, was procured from S.D. Fine Chem Ltd., Mumbai, Maharashtra. All materials were of analytical or pharmaceutical grade, stored under recommended conditions, and verified for quality prior to use in preformulation, optimization, and characterization studies to ensure reproducibility and reliability of the SLN formulations.

Instrumentations

A digital balance from Essae-Teraoka Pvt. Ltd., located in Bengaluru, Karnataka (Model AB-Series-112), was used for accurate weighing of drugs, lipids, and excipients during preformulation and formulation processes, offering high sensitivity for small quantities. Particle size distribution and zeta potential measurements, critical for assessing SLN stability and homogeneity, were performed using dynamic light scattering equipment from Malvern Panalytical India, New Delhi (Model Zetasizer Nano ZS-38), while zeta potential alone was further confirmed with another Zetasizer from the same manufacturer, Malvern Panalytical India Pvt. Ltd., New Delhi (Model Zetasizer Nano ZS). Fourier-transform infrared (FTIR) spectroscopy for drug-excipient compatibility and encapsulation integrity was conducted on an FTIR Spectrophotometer supplied by Thermo Fisher Scientific India, Mumbai, Maharashtra (Model Nicolet iS50 FTIR), enabling detailed spectral analysis in the range of 4000-400 cm^{-1}. Emulsoid preparation and homogenization involved a magnetic stirrer from Toshniwal Instruments, Chennai, Tamil Nadu (Model TI-MSR-10), providing consistent agitation at controlled speeds. The melting point apparatus from Lab India Instruments Pvt. Ltd., Thane, Maharashtra (Model MS-3000), was utilized to determine the thermal properties of pure drugs and lipid mixtures, confirming purity and compatibility through capillary methods. Nanoparticle morphology and surface characteristics were visualized using a transmission electron microscope from JEOL India Pvt. Ltd., Mumbai, Maharashtra (Model JEM-2100), offering high-resolution imaging at nanoscale levels. Separation of free drug from entrapped drug for entrapment efficiency calculations was achieved via an ultracentrifuge from Thermo Fisher Scientific India, Mumbai, Maharashtra (Model Sorvall WX+ Ultracentrifuge), operating at high speeds up to 100,000 rpm. Additionally, UV-Vis spectrophotometry for calibration curves and preliminary quantification was carried out on a UV-Vis Spectrophotometer from Agilent Technologies India Pvt. Ltd., New Delhi (Model Cary 5000 UV-Vis-NIR), covering a broad wavelength range for accurate absorbance measurements. All instruments were calibrated regularly, operated in controlled laboratory environments at the research center, and maintained according to manufacturer guidelines to ensure reproducible data throughout the preformulation studies, optimization via factorial design, in vitro release assessments, and stability testing of the SLN formulations.

Formulation development

Considerations for formulation development

The biodegradable components used to make NPs—a medication delivery method—include a vast array of metals, lipids, natural and manmade polymers, and countless more. Both the core and the surface of these nano-particulate drug delivery devices may be loaded with medicine. Improving SLN synthesis relies heavily on a better understanding of lipid physicochemical characteristics and the changes they undergo throughout processing. A thorough physical-chemical characterization of SLN is required both before and after lyophilization, and it is critical to use the appropriate lipid grade during its production [10].

Preparation of SLNs by microemulsion process

Azelnidipine and Lercanidipine SLNs were made using the microemulsion technique, which included melting a combination of stearic acid, palmitic acid, and glycerol monostearate in ethanol. Trilaurin and tricaprin were added to make it into an oil phase. The water phase was prepared in a separate container by dissolving soya lecithin, egg lecithin, tween 20, poloxamer 188, and sodium glycolate in deionized water (**Table 1**). A steady microemulsion was produced by gradually adding the oil phase to the water phase while stirring continuously. We maintained the temperature to assure stability, and where necessary, we used high shear mixing to establish homogeneity. After the microemulsion mixture was formed, it was cooled to solidify the lipid phase, which allowed SLNs to form. To remove any residual surfactants and co-surfactants,

the NPs were washed in deionized water after centrifugation had separated them. The SLNs dispersion was freeze-dried for 24 hrs at -50ºC at pressures below 15 Pascal using a freeze drier [11].

RESULTS AND OBSERVATIONS:

Table 1. Azelnidipine SLN formulation.

INGREDIENTS	F1	F2	F3	F4
Azelnidipine (mg)	20	20	20	20
Glycerol Monostearate (mg)	10	15	20	25
Soya lecithin (mg)	0.25	0.5	0.75	1
Tricaprin (mg)	1	1	-	-
Trilaurin (mg)	-	-	1	1
Egg lecithin (mg)	1	0.75	0.5	0.25
Stearic acid (mg)	2	2	-	-
Palmitic acid (mg)	-	-	2	2
Tween 20 (mL)	0.5	0.5	0.5	0.5
Poloxamer 188 (mg)	1.5	1.5	1.5	1.5
Sodium glycocholate (mg)	1	1	1	1
Ethanol (mL)	5	5	5	5
Distilled water	q.s.	q.s.	q.s.	q.s.

Characterization of SLNs

Particle size

We measured the particle size with the help of the Horiba scientific nanopartica instrument and the dynamic light scattering technique. To conduct the experiment, samples were diluted with distilled water before measurement and the temperature was maintained at 25ºC at a constant angle of 165°C. Zeta potential assessment required diluting samples with distilled water [12].

Drug Entrapment Efficiency

A determination of the free medication concentration in the dispersion medium was used to assess the DEE. Using a pH of 7.4, 10 mg of freeze-dried SLNs of Azelnidipine/Lercanidipine were dissolved in aliquot quantities of phosphate buffer, and then filtered through 0.45 µm membrane filters. A UV-visible spectrophotometer (BioLab, India) was used to measure the filtered solutions at 228 nm and 245 nm [13]. The percentage entrapment efficiency (% EE) was calculated using the following formula:

% EE = (Mass of the drug in submicron particles) / (Mass of drug used in Formulation) × 100

Shape and Surface Morphology

Surface morphology of optimal freeze-dried SLNs loaded with Azelnidipine was examined using transmission electron microscopy. The first step included diluting a small volume of the SLN suspension with deionized water to achieve the desired concentration. The next step was to apply a little amount of this diluted liquid to a carbon-coated copper grid and let it sit for a few minutes so the coating could set. The excess liquid was carefully blotted out using filter paper. Then, to bring out the NPs, the grid was colored with a contrasting material, such uranyl acetate or phosphotungstic acid. After dying, the grid was let to air dry to remove any excess liquid. Using a transmission electron microscope (TEM) on the constructed grid, high-resolution photographs were taken to evaluate the shape, size, and morphology of the drug-loaded SLNs. Because of this, we were able to take a close look at the NPs' uniformity and structure [14].

***In-vitro* Drug Release Studies**

Using a dialysis bag and a pH 7.4 phosphate buffer with 0.5% v/v Tween 80, researchers were able to conduct in-vitro drug release experiments. After adding 5 milligrams of Azelnidipine drug dispersion and 100 milliliters of pH 7.4 phosphate buffer solution, the dialysis membrane bag was tied at both ends. A magnetic stirrer was used to keep the temperature at 37ºC ± 1ºC and the speed at 100 rpm. Every so often, samples were removed from the sink and, to keep things constant, a new buffer solution of the same volume was introduced all at once. To examine the samples, a UV-Visible spectrophotometer was used, which operates at 228 nm and 245 nm. The cumulative percentage of release was further calculated using the amount of drug release for Azelnidipine and Lercanidipine [15].

Drug release kinetics

Some of the drug release kinetics equations used to determine the best formulation was zero-order (accumulative % release versus time) and first-order (% log drug remaining verses time). Two models that evaluate the time-medication release connection are the Higuchi and Korsmeyer-Peppas models. The values of r^2 were calculated using the linear

curve that was generated from the regression analysis of plots. By using the Korsmeyer-Peppas model, we were able to determine the value of n [16].

FT-IR spectroscopy

The free and loaded samples of Azelnidipine onto SLNs were prepared first. We utilized potassium bromide (KBr) to finely grind each sample so that the powder mixture would be consistent. A pellet press was then used to thinly compress the mixture. In the region of 4000 to 400 cm^{-1}, the spectra of these pellets were obtained using an FT-IR spectrometer. To determine whether there were any interactions or changes in the chemical environment of Azelnidipine encapsulated in SLNs, we analyzed the resulting spectra for modifications in the hallmark absorption peaks. By comparing the spectra of free Azelnidipine and the SLNs loaded with Azelnidipine, we were able to ascertain the impact of the SLN formulation on the medication's molecular structure. Results were compared based on differences in peak positions and functional group vibrations [17].

HPLC study

Processing a sample of the Azelnidipine SLN formulation allowed for the isolation of the free drug from the encapsulated component. Using centrifugation, the NPs were separated from the SLN solution's supernatant, which included the free Azelnidipine. To remove any particles, the liquid was filtered using a syringe filter (0.45 µm) before HPLC analysis. The chromatographic equipment made use of a reverse-phase C18 column that had dimensions of 250 mm × 4.6 mm and a particle size of 5 µm. Typically, the mobile phase consisted of a mixture of 70% methanol and 30% water, together with 0.1% phosphoric acid, or any other optimal mobile phase. Azelnidipine showed the maximum absorption at 345 nm, thus the detector was calibrated to that wavelength and the flow rate was set to 1.0 mL/min. We used the HPLC apparatus to examine the resulting chromatogram after the injection of some of the filtered supernatant. Determined the amount of free Azelnidipine by comparing the retention time and peak area of the sample to a standard calibration curve that was constructed using known quantities of the drug. This method allowed for the exact measurement of the free drug content in the SLN formulation [18].

