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Original Article

DESIGN, OPTIMIZATION AND CHARACTERIZATION OF AZELNIDIPINE LOADED SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM USING D-OPTIMAL MIXTURE DESIGN

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ABSTRACT

Objective: Azelnidipine (AZL), a biopharmaceutical classification system (BCS) class II calcium channel blocker, exhibits poor water solubility and limited oral bioavailability (22%) due to extensive first-pass metabolism. This study aimed to enhance its absorption by formulating it into a self micro-emulsifying drug delivery system (SMEDDS) and further converting it into a solid dosage form.

Methods: SMEDDS was developed using capmul MCMC8 (oil), transcutol HP (surfactant), and tween 80 (co-surfactant) depending on the results of solubility study. A ternary phase diagram identified the microemulsification region, while a D-optimal mixture design was used to optimize the formulation. Liquid SMEDDS was then converted into a solid powder using aeroperl 300 as adsorbing agent and ultimately converted into a tablet form.

Results: The optimized liquid SMEDDS exhibited a droplet size of 96.71 nm, solubility of 26.2 mg/ml, and emulsification time of 41 seconds. It was subsequently adsorbed onto a porous carrier to produce solid SMEDDS. Scanning electron microscopy (SEM) confirmed that the solid particles were discrete and non-agglomerated. *In vitro* drug release studies showed enhanced release profiles for both liquid and solid SMEDDS (~100%) compared to the marketed tablet available (72%) at 60 min. Thus SMEDDS showed a 1.3 fold increase in drug release. The formulation also remained stable for 6 mo under accelerated storage conditions (45 °C±2 °C and 75%±5% RH).

Conclusion: SMEDDS effectively improved the solubility, dissolution rate, and stability of azelnidipine. The application of D-optimal design enabled precise optimization of the formulation, supporting its potential as a promising strategy for enhancing the oral bioavailability of poorly water-soluble drugs.

Keywords: Azelnidipine, SMEDDS, Ternary plot, D-optimal mixture design, Adsorption, Bioavailability

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INTRODUCTION

Enhancing solubility is crucial in order to achieve the greatest effectiveness in newly generated medications because it is the key rate-limiting phase in the oral drug absorption mechanism. The relationship between dissolution and solubility is evident from the noyes-whitney equation, which states that a considerable increase in dissolution results in a corresponding rise in solubility. In addition to predicting *in vivo* outcomes like reduced bioavailability, increased inter-patient variability, etc., poorly soluble drugs also present several in vitro formulation challenges, such as a restricted selection of delivery methods and more complicated dissolution to *in vivo* absorption, when compared to highly soluble drugs [1]. Recently, there has been a growing interest in the formulation of water-insoluble drugs in lipids due to the revelation that the oral bioavailability of certain medications may be improved when they are taken with a meal high in fat. During the past several years, a variety of techniques and formulative procedures have been used to improve the solubility and dissolution. These include particle size reduction techniques such as micronization and nanocrystals, which enhance surface area but often suffer from agglomeration, poor physical stability, and limited improvement in saturation solubility. Solid dispersion systems using hydrophilic carriers have been widely investigated; however, their application is frequently constrained by drug recrystallization, moisture sensitivity, and scale-up challenges. Cyclodextrin inclusion complexes improve apparent solubility but are limited by low drug-loading capacity and potential gastrointestinal irritation at high concentrations. Salt formation is effective for ionizable drugs, yet it is not universally applicable and may result in chemical instability or altered pharmacokinetics.

Although lipid suspensions, solutions, and emulsions have all been employed to improve oral bioavailability, self micro-emulsifying drug delivery systems (SMEDDS) have received a lot of attention recently. For a medication that is poorly soluble in water, a lipid-based drug delivery method would be beneficial since it is hydrophobic, or more lipophilic [2]. SMEDDS, which are isotropic mixtures of natural or synthetic oils, surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants, have the unusual ability to form fine oil-in-water (o/w) micro emulsions when mild agitation is followed by dilution in aqueous media, such as GI fluids. The digestive motility of the stomach and intestines provides the agitation required to facilitate self-emulsification, and SMEDDS distributes easily in the gastro intestinal (GI) tract. As a result, SMEDDS may improve the rate and degree of absorption and produce more repeatable blood-time profiles for lipophilic medicinal molecules that exhibit dissolution rate-limited absorption.

The SMEDDS formulation is fairly simple in principle. Finding an oil-surfactant mixture that is appropriate for dissolving the medication at the necessary therapeutic concentration is a crucial step.

Azelnidipine (AZL) is a calcium channel blocker based on dihydropyridine. It has been used to treat myocardial infarction-related cardiac remodelling and ischaemic heart disease. It comes under the biopharmaceutical classification system (BCS) class II. Thus, because of its poor solubility, it has a very low bioavailability of 22% [3]. The purpose of this study is the development, optimization and evaluation of azelnidipine loaded SMEDDS fast-dispersing tablets. Azelnidipine is available in two different dosage forms, 8 mg and 16 mg, as tablets. 8 mg was chosen as the working dose for our investigation in order to restrict the overall formulation volume. Conversion of liquid SMEDDS into a fast dispersible tablet (FDT) was chosen to overcome handling and stability limitations associated with liquid formulations, while also offering rapid disintegration, improved patient compliance, and faster onset of action, which is clinically relevant for antihypertensive therapy. Compared to conventional tablets or capsules, the

FDT format ensures immediate dispersion of the SMEDDS in the gastrointestinal fluids, facilitating rapid microemulsion formation and consistent drug release.

MATERIALS AND METHODS

Chemicals and reagents

AZL was procured from purechem pvt. ltd., Ankleshwar, Gujarat. Various oils, surfactants, and co-surfactants essential for formulation development were obtained from abitech corporation. Transcutol HP (obtained from gatteffosse India pvt. limited, Mumbai,USP grade), span 20 (sorbitan monolaurate, analytical grade), tween 80 (polysorbate 80, analytical grade), and acrysol EL 135 (polyoxyl 35 castor oil, analytical grade) and castor oil (Laboratory grade were procured from abitech corporation Mumbai, India). syloid 244 FP,(99% analytical grade from grace division)aeroperl 300(from evonik industries), neusilin UFL 2(from fuji chemical industry), mannitol, lactose, and calcium carbonate were the different types of adsorbents that were studied and procured from abitech corporation.

Drug identification

AZL was characterized via ultraviolet (UV) spectroscopy, melting point determination, and fourier transform infra-red (FTIR) analysis. A methanolic solution of azelnidipine was scanned between 200–400 nm to determine the λmax using a UV spectrophotometer (shimadzu 1800). The melting point was measured by the capillary tube method on a digital melting point apparatus. FTIR spectra were recorded using a shimadzu FTIR spectrometer (model 8033) across the 400–4000 cm^{-1} range.

Solubility study

Excess AZL was added to various oils, surfactants, and co-surfactants. Each mixture (20 mg drug+2 ml vehicle) was vortexed, sonicated at 37 , and centrifuged at 3000 rpm for 15 min. Solubility was determined by incremental addition of drug until saturation, followed by filtration and UV analysis of the supernatant [4]. Saturation solubility was confirmed by repeating the measurements thrice until no significant change in drug concentration was observed between consecutive readings, indicating attainment of equilibrium.

Solvent system screening

Based on solubility data, the top two components from each category (oil, surfactant, and co-surfactant) were selected. Eight combinations were prepared (1 ml each component+8 mg azelnidipine) and assessed for emulsification efficiency, % transmittance, and precipitation.

Ternary phase diagram construction

Capmul MCM C8 (oil), transcutol HP (surfactant), and tween 80 (co-surfactant) were used to construct a ternary phase diagram using chemix school software version 13.5. Although the software is not specifically validated for pharmaceutical applications, it was utilized as a graphical plotting tool, while the identification of the microemulsion region was based on experimental observations. Preconcentrates were prepared at varying ratios of oil (5–80%), surfactant (10–90%), and co-surfactant (5–80%). Formulations were evaluated for emulsification time, % transmittance, and self-emulsification efficiency to define the microemulsion region, which guided further optimization [5].

Experimental design and optimization of liquid SMEDDS

The objective of pharmaceutical formulation optimization is to systematically evaluate and identify the optimal levels of formulation variables that influence critical quality attributes, thereby ensuring the development of a robust and efficacious product. In the context of mixture formulations, traditional experimental designs are inadequate because component proportions must collectively sum to unity, making the use of classical factorial designs inappropriate [6].

