Ind. J. Pharm. Edu. Res., 2026; 60(1):114-123.
https://www.ijper.org

Original Article

Formulation Development and Evaluation of Self-Microemulsifying Drug Delivery System (SMEDDS) of Azelnidipine for Hypertension

Rutik Jukti[1], Abhishek Kanugo[1,2]*

[1]Department of Pharmaceutics, SVKM NMIMS School of Pharmacy and Technology Management, Shirpur, Maharashtra, INDIA.
[2]Department of Pharmaceutical Quality Assurance, SVKM NMIMS Global University, Dhule, Maharashtra, INDIA.

ABSTRACT

Introduction/Objectives: Azelnidipine is a novel calcium channel blocker usually recommended for the management of an upsurge in blood pressure. The beneficial activity is circumvented because of extreme lipophilicity (Log P: 5.14). The present investigation is dedicated to the expansion of solubility and dissolution of Azelnidipine by self-microemulsifying drug delivery. **Materials and Methods:** The estimation of solubility of Azelnidipine was checked in several oils, surfactants, and solvents. The inertness of actives with the formulation components was confirmed with FTIR. The pseudo-ternary phase diagram illustrated the microemulsion area. **Results:** The extreme solubility was noted with oleic acid (oil), Labrasol (surfactant), and PEG 400 (cosolvent). The developed SMEDDS was assessed for globule size, zeta potential, robustness dilution, polydispersity index, viscosity, and *in vitro* drug release. The best results were displayed by 1:9 oil to S_{mix} ratio with a globule size of 309 nm, zeta potential (-18.3 mV) and PDI (0.377), self-emulsification time (30 sec), drug content (98%) and released within 25 min. The uniformity in globule size and spherical nature was confirmed by Transmission electron microscopy. **Conclusion:** The results conclude that a mark rise in the solubility, and dissolution rate of Azelnidipine was accomplished with the SMEDDS for their enhanced therapeutic benefits.

Keywords: SMEDDS, Azelnidipine, Hypertension, Microemulsion, Ternary Phase diagram.

Correspondence:
Dr. Abhishek Kanugo
Associate Professor, Department of Pharmaceutical Quality Assurance, SVKM NMIMS Global University, Dhule-424001, Maharashtra, INDIA.
Email: abhi.kanugo09@gmail.com

Received: 02-04-2025;
Revised: 28-05-2025;
Accepted: 16-07-2025.

INTRODUCTION

Azelnidipine (AZN) is an antihypertensive agent that belongs to the chemical class of dihydropyridine Calcium Channel Blocker (CCB) and is advised for the treatment of an exciting rise in blood pressure and other cardiovascular complications.[1] AZN is preferred over former CCB agents which diminishes the blood pressure with marginal rising heart rate. AZN is a highly lipophilic compound characterized by its log P value of 5.12 and practically insoluble in water (0.00082 mg/mL).[2] Hence, the therapeutic effectiveness of AZN is circumscribed due to their greater hydrophobic behavior. The current research focused on enhancing the solubility, and dissolution rate and thereby hastening the absorption, bioavailability, and therapeutic efficacy of AZN by developing microemulsion.

The Cardiovascular Disorders (CVDs) are the foremost reason for mortality globally. The high mortality rate is credited to the nonexistence of any indication or symptoms exposed by the body and hence recognized as a silent killer. The stated mortality rate is greater than 12.8% covering 7.5 million people in the world. In the last decade, the mortality rate has doubled affecting the age of 18-70 years' people.[3] The enormous surge in Cardiovascular Diseases (CVD) observed suddenly throughout the COVID-19 pandemic and post-pandemic also. Hypertension is not only affecting the heart but also the major organs of the body such as the brain, kidneys, and liver, etc.[4] The remarkable reasons for CVD are mainly genetic, age-related, obesity, unhealthy diet, and lifestyle, absence of physical exercise, kidney diseases, and diabetic conditions, etc.[5,6]

The highly acceptable, comfortable, and most convenient dosage form is oral drug delivery. The control solubility and dissolution rate of the active ingredient showed minimal therapeutic efficacy. Hence, to resolve this issue the improvement in the solubility and dissolution rate in the GIT seems a prime requirement for oral drug delivery. The active ingredient should have enough potential to cross through the GI barrier which is lipophilic, hence clinical trials developed the molecules with the greater lipophilicity.[7,8]

The Self-Micro Emulsifying Drug Delivery System (SMEDDS) overcomes the restrictions of oral drug delivery by augmenting

DOI: 10.5530/ijper.20266497

the solubility, dissolution rate, penetrability, and bioavailability of the active ingredients.[9,10] This is a lipid-based system comprised of an isotropic combination of three components namely oil, surfactant, and cosolvent.[11] The resultant mixture further developed into the microemulsion instantly upon exposure to the gastrointestinal fluids. The tiny globule size of these microemulsions generated a large surface area which favors the process of absorption.[12] Furthermore, SMEDDS is gaining popularity for accelerating permeability and imparting lymphatic circulation as well as suppressing the p-glycoprotein efflux transporters.[13] Thus, microemulsions possess significant stability comparatively with the conventional emulsion and other oral drug delivery systems.[14,15]