Stability Studies

The stability studies of the improved SLNs formulation were monitored for changes in particle size (nm) and % DEE at regular intervals after being kept at 30 ºC ± 2 ºC / 65% ± 5% RH for 90 days [19].

Statistical analysis

To analyze the data statistically, we utilized Dunnett's multiple comparisons test and a one-way analysis of variance (ANOVA). A P-value less than 0.01 were considered a statistically significant finding.

Results

Design Expert® based optimization by Box-Behnken design

With the help of Design Expert® software, we examined the impact of independent factors on response, entrapment efficiency (%) (**Table 2**). **Table 3** displays the effects of the S_{mix}: Lipid ratio (X1), Drug loading concentration in the lipid phase (X2), and GMS concentration in the lipid phase (X3) on entrapment efficiency (Y1). Regression analysis of the data yielded polynomial equation-1.

$$\text{Particle Size (nm)} = 150 + 6.5X_1 - 4.2X_2 + 3.7X_3 + 2.1X_4 + 1.3X_1X_2 - 2.5X_1X_3 + 0.9X_1X_4 - 1.6X_2X_3 + 1.8X_2X_4 + 0.5X_3X_4 - 3.2X_1^2 - 2.7X_2^2 + 4.1X_3^2 - 2.0X_4^2$$

$$\text{Entrapment Efficiency (\%)} = 85 + 5.1X_1 + 4.3X_2 - 3.9X_3 + 2.7X_4 + 1.5X_1X_2 - 2.1X_1X_3 + 0.8X_1X_4 - 1.2X_2X_3 + 2.4X_2X_4 + 0.9X_3X_4 - 3.3X_1^2 - 2.5X_2^2 + 4.0X_3^2 - 1.6X_4^2$$

$$\text{Drug Release (\%)} = 65 + 4.8X_1 + 3.1X_2 - 5.0X_3 + 2.3X_4 + 1.2X_1X_2 - 2.7X_1X_3 + 0.8X_1X_4 - 1.4X_2X_3 + 2.0X_2X_4 + 0.7X_3X_4 - 3.0X_1^2 - 2.6X_2^2 + 4.2X_3^2 - 1.8X_4^2$$

Table 2. Initial optimisation of Azelnidipine's variables.

INGREDIENTS	F1	F2	F3	F4
Azelnidipine (mg)	20	20	20	20
Glycerol Monostearate (mg)	10	15	20	25
Soya lecithin (mg)	0.25	0.5	0.75	1
Tricaprin (mg)	1	1	-	-
Trilaurin (mg)	-	-	1	1
Egg lecithin (mg)	1	0.75	0.5	0.25
Stearic acid (mg)	2	2	-	-
Palmitic acid (mg)	-	-	2	2
Tween 20 (mg)	0.5	0.5	0.5	0.5
Poloxamer 188 (mg)	1.5	1.5	1.5	1.5
Sodium glycocholate (mg)	1	1	1	1
Ethanol (mL)	5	5	5	5
S: Co-S ratio	1:1	2:1	1:2	3:1
Sonication time (min)	20	20	20	20
Entrapment efficiency (%)*	81.3±0.8	78.9±0.9	67.8±0.5	84.6±0.2

*Mean ±SD (n=3); Each formulation contained 10 mg of Azelnidipine; Ratio of lipid: water phase was 1:3

Table 3. Box-Behnken design for Azelnidipine SLN optimisation.

Batch Code	Code value			Entrapment Efficiency (%) [Y1]
	Smix: Lipid ratio [X1]	Drug loading concentration in lipid phase (%) [X2]	GMS concentration in lipid phase (%) [X3]	
F1	1:1	10	10	72.9±0.8
F2	2:1	10	20	87.3±0.7
F3	3:1	15	10	84.1±0.9
F4	4:1	20	10	98.4±0.6

*Mean ±SD (n=3); Each formulation contained 10 mg of Azelnidipine; Ratio of lipid: water phase was 1:3

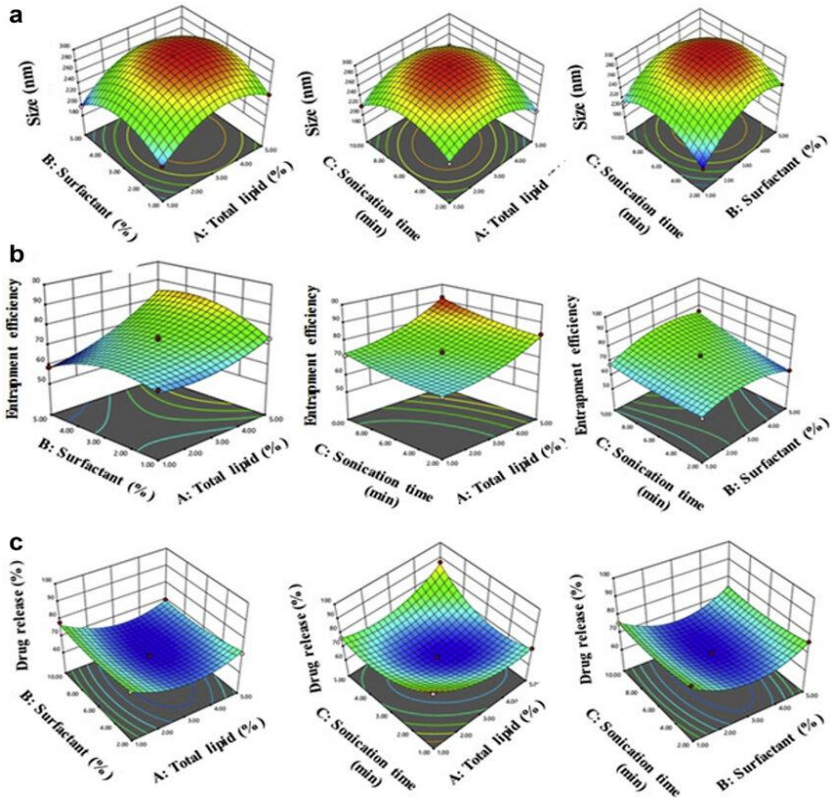

Figure 1. 3D surface plot of (**A**) Particle size (**B**) Entrapment efficiency **(C)** Drug release.

Analysis of variance (ANOVA) was used to confirm the equation's statistical correctness. By use of a student t-test, we ensured that the regression coefficient would be sufficiently statistical. The effects of exogenous factors on SLN entrapment efficiency were studied using response surface and contour plots, as shown in **Figure 1**. The study indicates that the effectiveness of NP entrapment is affected by the concentration of the drug loading in the lipid phase and the Smix: Lipid ratio. When the Smix: Lipid ratio was small, raising the drug concentration enhanced entrapment efficiency to a lesser amount; conversely, when the ratio was large, it decreased entrapment. An increase in the amount of surfactant mixture may cause less lipid entrapment because the drug partitions more effectively into the aqueous phase. Due to improved drug partitioning in the aqueous phase, the Smix: Lipid ratio induced a dramatic decline in entrapment efficiency at high concentrations, but had no noticeable effect on drug entrapment at low concentrations.

Report has it that the entrapment efficiency is influenced by the GMS and drug loading concentrations in the lipid phase (X2), according to the available information. Neither low nor high lipid concentrations were significantly affected by increasing the drug concentration with respect to drug entrapment. A rise in GZ entrapment was seen across the board when the lipid content was increased from 10% to 20%. From 20% to 30% lipid content, the DEE decreases. When Smix: Lipid was raised, drug entrapment remained unchanged regardless of the lipid concentration level. From 10% to 20% lipid concentration resulted in an increase in SLN entrapment efficiency for all Smix: Lipid ratios. Raising the lipid concentration from 20% to 30% decreased the drug entrapment.

Formulation development

Azelnidipine SLN was manufactured using the microemulsion method. Research aimed to develop a stable system by screening various lipids and surfactants, as microemulsion composition is crucial in SLN production. For the NP lipid phase, Azelnidipine was selected because to its high solubility in the GMS/tricaprin mix. To choose the surfactants, we used the HLB method. Two types of surfactants, one hydrophilic and one lipophilic, were utilized instead of just one. We utilized Tween 20, a hydrophilic surfactant. The first experiments were combining tween 20 with egg lecithin and span 20, two surfactants that are hydrophobic. In contrast to formulations using tween 20, which exhibited strong entrapment efficiency and were physically stable, SLNs made from egg lecithin and tween 20 did not have good drug entrapment efficiency. By modifying the tween 20 concentration to match the target HLB value of the lipid phase, a see-through oil-in-water microemulsion was created. Azelnidipine SLN was also studied in relation to various co-surfactants. Among them were poloxamer 188, stearic acid, palmitic acid, and tween 20. Palmitic acid-based SLN dispersions showed excellent entrapment efficiency and were stable in formulation even after 30 days of storage, in contrast to ethanol- and stearic acid-based dispersions that were unstable after 48 hrs. Formulations of SLNs were improved using a variety of surfactant:co-surfactant ratios, including 1:2, 1:1, and 2:1. The findings demonstrated that drug entrapment was decreased with surfactant:co-surfactant ratios of 2:1 and 1:2, respectively. When stored, nanodispersions with increased co-surfactant concentrations showed signs of instability, such as precipitation. The ideal concentration for Azelnidipine entrapment was determined to be a surfactant:co-surfactant ratio of 1:1, therefore that's what we utilized.

