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Design, Characterization, and Evaluation of Solid-Self-Nano-Emulsifying Drug Delivery of Benidipine with Telmisartan: Quality by Design Approach

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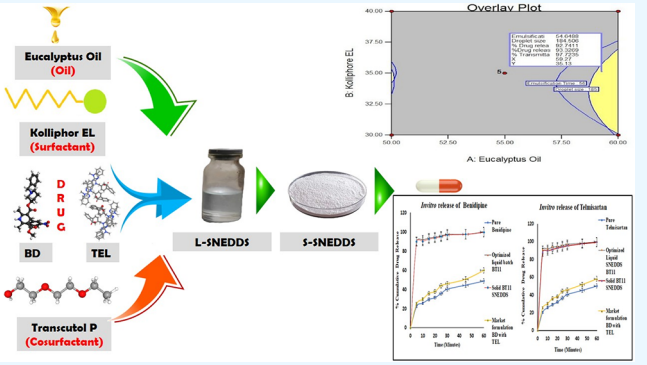
ABSTRACT: The main purpose of this study was to design and develop a solid self-nanoemulsifying drug delivery system (S-SNEDDS) for the oral administration of benidipine (BD) and telmisartan (TEL) using the adsorption method with eucalyptus oil, Transcutol P, and Kolliphor EL via the Box−Behnken design approach. The prepared SNEDDS formulations were characterized using FTIR, DSC, SEM, and PXRD techniques and evaluated for zeta potential, refractive index, drug concentration, resistance to dilution, viscosity, and thermodynamic stability. Additionally, *in vitro* and stability studies were conducted. The results revealed that all prepared formulations (BT1−BT15) exhibited favorable zeta potential (17.2−28.39 mV) and polydispersity index (PDI) values (0.226−0.354). Among them, formulation BT11 demonstrated a desirable droplet size of 175.12 ± 2.70 nm, a PDI of 0.226, a zeta potential of −24.98 ± 0.18 mV, a self-emulsification time of 53.00 ± 2.10 s, a transmittance percentage of 99.6 ± 0.3%, and a drug release of 92.65 ± 1.70% within 15 min. BT11 exhibited significantly faster drug release compared to the commercially available product benidipine T (4 mg/40 mg) and the pure drugs BD and TEL, releasing more than 96% of both drugs in 0.1 N HCl within 60 min. Furthermore, BT11 demonstrated stability throughout the product's stability testing. These findings suggest that the oral S-SNEDDS formulation of BD and TEL can enhance the drugs' water solubility, potentially improving therapeutic outcomes and increasing patient compliance.



1. INTRODUCTION

Delivery of drugs through the oral route is frequently encouraged for a number of reasons, including patient adherence, simplicity of self-medication, and cost-effectiveness. The Biopharmaceutical Classification System (BCS) identifies classes II and IV as the most significant issues in oral delivery due to their limited water solubility, resulting in decreased and inconsistent bioavailability.[1] Due to the increasing popularity of computer-aided drug design, almost 70% of newly developed drugs face this challenge. The decreased oral bioavailability has been linked to several factors, including fast first-pass metabolism, P-gp efflux, and presystemic elimination. To address these challenges, researchers use several formulation strategies to improve the absorption of medications. Solubilization, the process of achieving a uniform and stable distribution of compounds in a certain solvent, plays a major role in drug delivery.[2]

Optimizing solubility is critical to increasing oral bioavailability. Researchers have employed several common methods, including solid dispersions, nanoparticles, crystallization, supersaturable systems, micronization, and complexation, to enhance oral bioavailability and address the issue of low solubility.[3−5] Nanostructured lipid-based drug delivery technologies enhance the solubility of medications and bypass first-pass metabolism, thereby increasing their bioavailability when administered orally. In these cases, self-nanoemulsifying drug delivery systems (SNEDDS) receive attention. In gastrointestinal fluids, SNEDDS are isotropic composites that form fine oil-in-water nanoemulsions.[6] They swiftly disperse throughout the gastrointestinal tract, forming nano droplet-sized emulsions that the lymphatic system absorbs, thereby enhancing drug absorption. The stability and adaptability of SNEDDS make them suitable for production on a large scale. The increase in both the percentage and maintenance of drug absorption results in accurate blood concentration profiles.[7] SNEDDS development

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identifies a drug with a small dose, a significant logarithmic *P* value, and a low melting point.[8]

SNEDDS may be efficiently and systematically generated by combining components, making them suitable for commercial use because they can be manufactured in large quantities without requiring specialized equipment.[9] Inherently, the manufacturing process does not require high energy-consuming procedures, which may prove extremely useful for biopharmaceuticals. Concerns have been raised about the chemical and physical stability of liquid self-nanoemulsifying drug delivery systems (SNEDDS). Different solidification methods can turn liquid SNEDDS into powders that can flow freely. Furthermore, these powders can be transformed into several solid dosage forms, including tablets, capsules, or pellets.[10]

Benidipine, a dihydropyridine calcium channel-blocking agent, is used to treat angina and hypertension. The substance's hepatic breakdown and high lipophilicity (log *P* of 4.28) restrict its absorption, classifying it as a BCS class II agent.[11,12] Similarly, TEL, a class II angiotensin II receptor antagonist used to treat hypertension, faces challenges in terms of its oral bioavailability.[13,14] Frequently, it is administered in combination with other antihypertensive medications, particularly calcium channel blockers, to control hypertension associated with renal failure.[15,16] The literature has reported an extensive range of approaches to enhance the solubility of benidipine and telmisartan (TEL). These approaches include solid dispersion and complexation, among others.[17,18]

The primary aim of this study was to formulate and assess solid-state nanoemulsion drug delivery systems (S-SNEDDS) for benidipine and TEL using a quality by design (QBD) methodology. A review of the literature indicates that no techniques have been reported for improving the solubility of benidipine with TEL using S-SNEDDS, emphasizing the "novelty of our study." The Box−Behnken design (BBD) was used to evaluate the influence of formulation factors on the efficacy of the developed S-SNEDDS, including Neusilin US2, Aerosil 200, and Aeroperl 300. This study is crucial in optimizing oral delivery of benidipine and TEL by enhancing solubility, improving lymphatic transport, bypass first-pass metabolism, and ensuring complete release of the drug. The developed formulation strategies offer a scientifically robust approach to improve bioavailability and therapeutic efficacy.[19−21]

2. MATERIALS AND METHODS

2.1. Materials. Nikishan Pharmaceuticals and Torrent Research Center, respectively, have provided specimens of benidipine and TEL. Cremophor RH 40, Solutol HS 15, Labrafil M 2125 CS, and Transcutol P were originally supplied by BASF and Gettefose (Mumbai, India). The following chemicals were bought from SD. Fine Chem: Span 80 (sorbitan monooleate), Span 20 (sorbitan monolaurate), Tween 80 (polyoxyethylene sorbitan monooleate), Tween 20 (polyoxyethylene sorbitan monolaurate), propylene glycol (PG), polyethylene glycol (PEG) 200, PEG-400, sodium lauryl sulfate, peanut oil, olive oil, eucalyptus oil, oleic acid, sunflower oil, sesame oil, castor oil, cottonseed oil, and oleic acid. Water, which underwent repeated distillation, served as the solvent throughout the experiment. All of the other substances used during this experiment remained of research quality. Hard gelatin empty capsules were acquired from the Torrent Research Center.