Another advantage associated with the microemulsion is the protection of the active ingredient from the enzymatic hydrolysis. The microemulsion showed greater encapsulation efficiency, less viscous, and was capable of loading macromolecules, proteins, peptides, and other category molecules.[16] The microemulsion comprised of oil/water, water/oil, or multiple emulsions. The notable mechanism identified with the microemulsion is capability of minimizing the surface tension between the oil and water comparatively with the individual oil and water molecules. The o/w type of microemulsion showed greater aqueous solubility than others due to the rapid penetration capability through the mucus membrane of the GIT.[17,18]

MATERIALS AND METHODS

Azelnidipine was supplied from Ajanta Pharmaceuticals, Aurangabad. Tween 20, Tween 80, and Span 80, polyethylene glycol grades (200, and 400) were purchased from the Merck chemicals Mumbai. All other materials and the solvent utilized for the research work were of analytical grades only.

Selection of oil

The first criterion in the development of microemulsion was the selection of the most appropriate oil that solubilizes the active ingredient. The exceeded amount of AZN was dissolved in numerous oils, including oleic acid, castor oil, olive oil, and arachis oil to generate a supersaturated solution. The oil exhibiting the highest solubility was chosen for further investigation of saturation solubility. A surplus volume of AZN was mixed with oil and retained in a vial. The mixture was vigorously mixed using a cyclomixer and left undisturbed for approximately 24 hr. to achieve equilibrium. Subsequently, the resulting blend was imperiled to centrifugation at 5000 rpm for 10-15 min, after being kept at an orbital shaker for 72 hr and the clear solution was then appropriately diluted and investigated at 254 nm using a UV-visible spectrophotometer.[19,20]

Screening of surfactant and cosolvents

The second criterion was the selection of suitable surfactants and cosolvents which played a crucial role in achieving desirable emulsification properties. A proper amount of the active ingredient was mixed with the several surfactant and cosolvents followed by vortexing for about 24 hr. The mixture was then diluted and passed through a 0.45 µ filter. Finally, the absorbance was determined at 254 nm using a UV.[21,22]

Compatibility study

The powder sample of received AZN was identified using FTIR spectroscopy (Shimadzu Affinity 1-s) to confirm its presence. Further, compatibility studies were conducted to assess the interaction of AZN with selected oil, surfactant, and cosolvent.[23,24]

Creation of Pseudo Ternary Phase Diagram Study for Microemulsion (PTPDS)

It was developed by titrating oleic acid as the oil phase along with Labrasol and polyethylene glycol-400 (PEG-400) as the surfactant and cosurfactant to obtain a clear microemulsion. To generate the PTPD, the varying proportions of 1:1, 2:1, and 3:1 surfactant to cosolvent were selected. The selected mixtures of oil and surfactant mixtures were blended in the different ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 to achieve the maximum area of the ternary phase diagram. The objective was to establish the potential for self-emulsification,[25,26]

To evaluate the self-emulsifying capability, 1 g of the prepared blend was progressively titrated with deionized water, stirred gently, and observed for transparency. The transparency of the resulting emulsion indicated the capacity of the formulation to self-emulsify. The experimental data obtained from these observations were then utilized to create a TPD using Chemix software. The composition of SMEDDS-loaded AZN is depicted in Table 1.[27]

Evaluation of SMEDDS

Sturdiness to dilution

The developed microemulsion was thinned with DW, 0.1 N HCl, and phosphate buffers of pH 6.8 and 7.4. The dilutions were prepared at 50-, 100-, and 1000-proportions. Afterward, the diluted emulsions were set sidewise for around 24 hr. and visually inspected for the existence of any alterations, such as cloudiness, phase separation, or precipitation. The batch exhibiting a visually clear emulsion was preferred for further analysis and experimentation.[28,29]

Estimation of Globule Size (GS), and Polydispersity Index (PDI)

The formulations were diluted using deionized water and subjected to gentle agitation to achieve a clear and homogeneous dispersion. Subsequently, the droplet size and PDI were assessed

using a Zetasizer Nano ZS apparatus. The testers were placed inside a cuvette, which was positioned in a thermostatic chamber, and the scattering of light was recorded at a 90° angle at a temperature of 25°C.[30,31]

Emulsification time

A formulated emulsion, consisting of 1 g of substance, was introduced into 500 mL of 0.1 HCl at a temperature of 37°C while subjecting it to gradual agitation at a rate of 100 rpm. The duration required to achieve a visually transparent dispersion was recorded as the emulsification time.[32,33]

Determination of viscosity

The prepared batches of microemulsions were subsequently diluted using distilled water in beakers placed on a magnetic stirrer. The dilutions were carried out at dilution ratios of approximately 10-fold and 100-fold. The viscosity of these diluted samples was then measured using a Brookfield viscometer.[34]