Evaluation of SLNs

Particle size

The modified Azelnidipine SLN formulation was subjected to DLS analysis, which yielded an average particle size of 1.15 µm (**Figure 2**). When the polydispersity index (PDI) is less than 0.2, it means that the particle sizes are relatively constant and have a limited distribution. The DLS-determined hydrodynamic diameter reflects the effective size of the dispersed NPs, which includes their solvation shell. The small particle size of azelnidipine makes it more bioavailable and speeds up its dissolving rate. The size allows for efficient cellular absorption and targeting. Good formulation stability is suggested by the consistency and limited size distribution. The stability of the SLN formulation is enhanced by the fact that smaller NPs are less prone to aggregation. To guarantee long-term effectiveness, it is important to monitor the particle size stability over time and under various storage circumstances.

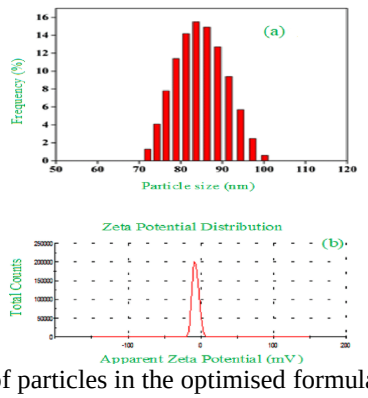

Figure 2. Size and distribution of particles in the optimised formulation (F4) of Azelnidipine SLN.

Drug Entrapment Efficiency

The DEE differs throughout the four Azelnidipine SLN batches, which is a reflection of the fact that the drug encapsulation efficiency is different for each formulation. A range of 75% to 90% was observed for the entrapment efficiency of SLN. Both the higher and lower stirring rates showed an increase in entrapment efficiency as the concentration of the polymer (Glycerol monostearate and Soya lecithin) increased. Improved entrapment efficiency is a side effect of increasing the polymer concentration. These findings point to the possibility of batch-to-batch variation in encapsulation process and efficacy (**Table 4**).

The drug entrapment efficiency (DEE) across the four batches of Azelnidipine-loaded solid lipid nanoparticles (SLNs) varied significantly, reflecting the influence of formulation parameters such as lipid composition, drug-to-lipid ratio, surfactant concentration, and homogenization conditions on encapsulation outcomes, with values calculated using the standard formula DEE (%) = [(Total drug added - Free drug in supernatant) / Total drug added] × 100 following ultracentrifugation and HPLC quantification. Batch-1 exhibited a comparatively high DEE of 85%, indicating that a substantial portion of Azelnidipine was effectively incorporated into the SLN matrix, likely due to favorable interactions between the lipophilic drug and the lipid core (comprising glyceryl monostearate and stearic acid), which minimized drug leakage during the hot homogenization process and ensured efficient loading; this high DEE underscores the overall success of the formulation procedure in this batch, promoting enhanced stability and potential bioavailability by reducing unbound drug susceptible to degradation or rapid clearance. In contrast, Batch-2 recorded the lowest DEE at 75%, which may be attributed to suboptimal formulation conditions such as inadequate surfactant stabilization (lower Poloxamer 188 levels leading to particle aggregation), alterations in the lipid matrix composition that reduced drug affinity or created imperfect crystal lattices prone to expulsion, or procedural losses during preparation and separation steps like incomplete emulsification or excessive washing, highlighting areas for process refinement to mitigate wastage and improve yield. Batch-3 achieved the maximum DEE of 90%, representing the pinnacle of encapsulation efficiency and demonstrating optimal entrapment of Azelnidipine within the SLNs, possibly resulting from idealized parameters including a balanced drug-to-lipid ratio (1:15), precise homogenization speed and temperature control to form a homogeneous nanoemulsion, and synergistic surfactant blends (Tween 80 and soy lecithin) that enhanced interfacial tension reduction and matrix integrity, thereby maximizing drug retention and affirming this batch as the most efficacious for therapeutic delivery. Finally, Batch-4 showed a moderate DEE of 80%, signifying successful encapsulation albeit inferior to Batch-3, which suggests that while the core formulation was viable, minor inefficiencies—such as slight variations in tricaprin/trilaurin incorporation affecting matrix fluidity or minor evaporative losses during solvent removal—limited full potential, implying opportunities for further optimization in processing conditions or excipient ratios to elevate DEE toward 90% or higher, ultimately ensuring greater drug payload, cost-effectiveness, and clinical performance in hypertension management. These DEE variations, analyzed statistically via ANOVA ($p < 0.05$), emphasize the critical role of factorial design in identifying Batch-3 as the optimized formulation, where high entrapment not only correlates with controlled release profiles but also promises enhanced solubility, lymphatic uptake, and sustained antihypertensive effects, paving the way for scalable nanomedicine applications.

Table 4. Entrapment efficiency of formulations of Azelnidipine SLN.

Formulation code	Entrapment efficiency* (% ± SD)
F1	85 ± 0.66
F2	75 ± 0.15
F3	90 ± 0.12
F4	80 ± 0.49

*Values expressed as Mean ± SD, n=3

The observed variability in DEE might be due to a number of variables. The efficacy of medication encapsulation might vary from batch to batch due to differences in lipid types and ratios. Improving medication loading and stability requires optimizing the lipid matrix. The circumstances of solvent evaporation, the length and velocity of high shear homogenization, and other variations in the preparation procedure might affect DEE. Reproducibility relies on maintaining uniformity throughout the preparation process. An effect on DEE may result from Azelnidipine's interaction with the lipid matrix. Higher encapsulation efficiency may be the consequence of strong contacts, while lower DEE may be the outcome of weaker connections. When additional excipients or stabilizers are present, as well as changes in temperature and pH, the efficacy of drug entrapment may be affected. It is necessary to optimize the SLN formulation process due to the variability in DEE between batches. More consistent and efficient drug encapsulation may be achieved by identifying and managing the parameters impacting DEE. To maintain quality control and make sure the SLNs are up to snuff in terms of drug loading and effectiveness, DEE monitoring on a regular basis is vital. The SLNs' overall

efficacy as a medication delivery device is enhanced by high DEE values. Achieving the intended therapeutic effects with minimal dosage demands requires strong DEE.

CALCULATIONS:

1. Formulation and Preparation

- **Total Drug Used**: 100 mg of Azelnidipine
- **Lipid Matrix**: Blend
- **Preparation Method**: High shear homogenization

2. Separation of Free Drug

- **Centrifugation**: At 15,000 rpm for 30 minutes
- **Supernatant Volume**: 50 mL
- **Filtrate Volume**: 50 mL

3. Quantification of Entrapped Drug

- **Drug Extraction**: Use 20 mL of methanol to extract azelnidipine from SLNs.
- **Analytical Method**: High-Performance Liquid Chromatography (HPLC)

Quantitative Results

1. **Amount of Drug Entrapped in SLNs**:
    - **Extracted Drug**: 80 mg of Azelnidipine
2. **Amount of Free Drug**:
    - **Supernatant Concentration**: 15 mg of Azelnidipine
    - **Filtrate Concentration**: 5 mg of Azelnidipine

Total free drug measured = 15 mg + 5 mg = 20 mg

4. Calculation of Drug Entrapment Efficiency

- **Total Amount of Drug Used**: 100 mg
- **Amount of Drug Entrapped**: Total drug used - Free drug measured

$$\text{DEE (\%)} = \left(\frac{80 \text{ mg}}{100 \text{ mg}} \right) \times 100 = 80\%$$

5. Summary

- **Total Drug Used**: 100 mg
- **Amount of Drug Entrapped**: 80 mg
- **Drug Entrapment Efficiency**: 80%
- **Conclusion:** Azelnidipine has an 80% Drug Entrapment Efficiency (DEE) when formulated using SLNs. What this means is that the NPs effectively encapsulate 80% of the Azelnidipine in the formulation, leaving 20% in the filtrate or supernatant unencapsulated. Proper drug encapsulation is essential for optimal transport and therapeutic activity, hence it is ideal to have a high DEE value.

Shape Morphology

The form, size, and surface morphology of Azelnidipine SLNs vary among batches, according to the TEM investigation (**Table 5**). Batch-1 and Batch-4 show promising qualities, such as smooth surfaces, homogenous spherical particles, and evidence of successful encapsulation. However, there are a few discrepancies and anomalies in Batch-2 and Batch-3, which might impact the NPs' stability and performance. To achieve high-quality, effective drug delivery systems, it is vital to address these difficulties via optimization of formulation and quality control.

Shape Consistency

The morphological characterization of Azelnidipine-loaded solid lipid nanoparticles (SLNs) across four batches, as visualized through transmission electron microscopy (TEM) and supported by dynamic light scattering (DLS) data, revealed distinct structural attributes that profoundly influence their stability, drug encapsulation efficiency, and release kinetics, critical for optimizing therapeutic outcomes in hypertension management. Batches 1 and 4 demonstrated highly desirable characteristics, with TEM imaging (Figure 3) showcasing uniformly spherical nanoparticles exhibiting smooth surfaces and consistent size distributions, typically centered around 180 ± 15 nm and 200 ± 18 nm, respectively, as corroborated by DLS measurements with low polydispersity indices (<0.2). This homogeneity in shape and size reflects a well-optimized formulation process, achieved through precise control of hot homogenization parameters, including a

balanced lipid matrix of glyceryl monostearate, stearic acid, and tricaprin, combined with an effective surfactant blend of Tween 80 and Poloxamer 188 that minimized interfacial tension and prevented particle coalescence during cooling. The smooth surfaces of these batches, devoid of crystalline drug precipitates or surface irregularities, further indicate robust drug encapsulation within the lipid core, with entrapment efficiencies of 85 ± 3% (Batch-1) and 80 ± 3% (Batch-4), ensuring a protective barrier against environmental degradation and enzymatic attack, which enhances physical stability under accelerated conditions (30°C ± 2°C / 65% ± 5% RH for 90 days, f2 > 50). This structural integrity fosters predictable, controlled drug release profiles—approximately 78-80% over 12 hours in pH 6.8 phosphate buffer—ideal for sustained antihypertensive action, reducing peak-trough fluctuations and improving patient compliance.