To address this, a D-optimal mixture design-recognized for maximizing the determinant of the information matrix and minimizing generalized variance-was employed. This approach is particularly suitable when the experimental region is constrained or irregularly shaped, as in the case of SMEDDS formulations. This design was selected in preference to conventional simplex lattice or simplex centroid designs due to its ability to accommodate component constraints and non-uniform design spaces, which are inherent to self-microemulsifying systems. Additionally, the D-optimal approach enables the development of robust polynomial models using a reduced number of experimental runs, thereby minimizing material consumption and experimental variability. The design was generated using design-expert® software (version 10.0.1, stat-ease inc., USA).

Based on the microemulsion region identified from the ternary phase diagram and solubility screening, the upper and lower concentration limits for the three formulation components-oil (A), surfactant (B), and co-surfactant (C)-were defined. In the D-optimal mixture design, the independent variables were defined as A: oil (capmul MCM C8), B: surfactant (transcutol HP), and C: co-surfactant (tween 80). The component proportions were constrained based on preliminary screening studies and ternary phase diagram analysis. The concentration ranges were fixed at A = 5–60% w/w, B = 10–90% w/w, and C = 5–80% w/w, with the total composition summing to 100%. These three variables were used as independent factors in the D-optimal design [7].

Formulations were prepared by combining the appropriate proportions of oil, surfactant, and co-surfactant in 25 ml screw-capped plastic tubes, followed by vortexing to ensure homogeneity. Each formulation batch was loaded with 8 mg of azelnidipine.

Five key dependent variables (responses) were measured to evaluate the performance of each formulation: droplet size (nm, R1), equilibrium solubility (mg/ml, R2), polydispersity index (PDI) (R3), percentage transmittance (R4), and emulsification time (seconds, R5) [8-10]. These responses were used to identify the optimal formulation exhibiting desirable physicochemical characteristics.

The D-optimal mixture design suggested 16 experimental runs, including two center points to evaluate model reproducibility. Each batch was prepared according to the design matrix with a fixed amount of azelnidipine (8 mg), and all experiments were conducted in a randomized sequence to minimize bias. The optimization strategy focused on maximizing the concentration of oil while minimizing the levels of surfactant and co-surfactant. The response constraints were defined to guide the formulation toward desirable characteristics: droplet size was restricted to the range of 80–180 nm, equilibrium solubility and percentage transmittance were set to be maximized, emulsification time minimized, and polydispersity index maintained between 0.1 and 0.5. These criteria were selected to ensure a stable and efficient SMEDDS formulation with enhanced biopharmaceutical performance [11].

Multiple linear regression and analysis of variance (ANOVA) were applied to assess the significance of formulation variables and their interactions. A predictive equation based on the D-optimal model was generated using response data from the sixteen formulations to estimate the attributes of prospective compositions. Contour plots were generated in order to visualize the influence of variables on each response. Model predictability was validated through checkpoint formulations, comparing observed and predicted values.

Characterization of optimized liquid SMEDDS

Percentage transmittance

Optical clarity of the SMEDDS formulation was assessed as an indirect measure of microemulsion formation. After dilution with distilled water (1:250), transmittance was measured spectrophotometrically at 650 nm using deionized water as the blank. Each sample was analysed in triplicate. A transmittance value approaching 100% indicates a clear and stable microemulsion [12].

Droplet size and polydispersity index

Average droplet size and polydispersity index (PDI) were determined using a zetasizer nano-ZS (malvern instruments) at a fixed angle of 90̊ and 25 . Formulations were diluted 1:100 (v/v) with double-distilled water to minimise multiple scattering effects [13]. The refractive index and viscosity parameters used for analysis were those of water. All measurements were conducted in triplicate.

Equilibrium solubility

SMEDDS formulations were prepared using the optimized composition, and excess azelnidipine was added. After vortex mixing for 3 min, samples were incubated in an isothermal sonicator at 37 for 48 h to achieve equilibrium. The samples were then centrifuged at 5000rpm for 10 min, and the supernatant was filtered, diluted with methanol, and analyzed spectrophotometrically for drug concentration [14].

Emulsification time

Self-emulsification time was evaluated using a USP Type II dissolution apparatus (electrolab, TDT-08L, Mumbai, India). 1 ml aliquot of SMEDDS was added to 200 ml of 0.1 N HCl at 37 ± 0.5 ℃ with paddle agitation at 50rpm. The time required to achieve complete emulsification was recorded [15].

Drug precipitation test

To assess physical stability, optimized preconcentrates were diluted (1:100 v/v) with 0.1 N HCl, phosphate buffer saline (PBS) pH 6.8, and PBS pH 7.4 under continuous stirring. To visually assess any instability, the produced microemulsions were centrifuged (ultra centrifuge, remi, India) for 30 min at 15,000rpm. The resulting microemulsions were visually assessed for precipitate formation after being left undisturbed for 48 h [16].

Emulsification efficiency

Self-emulsification was evaluated using the USP II dissolution apparatus. One millilitre of the formulation was added drop wise to 200 ml of 0.1 N HCl at 37 ℃± 0.5 ℃, and the emulsification time was recorded at 50 rpm [17]. The emulsion appearance qualitative grading (EAQG) was assigned based on visual inspection, as outlined in the grading table 1. This method evaluates the visual observation of emulsion after dilution. In this study, the term "rapidly" refers to an emulsification time of less than 1 min, as indicated in the grading criteria for grade A and grade B emulsions.

Table 1: Qualitative grading for emulsion

Appearance of emulsion	Grade
Forms rapidly (<1 min) with clear or slightly bluish appearance	A
Forms rapidly (<1 min) with less clear and bluish white appearance	B
Forms within 2 min (but more than 1 min) with bright white appearance	C
Takes more than 2 min with dull, greyish while emulsion, oily appearance	D
Poor emulsification, large oil droplets on surface	E

Grading is based on visual observation of emulsification behaviour.

Thermodynamic stability

Heating-cooling cycle

Undiluted AZL SMEDDS were subjected to a heating-cooling cycle, alternating between 40 and 45 , followed by cooling to 4 ℃. This cycle was repeated five times.

Centrifugation

Undiluted AZL SMEDDS were centrifuged at 3000 rpm for 30 min, and phase separation was visually examined.

Free-thaw cycle

AZL SMEDDS were frozen at 0 ℃ to 4 ℃ and then thawed at room temperature to assess stability [18].

Cloud point determination

To determine the cloud point, 1 ml of formulation was diluted in 250 ml distilled water. The emulsion's temperature was gradually increased by 2 ℃ increments, and the temperature at which turbidity appeared was recorded [19].

Preparation of solid SMEDDS

Solid SMEDDS (S-SMEDDS) are prepared by adsorbing optimized liquid SMEDDS onto inert solid excipients. For drugs with low water solubility, both water-soluble carriers (e. g., mannitol,sorbitol, lactose, maltodextrin, cyclodextrin, gum acacia) and water-insoluble carriers (e. g., calcium carbonate, neusilin ULF2, aerosil 200, syloid 244 FP) are used. The levigation method was employed to assess solidifying behaviour and screen potential solidifying agents.

The optimized formulation, composed of 15% capmul MCM (oil), 53.24% transcutol HP (surfactant), and 31.76% tween 80 (co-surfactant), was mixed to form a clear, uniform solution. The liquid SMEDDS was converted into a solid form by adsorption onto various solid carriers using the geometric dilution technique. AZL (10 mg) was incorporated into 1 ml of liquid SMEDDS under continuous mixing to obtain a liquid drug-loaded SMEDDS. Briefly, a predetermined quantity of the selected solid carrier was placed in a porcelain mortar, and the liquid SMEDDS was added drop wise with continuous

trituration using a pestle. Then carrier was added further in incremental portions, and thorough mixing was performed after each addition to ensure uniform adsorption of the liquid formulation. This process was continued until the powder exhibited free-flowing characteristics. The resulting powder was then passed through a suitable sieve to obtain a uniform free-flowing S-SMEDDS. The same procedure was followed for all carriers. The suitability of solid carriers was evaluated based on their solidifying capacity (SCmax), which reflects the maximum amount of liquid SMEDDS that can be adsorbed per unit weight of carrier while retaining acceptable flow properties. The solidifying capacity was calculated using the following equation: $SC\ max = \frac{V}{Q} \times 100$. V is the volume of liquid SMEDDS which is 1 ml and Q is the amount of solid carrier (gm) required to convert the liquid SMEDDS into free flowing powder [20]. Further the flow characteristics of different SMEDDS adsorbed on different carriers were evaluated to assess its suitability for further processing. Flow characteristics, including carr's index, hausner's ratio, and compressibility index, were assessed using standard pharmacopoeial methods.