2.2. Methods. *2.2.1. Quality by Design Approach.* The QbD methodology aligns with ICH guidelines (Q8−Q11) and facilitates systematic pharmaceutical development by identifying and controlling critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs) through risk-based management. Key components include the Quality Target Product Profile (QTPP), risk assessment (RA), design of experiments (DoE), design space (DS), and the establishment of a control strategy.[22−25]

QbD plays a crucial role in biopharmaceutical oral drug delivery, improving efficiency, preserving biological integrity, and reducing production timelines. The ICH Q11 guideline further refines QbD for biologics, addressing efficacy, immunogenicity, safety, pharmacokinetics, and challenges in technology transfer. The complexity of biopharmaceuticals complicates the correlation between CQAs and QTPP, necessitating advanced analytical methods for robust formulation development.[27]

2.2.1.1. Target Product (TPP). Table S1 outlines the characteristics of Benidipine with TEL L-SNEDDS. Key points include the preparation type (liquid-based self-nanoemulsifying system: L-SNEDDS), therapeutic dosage and strength for hypertension management, enhanced solubility and bioavailability mechanisms, improved pharmacokinetics with faster absorption, and specific packaging and storage conditions to maintain stability and efficacy.[26]

2.2.1.2. CQAs. CQAs were identified by examining the components of the L-SNEDDS for BD and TEL. These attributes were selected based on their impact on the product's stability, solubility, and bioavailability. A fishbone diagram was created to visually represent how material properties and manufacturing parameters influence the formulation. Key insights highlight the interdependence of lipid type, surfactant concentration, and mixing conditions in achieving optimal particle size, drug solubility, and release profile, ensuring desired therapeutic outcomes.[27]

2.2.1.3. Risk Assessment. A preliminary RA evaluated potential hazards associated with CQAs, focusing on lipid, surfactant, and cosurfactant quantities due to their significant influence on formulation performance. The cumulative risk was assessed by combining the degree of risk, probability, and significance of each factor. This analysis guided the selection of parameters to minimize variability and enhance product quality.[28]

2.2.2. Estimation Method for Benidipine and TEL. UV spectroscopy was performed within the wavelength range of 200 to 400 nm. In this investigation, methanol was used as a reference blank. The wavelength at which each drug exhibited maximum absorbance (λmax) was determined from the overlapping spectra. This technique enables the measurement of benidipine and TEL using a dual-wavelength approach, as explained in previous research studies. A statistical assessment was conducted to evaluate the accuracy and precision of the procedure.[30,31] A statistical evaluation was performed to ascertain and evaluate the accuracy as well as precision of the method.

2.2.3. Screening of Oil, Surfactants, and Cosurfactants. 2.2.3.1. Screening of Oils. Various oils were evaluated using the shake flask method based on clarity and emulsification speed. Clarity was assessed by measuring percentage transmittance at 638.2 nm by a Shimadzu UV−vis spectrophotometer. Emulsification speed was determined by counting flask inversions required to achieve homogeneity. Oils tested included oleic acid, sunflower oil, eucalyptus oil, and others. Excess BD and TEL were added to 2 mL of each oil, agitated for 72 h at 37 ± 0.2 °C, and centrifuged. Solubility was calculated

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using the supernatant. Results identified optimal oils for formulation based on clarity and emulsification performance. The study was performed three times and reported the average results.[32,33]

2.2.3.2. Screening of Surfactants and Cosurfactants. The emulsification efficiency of surfactants (Tween 80, Cremophor RH 40, etc.) and cosurfactants (Transcutol P, PEG-400, etc.) was evaluated. By measuring transmittance at 638.2 nm, surfactant and cosurfactant combinations effectively screen based on their ability to form transparent, nanosized emulsions with eucalyptus oil, ensuring optimal formulation performance. 638.2 nm is chosen because it minimizes light scattering from nanosized droplets, and it allows a clear differentiation between nanoemulsions and microemulsions. Clarity was measured by transmittance at 638.2 nm, and emulsification speed was gauged by flask inversions. Surfactant and cosurfactant combinations were vortexed with eucalyptus oil and tested for nanoemulsification capacity. Double-distilled water served as the control. Optimal combinations were identified based on clarity and rapid emulsification.[34]

2.2.4. Construction of the Ternary Phase Diagram (TPD). TPD was constructed using ProSim Ternary Diagram version 1.0 software to establish the boundaries of the nanoemulsion zone. Lipid-to-emulgent ratios ranging from 1:9 to 9:1 were tested at 37 °C. Smix ratios (surfactant to cosurfactant) of 1:1, 2:1, 3:1, 1:2, and 1:3 were used. The oil phase was blended with each Smix ratio using vortexing for 2−3 min, followed by incubation at 37 °C to achieve equilibrium. Transparency of the mixtures was assessed optically, and samples with clarity or a light blue tint were selected as nanoemulsions. All tests were conducted in triplicate for accuracy and reproducibility.[35]

2.2.5. Thermodynamic Stability and Dispersibility of L-SNEDDS. Thermodynamic stability was evaluated using centrifugation at 5000 rpm for 30 min, a heating−cooling cycle alternating between 45 and 0 °C for 48 h, and a freeze−thaw cycle alternating between −21 and 21 °C for 24 h. Samples showing no phase separation were considered stable. Dispersibility was tested using USP paddle apparatus. 1 mL of SNEDDS was added to 500 mL of distilled water or 0.1 N HCl at 37 ± 0.5 °C, with the paddle rotating at 50 rpm. Visual grading categorized emulsification as (A) rapid (<1 min), transparent/bluish; (B) partially transparent, bluish; (C) milky (<2 min); (D) dull/grayish (>2 min); (E) poor emulsification with visible oil globules.[36]

2.2.6. Fabrication of Benidipine-TEL-SNEDDS. Formulations were optimized using Box−Behnken design (BBD) in Design-Expert 13 software. BBD evaluated the effects of independent variables (oil, surfactant, and cosurfactant) on critical quality characteristics (CQAs) for L-SNEDDS of Benidipine with Telmisartan, along with their related explanations. A total of 15 formulations were prepared based on three variables and three levels. Precisely, 4 mg of benidipine and 40 mg of TEL were mixed with predefined quantities of oil, surfactant, and cosurfactant. The mixture was homogenized by vortexing and then sonicated for 15 min at ambient temperature.[36]