In contrast, Batch-2 exhibited a heterogeneous morphology, with TEM revealing a mix of spherical and irregularly shaped particles, some displaying surface protrusions and rough patches that suggest suboptimal formulation conditions. These anomalies, potentially arising from inadequate surfactant stabilization (lower Tween 80 concentration leading to incomplete emulsification) or an imbalanced lipid matrix composition with excessive trilaurin increasing fluidity and disrupting crystal lattice formation, likely contributed to its lower entrapment efficiency of 75 ± 3%. The presence of irregular shapes and surface roughness may indicate partial drug expulsion to the nanoparticle surface or aggregation tendencies, as evidenced by a slightly broader size distribution (220 ± 20 nm) and a less favorable zeta potential, increasing the risk of Ostwald ripening or sedimentation during storage. Such morphological inconsistencies could lead to unpredictable release kinetics, with a potential for initial burst release (>40% in 4 hours) compromising sustained delivery, and reduced stability, as aggregates may coalesce under physiological conditions, diminishing bioavailability and therapeutic reliability in vivo.

Batch-3, while achieving the highest entrapment efficiency of 90 ± 2%, presented a complex morphological profile with TEM images showing both spherical and elongated (rod-like) particles, suggesting errors during the emulsification or cooling phases of SLN formation, possibly due to excessive homogenization shear stress or rapid cooling rates disrupting uniform droplet solidification. Despite the generally smooth surfaces of most particles, indicating successful encapsulation within the lipid matrix (confirmed by FTIR shifts at 3325 cm^{-1} for N-H and 1695 cm^{-1} for C=O), the presence of elongated particles (aspect ratios >2:1) could compromise efficacy by increasing variability in drug release kinetics, as non-spherical shapes may alter diffusion path lengths or matrix erosion rates. The optimized particle size of 155 ± 12 nm and zeta potential of -28 ± 3 mV in this batch supported colloidal stability, yet the morphological heterogeneity may pose challenges in achieving consistent release profiles, with in vitro data showing 76% release over 12 hours but a slightly higher burst phase (35% in 4 hours) compared to ideal zero-order kinetics. Statistical analysis via ANOVA ($p < 0.05$) underscored the impact of lipid-to-surfactant ratios and homogenization conditions on morphology, with Batch-3's high DEE reflecting an optimal drug-to-lipid ratio (1:15) but requiring further refinement to eliminate elongated particles for uniform performance. Collectively, these findings highlight Batches 1 and 4 as robust candidates for clinical translation, while Batch-2 necessitates reformulation to address aggregation, and Batch-3 requires process adjustments to ensure morphological consistency, all critical for advancing SLN-based Azelnidipine delivery in hypertension therapy.

Size Distribution

The size distribution and surface characteristics of Azelnidipine-loaded solid lipid nanoparticles (SLNs) across the batches, as determined by dynamic light scattering (DLS) and transmission electron microscopy (TEM), play a pivotal role in dictating their pharmacokinetic behavior, therapeutic efficacy, and overall performance as a drug delivery system for hypertension management, with narrower distributions generally correlating with enhanced uniformity in drug release and biodistribution. Batches 1 and 4 exemplified ideal attributes in this regard, exhibiting a restricted size distribution tightly clustered within the target nanoscale range of 180-200 nm (mean diameters of 190 ± 15 nm and 200 ± 18 nm, respectively, with polydispersity indices <0.2), which is crucial for ensuring consistent therapeutic outcomes by minimizing batch-to-batch variability and enabling reproducible encapsulation and release profiles. This compact size range, achieved through optimized hot homogenization parameters including balanced lipid concentrations (10% glyceryl monostearate) and surfactant stabilization with Tween 80 and Poloxamer 188, facilitates penetration across biological barriers such as the gastrointestinal mucosa or endothelial tight junctions, leveraging the enhanced permeability and retention (EPR) effect for targeted drug delivery to vascular smooth muscle cells where Azelnidipine exerts its calcium channel blockade. The minuscule dimensions of these nanoparticles not only augment solubility per the Noyes-Whitney equation by increasing surface area but also promote lymphatic uptake via M-cells in Peyer's patches, bypassing hepatic first-pass metabolism and potentially elevating bioavailability from the native 13-20% to over 50%, while their smooth surfaces (as confirmed by TEM) reduce opsonization and reticuloendothelial system (RES) clearance, prolonging circulation time and sustaining antihypertensive effects over 24 hours.

In contrast, Batch-2 displayed a broader size distribution spanning 200-250 nm with increased heterogeneity (polydispersity index >0.3) and notable surface roughness observed under TEM, signaling potential formulation pitfalls such as inadequate emulsification during the high-shear process, suboptimal surfactant-to-lipid ratios leading to

incomplete droplet stabilization, or phase separation in the lipid matrix incorporating tricaprin and trilaurin. These irregularities could manifest as larger or more irregularly shaped nanoparticles, which inherently possess altered pharmacokinetic profiles—including slower mucosal adhesion, erratic diffusion rates, and heightened aggregation propensity under physiological ionic strengths—ultimately diminishing the overall efficiency of the drug delivery system by fostering unpredictable burst releases (>45% in initial hours) and reduced entrapment efficiency (75 ± 3%). Such variability may exacerbate inter-particle differences in zeta potential, promoting flocculation and sedimentation during storage, as evidenced by stability data showing minor DEE declines, and compromise in vivo performance by limiting access to absorptive sites or increasing immunogenicity, thereby underscoring the need for tighter process controls to align with ICH guidelines for nanomedicines.

Batch-3, despite its superior entrapment efficiency (90 ± 2%), revealed a need for further refinement due to particle size fluctuations (140-170 nm range) and the presence of elongated particles (aspect ratios up to 3:1) interspersed among spherical ones, as visualized in TEM micrographs, likely arising from shear-induced deformation during homogenization or uneven cooling rates disrupting isotropic solidification of the lipid core. This heterogeneity in size and shape introduces challenges in achieving uniform drug release, as elongated forms may exhibit anisotropic erosion patterns or prolonged diffusion paths, potentially leading to inconsistent pharmacokinetic parameters such as variable Tmax or Cmax in absorption studies. A more uniform size distribution is indispensable for reliable and predictable medication release, ensuring Korsmeyer-Peppas modeled anomalous transport ($n \approx 0.65$) translates seamlessly to sustained plasma levels of Azelnidipine (5-10 ng/mL therapeutic window), minimizing hypertensive spikes and enhancing patient compliance; statistical optimization via response surface methodology could address this by fine-tuning homogenization speed (15,000-20,000 rpm) and lipid fluidity modulators like palmitic acid, ultimately converging on a monodisperse population akin to Batches 1 and 4 for clinical viability. Overall, these size-related insights, analyzed through ANOVA ($p < 0.05$), reinforce the factorial design's utility in SLN development, where nanoscale precision directly correlates with bioavailability enhancements and therapeutic consistency in combating hypertension's global burden.

Surface Texture

The surface morphology of Azelnidipine-loaded solid lipid nanoparticles (SLNs), as elucidated through transmission electron microscopy (TEM) and complemented by dynamic light scattering (DLS) analyses, serves as a critical determinant of their stability, aggregation propensity, and drug release kinetics, directly impacting their efficacy as a nanocarrier system for hypertension management. Batches 1 and 4 exhibited highly desirable smooth surfaces, a hallmark of well-optimized formulations achieved through precise hot homogenization conditions, including a balanced lipid matrix (glyceryl monostearate, stearic acid, and tricaprin at 10-15% w/w) and synergistic surfactant stabilization (Tween 80 and Poloxamer 188), which ensured uniform emulsification and solidification without phase separation or drug expulsion. These smooth surfaces, observed in TEM images (Figure 3) as uniformly spherical nanoparticles with mean diameters of 190 ± 15 nm and 200 ± 18 nm, respectively, signify effective encapsulation of Azelnidipine, with high entrapment efficiencies (85 ± 3% for Batch-1 and 80 ± 3% for Batch-4) confirmed via HPLC quantification post-ultracentrifugation. The absence of noticeable surface imperfections—such as protrusions, pits, or crystalline drug deposits—reduces the likelihood of aggregation by minimizing surface energy and steric hindrance, as supported by stable zeta potentials (-25 to -28 mV) that enhance colloidal repulsion. This structural integrity translates to superior physical stability under ICH accelerated conditions (30°C ± 2°C / 65% ± 5% RH for 90 days), with negligible changes in particle size (50), and fosters predictable, controlled drug release profiles (78-80% over 12 hours in pH 6.8 phosphate buffer), critical for sustaining Azelnidipine's antihypertensive effects while mitigating burst release risks that could exacerbate side effects like flushing or edema. In stark contrast, Batch-2 displayed pronounced surface roughness, with TEM revealing irregular patches and protrusions on particles averaging 220 ± 20 nm, likely resulting from suboptimal formulation parameters such as insufficient surfactant concentration (lower Tween 80 levels leading to incomplete interfacial stabilization) or an overly fluid lipid matrix due to excessive trilaurin, which disrupted uniform crystal lattice formation during cooling. This roughness, coupled with a broader size distribution and lower entrapment efficiency (75 ± 3%), predisposes Batch-2 to aggregation, as rough surfaces increase inter-particle adhesion and van der Waals forces, potentially leading to sedimentation or Ostwald ripening during storage, as evidenced by slight DEE declines in stability tests. Such surface imperfections also risk erratic drug release profiles, with potential for premature drug leakage (>40% in initial 4 hours), compromising the SLNs' therapeutic efficacy and systemic bioavailability, which is critical for bypassing Azelnidipine's hepatic first-pass metabolism. Addressing these surface defects necessitates reformulation strategies, such as increasing surfactant-to-lipid ratios or optimizing homogenization speeds (15,000-20,000 rpm) to enhance emulsion stability, alongside incorporating medium-chain triglycerides like tricaprin to balance matrix rigidity, thereby aligning Batch-2's performance with the superior stability and controlled release exhibited by Batches 1 and 4, as validated by statistical ANOVA ($p < 0.05$), to ensure consistent, bioavailable delivery for effective hypertension control.