Conversion of S-SMEDDS into azelnidipine tablets

Based on solidifying capacity and flow properties, aeroperl 300 was selected as the optimal adsorbent, requiring 320 mg to adsorb 0.8 ml of liquid SMEDDS. The mixture was converted into fast-dispersible tablets via direct compression. To ensure uniformity, larger agglomerates were removed using a 1000 µm mesh sieve. The blend was then combined with lubricants, glidants, disintegrants, and binders. Tablets (500 mg), each containing 8 mg of azelnidipine, were compressed using a rotary tablet press (karnavati) equipped with 12.0 mm flat-faced round punches [21].

Characterization of SMEDDS tablets

Tablet diameter and thickness were measured with a vernier calliper, and weight was assessed using a mettle toledo balance. Mechanical strength was evaluated using a pfizer hardness tester. Disintegration time and friability were assessed using electro lab instruments (electrolab ED-2L, Mumbai, India and electrolab EF-2, Mumbai, India respectively).

***In vitro* drug release**

Dissolution studies were conducted for optimized liquid SMEDDS, tablet form of SMEDDS and available marketed tablet of 8 mg dose using USP Type II apparatus with 900 ml of 0.1N HCl at 37±0.5 °C and 50 rpm. Invitro drug release of liquid SMEDDS was studied using the dialysis bag method. Aliquots (5 ml) were withdrawn at predefined time points (0, 5, 10, 15, 30, 45, 60 min), filtered, and replaced with fresh medium. Samples were diluted as needed and analyzed spectrophotometrically at 255 nm [22]. Experiments were conducted in triplicate, and mean values were reported.

Stability studies

Accelerated stability studies for both liquid and S-SMEDDS were performed by storing samples at 45°±2 ° and 75%±5% RH. Physical and chemical stability parameters were monitored over 6 mo.

RESULTS

Drug identification

AZL exhibited a characteristic absorption maximum at 255 nm, consistent with literature reports. FTIR spectral analysis further confirmed the identity of the drug (fig. 1). The observed melting point of 193±0.86 °C corroborates the reported range of 193–195 °C.

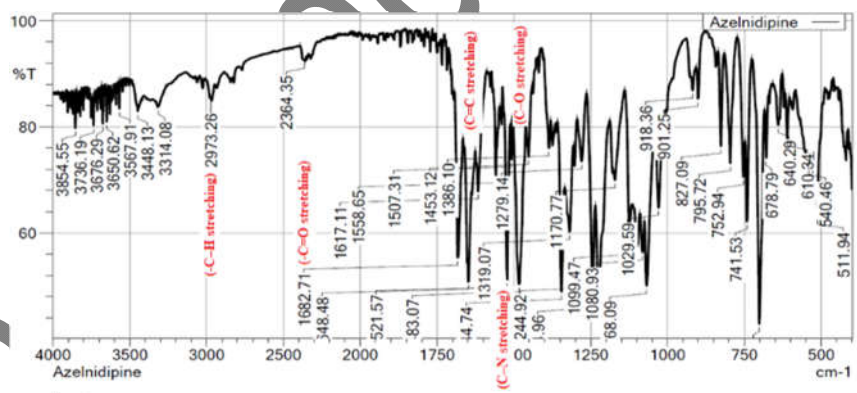

Fig. 1: FTIR spectrum of pure AZL showing characteristic absorption bands 2973 cm^{-1} (-C–H stretching), 1682 cm^{-1} (-C=O stretching), 1648 cm^{-1} (C=C stretching), 1279 cm^{-1} (C–N stretching), and 1224 cm^{-1} (C–O stretching)

The data of solubility study is shown in fig. 2. It was found that in surfactants transcutol HP and acrysol EL 135 shows maximum drug solubility whereas in co-surfactants span 20 and tween 80 shows maximum solubility

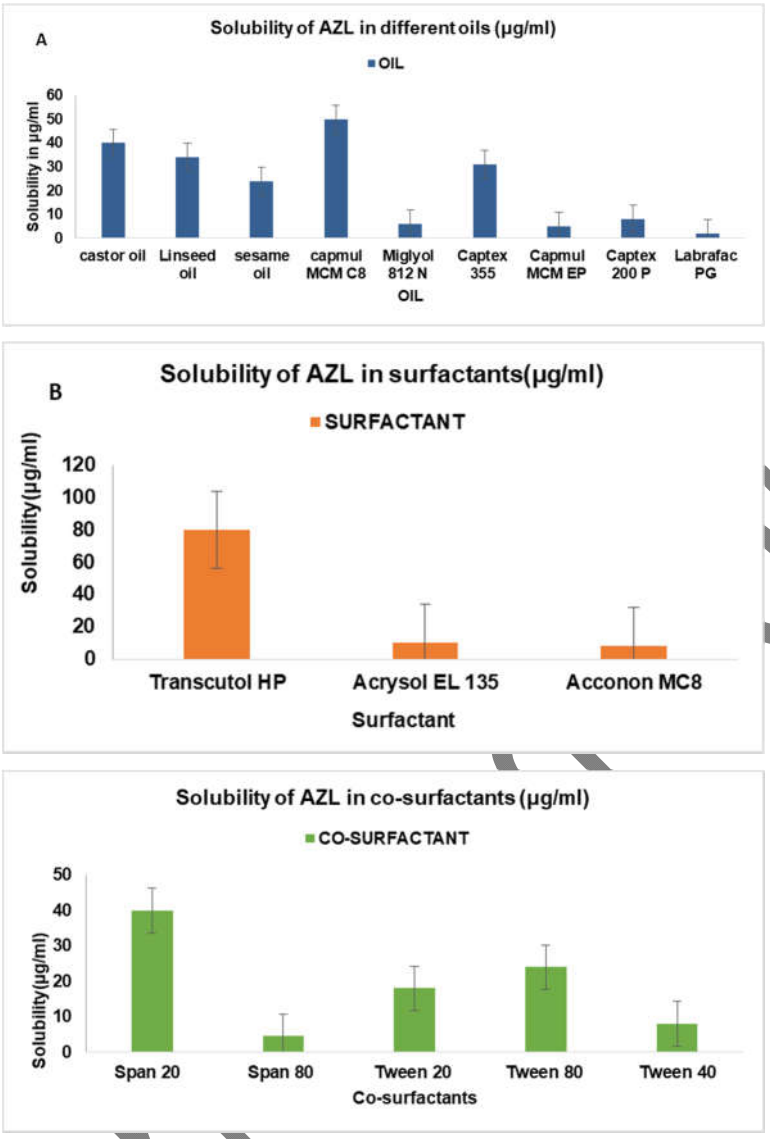

Fig. 2: Results of solubility study of azelnidipine in various (A) oils, (B) surfactants and (C) co-surfactants (Data represented as mean±SD, n = 3)

Solvent system screening

Based on solubility studies, multiple formulations (table 2) were evaluated for emulsification efficiency, percent transmittance, and drug precipitation. Batch AZL 6 demonstrated superior performance, exhibiting grade a emulsification, 92% transmittance, and no drug precipitation. Consequently, AZL 6, comprising capmul MCM C8 (oil), transcutol HP (surfactant), and tween 80 (co-surfactant) was selected as the solvent system. All preliminary batches were prepared using a fixed oil: surfactant: co-surfactant ratio of 1:1:1 (v/v/v) to enable unbiased comparison of emulsification efficiency percent transmittance and drug precipitation.