Cloud point estimation

The microemulsion was diluted up to 250 mL and positioned in a water bath which raises the temperature gradually. The temperate at which there was initiation of cloud was noted.[35,36]

Transmission Electron Microscopy (TEM)

The surface characteristics of the improved microemulsion batch were assessed using TEM with an advanced microscope. A diluted sample of the optimized batch of microemulsion was applied to a film-coated 200-mesh gold specimen grid, and a negative staining technique was employed. The grid was then set aside for approximately 10 min. Subsequently, a drop of phosphotungstic acid was applied to the grid for staining, followed by drying. Finally, the grid was examined using electron microscopy for further analysis.[37,38]

In vitro dissolution studies

The microemulsion was investigated using a USP Type I dissolution machine. The apparatus comprised 900 mL of HCl with a pH of 1.2. The dissolution apparatus, equipped with a paddle, was set to rotate at a velocity of 100 rpm, and 37±0.5°C. To assess the release profile, aliquots of samples were withdrawn at 5-min intervals. Immediately after withdrawal, the dissolution level was replenished with phosphate buffer to ensure consistent conditions. The introverted fluids were diluted, and the absorbance was estimated at a wavelength of 254 nm using a UV-visible spectrophotometer.[39,40]

Thermodynamic Stability Studies (TST)

An optimized batch of SMEDDS formulation underwent stability testing, including centrifugation, heating-cooling cycles, and freeze-thaw cycles. In the centrifugation study, the formulation was diluted with distilled water (1:25) and centrifuged at 5000 rpm for 30 min. Visual examination was conducted to detect any signs of unsteadiness such as phase separation, creaming, or cracking. The sample was to heating-cooling cycles at 40°C and 4°C for 48 hr. to assess its stability. Additionally, an accelerated study was performed at -21°C and 25°C for 48 hr., tailed by examination for any instability. Shelf-life and degradation studies were conducted for the optimized batch.[41,42]

RESULTS AND DISCUSSION

Screening of oil

Among the several oils tested, oleic acid exhibited the highest solubility of AZN (61.92±0.11 mg/mL), trailed by olive oil (44.47±0.21 mg/mL), castor oil (37.69±0.45 mg/mL) and Arachis oil (23.52±0.37 mg/mL). Therefore, oleic acid was chosen as the most suitable oil for developing SMEDDS formulations.

Screening of surfactant and cosolvent

The highest solubility of AZN was found in the Labrasol and PEG 400 hence selected as the best surfactant and cosolvent correspondingly. The solubility of AZN among the several surfactants and cosolvent was found in the following order.

Labrasol > Tween 20> Tween 80> Span 20 > Span 80

PEG 400> PEG 200> PG> Methanol

Table 1: Composition of Azelnidipine SMEDDS.

Batch	Drug (mg)	Oil (% w/w)	Surfactant (% w/w)	Co-surfactant (% w/w)
A1	8	10	45	45
A2	8	20	40	40
A3	8	30	35	35
A4	8	40	30	30
A5	8	50	25	25
A6	8	60	20	20
A7	8	70	15	15
A8	8	80	10	10
A9	8	90	5	5

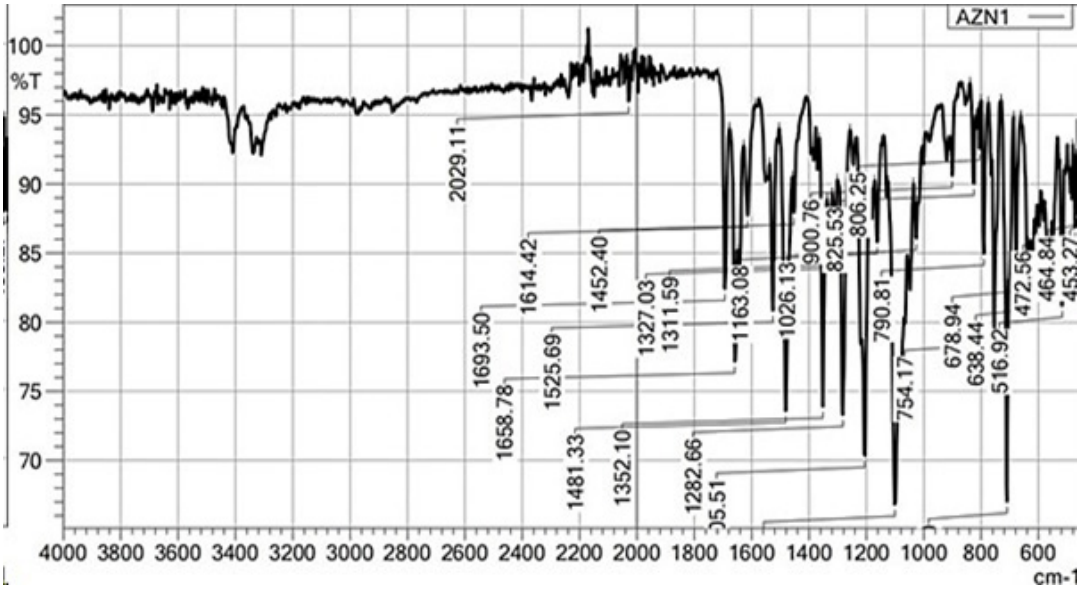

Figure 1: FTIR Spectra of Azelnidipine.