2.2.7. Factor Screening Studies. Box−Behnken design (BBD) was employed to assess the effects of oil (X1), surfactant (X2), and cosurfactant (X3) on SNEDDS properties. Regression analysis identified significant factors influencing CQAs. Eucalyptus oil, Kolliphor EL, and Transcutol P were used as components for screening. Table 1 summarizes the experimental design and results for optimizing SNEDDS formulations.[36]

Table 1. Design Plan of Box−Behnken Design Batches for the Prepared SNEDDS of Benidipine with TEL[a]

	coded level			X1	X2	X3
batch	X1	X2	X3	%eucalyptus oil	%Kolliphor EL	%Transcutol P
BT1	1	1	0	60	40	12.5
BT2	0	0	0	55	35	12.5
BT3	0	1	−1	55	40	10
BT4	−1	0	1	50	35	15
BT5	−1	0	−1	50	35	10
BT6	−1	1	0	50	40	12.5
BT7	0	0	0	55	35	12.5
BT8	1	0	1	60	35	15
BT9	1	−1	0	60	30	12.5
BT10	0	1	1	55	40	15
BT11	1	0	−1	60	35	10
BT12	0	−1	−1	55	30	10
BT13	0	0	0	55	35	12.5
BT14	0	−1	1	55	30	15
BT15	−1	−1	0	50	30	12.5

[a]BT: Benidipine with TEL responses.

Self-emulsification time (Y1), droplet size (Dnm) (Y2), percentage of BD release in 15 min (Y3), percentage of transient TEL release in 15 min (Y4), and transmittance percentage (Y5) were the response variables investigated. Multiple regression analysis was utilized to develop a second-order polynomial model complementary to the BBD model, enabling in-depth analysis of relationships among variables and their influence on SNEDDS characteristics.[37]

2.2.7.1. Assessment of SNEDDS for Selected Responses. The study systematically assessed key factors, including droplet size (Dnm), emulsification time (Temul), % transmittance (% *T*), and the proportion of pure drug delivered within 15 min. Each formulation was diluted with water in a 1:100 ratio and gently agitated to produce a homogeneous dispersion. The Malvern Zeta sizer was employed to determine the average droplet size across 15 formulations of L-SNEDDS. Optical transmission measurements were conducted using a UV−visible spectrophotometer (UV1800, Shimadzu, Japan) at a wavelength of 638.2 nm. To evaluate self-emulsification effectiveness, each mixture was introduced into water at 37 ± 0.5 °C and rotated at 50 rpm. Dissolution studies were performed with USP Apparatus II, using 0.1 N HCl as the dissolving medium. Samples were analyzed spectrophotometrically at specified wavelengths for Benidipine and TEL. Drug release was evaluated at 15 min across formulation batches.[38]

2.2.8. Characterization of Liquid SNEDDS (L-SNEDDS) Formulations. 2.2.8.1. Visual Characterization. Self-emulsification of liquid preconcentrates of BD generated with TEL was evaluated. To prepare blank preconcentrates, 0.1 mL of solution was mixed with distilled water in a 1:100 ratio using a magnetic stirrer at 37 °C and 150 rpm. Samples were visually inspected for clarity, coalescence, and phase separation immediately after processing and after 7 days at room temperature. A grading technique as per Singh et al. was employed.[39]

2.2.8.2. Self-Emulsification Time. Diluted BD samples containing TEL-SNEDDS were mixed with 250 mL simulated gastric fluid (SGF) at pH 1.2. Stirring was performed at 50 rpm

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using a USP dissolving equipment-II paddle technique at 37 ± 0.5 °C. The self-emulsification time was recorded.[40]

2.2.8.3. Cloud Point Temperature Measurement Benidipine with TEL. Cloud point temperature was determined by stirring 1 mL of Benidipine with TEL-SNEDDS on a hot plate magnetic stirrer. The temperature was gradually increased until the nanoemulsion transitioned to a cloudy state.[41]

2.2.8.4. Refractive Index. The refractive index (RI) of the optimized liquid SNEDDS formulation was determined using a Digital Abbe Refractometer (Model: HV-1317, Hover Laboratories, India) at 25 °C. The small quantity of the formulation had been applied to the glass prism, and its RI had been recorded. Distilled water (RI = 1.333) has been employed to calibrate the instrument prior to each measurement. The analysis was conducted in triplicate, and the mean ± standard deviation was reported.[42]

2.2.8.5. Droplet Size, Polydispersity Index, and Zeta Potential. Dynamic light scattering (DLS) was utilized to measure average droplet size (ADS), polydispersity index (PDI), and zeta potential (ZP) using the Malvern Zetasizer Nano model with a He−Ne laser at 633 nm. Samples were prepared from centrifuged formulations diluted in water. Surface morphology of compositions was examined via scanning electron microscopy (SEM).[37]

2.2.8.6. pH Level. Drug-loaded L-SNEDDS formulations were mixed with water (1:250), and their pH was measured using a digital pH meter (Systronics, India).[43]

2.2.8.7. In Vitro Dissolution Studies. *In vitro* dissolution was conducted using the USP paddle method (Electrolab, Mumbai, India). The BD with the TEL-loaded SNEDDS mixture, encapsulated in HPMC capsules, was tested in three media—SGF, SIF, and distilled water—under controlled conditions. Drug release was monitored at specified intervals (5 to 60 min) using a UV−visible spectrophotometer. Experiments were conducted in triplicate to ensure statistical reliability.[44]

2.2.8.8. Drug Entrapment Efficiency. Drug entrapment efficiency was assessed by centrifuging formulations at 4000 rpm for 15 min. The supernatant was diluted and analyzed spectrophotometrically for BD and TEL content.[45]

2.2.8.9. Rheological Study. Viscosity measurements were performed using a Brookfield viscometer at 20 rpm and 25 °C. Samples were diluted with water at a 1:250 ratio prior to measurement.[46]

2.2.8.10. Conductivity Measurement. Electrical conductivity of SNEDDS was evaluated using a conductivity meter at 30 °C. Dilutions were prepared in a 1:50 ratio.[47]

2.2.8.11. Robustness to Dilution and pH Change. Robustness was assessed by diluting BD with TEL-loaded SNEDDS in 0.1 N HCl, pH 6.8 phosphate buffer, and water at varying volumes (10 to 1000 mL). Samples were observed for purity or precipitation over 3 h.[48,49]

2.2.9. Preparation of S-SNEDDS. L-SNEDDS, distinguished by their large surface areas, may result in problems such as inadequate stability, drug leakage, and interactions between SNEDDS and capsule shells. The S-SNEDDS combines the advantages of a solid controlled-release pharmaceutical formulation, comprising enhanced safety, controlled drug release, and industrial as well as commercial benefits. The adsorption of L-SNEDDS onto solid carriers may be achieved by combining carriers such as Aerosil 200, Aeroperl 300, and Neusilin US2 in order to produce freely flowing powder in different weight ratios of 1:1, 1:1.5, and 1:2, respectively, as shown in Table S5.