Table 2: Preliminary trial batches

Batch no	Oil	Surfactant	Co-S	Emulsification efficiency	% T	Drug precipita-tion
AZL 1	Castor oil	Transcutol HP	Span 20	D	20±0.16	NO
AZL 2	Castor oil	Transcutol HP	Tween 80	D	22±0.34	NO
AZL 3	Castor oil	Acrysol EL135	Tween 80	E	20±0.89	NO
AZL 4	Castor oil	Acrysol EL135	Span 20	E	19±1.1	NO
AZL 5	Capmul MCM C8	Transcutol HP	Span 20	B	56±0.72	NO
AZL 6	Capmul MCM C8	Transcutol HP	Tween 80	A	92±1.02	NO
AZL 7	Capmul MCM C8	Acrysol EL135	Span 20	B	42±0.42	NO
AZL 8	Capmul MCM C8	Acrysol EL135	Tween 80	B	59±0.11	NO

(Data are expressed as mean±SD, n = 3).

Ternary phase diagram construction

Formulations were prepared based on a ternary phase diagram with varying concentrations of the selected solvent system. Each batch was evaluated for emulsification efficiency, percent transmittance, and emulsification time. The batches which shows emulsification efficiency of grade A or B as per table 1, percentage transmittance greater than 90% and emulsification time less than 180 seconds were selected for creation of microemulsification region. Batches AZL 9, AZL 10, AZL 19, and AZL 22 exhibited optimal performance and were subsequently used to define the microemulsification region (fig. 3).

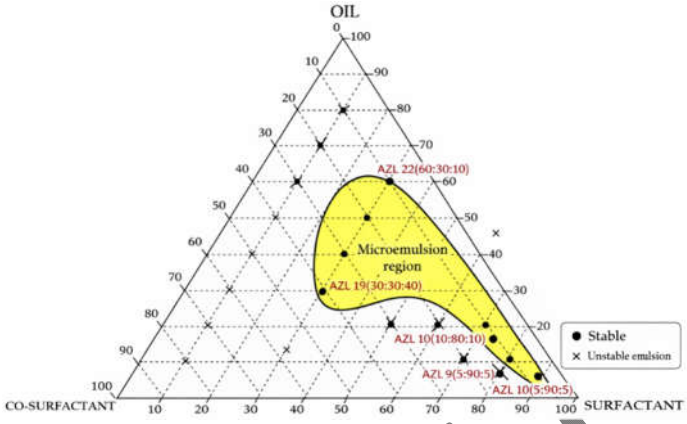

Fig. 3: Ternary phase diagram of oil, surfactant, and co-surfactant showing the shaded microemulsion region. Solid circles represent stable microemulsions, while crosses represent unstable emulsions. Formulations located outside the shaded microemulsion region were classified as unstable emulsions

Experimental design and optimization of liquid SMEDDS

Batches AZL 31 to AZL 46 (table 2)were prepared and evaluated for droplet size, equilibrium solubility, PDI, percent transmittance and emulsification time. Table 3 shows the results for different dependent variables. Fig. 4 and fig. 5, respectively, show the interaction of dependent and independent variables using a contour plot and response surface plot.

Table 3: Results of D-optimal design batches

Batch No	A (Oil)	B (surfactant)	C(Co-surfactant)	R1-Droplet size (nm)	R2-Equilibrium solubility (mg/ml)	R3-PDI	R4-% T	R5 Emulsification time (sec)
AZL 31	5	75.175	19.825	90.2±0.33	68.2±0.45	0.404±0.89	99.1±0.44	53±0.75
AZL 32	5	90	5	167.6±0.43	103.2±0.61	0.168±0.74	49.3±0.76	20±0.12
AZL 33	5	90	5	83.8±0.09	45.6±0.76	0.323±0.15	98.3±0.74	77±0.67
AZL 34	5	55	40	139±0.71	76.6±0.80	0.299±0.93	64.1±0.42	44±0.54
AZL 35	5	55	40	122±0.12	73.2±0.65	0.328±1.03	68.1±0.70	46±0.82
AZL 36	5	55	40	130±0.14	69.1±0.62	0.374±0.07	70.2±0.54	48±0.32
AZL 37	18.2811	59.4552	22.2637	152.8±0.86	94.3±0.31	0.291±0.09	60.5±0.98	27±0.65
AZL 38	19.645	75.355	5	83.8±0.76	48.2±0.42	0.394±0.87	98.2±0.43	74±0.74
AZL 39	30	30	40	86.4±0.11	52.2±0.53	0.366±0.62	79±0.08	54±0.09
AZL 40	30	30	40	100.8±0.11	97.6±0.04	0.291±0.09	56.2±0.75	30±0.86
AZL 41	34.1519	46.0735	19.7745	90.4±0.54	58.1±0.76	0.397±0.24	98.4±0.61	72±0.05
AZL 42	34.932	60.068	5	92.4±0.82	69.3±0.04	0.389±0.84	98.2±0.01	60±0.04
AZL 43	44.9461	30	25.0539	93.7±0.02	60.8±0.64	0.374±0.71	95.4±0.84	58±0.06
AZL 44	49.327	45.673	5	167.4±0.96	98.7±0.41	0.182±0.80	56.6±0.03	26±0.64
AZL 45	60	30	10	90.5±0.98	64.6±0.22	0.399±0.65	93.2±0.01	50±0.32
AZL 46	60	30	10	104.2±0.21	76.1±0.42	0.319±0.64	68.2±0.61	35±0.07

A (oil), B (surfactant), and C (co-surfactant) are expressed as percentage composition (% v/v), and the sum of A+B+C equals 100% for all formulations. (Data are expressed as mean±SD,n = 3)).

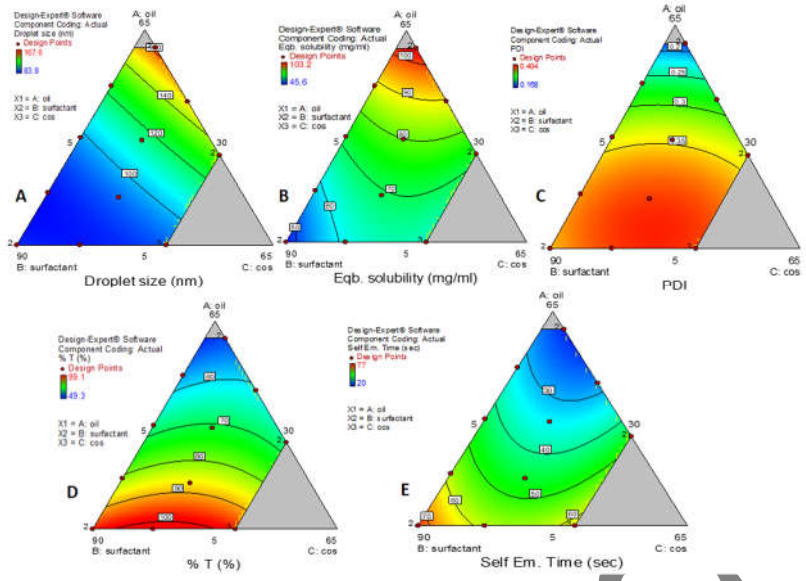

Fig. 4: Contour plot for (A) droplet size, (B) equilibrium solubility, (C) PDI, (D)% T, (E) self emulsification timeshowing the effect of formulation variables on the response. The color gradient represents the magnitude of the response, with blue indicating lower values and red indicating higher values, as shown on the scale bar

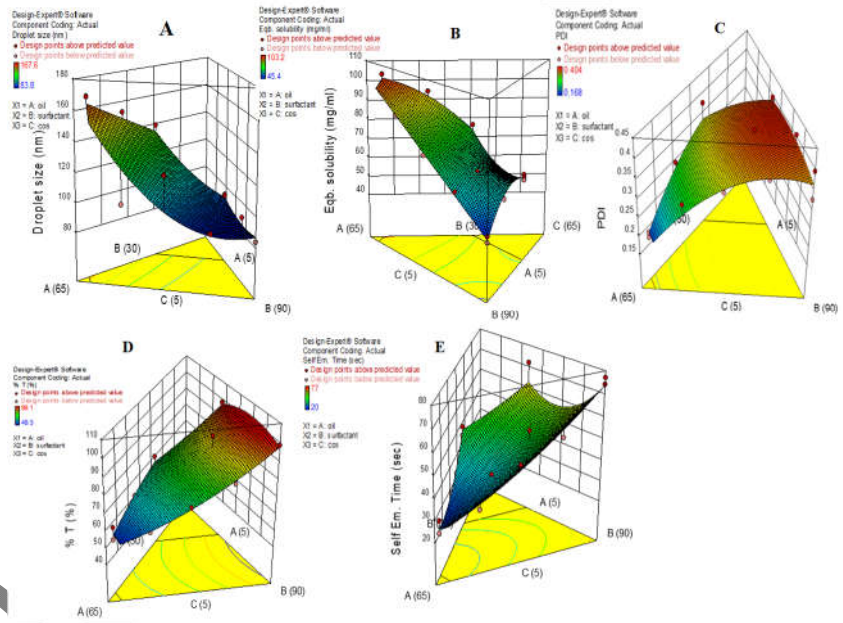

Fig. 5: Response surface plot for droplet size(A), equilibrium solubility(B), PDI(C), % T(D), self emulsification time(E). The color gradient represents the magnitude of the response, with blue indicating lower values and red indicating higher values, as shown on the scale bar

Model validation and optimization

To validate the mixture design model, experimentally measured responses were compared with predicted values using checkpoint batches. Prediction errors, calculated via desirability functions, were all below 4%, indicating high model accuracy and reliability. These results confirm the model's effectiveness in optimizing the AZL-loaded SMEDDS formulation.