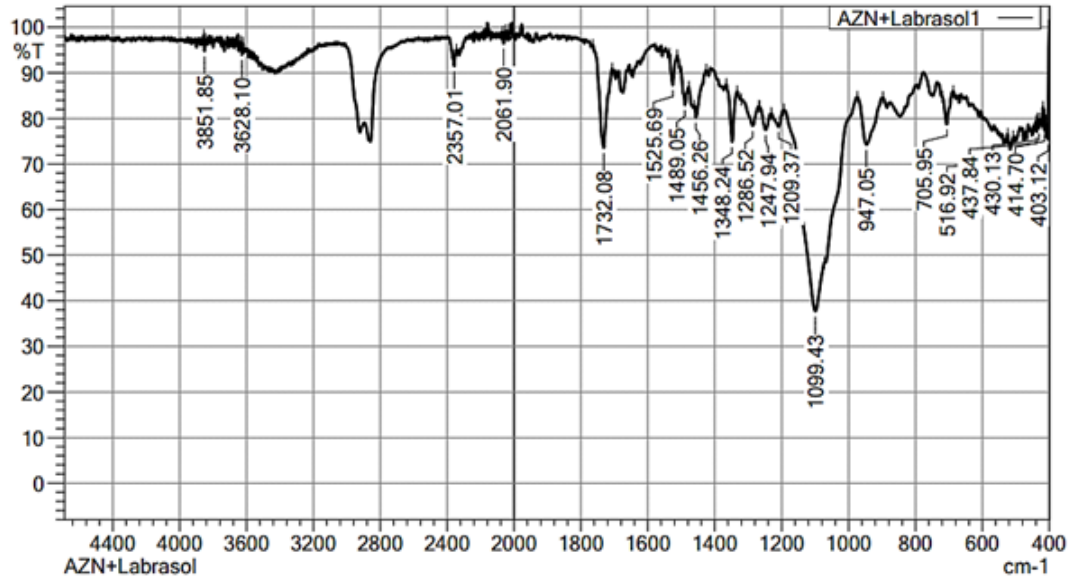

Figure 2: FTIR spectrum of AZN+Labrasol.

Compatibility studies

To assess the probability of interface amongst AZN and the excipients used, Fourier Transform Infra-Red Spectroscopy (FTIR) analysis was conducted. The FTIR spectra of pure AZN revealed specific peaks at 3267 cm-1 (carboxylic group), 2935 cm-1 (alkanes group stretching), 1724 cm-1 (carbonyl group stretching), 1292 cm-1 (amines stretching), and 1088 cm-1 (halogen group presence). The FTIR spectrum is displayed in Figures 1-4.

Creation of Pseudo Ternary Phase Diagram Study for Microemulsion (PTPDS)

Solubility analysis and emulsification potential were assessed to recognize the self-emulsification zone and regulate suitable proportions of oil, surfactant, and cosurfactant for the development of SMEDDS (Self-Microemulsifying Drug Delivery Systems). It is important to determine the optimal concentration of surfactant that can effectively emulsify the system without irritating. Various extents of components (oil, surfactant, co-surfactant mixture, and water) were evaluated for formulating 0.5% w/w AZN microemulsions. The pseudo ternary plot was showed in Figure 5.

Characterization of SMEDDS

Sturdiness to dilution

To assess the nonappearance of drug molecule precipitation at upper dilutions, which could disturb absorption. Multiple batches of SMEDDS (Self-Microemulsifying Drug Delivery Systems) were diluted in 0.1 N HCl and phosphate buffer (pH 6.8) to simulate *in vivo* conditions and confirm the uniformity of the micro-emulsions. Batch A1 exhibited clear solutions even after 50-, 100-, and 1000-fold dilutions.

Determination of Globule Size (GS), Zeta Potential (ZP), and Polydispersity Index (PDI)

The Zetasizer ZS Malvern instrument was employed to measure the average GS and PDI. A smaller globule size is desirable for enhancing drug diffusion and absorption, thereby increasing the interfacial area. This requirement holds for both nano and micro-sized globules in the progress of SMEDDS. The globule size assessed by the Malvern Zetasizer was observed in the series of 309 nm to 428 nm. The PDI of the microemulsion was series from 0.327 to 0. 425. The ZP was recorded in the series of -5 mV to - 30 mV.

Batch A1 exhibited a globule size of 309.3 nm, a zeta potential of -18.3 mV, and a Polydispersity Index (PDI) of 0.377. These favorable measurements led to the selection of batch A1 as the optimized batch. Additionally, a smaller PDI is crucial for achieving uniformity in globule size distribution during self-emulsification. Moreover, achieving ultrafine globule sizes is essential for maintaining kinetic stability, ensuring that the prepared microemulsions do not exhibit flocculation, coalescence, creaming, or phase separation. The PS, PDI, and ZP of an optimized batch was reflected in Figure 6.