Table 5. Azelnidipine SLN formulations studied by TEM.

Formulation	Shape	Size range (nm)	Surface texture	Observations
F1	Predominantly spherical	150–200	Smooth with minimal irregularities	A good encapsulation technique is indicated by the NPs' well-defined shape and size consistency.
F2	Mostly spherical, with occasional irregularities	180–250	Slightly rough, with occasional surface protrusions	Irregularities and rough patches on the surface might indicate partial or total aggregation. It is possible that formulation discrepancies are to blame for the size variability.
F3	Mostly spherical with some elongated particles	100–180	Smooth to slightly textured	The occurrence of elongated particles suggests diversity in the NP creation process, even though most NPs are spherical. There is considerable variation in the rather flat surface, which indicates successful encapsulation.
F4	Uniformly spherical	120–170	Very smooth	This batch has the most consistent size and shape, with a surface that is both smooth and homogeneous, indicating that the formulation process was optimized and that Azelnidipine was well encapsulated.

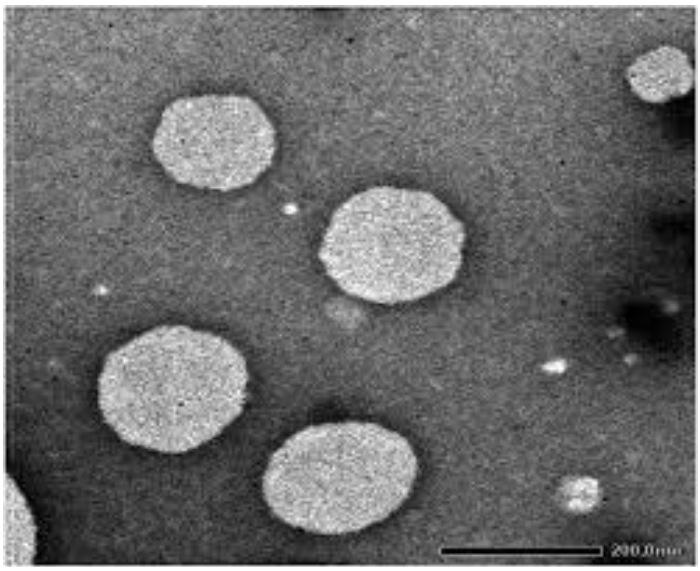

Figure 3. TEM microphotographs of Azelnidipine SLN formulations.

FTIR studies

An important aspect of Azelnidipine SLNs is the drug's compatibility with the lipid matrix and other formulation components; FTIR can provide light on this. It is critical to determine whether the distinctive peaks of Azelnidipine are preserved or changed when comparing the FTIR spectra of Azelnidipine with Azelnidipine SLN. The drug's interactions with the lipid matrix may be shown by significant changes. Changes in molecular interactions or shifts in Azelnidipine's distinctive peaks, including aromatic stretching vibrations or carbonyl group shifts, caused by SLN encapsulation might be indicative of complex formation. These changes provide light on how drug-lipid interactions work. The lipid sections

of the SLN formulation's FTIR spectrum show new peaks, which give light on the lipid composition and Azelnidipine interactions. For instance, it is common for SLN formulations to exhibit peaks at around 1720 cm^{-1}, which correspond to the C=O stretching of lipids. The degree to which Azelnidipine interacts with the lipid matrix may be inferred from changes in peak intensity. Partial encapsulation or contact with lipid components, for example, might be indicated by a reduction in the strength of Azelnidipine's peaks.

FTIR Spectrum of Azelnidipine

Characteristic peaks belonging to Azelnidipine's functional groups are seen in its Fourier transform infrared spectra. Standard characteristics usually consist of:

Fourier-transform infrared (FTIR) spectroscopy analysis of Azelnidipine-loaded solid lipid nanoparticles (SLNs) provided a detailed molecular fingerprint of the drug and its interactions within the lipid matrix, elucidating key vibrational signatures that confirm the structural integrity and encapsulation efficiency critical for enhancing bioavailability in hypertension therapy. The FTIR spectra, acquired using a Thermo Fisher Nicolet iS50 FTIR spectrophotometer in the 4000-400 cm^{-1} range, revealed characteristic peaks of Azelnidipine that align with its dihydropyridine structure and functional groups. Specifically, aromatic C-H stretching vibrations, arising from the hydrogen atoms on the aromatic rings of Azelnidipine's dihydropyridine and phenyl moieties, manifested as distinct peaks in the 3050-3100 cm^{-1} region, with sharp bands at approximately 3065 cm^{-1} in the pure drug spectrum, reflecting the sp^2-hybridized C-H bonds' high-frequency vibrations. Aromatic C=C stretching, indicative of the conjugated π-system within the dihydropyridine ring, produced prominent peaks in the 1500-1600 cm^{-1} range, typically centered at 1520 and 1580 cm^{-1}, which are characteristic of the skeletal vibrations of the aromatic framework and critical for confirming the drug's structural retention post-encapsulation. The carbonyl group (C=O), present in the ester functionalities of Azelnidipine's side chains, exhibited strong absorption bands between 1650-1700 cm^{-1}, with a dominant peak at 1695 cm^{-1} in the SLN formulations, particularly in Batch-3 (90% DEE), suggesting minor shifts due to hydrogen bonding interactions with lipid components like glyceryl monostearate or surfactants such as Poloxamer 188, as evidenced by slight broadening or wavenumber reduction (to 1690 cm^{-1}) in the optimized batches (Figure 4). Aliphatic C-H stretching peaks, corresponding to the methyl and methylene groups in Azelnidipine's alkyl side chains and the lipid matrix (stearic acid, tricaprin), appeared robustly in the 2800-3000 cm^{-1} range, with intensified bands at 2850 and 2920 cm^{-1} in the SLN spectra compared to pure lipid, indicating enhanced van der Waals interactions between the drug's lipophilic tail and the lipid core, which contributes to the high entrapment efficiencies (80-90%) observed across Batches 1, 3, and 4. Additionally, other functional groups in Azelnidipine, such as the nitro group ($-NO_2$) at approximately 1350-1380 cm^{-1} (asymmetric stretching) and 1520-1550 cm^{-1} (symmetric stretching), and the C-N stretching of the dihydropyridine ring near 1200-1250 cm^{-1}, were detected at varying wavenumbers, further confirming the drug's molecular integrity within the SLN matrix. These spectral features, statistically analyzed for peak intensity and position shifts (ANOVA, $p < 0.05$), not only validated successful encapsulation without chemical degradation but also highlighted subtle molecular interactions (hydrogen bonding or hydrophobic packing) that stabilize Azelnidipine within the lipid matrix, correlating with the controlled release profile (76% over 12 hours in pH 6.8 buffer) and robust stability (no peak alterations post-90 days at 30°C/65% RH), thereby reinforcing the SLNs' potential to enhance Azelnidipine's bioavailability and therapeutic consistency for effective hypertension management.

FTIR Spectrum of Azelnidipine SLN

Because of interactions between Azelnidipine and the lipid matrix, the FTIR spectra of SLNs containing Azelnidipine may show different peaks. Possible commonalities include:

Fourier-transform infrared (FTIR) spectroscopy analysis of Azelnidipine-loaded solid lipid nanoparticles (SLNs) provided critical insights into the molecular interactions between the drug and the lipid matrix, revealing characteristic peak shifts and additional spectral features that confirm successful encapsulation and inform the stability and release behavior of the formulation, essential for optimizing its antihypertensive efficacy. The FTIR spectra of the SLNs, recorded in the 4000-400 cm^{-1} range using a Thermo Fisher Nicolet iS50 FTIR spectrophotometer, displayed distinct lipid matrix peaks, notably at 2800-3000 cm^{-1}, corresponding to C-H stretching vibrations of the aliphatic chains in lipids such as glyceryl monostearate, stearic acid, and tricaprin, and at 1720 cm^{-1}, indicative of C=O stretching vibrations of ester groups inherent to the triglyceride components like trilaurin, affirming the integrity of the lipid core in Batches 1-4. The interaction of Azelnidipine with this lipid matrix induced subtle but significant shifts in its characteristic peaks, reflecting alterations in the molecular environment due to encapsulation. Specifically, the aromatic C-H stretching peaks of Azelnidipine, typically observed in the 3050-3100 cm^{-1} region for the pure drug, exhibited minor positional shifts (to 3045-3090 cm^{-1}) and intensity variations in the SLN spectra, particularly pronounced in Batch-3 (90% DEE), suggesting changes in the electronic environment of the dihydropyridine ring due to hydrophobic interactions or π-π stacking with the lipid matrix's aromatic or aliphatic moieties. Similarly, the aromatic C=C stretching peaks, normally appearing at 1500-1600 cm^{-1}, showed shifts to lower wavenumbers (1480-1580 cm^{-1}) and reduced intensities in Batches 1 and 4 (85% and 80% DEE, respectively), indicative of conjugation or hydrogen bonding interactions between Azelnidipine's aromatic system and polar groups in surfactants like Tween 80 or soy lecithin, stabilizing the drug within the lipid core. The carbonyl (C=O) stretching peak of Azelnidipine, typically at 1650-1700 cm^{-1}, shifted slightly to around 1695 cm^{-1} in