The design yielded 15 optimized solutions, from which the formulation with the highest desirability (0.792) was selected. Table 4 shows the evaluation of optimized liquid SMEDDS. Batch AZL 49, prepared using the optimized composition,(oil-15%,surfactanat-53.24%, co-surfactant-31.76%) was further evaluated and found to me*et al.* l performance criteria. While the model demonstrated high precision, formulation outcomes remain material-dependent and warrant further investigation.

Table 4: Evaluation of optimized formula

Formulation code	R1(Droplet size nm)	R2 (Equilibrium solubility(mg/ml)	R3 (PDI)	R4 (% Transmittance)	R5 (Emulsification time in sec)

	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual
AZL 49	95.9	96.7±0.21	27.21	26.2±0.17	0.36	0.37±0.24	94.8	93±0.34	42	41±0.11

Response variables R1–R5 and their corresponding units are indicated in the table column headings (Data represented as mean±SD,n = 3)

Characterization of optimized liquid SMEDDS

The optimised AZL SMEDDS formulation appeared as a transparent and homogenous liquid. The droplet size of optimized AZL-SMEDDS is shown in fig. 6. A lower PDI signifies a homogeneous system, ensuring stability, consistent drug solubilisation, and improved absorption. It was found that 1 ml of the solvent system solubilizes 26.2 ±0.17 mg of drug. It helps in determining the maximum amount of a drug that can dissolve in a given medium under equilibrium conditions. The self-emulsification time was found to be 41 ±0.11 seconds. There was no sign of precipitation. Thermodynamic stability was assessed by heating-cooling cycle, centrifugation and freeze-thaw cycle. There were no visual signs of drug precipitation, phase separation or creaming. The cloud point temperature was found to be 72±1.37 . It helps to assess the stability of the formulation at physiological temperatures [23].

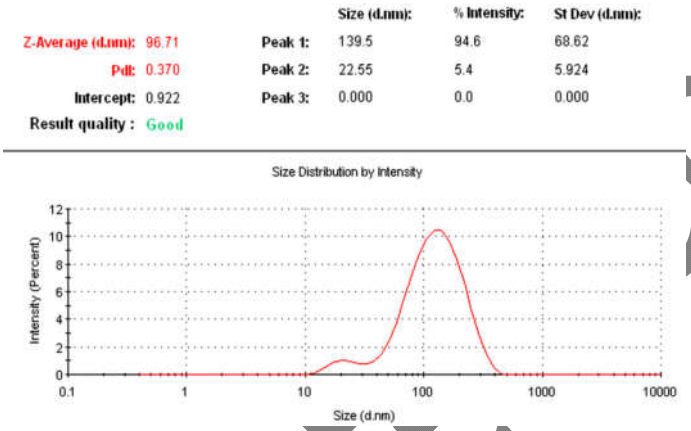

Fig. 6: Droplet size distribution of the optimized liquid SMEDDS measured by dynamic light scattering

Preparation of S-SMEDDS and conversion into AZL tablets

Aeroperl 300 was identified as the most effective adsorbent based on its superior solidifying capacity and flow properties based on table 5 [24]. This highly porous silica-based material, with excellent surface area and adsorption capacity, enables efficient loading of lipid-based SMEDDS while preserving self-emulsification, flowability, and compressibility-key factors for tablet and capsule formulation.

Table 5: Solidifying capacity of different carriers

Carrier	Min. amount of solid carrier added (mg) (Q)	SC_{max} = V/Q	Flow Properties		
			Carr's index	Hausner'sratio	Angle of repose
Lactose	742±0.11	0.00134±0.12	42±0.51	1.68±0.22	46±0.45
Mannitol	685±0.59	0.00146±0.30	36±0.14	1.82±0.32	41±0.67
Neusilin ULF 2	480±0.51	0.00208±0.18	22.3±0.12	1.48±0.14	34.5±0.16
Syloid 244 FP	435±0.44	0.00229±0.13	27.34±0.12	1.35±0.33	32±0.34
Aeroperl 300	320±0.65	0.00312±0.44	17.81±0.56	1.21±0.54	22.5±0.66

(Data represented as mean±SD, n = 3)

To solidify the formulation, 320 mg of aeroperl 300 was required to adsorb 1 ml of liquid SMEDDS. The SEM image shown in fig. 7 displays a porous or granular structure where liquid droplets are adsorbed on solid adsorbents.

The resulting S-SMEDDS was further processed into a FDT using direct compression with the incorporation of necessary excipients. The formula is shown in table 6.

Table 6: Ingredients of AZL loaded FDT

Ingredients	Role of excipients	Quantity for 1 tablet
Liquid SMEDDS	Carrier incorporating drug	0.6 ml (contains 8 mg AZL)
Aeroperl 300	Adsorbent	320 mg
Cellulose microcrystalline (avicel PH 102)	Diluent and binder	130 mg
Cross carmellose sodium	Superdisintegrant	25 mg
Talc	Glidant	10 mg
Magnesium stearate	Lubricant	15 mg

Total weight	500 mg

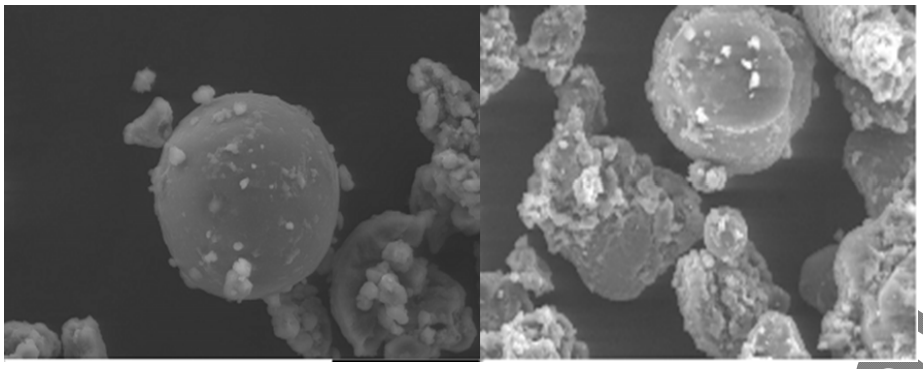

Fig. 7: SEM image of the optimized S-SMEDDS showing a porous surface morphology with uniform adsorption of liquid SMEDDS within the carrier matrix. The image was captured at ×1500 magnification, and the scale bar represents 50 µm

Characterization of SMEDDS tablets

The hardness of the tablet was found to be 3±0.63 kg. The friability of AZL fast dispersible tablet was found to be 0.8±0.49 % and passes the IP limit of 1%. The batches showed no weight variation, and the drug content was found to be 101.65±2.5 %. A good disintegration time of 2.31±0.54 min was obtained, which was a prerequisite for fast-dispersible tablets. According to the Indian Pharmacopoeia, fast-dispersing tablets should disintegrate within 3 min, and the formulated tablets complied with this pharmacopoeial requirement. Tablets are made of a thickness of 4.2±1.20 mm and a diameter of 12±0.64 mm.