The L-SNEDDS were steadily introduced into an adsorbent using a mortar and pestle, blended in order to improve adsorption onto a solid substrate, and then passed through a #BSS 30 sieve to produce a homogeneous and smooth powder. For the convenience of further study, the powder was prepared and then incorporated into hard hydroxypropyl methylcellulose (HPMC) capsules.[50,51] Measurements of the powders' bulk and tapped density, Hausner's ratio (HR), Carr's index (CI), and angle of repose (AR) were conducted using micromeritic methods for analysis. Calculations of HR and CI have been carried out employing bulk density principles as described in the prior research. The evaluation of AR was carried out utilizing the static funnel methodology. To assess the flow capacities of the porous carriers, a flow property analysis was conducted utilizing the micromeritic data. Therefore, considering the above remarks, the most favorable ratio of solid carrier to L-SNEDDS was chosen.[52]

2.2.9.1. Fourier Transform Infrared Spectroscopy (FTIR) Study. To assess any possible interactions among drugs and excipients, FTIR spectroscopy tests have been performed employing an FTIR spectrometer (Bruker Alpha, Germany) utilizing the potassium bromide-pressed disc methodology. The absorbance of all the specimens has been determined within a wavelength range of 600−4000 cm^{-1}. The spectra obtained are the average of 128 successive scans executed with a wavelength resolution of 4 cm^{1} and include adjustments for CO_2 and H_2O. The spectrum of the graphs has been employed in the assessment of the outcome with the objective of figuring out whether it showed any interactions.[53]

2.2.9.2. Differential Scanning Calorimeter (DSC). DSC has been used to evaluate the crystallinity of the substances. The DSC thermograms of the pure medication and S-SNEDDS were obtained using a differential scanning Linseis electron thermal analyzer (SPA PT-1600). The samples and reference pans were placed in the heating chamber and heated from 100 to 400 °C with an average scanning speed of 10 °C/min through a steady supply of nitrogen gas.[49]

2.2.9.3. Morphology Analysis of S-SNEDDS. SEM was applied to investigate the surface appearance of the generated formulation of S-SNEDDS of Benidipine with TEL. Individual specimens of pure medicines and powdered S-SNEDDS were precisely attached to aluminum stubs using dual-sided tape (ZEISS EVO 18). An analysis was conducted on the gold-coated sample using an 8 mm working distance and a 15 kV activation voltage.[50]

2.2.9.4. Powder X-ray Diffraction (PXRD). The crystal structural analysis of the pure drug and the S-SNEDDS of BT11 was conducted using the X-ray-based particle diffraction method.[51,52] X-ray diffraction patterns of pure drug and powder S-SNEDDS of BT11 were acquired using a powder X-ray diffractometer that was fitted with Ni-filtered CuK radiation as the source. The measurements were done at a voltage of 40 kV and an electric current of 25 μA. An analysis of the diffraction pattern was conducted using a 20° spectrum spanning from 10 to 80°, acquired at a scanning rate of 1° per minute.

2.2.10. Comparison of In Vitro Dissolution of S-SNEDDS of BT11 with Other Formulations. Drug release investigations of the pure medication (Benidipine with TEL), liquid SNEDDS of BT11, S-SNEDDS of BT11 formulations, and the marketed tablet Benidip T 4 mg/40 mg Tab (Precia Pharma Pvt., Ltd.) in Thane, India, were performed utilizing USP dissolution apparatus II. For the purpose of testing *in vitro* drug dissolution capability, L-SNEDDS and S-SNEDDS of BT11 have been

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placed into hard HPMC capsules and introduced through dissolution equipment comprising 900 mL of 0.1 N HCl at 37 ± 0.5 °C. Initially, capsule sinkers were employed to prevent the capsule from floating in its dissolution media. The monitoring techniques employed in the above method were 50 rpm and 37 ± 0.5 °C ambient temperature. After the collection and filtration of 5 mL samples, an equal volume of the fresh medium was added at different time intervals. Each sample was examined using a UV−visible spectrophotometer. The experiments were repeated three times to obtain a robust and reliable mean result. The total correcting value has been utilized for the purpose of accounting for the dilution of removed samples in released tests.[52−54]

2.2.11. Optimization of S-SNEDDS of BD with TEL Formulation. Using rigorous statistical approaches, an investigation has been undertaken to assess the efficiency and precision of the SNEDDS of Benidipine with TEL. This optimization approach utilizes multiple linear regression analysis (MLRA) to effectively examine experimental data by formulating a second-order quadratic polynomial model that incorporates interaction components. Following that, a one-way analysis of variance (ANOVA) was conducted to evaluate the fundamental model parameters, such as the *p*-value, coefficient of correlation (r^2), and predicted error sum of squares (PRESS). Furthermore, a contour plot analysis was conducted to provide comprehensive data on the interactions among the analyzed components and their impact on the response variables. By utilizing the goal in mind, the optimum formulation has been identified and specified in the DS.[55] In order to validate the optimization process, numerous checkpoint combinations were generated inside the design area, and the most efficient formulation had been selected. A comparison was made between the outcomes reported of these checkpoint compositions and the observed results to evaluate the accuracy and validity of the optimization procedure.

2.2.12. Research on Accelerated Stability. The enhanced L-SNEDDS of BT11 formulations undergo a 6-month accelerated stability investigation in the stability chamber of Nova Instruments Private Limited, India. The experiments were conducted at a standard temperature of 40 ± 2 °C and a relative humidity of 75 ± 5%. The L-SNEDDS developed from the optimized BT11 formulations were enclosed in HPMC capsules, tightly sealed, and stored in glass bottles with cotton plugs in a stability chamber. The samples have been collected and subjected to careful evaluation for emulsification efficacy, droplet size, percentage of transmittance, and release of drugs at time intervals of 0, 1, 2, 3, and 6 months.[54]

3. RESULTS AND DISCUSSION

3.1. Estimation Technique for Benidipine with TEL. Four wavelengths, namely, 229.30 and 246.32 nm for Benidipine and 280.10 and 315.29 nm for TEL, were chosen for the study of the two drugs (BD and TEL) using the dual-wavelength spectrophotometric approach. The BD and TEL methods were found to exhibit linearity within the range of 1−5 and 10−50 μg/mL, respectively. Statistical analysis of market preparations at three different levels (80, 100, and 120%) has demonstrated the dependability of the used approach. The percentage recovery for Benidipine and TEL was found to range from 99.20 to 105.10% for both drugs, as shown in Table S3.

3.2. Excipient Screening. Thus, the solubility of the drugs in the oil serves as an essential indicator of the effectiveness of the SNEDDS formulation in maintaining the drug in a solubilized state throughout storage. Table 2 displays the results for the solubility of Benidipine with TEL in different oils, surfactants, and cosurfactants.