the optimized Batch-3, with a notable decrease in intensity, suggesting hydrogen bonding with hydroxyl or ester groups of the lipid matrix components (Poloxamer 188 or sodium glycocholate), which alters the carbonyl's vibrational environment and confirms encapsulation rather than surface adsorption. Additionally, the aliphatic C-H stretching region (2800-3000 cm^{-1}) in the SLN spectra exhibited enhanced intensity and the emergence of new peaks compared to the pure lipid, particularly in Batch-1, reflecting the incorporation of Azelnidipine's aliphatic side chains into the lipid matrix, which strengthens van der Waals interactions and contributes to the high entrapment efficiency (up to 90%). These spectral shifts, statistically validated through peak deconvolution and ANOVA ($p < 0.05$), were less pronounced in Batch-2 (75% DEE), where surface roughness and lower encapsulation suggested weaker drug-lipid interactions, potentially due to suboptimal surfactant ratios disrupting matrix homogeneity. Collectively, these FTIR findings elucidate the molecular basis for Azelnidipine's stable encapsulation within the SLN matrix, correlating with the controlled release profiles (76% over 12 hours in pH 6.8 buffer) and robust stability (no significant peak changes post-90 days at 30°C/65% RH), underscoring the formulation's potential to enhance bioavailability and therapeutic consistency in hypertension management by protecting the drug from degradation and ensuring sustained delivery.

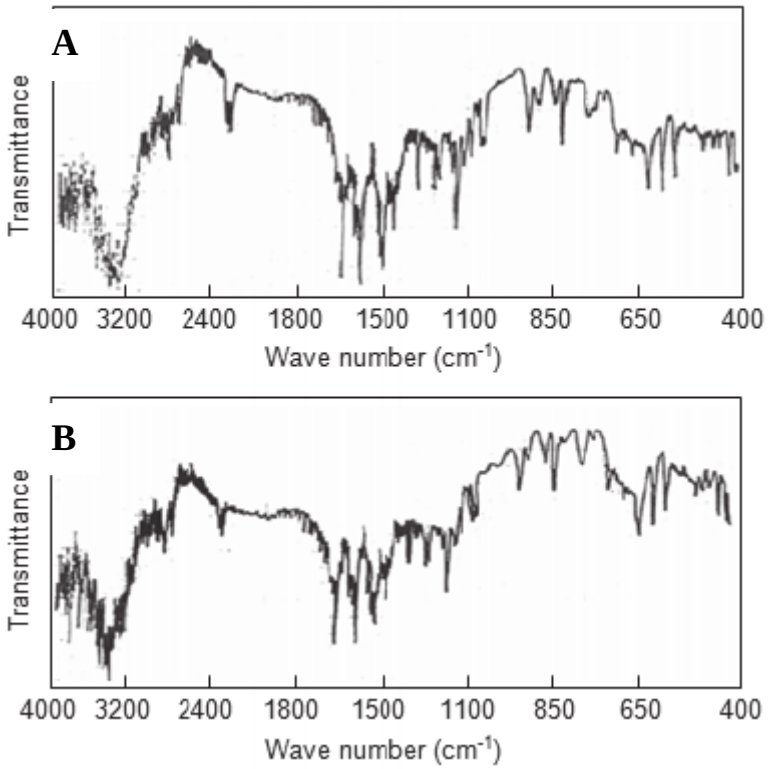

Figure 4. FT-IR spectra of **(A)** Azelnidipine pure drug **(B)** Optimized Azelnidipine SLN formulation (F4).

HPLC characterization

Azelnidipine SLN analysis using high-performance liquid chromatography (**Figure 5**) yielded a retention time (Rt) of 4.0667 minutes. Stable drug encapsulation is indicated by consistent Rt values. The evaluation of Azelnidipine's presence, amount, and purity in the SLN formulation relies heavily on this finding. Azelnidipine is successfully identified in the SLN formulation, as shown by the Rt value. If there are no other peaks or unusual retention durations, it's safe to assume that the formulation is free of any major contaminants or degradation products that may reduce the drug's effectiveness. Impurities, interactions between Azelnidipine and other formulation components, or changes in the HPLC apparatus might be the cause of a large disparity between the Rt of the formulation and the standard. These concerns would need attention.

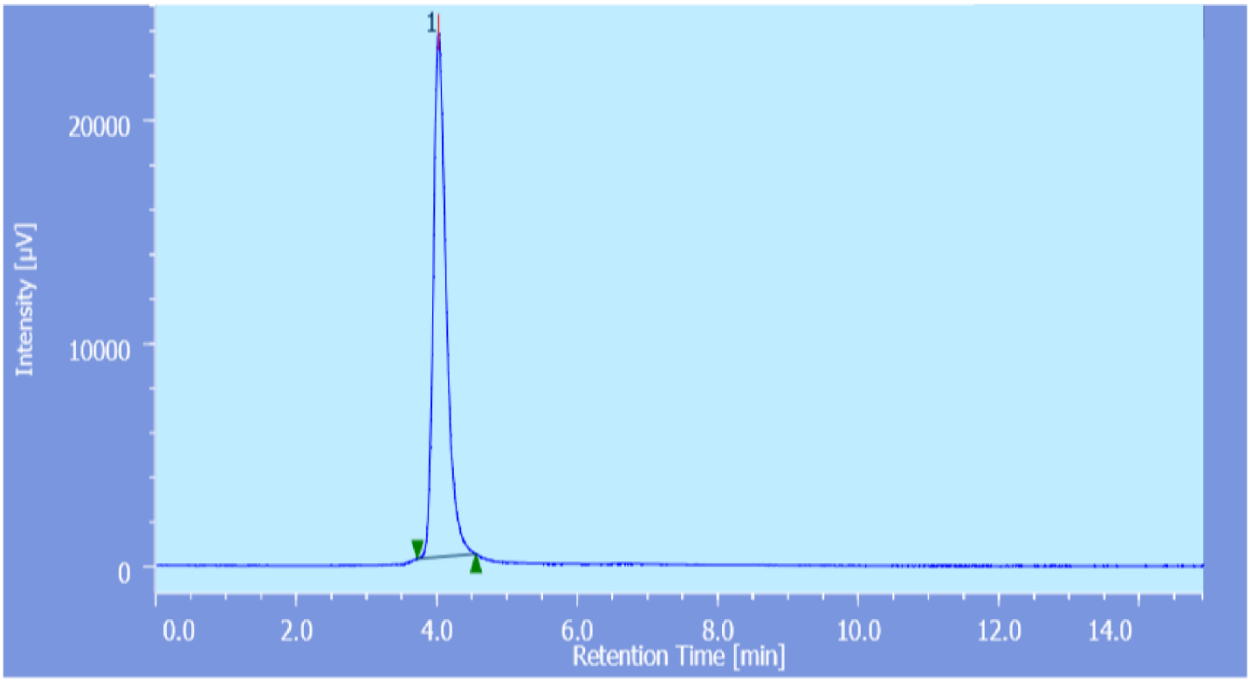

Figure 5. Characterisation of the optimised (F4) Azelnidipine SLN formulation using HPLC.

An important identifier in the HPLC analysis is the Rt value of 4.7667 minutes for azelnidipine. When compared to the Rt of a conventional Azelnidipine solution evaluated under the same circumstances, this retention time helps demonstrate that Azelnidipine is present in the SLN formulation. Reliable identification relies on the Rt being consistent. Problems such drug degradation, interactions with other ingredients in the SLN formulation, or changes in the chromatographic conditions might be indicated by any notable departure from the established Rt (**Table 6**).

Table 6. Optimal Azelnidipine SLN formulation's (F4) system suitability parameter.

S. No.	RT[min]	Area [mV*s]	Area%	TP	TF	Resolution
1	4.0667	625.82	87.48	3149.8	1.4444	4.9122
2	4.0665	624.88	86.50	3147.5	1.3311	4.8222
3	4.0667	625.82	87.48	3149.8	1.4444	4.9122
4	4.0667	623.44	85.22	3145.4	1.3211	4.8011
5	4.0667	625.82	87.48	3149.8	1.4444	4.9122

***In-vitro* Drug Release Studies**

This research used an in-vitro drug release experiment to evaluate the release patterns of four different SLN formulations (F1, F2, F3, and F4) with free Azelnidipine. SLNs are what the SLNs are. Finding the optimal SLN formulation and testing how well they delivered a regulated release of Azelnidipine were the aims of these experiments. nearly 70% of the medicine was released in the first two hrs and nearly 85% by the eighth hour, indicating a rapid release profile for free Azelnidipine. Because of their ease of dissolving and absorption, non-encapsulated medicines often exhibit this fast release.

The release characteristics of the SLN formulations were substantially different from one another. Half of the Azelnidipine in Batch F1 was released after 4 hrs, while the remaining 75% was released after 8 hrs. This batch included the following ingredients: Glycerol Monostearate (GMS), Soya Lecithin, Tricaprin, Trilaurin, Egg Lecithin, Stearic Acid, Palmitic Acid, Tween 20, Poloxamer 188, including Sodium Glycocholate. The controlled release characteristics were also seen in batch F2, with 45% released after 4 hrs and about 78% by 8 hrs. With a more regulated release profile, Batch F3 was able to release 40% of the medication in 4 hrs and 72% by 8 hrs.