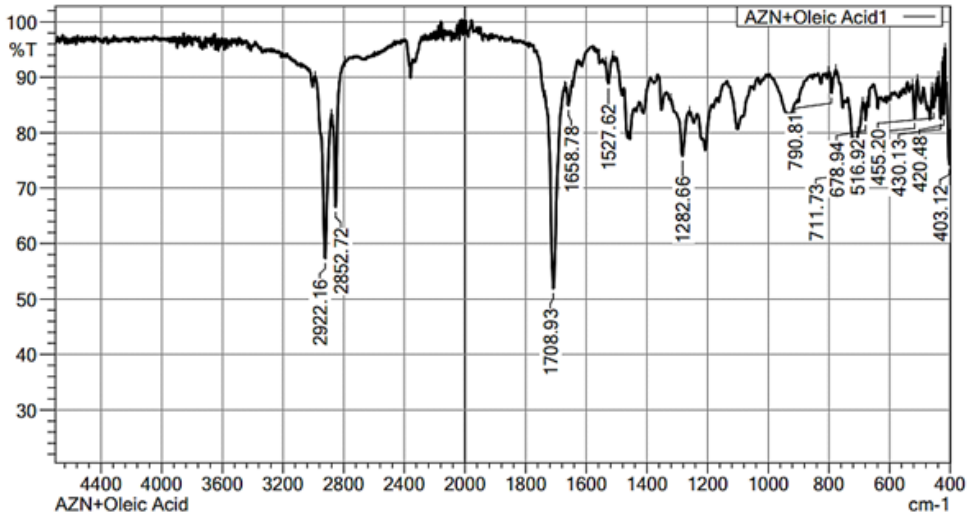

Figure 3: FTIR spectrum of AZN+Oleic acid.

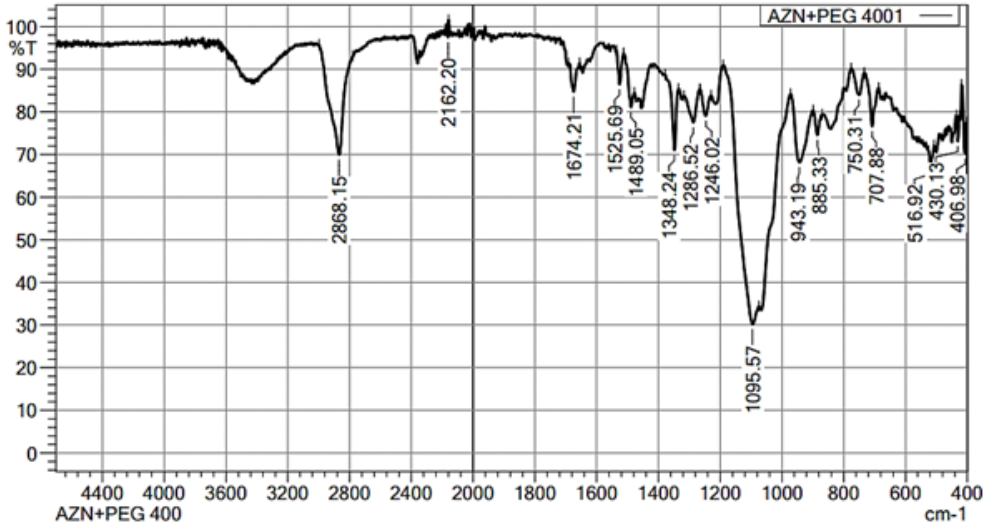

Figure 4: FTIR spectrum of AZN+PEG-400.

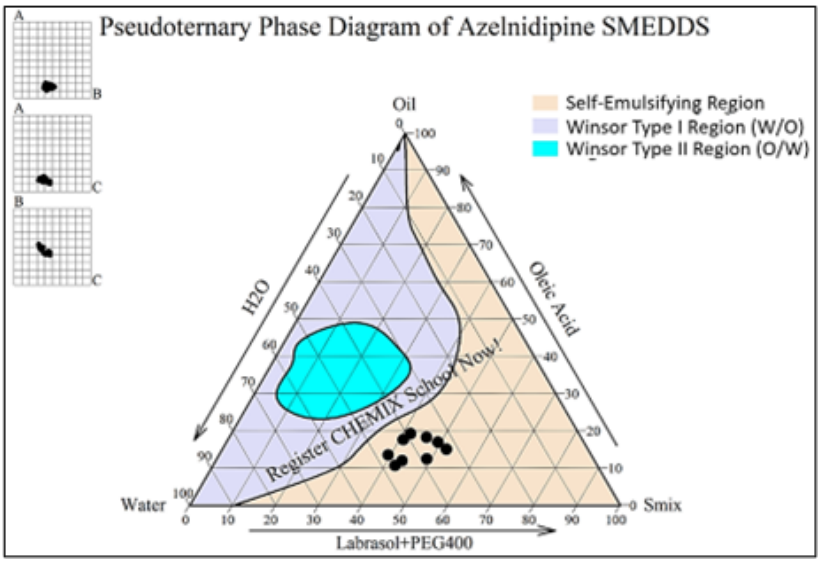

Figure 5: Pseudo ternary Phase Diagram of AZN SMEDDS.