Table 2. Solubility Study of BD and TEL in Various Excipients

	solubility[a] (mg/mL)	
oils	BD	TEL
oleic acid	6.02 ± 1.10	11.24 ± 1.37
sunflower oil	3.33 ± 0.51	10.43 ± 0.81
olive oil	5.54 ± 0.63	13.24 ± 0.98
castor oil	4.55 ± 0.33	10.35 ± 0.77
sesame oil	4.32 ± 0.31	15.14 ± 1.45
peanut oil	5.54 ± 0.41	12.15 ± 0.80
eucalyptus oil	6.55 ± 0.65	18.34 ± 1.57
cotton seed oil	4.53 ± 0.36	16.26 ± 1.30
soyabean oil	3.16 ± 0.44	14.10 ± 1.23
Labrafil M 2125CS	8.43 ± 0.87	14.24 ± 1.08
	solubility[b] (mg/mL)	
surfactant and cosurfactant	BD	TEL
Cremophor RH	6.40 ± 0.80	14.25 ± 1.03
Tween 20	8.84 ± 0.90	8.17 ± 0.84
Tween 80	3.44 ± 0.43	10.26 ± 0.75
Span 20	9.35 ± 0.91	16.27 ± 1.28
Span 80	8.23 ± 0.82	12.43 ± 1.05
Solutol HS 15	8.95 ± 0.85	14.24 ± 1.20
Kolliphor EL	6.46 ± 0.50	16.42 ± 1.33
alcohol	4.46 ± 0.50	16.38 ± 1.30
PEG-200	5.65 ± 0.76	12.32 ± 1.08
PEG-400	7.65 ± 0.87	12.45 ± 1.10
propylene glycol	4.75 ± 0.55	8.48 ± 0.89
Transcutol P	6.54 ± 0.84	18.25 ± 1.56

[a]Data are expressed as mg/mL ± SD (n = 3). [b]Values are for the 10% w/w surfactant solution.

The available data demonstrate a significant difference in the solubility of both medications among various oils, with a prominent difference between the minimum and maximum solubilities. The graph represents the ordered solubility of BD in different oils in the following sequence. The oils are arranged in order of increasing efficacy as follows. The chart reveals the order of BD solubility in various oils, as follows. The order of oils, from least to most effective, is soybean oil < sunflower oil, sesame oil, cottonseed oil < castor oil < peanut oil < olive oil < oleic acid < eucalyptus oil, < Labrafil M 2125 CS. The order in which TEL solubility was determined in different oils was as follows: The order of oils, from least to most effective, is castor oil < sunflower oil< peanut oil < olive oil< soybean oil < Labrafil M 2125 CS < sesame oil < cotton seed oil < eucalyptus oil. Eucalyptus oil was selected as the oil having the greatest solubility for the drug in use.

In further investigations, the identification of the surfactant and cosurfactant has been confirmed based on the efficacy of emulsification and the solubilization characteristic of Benidipine and TEL. During the early phases, the selection of the surfactant was carefully made, and particular attention is given to the continuous phase of the nanoemulsion. The hydrophilic surfactant was employed in the formation of the nanoemulsion, while the water phase served as the dispersion substance, and vice versa. Table 3 summarizes the results of the emulsification

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study using eucalyptus oil for the purpose of selecting surfactants and cosurfactants for Benidipine and TEL mixtures.

Table 3. Emulsification Study of Eucalyptus Oil for Surfactant and Cosurfactant Selection for Benidipine and TEL

	no. of inversion (BD)	(%) transmittance (BD)	no. of inversion (TEL)	(%) transmitance (TEL)
Surfactant				
Cremophor RH40	35	84.5	38	83.10
Tween 20	21	87.3	24	86.65
Tween 80	45	82.2	49	80.30
Span 20	22	85.5	24	84.65
Span 80	18	96.5	20	97.20
Solutol HS 15	20	92.5	23	93.50
Kolliphor EL	17	99.5	19	99.65
Cosurfactant				
PEG-200	27	94.25	25	92.25
Transcutol P	15	97.50	13	98.85
PEG-400	21	96.75	18	95.50
propylene glycol	35	92.25	32	90.65

The evaluation of the emulsification characteristics of various surfactants and cosurfactants was conducted by taking into account the solubility of the drugs in these substances, together with the frequency of inversions and the percentage of transmission.[56]

Based on the systematic evaluation, the selection of oil, surfactant, and cosurfactant was finalized considering their individual contributions to forming a stable nanoemulsion system. Nonionic surfactants were chosen due to their lower toxicity compared to ionic surfactants. Seven nonionic surfactants with varying hydrophilic−lipophilic balance (HLB) values were evaluated, as illustrated in Table 2 and Figure S1. The molecular solubility of the drug in these surfactants followed the sequence Tween 80 < Cremophor RH 40 < Span 20 < Tween 20 < Solutol HS 15 < Span 80 < Kolliphor EL. Among these, Kolliphor EL exhibited superior emulsification capabilities, producing the smallest droplet sizes when the emulgent concentration was increased. It also demonstrated excellent clarity with a transmittance of 99.50% and formed a transparent mixture with the oil. In contrast, formulations containing Span 80 showed unsatisfactory self-emulsification efficiency and produced turbid solutions. Furthermore, Kolliphor EL is known to enhance bioavailability by inhibiting certain CYP enzymes and intestinal P-glycoprotein. Thus, Kolliphor EL was selected as the surfactant due to its superior