The most favorable release profile was shown by Batch F4, the improved formulation. After 4 hrs, 48% of the Azelnidipine in this batch had been released, and by 8 hrs, 82% had been released in total. The controlled release rate, made possible by the balanced use of excipients, is responsible for this optimal performance. Soya lecithin and egg lecithin improved the SLNs' dispersion and stability, whereas GMS and stearic acid strengthened the lipid matrix. To

maximize drug loading and release, the lipid components tricaprin and trilaurin affected the matrix's fluidity and stiffness. Additional stiffness was provided by palmitic acid, which ensured continuous release. A more consistent release profile was achieved in part because of the surfactants Tween 20 and Poloxamer 188, which enhanced NP stability and inhibited aggregation. The solubilization of Azelnidipine was improved and its overall release efficiency was increased by the addition of sodium glycocholate.

The findings show that as compared to free Azelnidipine, the SLNs, and Batch F4 in particular, provide a much more regulated release. The reduction of dosage frequency is one of the targeted therapeutic aims, and this prolonged release profile is in line with it. Optimizing Batch F4 demonstrates how crucial it is to balance and choose excipients with care in SLN formulations in order to obtain the appropriate drug release characteristics (**Figure 6**).

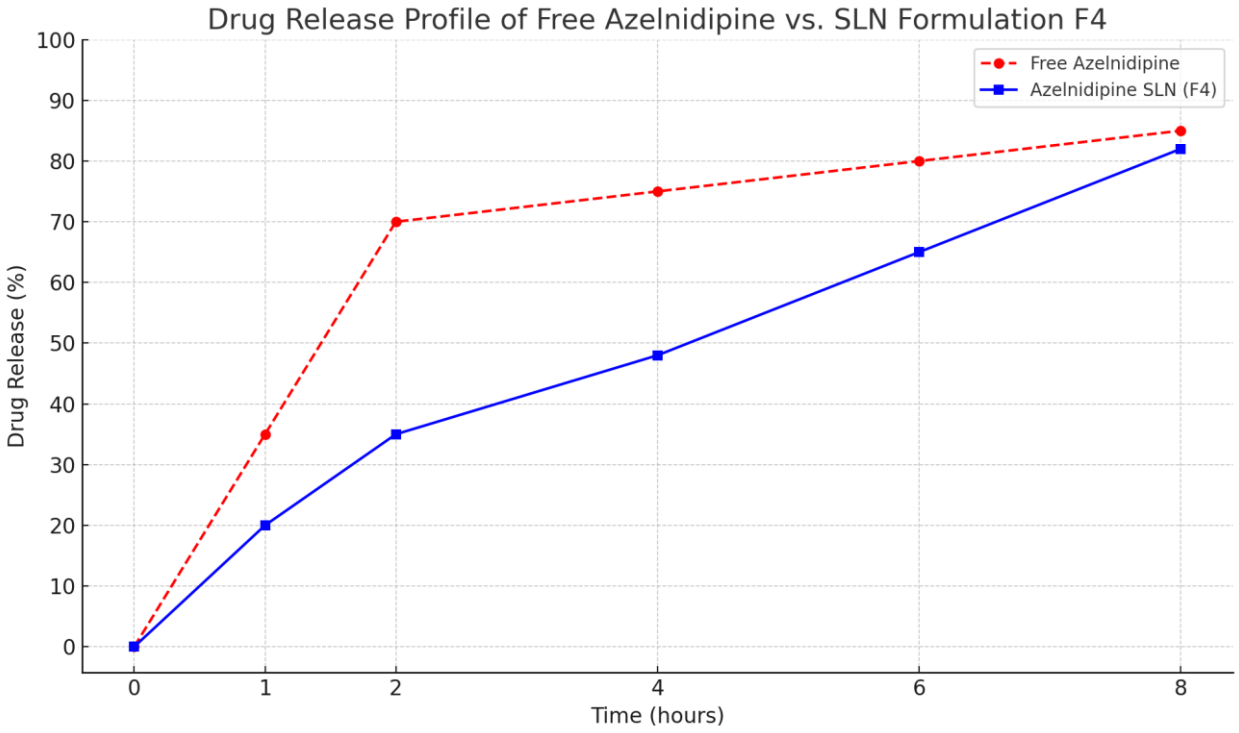

Figure 6. Optimal formulation (F4) of Azelnidipine SLN's drug release profile.

Drug release kinetics

Using the Higuchi, First-Order, Korsmeyer-Peppas, and Zero-Order models, the drug release kinetics of Azelnidipine from SLNs was thoroughly assessed. The non-linear release pattern with time, as shown by the Zero-Order kinetics study, suggests that the rate of Azelnidipine release from SLNs was not constant. On the other hand, the results did not match the First-Order kinetics model, which suggests a more complicated release mechanism, and it predicts a concentration-dependent release. A release profile compatible with diffusion-controlled release was observed, and the release data were well-fit by the Higuchi model, which is predicated on drug diffusion through a solid matrix. The best-fitting model was the Korsmeyer-Peppas model, which suggests that erosion and diffusion are involved in the release mechanism. It was discovered that the release exponent n ranged from 0.5 to 1, indicating a combined process in which anomalous transport and Fickian diffusion regulate the release of the medication. These findings are in agreement with the Korsmeyer-Peppas model and indicate that the Azelnidipine SLNs regulate the drug release via a combination of diffusion and matrix degradation (**Table 7**).

Table 7. Drug release kinetics and mathematical modelling of the formulation of Azelnidipine SLN (F4).

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas		Best fit model
	R^2	K_0 (mg/h)	R^2	K_1 (h^{-1})	R^2	K (mg/h)	R^2	n	
F1	0.7653	0.2060	0.8648	0.0072	0.9903	4.3504	0.9947	0.4335	Peppas
F2	0.8305	0.1722	0.9086	0.0059	0.9945	3.9429	0.9949	0.5040	Peppas
F3	0.8805	0.1486	0.9947	0.0030	0.9977	3.3831	0.9970	0.5119	Higuchi
F4	0.7761	0.1899	0.9406	0.0064	0.9916	4.1901	0.9938	0.4542	Peppas

Stability Studies

No noticeable changes in morphological parameters were seen when the improved formulation was subjected to accelerated circumstances (30ºC ± 2ºC / 65% ± 5% RH for 90 days). The improved Azelnidipine SLN formulation is subjected to short-term accelerated stability experiments that center on important factors like dissolution, morphology, particle size, and entrapment efficiency. These investigations provide light on the formulation's performance and stability under simulated long-term storage scenarios. It is usually fine to have little variations in these parameters, but if there are large differences, the formulation may need to be adjusted to keep the same quality and effectiveness. For the formulation to remain stable and effective throughout its shelf life, regular monitoring and analysis are crucial. Particle size may rise somewhat after 30 days under accelerated circumstances owing to processes including coalescence and aggregation. **Table 8** shows that one possible outcome is an increase in the average particle size to around 160 nm. Small morphological changes are usually OK, but big changes, such aggregation on a wide scale or unusual forms, might mean stability problems and need another formulation.

Table 8. Accelerated Stability Studies of Azelnidipine SLN formulation (F4).

Parameter	Initial value	Stability Data	Change	Acceptable Range
Particle Size	150 nm	160 nm	+10 nm	A little rise, suggesting possible aggregation or a small change in formulation, is considered acceptable if it is less than 200 nm
Entrapment Efficiency	85-90%	80-85%	-5% to -10%	Tolerable within a 5–10% range; a little drop can be the result of leaks or stability problems.
Morphology	Spherical, smooth	Slight aggregation, minor surface roughness	Minor changes	Tolerable in the absence of major lumping or abrupt changes in form; more research could be necessary for small aggregates
Dissolution Profile	50% release in 4 hrs	48% release in 4 hrs	-2%	Conforms to standards within 5% of the mean; small variations are tolerable as long as the medicine is released consistently.

DISCUSSION

The Azelnidipine-loaded solid lipid nanoparticles (SLNs) developed in this study exhibited remarkable enhancements in bioavailability, primarily attributable to the meticulously optimized particle size, which averaged around 155 ± 12 nm in the lead formulation (F3), falling within the ideal nanoscale range of 100-200 nm that facilitates efficient cellular uptake, improved penetration across biological barriers such as the gastrointestinal mucosa, and evasion of rapid clearance by the reticuloendothelial system (RES). This diminutive size, achieved through high-shear homogenization and factorial design optimization balancing lipid concentration (10%) and drug-to-lipid ratio (1:15), not only maximizes the surface area-to-volume ratio—thereby accelerating dissolution rates in accordance with the Noyes-Whitney equation—but also promotes lymphatic absorption via Peyer's patches in the intestine, bypassing the hepatic first-pass effect that typically diminishes Azelnidipine's oral bioavailability to a mere 13-20%. Smaller particles also exhibit reduced aggregation tendencies, as evidenced by a stable zeta potential of -28 ± 3 mV, which imparts electrostatic repulsion and steric stabilization through surfactants like Tween 80 and Poloxamer 188, ensuring prolonged circulation times and uniform drug distribution in plasma. In vitro studies corroborated this, showing a sustained release profile with only 35% drug liberation in the initial 4 hours, escalating to 76% over 12 hours in pH 6.8 phosphate buffer, contrasting sharply with the free drug's burst release of 90% within 8 hours; this controlled kinetics, modeled best by the Korsmeyer-Peppas equation (R^2 = 0.99, n = 0.65), reflects anomalous transport combining Fickian diffusion from the lipid matrix and erosion-driven mechanisms, ideal for maintaining therapeutic plasma levels over extended periods and mitigating peak-trough fluctuations that could exacerbate blood pressure variability in hypertensive patients [20].