In vitro drug release study

The in vitro drug release profiles (fig. 8) show a markedly improved dissolution performance of both L-SMEDDS and S-SMEDDS tablets compared with the marketed formulation. L-SMEDDS and S-SMEDDS achieved rapid release within the first 10 min (≈80–90% CDR), whereas the marketed product released only ~40–45%, indicating dissolution-limited behaviour. The enhanced release from SMEDDS is attributed to the spontaneous formation of nanoemulsion droplets that provide a larger interfacial area and maintain the drug in a solubilized state, thereby preventing precipitation. Notably, the solidified SMEDDS exhibited release kinetics comparable to the liquid system, confirming retention of emulsification efficiency after solidification. At 60 min., both SMEDDS formulations reached ~100% CDR versus ~70–75% for the marketed formulation, demonstrating the superiority of SMEDDS for improving the dissolution of poorly water-soluble drugs

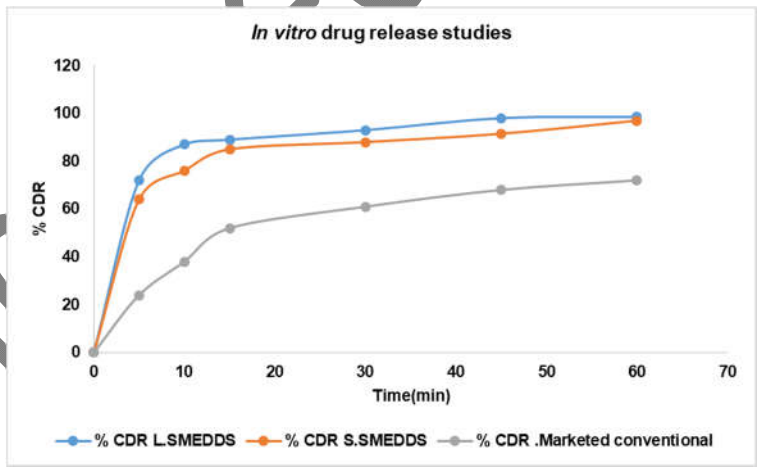

Fig. 8: In vitro drug release studies release profiles of liquid SMEDDS, S-SMEDDS, and marketed formulation in pH 6.8 phosphate buffer. (Data are expressed as mean±SD, n = 3)

The *in vitro* dissolution data of liquid SMEDDS, S-SMEDDS, and the marketed formulation were subjected to kinetic modeling using zero-order, first-order, higuchi, and korsmeyer–peppas equations in order to elucidate the drug release mechanism. Table 7 provides an overview of the correlation coefficients (R^2) derived from linear regression analysis.

Both the liquid and S-SMEDDS formulations exhibited the highest linearity with the first-order kinetic model, with R^2 values of 0.952 and 0.935, respectively. In contrast, the marketed formulation showed a comparatively lower correlation with the first-order model and demonstrated better fitting to the higuchi model (R^2 = 0.921), indicating diffusion-controlled release. The zero-order model showed lower R^2 values for all formulations, suggesting that constant release over time was not the predominant release mechanism. The korsmeyer–peppas model was applicable only to the initial release phase of the marketed formulation (≤60% drug release), where a high correlation coefficient was observed, indicating diffusion-dominated drug transport.

Table 7: Provides an overview of the correlation coefficients (R^2) derived from linear regression analysis

Kinetic model	Liquid SMEDDS	S-SMEDDS	Marketed formulation
Zero order	0.715	0.79	0.833
First order	0.952	0.935	0.919
Higuchi	0.817	0.877	0.921
Korsmeyer–Peppas*	-	-	0.998

R^2 values were obtained from linear regression analysis of mean dissolution data (n = 3).

To statistically compare dissolution profiles, the similarity factor (f_2) was calculated using mean percentage drug release values at identical time points. The f_2 values for liquid SMEDDS and S-SMEDDS when compared with the marketed formulation were 19.6 and 22.6, respectively, indicating statistically dissimilar dissolution profiles. In contrast, the f_2 value obtained for the comparison between liquid and S-SMEDDS was 56.7, demonstrating similarity between the two SMEDDS formulations. Dissolution profile comparison was performed using the similarity factor (f_2), as recommended by regulatory guidelines for time-dependent dissolution data. Point-wise statistical tests such as ANOVA were not applied due to the non-independent nature of dissolution time points.

Stability studies

The stability study of both liquid (L. AZL) and tablet (AZL TAB) formulations was conducted over 6 mo. Emulsification time for L. AZL remained stable, ranging from 41 to 42 seconds, well within the acceptable limit of not more than 15% deviation from the initial value. Transparency values exceeded 94% throughout the study, meeting the criterion of not less than 90%. No signs of drug precipitation were observed at any time point. The droplet size and PDI of L. AZL remained stable throughout the study period with values ranging from 78.4 nm to 80.1 nm for droplet size and 0.21 to 0.23 for PDI. For the AZL tablet, the physical parameters such as diameter (12 mm) and thickness (4.3 mm) consistently complied with specifications. Disintegration time remained within acceptable limits, ranging from 3.27 to 3.87 min. Drug content was maintained within the ±15% range of the label claim (8 mg), with values between 8.12% and 8.86%, indicating the formulation's stability over the test period.

DISCUSSION

The present study demonstrates that the strategic application of lipid-based formulation principles, supported by D-optimal mixture design, enabled the development of an efficient SMEDDS for AZL, a drug whose biopharmaceutical limitations are primarily driven by poor aqueous solubility. The findings collectively indicate that the selected excipient system and optimized component ratios were appropriate for achieving micro emulsification, improved solubilisation capacity, and enhanced dissolution behaviour.

In addition to improved solubility and dissolution, several formulation-related mechanisms may contribute to the enhanced oral bioavailability of azelnidipine from the developed SMEDDS. The best approach to transfer drugs without first-pass metabolism is through the intestinal lymphatic system. Fat is absorbed by the colon by both protein-facilitated transfer and passive diffusion. Food-derived lipids and fat-soluble vitamins are transported to the cells by the exogenous lipoprotein pathway, which uses chylomicrons, the fat carriers assembled in the intestinal epithelium. Lipid-based medication formulations can therefore be absorbed from the intestine via lymphatic transport via the chylomicron pathway and enter the circulation through the thoracic lymph duct by focussing on the chylomicrons in enterocytes [25].

P-glycoprotein (P-gp) is essential for the active transport of different substrates with different structures out of cells, which leads to restricted bioavailability after oral administration and poor intestinal penetration. P-gp inhibitors have been used to improve the oral absorption and bioavailability of numerous p-gp substrates by overcoming p-gp efflux. Notably, because of the formulation itself and the excipients' p-gp inhibitory actions, they can be added to pharmaceutical formulations to improve medication solubility, absorption, and bioavailability. Micelles, emulsions, liposomes, solid lipid nanoparticles, and other formulations having intrinsic p-gp inhibitory activity [26]. These formulations themselves can enhance drug solubility and affinity to the intestinal membrane, encourage paracellular transit and endocytic absorption, and facilitate the lymph transport channel, all of which contribute to enhanced oral bioavailability in addition to the excipients' p-gp inhibitory impact. Additionally, the formation of nano-sized emulsion droplets ensures maintenance of the drug in a solubilized state in the gastrointestinal environment, reducing the likelihood of precipitation upon dilution and thereby sustaining a higher concentration gradient for absorption. The improved in vitro performance of the optimized SMEDDS may be attributed to several potential mechanisms associated with lipid-based drug delivery systems. These include enhanced solubilisation and maintenance of the drug in a dissolved state, as well as possible lymphatic transport and modulation of efflux transporters such as p-glycoprotein, as reported for similar lipid-based formulations in the literature. However, it should be noted that lymphatic uptake and P-gp inhibition were not directly investigated in the present study, and therefore these mechanisms are hypothesized rather than experimentally confirmed. Further *in vivo* studies would be required to substantiate these effects.

The solvent screening and ternary phase mapping showed that the capmul MCM–transcutolHP, tween 80 system possessed a broad micro emulsification region. This behaviour is consistent with earlier reports where medium-chain mono-and triglycerides combined with hydrophilic surfactant/co-surfactant pairs produced stable micro emulsions for BCS II drugs [27]. SMEDDS, where transcutol-containing systems improved clarity and emulsification efficiency. The close agreement suggests that the polarity and interfacial flexibility provided by transcutolHP and tween 80 facilitate rapid droplet formation even at moderate surfactant levels.