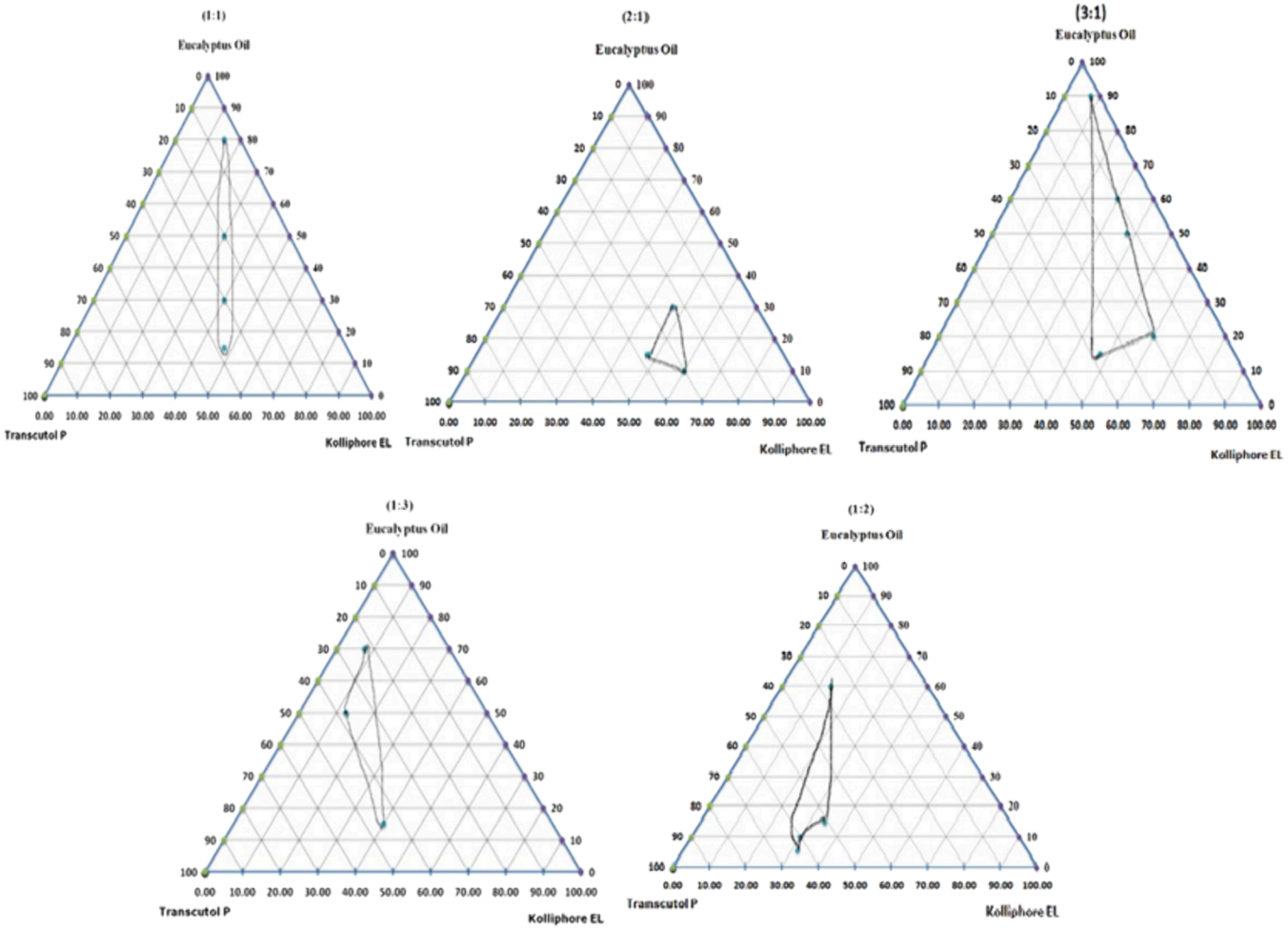

Figure 1. Ternary phase diagrams of the o/w emulsified regions of 1:1, 2:1, 3:1, 1:3, and 1:2 ratios of eucalyptus oil, Kolliphor EL, and Transcutol P.

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ACS Omega 2025, 10, 16440−16456

solubility, emulsification efficiency, and bioavailability-enhancing properties.[39]

The role of cosurfactants was to provide flexibility to the surfactant layer, reduce surface tension, and improve the fluidity necessary for forming nanoemulsions across various compositions. The solubility of the drug (benidipine and TEL) in different cosurfactants was also assessed, as shown in Table 2. The solubility order was observed as propylene glycol < PEG-400 < PEG-200 < Transcutol P. Transcutol P demonstrated the highest solubility and produced emulsions with excellent transparency, making it the ideal choice as a cosurfactant.[34]

For the oil phase, eucalyptus oil was selected based on its solubilization capacity and emulsification efficiency, which complemented the properties of Kolliphor EL and Transcutol P. This combination of eucalyptus oil, Kolliphor EL, and Transcutol P proved optimal for forming a stable nanoemulsion system with excellent solubilization, emulsification, and bioavailability enhancement properties.

3.3. TPDs. The nanoemulsion can be considered the region of the isotropy in the phase diagram, known for the creation and confirmation of transparent formulations by visual examination. By employing solubility and emulsification investigations, a TPD has been constructed to precisely determine the nanoemulsifying zone (Z-avg <200 nm, T% >90%). Furthermore, the composition of the nanoemulsion assists in identifying the concentration range of the elements required for its creation. Figure 1 displays an extensive collection of five tertiary phase diagrams that were generated using various proportions of oil phase, surfactant, and cosurfactant (1:1, 2:1, 3:1, 1:3, and 1:2).

Based on the study information, it was discovered that when a 2:1 ratio was used, the nanoemulsion region obtained was basically small. However, the phase diagram with the (3:1) ratio displayed the most desirable phase diagram. In contrast to the smallest emulsified sections (2:1), the remaining phase diagrams with (1:2) and (1:3) ratios had significant nanoemulsification zones. An increase in surfactant concentration from 2:1 to 3:1 resulted in an expansion of the nanoemulsion zone. An additional significant finding was the absence of any easily noticeable transition from the water-in-oil (w/o) to the oil-in-water (o/w) nanoemulsion. The residual portion of the phase diagram exhibited turbid and typical emulsions. The phase diagram, which contains the largest nanoemulsification zone and was achieved using the 3:1 ratio, has been selected based on the data collected for the development of Benidipine with TEL-SNEDDS formulations.

3.4. Thermodynamic Stability and Dispersibility Studies. Thermodynamic stability studies have been performed to investigate the effect of temperature variations, centrifugation, and freeze−thaw cycles on SNEDDS formulations prepared with a Smix ratio of 3:1. The results, as detailed in Table 4, are summarized in the following.

3.4.1. Heating and Cooling Cycles. All analyzed oil-to-water ratios, with one exception of 9:1, successfully passed the heating and cooling cycle tests. The 9:1 ratio showed instability during freeze−thaw cycles, suggesting its susceptibility to phase separation and precipitation under stress conditions.

3.4.2. Centrifugation Stability. All formulations successfully survived centrifugation tests, thereby confirming their capacity for sustaining phase separation under increasing forces of rotation.

3.4.3. Freeze−Thaw Stability. Formulations at oil-to-water ratios from 8:2 to 1:9 showed no signs of phase separation or precipitation, even after multiple freeze−thaw cycles. However, the 9:1 ratio could not maintain stability under these conditions, thereby confirming that it was excluded as a suitable formulation.

Table 4. Results of the Thermodynamic Study and Dispersibility Test of Various Liquid Self-Nanoemulsifying Drug Delivery Systems Prepared Using a Smix Ratio of 3:1

	thermodynamic stability			dispersibility test	
oil:water ratio	heating−cooling cycle	centrifugation cycle	freeze−thaw cycle	water	0.1 N HCl
9:1	pass	pass	fail	C	C
8:2	pass	pass	pass	A	A
7:3	pass	pass	pass	A	A
6:4	pass	pass	pass	A	A
5:5	pass	pass	pass	A	A
4:6	pass	pass	pass	A	A
3:7	pass	pass	pass	A	A
2:8	pass	pass	pass	A	A
1:9	pass	pass	pass	A	A

The dispersibility tests conducted in both water and 0.1 N HCl indicated that all formulations, with the one exception of the 9:1 ratio, acquired grade A dispersibility, characterized by rapid and uniform nanoemulsion formation. The 9:1 ratio attained merely a grade C, signifying inadequate dispersibility and nonhomogeneous emulsions.