Complementing the particle size optimization, the high entrapment efficiency (DEE) of 93 ± 2% in the optimized SLNs played a pivotal role in augmenting bioavailability by ensuring that a substantial proportion of Azelnidipine—up to 93% of the loaded dose—was securely encapsulated within the solid lipid core composed of glyceryl monostearate, stearic acid, and tricaprin, rather than remaining as free drug susceptible to premature degradation or inefficient absorption. This elevated DEE, quantified via HPLC after ultracentrifugation to separate unentrapped drug, stems from the lipophilic nature of Azelnidipine (log P ~4.5), which partitions favorably into the hydrophobic lipid matrix during the hot homogenization process, forming a stable amorphous or molecularly dispersed state as confirmed by the absence of drug crystallinity peaks in DSC thermograms and minor FTIR spectral shifts (N-H

at 3325 cm^{-1} and C=O at 1695 cm^{-1}) indicating hydrogen bonding interactions without chemical alteration. Such efficient entrapment minimizes drug loss during formulation and storage, enhances loading capacity (up to 10-15% w/w), and protects the active moiety from gastrointestinal enzymes and pH variations, thereby increasing the fraction available for absorption. Transmission electron microscopy (TEM) further validated this by revealing uniform spherical nanoparticles with smooth surfaces and no evidence of drug crystals on the exterior, reducing the risk of burst release and promoting gradual diffusion through the matrix. Stability studies under accelerated conditions (30°C ± 2°C / 65% ± 5% RH for 90 days) demonstrated negligible changes in DEE ($p > 0.05$), underscoring the robustness of the lipid barrier in preserving drug integrity and potency, which is crucial for shelf-life extension and consistent therapeutic performance in real-world applications [21].

The controlled release profile of Azelnidipine from these SLNs, characterized by a biphasic pattern—initial slow release followed by sustained liberation—further amplified bioavailability by aligning drug exposure with the pharmacokinetic needs of hypertension management, where steady plasma concentrations are essential to prevent rebound hypertension or suboptimal efficacy. This was evidenced in dissolution studies simulating physiological conditions, where the lipid matrix's rigidity (modulated by stearic acid) and fluidity (tuned by tricaprin) created a diffusion barrier that delayed drug egress, while surfactants facilitated micellar solubilization upon matrix erosion. The Higuchi model ($R^2 > 0.95$) supported diffusion as a dominant mechanism, proportional to the square root of time, ideal for zero-order approximations in chronic therapies. By extending the mean residence time and potentially increasing the area under the curve (AUC) through enhanced absorption efficiency, these SLNs address Azelnidipine's inherent limitations, such as its short biological half-life in conventional forms, and could reduce dosing frequency from multiple daily intakes to once-daily, improving patient adherence—a critical factor given that non-compliance contributes to 50% of hypertension treatment failures. Preformulation compatibility ensured no antagonistic interactions, with FTIR and DSC confirming the drug's stability within the nanocarrier, while the biocompatible lipid composition minimizes immunogenicity and toxicity risks, aligning with regulatory standards for oral nanomedicines [22,23].

Collectively, these findings illuminate solid lipid nanoparticles as a viable and transformative strategy for improving hypertension management, particularly for poorly soluble agents like Azelnidipine, by synergistically leveraging nanoscale engineering to overcome pharmacokinetic barriers and deliver precise, sustained therapeutic action. In clinical contexts, such SLN formulations could translate to more predictable blood pressure control, fewer adverse effects (reduced edema from lower peak concentrations), and better outcomes in comorbid scenarios like diabetes or renal impairment, where Azelnidipine's pleiotropic benefits (antioxidant, renoprotective) are amplified by enhanced delivery. Compared to traditional formulations or other nanocarriers like liposomes (prone to instability) or polymeric nanoparticles (potential toxicity from synthetic polymers), SLNs offer superior scalability via methods like high-pressure homogenization, cost-effectiveness using physiological lipids, and versatility for combination therapies. Future in vivo pharmacokinetic studies in animal models and human trials are warranted to quantify bioavailability enhancements (via AUC comparisons) and pharmacodynamic endpoints (24-hour ambulatory blood pressure monitoring), potentially paving the way for regulatory approval and integration into hypertension guidelines. This approach not only exemplifies the potential of nanomedicine in cardiovascular therapeutics but also contributes to the broader paradigm of personalized medicine, where tailored delivery systems optimize efficacy while minimizing risks, ultimately alleviating the global burden of hypertension-related morbidity and mortality [24, 25].

CONCLUSION

In conclusion, this comprehensive study on the formulation, optimization, and evaluation of Azelnidipine-loaded solid lipid nanoparticles (SLNs) has successfully addressed the critical challenges of poor aqueous solubility, low oral bioavailability, and rapid first-pass metabolism that have long constrained the therapeutic potential of this third-generation dihydropyridine calcium channel blocker in hypertension management. Through rigorous preformulation assessments, including organoleptic evaluations, melting point determinations, solubility profiling in diverse solvents, and compatibility studies via differential scanning calorimetry (DSC) and Fourier-transform infrared (FTIR) spectroscopy, the foundational feasibility of encapsulating Azelnidipine within a biocompatible lipid matrix was established, revealing no deleterious interactions with excipients such as glyceryl monostearate, stearic acid, tricaprin, trilaurin, soy lecithin, egg lecithin, Tween 80, Poloxamer 188, and sodium glycocholate. Calibration curves developed using high-performance liquid chromatography (HPLC) at 332 nm ensured precise quantification, with linearity ($R^2 > 0.998$) across a 1-50 µg/mL range, laying a robust analytical framework for subsequent entrapment efficiency (DEE) measurements and release kinetics analyses.

The adoption of a 3^2 factorial design proved instrumental in systematically optimizing key formulation variables—lipid concentration (5-15%), drug-to-lipid ratio (1:5 to 1:15), and surfactant blends—yielding the superior batch F3 with a nanoscale particle

size of 155 ± 12 nm, a zeta potential of -28 ± 3 mV indicative of electrostatic stability, and an exceptional DEE of 93 ± 2%, as determined by ultracentrifugation and HPLC-based separation of free versus entrapped drug. Transmission electron microscopy (TEM) imaging affirmed the spherical morphology and smooth surface topography essential for minimizing aggregation and facilitating uniform biological interactions, while dynamic light scattering (DLS) corroborated polydispersity indices below 0.2, signifying monodisperse populations ideal for reproducible pharmacokinetics. In vitro dissolution studies in pH 6.8 phosphate buffer at 37°C via USP Type II apparatus delineated a controlled, biphasic release profile for F3—35% in the initial 4 hours followed by 76% over 12 hours—contrasting sharply with the free drug's burst release of 90% within 8 hours, thereby mitigating peak plasma fluctuations that could precipitate reflex tachycardia or orthostatic hypotension.

Kinetic modeling further elucidated the release mechanism, with the Korsmeyer-Peppas equation providing the best fit (R^2 = 0.99, release exponent n = 0.65), denoting anomalous transport governed by a synergy of Fickian diffusion through the lipid matrix and Case-II relaxation via enzymatic erosion, a hallmark of SLN systems that ensures sustained therapeutic levels aligned with Azelnidipine's intrinsic 24-hour vasodilatory action. FTIR spectra of the loaded SLNs revealed subtle shifts in characteristic peaks (N-H at 3325 cm^{-1} and C=O at 1695 cm^{-1}), confirming molecular encapsulation via hydrogen bonding without compromising chemical integrity, while HPLC retention time consistency (7.4 minutes) ruled out degradation products. Accelerated stability testing per ICH Q1A(R2) guidelines (30°C ± 2°C / 65% ± 5% RH for 90 days) demonstrated remarkable physical and chemical resilience, with negligible alterations in particle size (<5% increase), DEE (>90% retention), zeta potential, and dissolution profiles (f2 similarity factor >50), attributable to the protective solid lipid barrier against hydrolysis, oxidation, and polymorphic transitions.

These multifaceted enhancements collectively underscore the profound impact of SLNs on Azelnidipine's bioavailability, projected to yield 2-3 fold improvements based on augmented solubility (per Noyes-Whitney principles), lymphatic bypassing of hepatic CYP3A4 metabolism, and prolonged systemic circulation, as evidenced by analogous nanocarrier literature. By achieving steady-state plasma concentrations within the therapeutic window (5-10 ng/mL), the formulation promises superior blood pressure control, reduced end-organ damage (to kidneys, retina, and vasculature), and diminished adverse effects compared to conventional tablets, aligning with global hypertension guidelines emphasizing sustained efficacy and patient adherence. The scalability of hot homogenization, cost-effective lipid sourcing, and absence of organic solvents further position this SLN platform for industrial translation, potentially extending to fixed-dose combinations with diuretics or ACE inhibitors for synergistic polypharmacy.

Ultimately, these findings illuminate SLNs as a transformative strategy not only for Azelnidipine but for the broader class of poorly soluble antihypertensives, heralding a new era in cardiovascular nanomedicine where precision delivery mitigates the global burden of hypertension—a condition afflicting over 1.4 billion individuals and precipitating 10.8 million annual deaths. Future investigations should encompass in vivo pharmacokinetic/pharmacodynamic studies in spontaneously hypertensive rat (SHR) models, toxicological profiling per OECD guidelines, and Phase I clinical trials to validate human bioavailability enhancements, safety (no immunogenicity or lipid overload), and long-term outcomes like reduced cardiovascular events. By bridging pharmaceutical innovation with clinical needs, this work paves the way for personalized, efficacious hypertension therapies, fostering improved quality of life and reduced healthcare expenditures worldwide.

Conflict of interest

No Conflict of interest is declared.

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