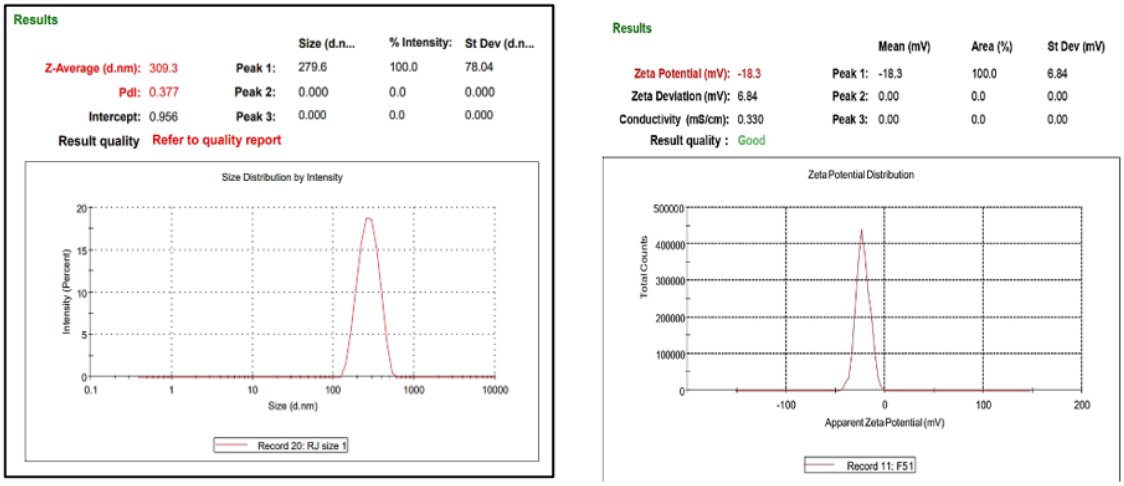

Figure 6: Particle size, PDI and ZP of optimized batch A1.

Emulsification time

The outcomes exposed the self-emulsification time of the L-SMEDDSs was in the range of 27 s to 40 s and the optimized batch showed the 30±0.22 s, indicating a rapid and efficient emulsification process.

Determination of viscosity

The results showed that the viscosity of L-SMEDDS was relatively high (120.31±0.11 cps), which could be accredited to the superior extent of surfactant and co-surfactant. During the preparation of L-SMEDDS, the ratio of oil and surfactant was preserved as 1:9, which resulted in an extraordinary concentration of surfactant and co-surfactant (90%).

Cloud point estimation

Among the 9 batches, 5 batches showed good stability, and cloud point was observed at 77°C to 81°C. Furthermore, few batches were found less stable, and cloud points were noted between 61 to 64°C.

TEM

The morphology of AZN L-SMEDDS was scrutinized using a TEM. The micro-emulsion exhibited a dark appearance with a bright surrounding, indicating a positive image. The droplet size of the sample was below 350 nm, and the droplets were observed to be circular. No coalescence or agglomerations were observed within the system. The TEM image is displayed in Figure 7.

In vitro dissolution studies

This is an essential aspect of evaluating the performance and quality of drug delivery systems. In this study, the *in vitro* dissolution behavior of Azelnidipine (AZN) loaded in L-SMEDDS was investigated in HCl buffer (pH 1.2). The results showed that the L-SMEDDS containing 10% oleic acid exhibited

a significantly higher release of AZN (99.25±0.26) within the first hour compared to the marketed tablet. The release pattern is shown in Figure 8.

Thermodynamic Stability Studies (TST)

The constancy of the ready SMEDDS was evaluated through centrifugation, heating-cooling, and freeze-thaw cycle studies. The developed microemulsion doesn't indicate phase separation and instability. The microemulsion retained its viscosity, pH, and emulsification characteristics.

DISCUSSION

The primary consideration in developing Self-Microemulsifying Drug Delivery Systems (SMEDDS) is selecting the appropriate oil based on the drug's characteristics. Other important factors include the oil's ability to solubilize the drug, promote effective emulsification, and prevent precipitation. To determine solubility characteristics, AZN was dissolved in various oils under standardized conditions. The superior solubility was showed in oleic acid, hence selected for the development of SMEDDS. The selection of a suitable surfactant is crucial in the prepared microemulsions which significantly minimizes interfacial tension and facilitates the rapid formation of microemulsions by establishing a film at the oil-water boundary. According to Bancroft's rule (Bancroft WD, 1913), emulsifiers with predominantly hydrophilic properties stabilize oil-in-water emulsions. Therefore, for the creation of oil-in-water microemulsions, surfactants with high Hydrophilic-Lipophilic Balance (HLB) values were considered. Accordingly, the highest solubility of AZN was attained in Labrasol and PEG 200.