So, formulations with oil-to-water ratios ranging from 8:2 to 1:9 exhibited excellent thermodynamic stability and dispersibility. The Smix ratio of 3:1 was particularly significant for its capacity to generate a substantial nanoemulsion area, outstanding thermodynamic stability, and exceptional dispersibility across various oil-to-water ratios. These characteristics make it an ideal candidate for further development utilizing a full factorial design.

3.5. Quality by Design Approach. The current study was designed to discover a self-emulsifying capsule containing Benidipine and TEL as a model biopharmaceutical for the final dosage form of QTPP. A systematic risk assessment approach has been developed to detect possible interactions between drugs and excipients throughout various unit operations. Utilizing Minitab 16 software, an Ishikawa fishbone diagram was created to examine the elements and subfactors that impact the quality attributes (CQAs) of the pharmaceutical product. Furthermore, a risk estimate matrix (REM) was created to assign values (low, medium, and high) to product features and process parameters in order to identify the components with a high level of risk and their potential impact on critical quality attributes (CQAs).

Table S2 shows that CQAs are extremely important for the biopharmaceutical effectiveness of BD and TEL liquid SNEDDS, including droplet size, zeta potential, liquefaction time, emulsification time, mean dissolution time, drug release rate (Rel_{60min}), and transmittance. These characteristics directly impact drug solubilization, absorption, and stability, ensuring better bioavailability and therapeutic effectiveness.

3.6. SNEDDS Optimization Using Experimental Design. The experimental design was created using the software Design-Expert 13. Table 5 provides a concise overview of the CQAs defined for Benidipine with TEL formulations according to the BBD design. The CQAs are categorized by response self-emulsification time (Y_1), droplet size Dnm (Y_2), percentage of BD release in 15 min (Y_3), percentage of TEL release in 15 min

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ACS Omega 2025, 10, 16440−16456

Table 5. Overview of the CQAs Observed for Formulations of BD with TEL Created by the BBD Design

formulation	T_{emul} (sec)[a]	D_{nm} (nm)[a]	%Rel 15 min[a]		%transmittance[a] (%)
			BD	TEL	
BT1	60.60 ± 2.03	186.01 ± 3.10	91.5 ± 1.2	92.7 ± 0.5	97.1 ± 1.5
BT2	57.71 ± 2.10	195.23 ± 3.25	92.3 ± 1.4	92.9 ± 1.9	89.1 ± 1.2
BT3	58.50 ± 2.15	183.14 ± 3.00	89.7 ± 0.6	89.5 ± 1.2	92.3 ± 0.5
BT4	53.12 ± 2.10	191.32 ± 3.30	91.6 ± 1.3	92.4 ± 1.1	96.1 ± 1.9
BT5	55.10 ± 2.05	184.23 ± 3.20	91.6 ± 0.9	91.6 ± 1.7	95.3 ± 1.2
BT6	61.15 ± 2.10	192.23 ± 3.10	91.7 ± 1.7	92.4 ± 1.6	96.9 ± 1.5
BT7	57.30 ± 2.15	184.03 ± 2.90	92.3 ± 0.8	92.9 ± 1.2	89.2 ± 0.4
BT8	56.22 ± 2.10	189.10 ± 2.80	92.5 ± 0.6	92.9 ± 1.4	98.2 ± 1.1
BT9	55.16 ± 1.95	182.43 ± 2.75	91.9 ± 0.4	91.7 ± 1.4	96.1 ± 1.7
BT10	62.90 ± 2.50	199.75 ± 2.90	92.1 ± 1.6	92.1 ± 1.6	92.9 ± 1.6
BT11	53.00 ± 2.10	175.12 ± 2.70	93.5 ± 0.8	93.7 ± 0.7	99.6 ± 0.3
BT12	60.30 ± 2.10	199.12 ± 2.60	91.4 ± 1.5	92.5 ± 0.5	86.5 ± 0.5
BT13	57.10 ± 2.20	164.50 ± 2.50	92.3 ± 0.6	93.0 ± 1.6	89.0 ± 0.6
BT14	59.25 ± 1.97	156.20 ± 2.40	91.3 ± 1.2	91.6 ± 0.2	88.6 ± 0.7
BT15	60.12 ± 2.00	161.21 ± 2.50	91.8 ± 0.6	91.9 ± 0.4	93.9 ± 0.4

[a]Average ± SD (n = 3).

(Y_4), and % transmittance %T (Y_5). The prepared SNEDDS have been evaluated using a number of parameters, including the application of multiple regression analysis. The BBD model was specifically developed to precisely represent the second-order polynomial model. Table 6 presents the outcomes of a

Table 6. Outcomes of the ANOVA Test for the Benidipine with TEL-Loaded SNEDDS

responses	suggested model	model p value	R^2	adjusted R^2	adequate precision
T_{emul} (sec) (Y_1)	quadratic	0.0363	0.9691	0.9457	48.4592
Dnm(μ) (Y_2)	quadratic	0.0251	0.9264	0.9048	75.4515
% BD Rel_{15min} (Y_3)	linear	0.0045	0.9641	0.9401	34.1506
% TEL Rel_{15min} (Y_4)	linear	0.0048	0.9502	0.9321	37.3245
%T (Y_5)	linear	0.0054	0.9255	0.9083	28.1570

regression analysis conducted with design batches of Benidipine with TEL-loaded SNEDDS. Polynomial equations were created to characterize the mathematical correlations between possible responses:

$$Y_1 = 52.779 + 0.355X_1 - 0.921X_2 + 0.026X_3 + 1.125X_1X_2 - 1.375X_2X_3 + 0.02X_1X_3 + 1.0271X_1^2 + 1.895X_2^2 - 1.718X_3^2 \quad (1)$$

$$Y_2 = 184.50 + 0.118X_1 + 0.977X_2 - 0.311X_3 + 1.054X_1X_2 + 0.379X_2X_3 - 0.741X_1X_3 + 12.657X_1^2 + 11.523X_2 + 1.673X_3^2 \quad (2)$$

$$Y_3 = 86.768 + 3.322X_1 - 0.011X_2 - 1.112X_3 - 5.795X_1X_2 - 2.066X_2X_3 - 2.827X_1X_3 - 0.518X_1^2 - 0.845X_2^2 - 1.754X_3^2 \quad (3)$$

$$Y_4 = 162.30 + 6.62X_1 - 57.31X_2 - 2.69X_3 - 43.87X_1X_2 - 6.70X_2X_3 - 20.20X_1X_3 + 42X_1^2 + 19.21X_2^2 + 0.451X_3^2 \quad (4)$$

$$Y_5 = 97.73 - 2.852X_1 + 2.268X_2 + 0.396X_3 + 2.975X_1X_2 - 0.35X_2X_3 + 0.6X_1X_3 - 2.2923X_1^2 - 1.794X_2^2 - 0.643X_3^2 \quad (5)$$

In the study investigation, a positive sign denotes a synergistic effect, whereas a negative sign corresponds to an antagonistic interaction. In order to enhance understanding of the correlation between dependent and independent variables, further analysis has been conducted using contour plots.