Optimization using D-optimal design clearly explained how excipient proportions influenced critical responses. The positive association between oil content and droplet size, and the counterbalancing effect of surfactant/co-surfactant, align with trends observed in previous SMEDDS optimization studies. In SMEDDS, droplet size critically influences formulation quality and bioavailability. Smaller droplets enhance absorption by increasing the interfacial surface area. Literature suggests optimal microemulsion sizes range from 20–200 nm. Hence, droplet size post-dilution is a key in vitro parameter. Equilibrium solubility of AZL in various oil, surfactant, and co-surfactant compositions was selected as a key response, given its critical role in determining excipient load during conversion to solid dosage forms. Enhanced drug solubility in the solvent system minimizes the required quantities of oil, surfactant, and co-surfactant, which is beneficial since high surfactant/co-surfactant levels can cause gastrointestinal irritation. Additionally, improved solubility reduces the need for adsorbents, aiding in the reduction of formulation bulk. Percent transmittance was used to assess microemulsion clarity, with values ≥98% indicating high transparency. Larger droplet sizes typically reduce transmittance. Self-emulsification time is a critical parameter reflecting the efficiency of SMEDDS dispersion upon aqueous dilution. Faster emulsification enhances bioavailability by promoting rapid drug release. The model's predictive accuracy (error<4%) further confirms the suitability of D-optimal mixture design for formulations where component ratios must sum to unity and interactions are non-linear.

The optimized formulation demonstrated a nanoscale droplet size with a narrow distribution, supporting the premise that self-micro emulsifying systems can provide favourable interfacial area for drug release. SMEDDS studies on other poorly soluble drugs show similar nanoparticle behaviour. Raloxifene SMEDDS showed droplet size around 147.1 nm with PDI ≈0.227, indicating a narrow size distribution consistent with efficient self-emulsification. Phillygenin SMEDDS showed optimized formulation droplets around 40 nm with PDI ≈0.15, demonstrating highly uniform size and suggesting great potential for enhanced absorption. Other lipid-based systems: literature suggests that PDI values<0.3 are generally accepted for stable SMEDDS dispersions, with lower values (<0.2) indicating narrow size distribution and predictable in vitro performance. Previous work on AZL solid lipid nanoparticles reported similar improvements in dissolution attributed to increased surface area, reinforcing that particle size reduction-whether through emulsification or nanostructuring-plays a dominant role in enhancing AZL's dissolution-rate-limited absorption. The enhanced in vitro dissolution of the optimized AZL SMEDDS formulation also aligns with literature trends showing that SMEDDS significantly improves drug release profiles compared to pure drugs or marketed tablets, which is attributed to the increased surface area and solubilisation provided by nano-sized droplets.

Conversion to S-SMEDDS using aeroperl 300 was successful without compromising emulsification behaviour. Aeroperl 300, a silicate with high porosity and mechanical stability, has been highlighted in other S-SMEDDS studies (e. g., atorvastatin calcium and fenofibrate) as an effective adsorbent capable of preserving the self-emulsifying characteristics of the lipid formulation. The SEM observations in the present study mirrored these reports, showing non-agglomerated adsorbate structures, indicative of efficient liquid entrapment and surface distribution.

The markedly enhanced dissolution from both liquid and S-SMEDDS compared to pure drug suspension can be attributed to multiple mechanisms: improved apparent solubility, formation of nano-sized droplets, prevention of drug precipitation upon dilution, and increased wettability in tablet form. Kinetic modelling of the dissolution data revealed distinct release behaviours between the SMEDDS formulations and the marketed product. The superior fitting of both liquid and S-SMEDDS to the first-order kinetic model indicates that drug release from these systems is concentration-dependent, which is characteristic of lipid-based self-emulsifying drug delivery systems. Upon aqueous dilution, SMEDDS rapidly form fine oil-in-water emulsions, facilitating immediate drug partitioning into the dissolution medium and resulting in accelerated release.

The comparatively lower correlation with the zero-order model confirms that SMEDDS do not exhibit controlled or constant drug release, which is expected due to their spontaneous emulsification and absence of a release-controlling matrix. The moderate fitting to the higuchi model further suggests that diffusion from emulsion droplets contributes to the overall release mechanism, although it is not the sole governing process.

In contrast, the marketed formulation followed the higuchi release model, indicating a diffusion-controlled mechanism typical of conventional solid dosage forms. The applicability of the korsmeyer–peppas model to the initial release phase of the marketed product further supports the dominance of diffusion-based drug transport during early dissolution.

Importantly, the similarity in kinetic behaviour between liquid and S-SMEDDS demonstrates that solidification of the liquid SMEDDS did not adversely affect the release mechanism. The low f_2 values obtained for comparisons involving the marketed formulation demonstrate a significant difference in dissolution behaviour when compared with SMEDDS formulations. This dissimilarity is attributed to the rapid self-emulsification of SMEDDS, resulting in enhanced drug dispersion and faster release. The f_2 value above 50 for liquid and solid SMEDDS indicates that solidification of the liquid SMEDDS did not significantly alter the dissolution profile, confirming preservation of self-emulsifying characteristics

Stability assessment showed that neither phase separation nor drug precipitation occurred under accelerated storage. This stability profile is comparable to that of other SMEDDS systems containing transcutol and tween 80, which are known to maintain thermodynamic stability due to low interfacial tension and robust solubilisation capacity.

Overall, the study confirms that the combined approach of rational excipient selection, design-of-experiments-based optimization, and adsorption solidification can successfully overcome the solubility and dissolution limitations of AZL. The performance of the developed system is consistent with contemporary findings in SMEDDS research and underscores its potential for improving the oral delivery of poorly water-soluble, highly lipophilic drugs.

Despite the promising *in vitro* performance of the developed a AZL-loaded SMEDDS, certain limitations of the present study should be acknowledged. First, the evaluation was restricted to *in vitro* characterization and dissolution studies, and the absence of *in vivo* pharmacokinetic or bioavailability data limits direct correlation between enhanced dissolution and clinical performance. Future *in vivo* studies are therefore necessary to confirm the extent of bioavailability improvement and lymphatic uptake potential of the formulation.

Second, the conversion of liquid SMEDDS into solid dosage form was achieved using an adsorption technique with aeroperl 300, which, although effective at the laboratory scale, may present scalability and process-control challenges during large-scale manufacturing, such as uniform adsorption and batch-to-batch reproducibility. Further investigation into scalable solidification approaches and process optimization would be required prior to industrial translation. Nevertheless, these limitations do not diminish the significance of the present study, which provides a rational formulation framework for improving the solubility and dissolution behaviour of poorly water-soluble drugs through SMEDDS technology and supports earlier findings demonstrating the effectiveness of lipid-based delivery systems in enhancing oral bioavailability [26].

CONCLUSION

In the current study azelnidipine SMEDDS was successfully formulated and converted to solid dosage form. Formulating water insoluble AZL as SMEDDS will promote its absorption by lymphatic system and by-pass the first pass metabolism.

Thus, it may help to overcome the bioavailability problem. Selection and optimum concentration of oil, surfactant and co-surfactant play a crucial role in the success of emulsification. The formulation was optimized by d-optimal design to get optimized formulation with desired desirability. Optimized batch shows droplet size of 96.71 nm, equilibrium solubility as 26.2 mg/ml and rate of emulsification as 41 seconds. The formulated liquid SMEDDS was successfully converted to S-SMEDDS with the help of aeroperl 300 as adsorbent. The SEM image shows liquid SMEDDS adsorbed on aeroperl 300 which was used as the adsorbent. The *in vitro* study shows improved drug release of azelnidipine from liquid and S-SMEDDS as compared to pure suspension. The stability study reveals that the formulation is stable at 45 ±2 and 75%±5% RH. The developed liquid and S-SMEDDS formulations demonstrated significantly enhanced *in vitro* drug release compared to the marketed formulation, attributed to rapid self-emulsification and concentration-dependent release behaviour. Although *in vivo* bioavailability studies were not conducted, the markedly improved dissolution performance and favourable release kinetics suggest a strong potential for enhanced oral bioavailability of the drug. These findings indicate that the optimized SMEDDS may serve as a promising approach for improving the oral delivery of poorly water-soluble drugs, warranting further *in vivo* investigation. Finally, it can be concluded that azelnidipine SMEDDS can be promising for increasing bioavailability problems with improved patient compliance.