The compatibility of AZN with formulation ingredients (oleic acid, Labrasol, and PEG 200) was analyzed by FTIR. Upon mixing AZN with oleic acid, Labrasol, and PEG-400, it was observed that the characteristic peaks of AZN remained unchanged. This indicates that the excipients used, as well as any other materials present, do not modify the position of the distinctive peaks of the drug, suggesting compatibility between the excipients and the drug.

The self-emulsifying zone, characterized by clear isotropic regions, was determined through optical observation. TPDS was created for different surfactant to co-surfactant ratios to identify and optimize o/w micro-emulsion regions. A surfactant-to-co-surfactant ratio of 5:1 exhibited a significant micro-emulsion area, indicating its potential for use in SMEDDS development.

To minimize gastrointestinal irritation, it was necessary to incorporate a co-surfactant with the surfactant in a ratio of 5:1. This resulted in the formation of a larger area of oil-in-water (o/w) micro-emulsion. This observation can be attributed to the improved permeation of the oil phase into the hydrophobic region of the surfactant monomers. Another contributing factor could be the increase in system entropy.

Upon rapid dilution, the L-SMEDDSs were observed as clear and bluish emulsions, which further confirms their efficient self-emulsification behavior. The L-SMEDDSs were graded as 'A' according to the visual grading system, indicating their high degree of spontaneity and emulsification efficiency. The emulsification time was found to be less than 1 min, suggesting

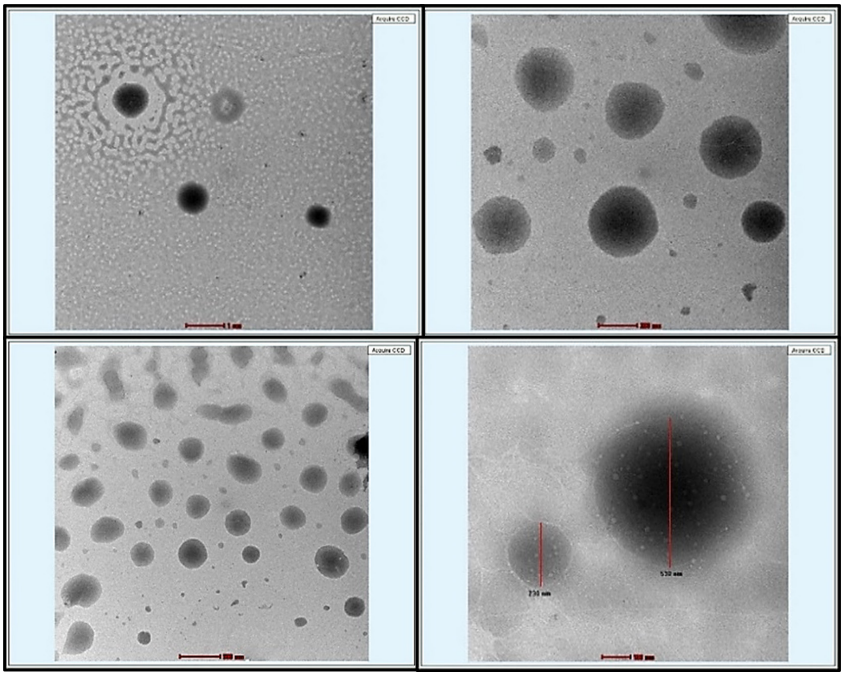

Figure 7: TEM Image Showing Quality of SMEDDS.

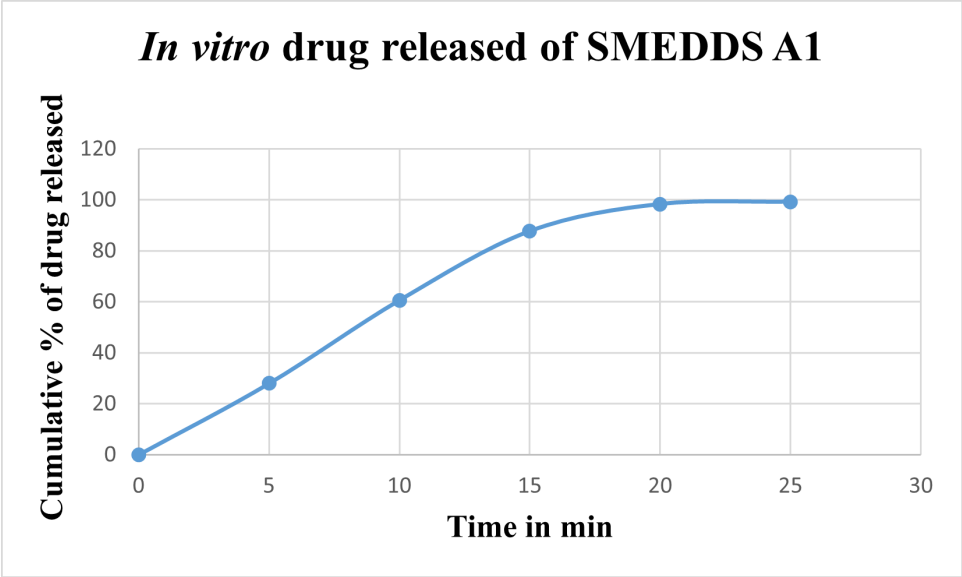

Figure 8: *In vitro* drug release profile of an optimized batch A1.

that the proportion of surfactant in the formulation was high, which promotes the spontaneity of emulsification.

The *in vitro* drug release studies indicated rapid discharge of actives from SMEDDS. These liquids quickly transform into microemulsions upon contact with the gastric fluids.[43] Hence, the release of medicament is much faster. The rapid release of 27.95% was attained after 5 min indicating the Azelnidipine showed excellent solubility in the preferred oil and S_{mix}. The oil (oleic acid), surfactant (Labrasol), and cosolvent (PEG 400) showed excellent solubilization of Azelnidipine.[44,45] The plain drug was also evaluated for its dissolution profile at the same media but active was precipitated and marginally soluble in the fluid due to high lipophilicity.[46,47]

The cumulative percentage of drugs released after 10 min was 60.57%. The highest drug release of 99.25% was achieved after 25 min and indicated that mark improvement in solubility and dissolution of Azelnidipine was attained with SMEDDS. One of the reasons for rapid drug release is the existence of small globule size of the emulsion which facilitates rapid dissolution.[48,49]

The marketed tablets of Azelnidipine were assessed for *in vitro* dissolution testing using similar conditions opted for the SMEDDS of Azelnidipine. The discharge of active ingredients from the marketed tablet is very slow and less after 5 min. The liquid SMEDDS released 27.95% of actives but the marketed tablet showed a cumulative drug release of only 9.38%. The 98.32% of active was liberated in 20 min from the liquid SMEDDS. After 20 min, the cumulative drug release was 54.89%. The maximum content was released after 25 min (99.25%) from the liquid SMEDDS but the marketed tablet took 45 min to dissolve entirely with a cumulative release of a maximum of 87.30%. hence, comparatively an optimized batch is much superior in availing greater bioavailability and therapeutic efficacy than a marketed formulation.

The assessed results of thermodynamic stability testing interpreted that the optimized SMEDDS has high stability. The microemulsion does not show any signs of drug precipitation, or phase separation. After centrifugation, the emulsion does not show any signs of separation. The emulsion has not shown creaming, cracking, flocculation, and phase inversion at various temperatures. Furthermore, the viscosity, pH, and globule size are marginally changed reflecting greater stability.

The enhanced early phase maximum release within one hour indicates the potential of L-SMEDDS in improving the solubility and bioavailability of AZN. These findings highlight the importance of L-SMEDDS as an auspicious system for augmenting the dissolution rate and enhancing the therapeutic efficacy of poorly soluble drugs like AZN. Overall, the research demonstrated cherished perceptions of the formulation optimization of L-SMEDDS for effective drug delivery applications.

CONCLUSION

SMEDDS is highly preferred over emulsion and conventional medications for offering multiple benefits and steadiness. These structures meaningfully expand the solubility, dissolution rate, absorption, and bioavailability of the hydrophobic moieties. Moreover, greater therapeutic benefits are achieved with these technologies. Among the numerous liquid vehicles, oleic acid, Labrasol, and PEG 400 showed marked improvement in the solubility of AZN. The desired globule size of 309 nm, PDI of 0.377, and ZP of -18.3 mV was attained. The microemulsion showed prompt dispersion when reacted with the gastric fluids.

The limitations of scalability and higher cost production of SMEDDS were overcome with the solidified SMEDDS.

ACKNOWLEDGEMENT

The authors are thankful to Ajanta Pharmaceutical for providing the gift sample of the drug. The authors are also thankful to the SVKM NMIMS SPTM Shirpur and SVKM NMIMS SPPSPTM Mumbai for providing the necessary research facilities for the completion of the work.

ABBREVIATIONS

AZN: Azelnidipine; **SMEDDS:** Self-Micro Emulsifying Drug Delivery System; **CCB:** Calcium channel blocker; **CVDs:** Cardiovascular disorders; **PTPD:** Pseudo ternary phase diagram system.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

The marked improvement in the solubility and dissolution rate was attained with the SMEDDS. The highly lipophilic molecule showed superior solubility in the oil (oleic acid), surfactant (Labrasol), and co-solvent (PEG 400). The preferred batch A1 indicated the desired lowest globule size of 309 nm, PDI of 0.377, and ZP (-18.3 mV). The microemulsion qualifies for entire evaluation parameters and observed stable. This batch is further recommended for the pilot plant transfer for the commercialization.

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Cite this article: Kanugo A. Formulation Development and Evaluation of Self-Microemulsifying Drug Delivery System (SMEDDS) of Azelnidipine for Hypertension. Indian J of Pharmaceutical Education and Research. 2025;60(1):114-23.