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Artificial intelligence–assisted tools (quill-bot, chatGPT) were used solely for language editing and gmatical refinement of the manuscript. No AI tools were used for data analysis, data interpretation, or generation of scientific content. All scientific conclusions and interpretations remain the responsibility of the authors.

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICTS OF INTERESTS

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. Authors, Dr. Kunal N Patel supervised the project, validated the methodology, and critically revised the manuscript. Ms. Amrutha Mohandas designed the study, performed experiments, analyzed data, and drafted the manuscript. Dr. Dashrath M. Patel and Dr. Pankaj Prajapati assisted in methodology development and supervised the project. All authors reviewed and approved the final manuscript.

REFERENCES

1. Vilas PC, Gujarathi NA, Rane BR, Pawar SP. A review on self microemulsifying drug delivery system. Pharma science monitor. Vol. 4(1); 2013 Jan 1.
2. Vithani K, Hawley A, Jannin V, Pouton C, Boyd BJ. Solubilisation behaviour of poorly water-soluble drugs during digestion of solid SMEDDS. Eur J Pharm Biopharm. 2018 Sep 1;130:236-46. doi: 10.1016/j.ejpb.2018.07.006, PMID 29981444.
3. Dugad T, Kanugo A. Design optimization and evaluation of solid lipid nanoparticles of azelnidipine for the treatment of hypertension. Recent Pat Nanotechnol. 2024 Feb 1;18(1):22-32. doi: 10.2174/1872210517666221019102543, PMID 36278461.
4. Singh D, Tiwary AK, Bedi N. Canagliflozin loaded SMEDDS: formulation optimization for improved solubility, permeability and pharmacokinetic performance. J Pharm Investig. 2019 Jan 15;49(1):67-85. doi: 10.1007/s40005-018-0385-5.
5. Detholia K, Mohandas A, Varia U, Jadeja M, Katariya H. Development and optimization of ropinirole loaded self-nanoemulsifying tablets. Future J Pharm Sci. 2023 Aug 9;9(1):66. doi: 10.1186/s43094-023-00516-x.
6. Holm R, Jensen IH, Sonnergaard J. Optimization of self-microemulsifying drug delivery systems (SMEDDS) using a D-optimal design and the desirability function. Drug Dev Ind Pharm. 2006 Jan 1;32(9):1025-32. doi: 10.1080/03639040600559024, PMID 17012115.
7. Barot BS, Parejiya PB, Patel HK, Gohel MC, Shelat PK. Microemulsion-based gel of terbinafine for the treatment of onychomycosis: optimization of formulation using D-optimal design. AAPS PharmSciTech. 2012 Mar;13(1):184-92. doi: 10.1208/s12249-011-9742-7, PMID 22187363.
8. Lee DW, Marasini N, Poudel BK, Kim JH, Cho HJ, Moon BK et al. Application of Box–Behnken design in the preparation and optimization of fenofibrate-loaded self-microemulsifying drug delivery system (SMEDDS). J Microencapsul. 2014 Feb 1;31(1):31-40. doi: 10.3109/02652048.2013.805837, PMID 23834315.
9. Wang H, Li L, Ye J, Dong W, Zhang X, Xu Y et al. Improved safety and anti-glioblastoma efficacy of cat3-encapsulated SMEDDS through metabolism modification. Molecules. 2021 Jan 18;26(2):484. doi: 10.3390/molecules26020484, PMID 33477555.
10. Sanka K, Suda D, Bakshi V. Optimization of solid-self nanoemulsifying drug delivery system for solubility and release profile of clonazepam using simplex lattice design. J Drug Deliv Sci Technol. 2016 Jun 1;33:114-24. doi: 10.1016/j.jddst.2016.04.003.
11. Shazly G, Mohsin K. Dissolution improvement of solid self-emulsifying drug delivery systems of fenofibrate using an inorganic high surface adsorption material. Acta Pharm. 2015 Mar 31;65(1):29-42. doi: 10.1515/acph-2015-0003, PMID 25781702.
12. Borhade V, Nair H, Hegde D. Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS PharmSciTech. 2008 Mar;9(1):13-21. doi: 10.1208/s12249-007-9014-8, PMID 18446456.
13. Dumpala RL, Khodakiya A. Formulation and statistical optimization of S-SMEDDS of nicardipine hydrochloride by using BBD and PCA design. Int J Pharm Sci Res. 2021;12(3):1860-74.
14. Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS) – challenges and road ahead. Drug Deliv. 2015 Aug 18;22(6):675-90. doi: 10.3109/10717544.2014.896058, PMID 24670091.
15. Rahman MA, Hussain A, Hussain MS, Mirza MA, Iqbal Z. Role of excipients in successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS). Drug Dev Ind Pharm. 2013 Jan 1;39(1):1-19. doi: 10.3109/03639045.2012.660949, PMID 22372916.
16. Patel PV, Patel HK, Panchal SS, Mehta TA. Self micro-emulsifying drug delivery system of tacrolimus: formulation, in vitro evaluation and stability studies. Int J Pharm Investig. 2013 Apr;3(2):95-104. doi: 10.4103/2230-973X.114899, PMID 24015381.
17. Pandey V, Kohli S. SMEDDS of pioglitazone: formulation, in-vitro evaluation and stability studies. Future J Pharm Sci. 2017 Jun 1;3(1):53-9. doi: 10.1016/j.fjps.2017.02.003.
18. Yeom DW, Son HY, Kim JH, Kim SR, Lee SG, Song SH et al. Development of a solidified self-microemulsifying drug delivery system (S-SMEDDS) for atorvastatin calcium with improved dissolution and bioavailability. Int J Pharm. 2016 Jun 15;506(1-2):302-11. doi: 10.1016/j.ijpharm.2016.04.059, PMID 27125455.
19. Cirri M, Roghi A, Valleri M, Mura P. Development and characterization of fast-dissolving tablet formulations of glyburide based on solid self-microemulsifying systems. Eur J Pharm Biopharm. 2016 Jul 1;104:19-29. doi: 10.1016/j.ejpb.2016.04.008, PMID 27091783.
20. Hintzen F, Perera G, Hauptstein S, Müller C, Laffleur F, Bernkop-Schnürch A. *In vivo* evaluation of an oral self-microemulsifying drug delivery system (SMEDDS) for leuprorelin. Int J Pharm. 2014 Sep 10;472(1-2):20-6. doi: 10.1016/j.ijpharm.2014.05.047, PMID 24879935.
21. Moravkar KK, Korde SD, Bhairav BA, Shinde SB, Kakulade SV, Chalikwar SS. Traditional and advanced flow characterization techniques: a platform review for development of solid dosage form. Indian J Pharm Sci. 2020 Nov 1;82(6):945-57. doi: 10.36468/pharmaceutical-sciences.726.
22. Singh AK, Chaurasiya A, Awasthi A, Mishra G, Asati D, Khar RK et al. Oral bioavailability enhancement of exemestane from self-microemulsifying drug delivery system (SMEDDS). AAPS PharmSciTech. 2009 Sep;10(3):906-16. doi: 10.1208/s12249-009-9281-7, PMID 19609837.
23. Jayapal NA, Vamshi Vishnu Y. Formulation and *in vivo* evaluation of self-nanoemulsifying drug delivery system of ramipril in Wistar rats. Asian J Pharm Clin Res. 2021 Jul;14(7):126-36. doi: 10.22159/ajpcr.2021.v14i7.42003.
24. Mathew RO, Varkey JO. Formulation and in vitro evaluation of self nano emulsifying drug delivery system of quercetin for enhancement of oral bioavailability. Int J Curr Pharm Sci. 2022 Jan 15;14(1):60-9. doi: 10.22159/ijcpr.2022v14i1.44113.
25. Jyothi Nakka VN, Gubbiyappa KS, Nagaraju NA. Enhancement of dissolution and bioavailability of simvastatin by solid dispersion technique using sugar-based carriers. Int J Appl Pharm. 2024;16:239-45. doi: 10.22159/ijap.2024v16i1.49442.
26. Shukla S, Kumar K, Tayal S, Tiwari P, Soni AK. Formulation and evaluation of Argemone mexicana oil-based nano-emulsion using low-energy method and its antimicrobial assessment. Int J Pharm Pharm Sci. 2025;7(2):47-51. doi: 10.33545/26647222.2025.v7.i2a.194.