The variability of the response outcomes was assessed using the R^2 and adjusted R^2 values. R^2 and adjusted R^2 values greater than 0.9 indicated a high level of agreement between the experimental data and the fitted values for each response. The precision of the statistical models in navigating the DS was tested using the acceptable precision levels. A number larger than 4 suggested that the statistical model might be reliably applied for navigating the DS. Interestingly, all the statistical models revealed similar R^2 and adjusted R^2 values, with the difference between the two being <0.2. This shows an excellent match for all the models, showing that the experimental data aligned well with the calculated values.[28] The results of the ANOVA test for the Benidipine with TEL-loaded SNEDDS, as shown in Table 6.

3.7. Influence of Formulation Factors on the Responses. *3.7.1. Self-Emulsification Time (Temul).* Self-emulsification time (53.00 ± 2.10 s) confirms the spontaneous emulsification of L-SNEDDS, with decreased Temul facilitating the formation of clear dispersions with nanoscale droplets. A transmission rate of >98% indicates a rapid emulsification process (Table 4).

As per eq 1, emulsification time (Y_1) is influenced by X_1 (oil concentration): slight positive effect, increasing emulsification time due to higher viscosity. X_2 (surfactant concentration): negative effect, reducing Temul by enhancing interfacial disruption. X_3 (cosurfactant concentration): negligible effect, indicating minimal influence on emulsification kinetics.

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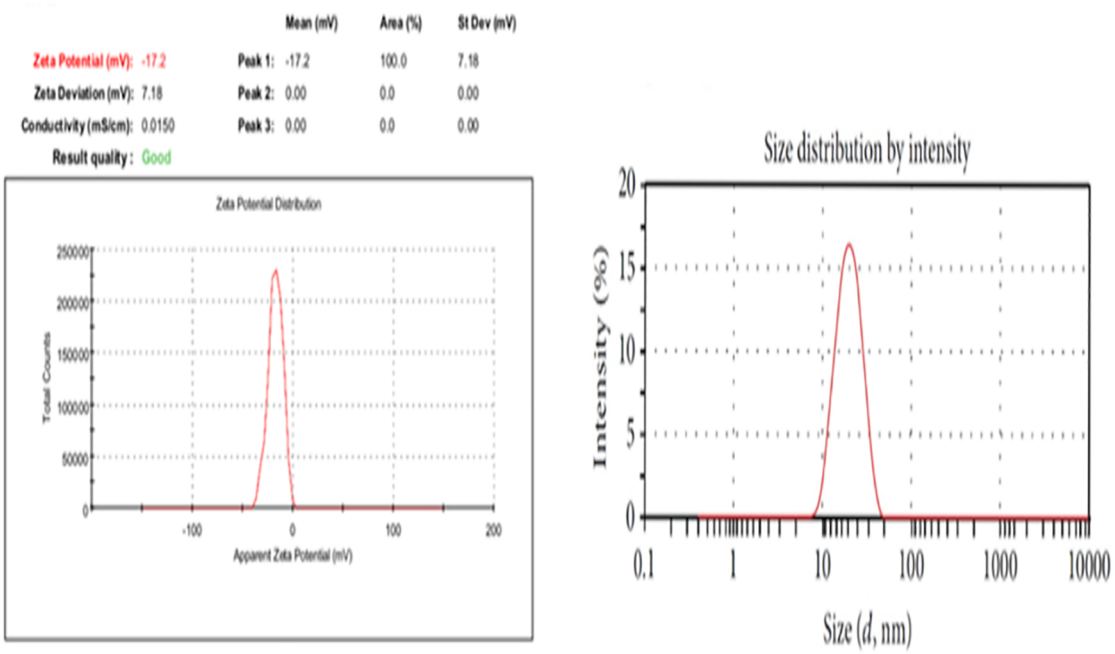

Figure 2. Zeta potential and droplet size distribution of optimized liquid SNEDDS of Benidipine with TEL BT11.

Table 7. Evaluation of L-SNEDDS BT1 to BT15 Formulation of Design

formulation	polydispersity index[a]	cloud point (°C)[a]	zeta potential (mV)[a]	refractive index[a]	viscosity (cP)[a]
BT1	0.324	75.6 ± 1.7	−24.26	1.798	90 ± 3.6
BT2	0.332	72.8 ± 2.2	−21.21	1.765	85 ± 2.4
BT3	0.354	85.6 ± 2.6	−23.24	1.745	80 ± 2.8
BT4	0.258	83.7 ± 2.8	−22.32	1.752	75 ± 2.9
BT5	0.264	75.8 ± 1.7	−20.65	1.742	78 ± 3.4
BT6	0.325	73.2 ± 1.9	−28.39	1.761	70 ± 2.6
BT7	0.331	73.9 ± 1.7	−22.14	1.762	84 ± 2.8
BT8	0.256	69.7 ± 1.1	−24.21	1.789	83 ± 3.3
BT9	0.260	74.4 ± 1.5	−24.36	1.739	96 ± 2.5
BT10	0.265	68.7 ± 1.4	−23.91	1.773	74 ± 3.1
BT11	0.226	79.6 ± 1.7	−17.20	1.742	87 ± 3.2
BT12	0.321	64.2 ± 1.5	−25.96	1.745	72 ± 2.5
BT13	0.325	71.5 ± 2.2	−22.62	1.761	85 ± 2.7
BT14	0.299	68.9 ± 1.7	−24.36	1.746	72 ± 2.3
BT15	0.305	64.5 ± 1.7	−23.63	1.734	79 ± 2.8

[a]All the values are in mean ± SD (n = 3). BT: Benidipine with TEL.

Optimizing surfactant concentration is essential for rapid emulsification, while oil levels must be carefully controlled to prevent extended Temul.

3.7.2. Droplet Size. Regression analysis (eq 2) indicated that oil content (X_1) positively affected droplet size, whereas surfactant (X_2) and cosurfactant (X_3) had negative impacts. Increasing oil concentration led to larger lipophilic droplets, possibly increasing the emulsification process. Droplet sizes varied from 176.24 ± 1.90 to 194.20 ± 2.10 nm, with a negative connection observed between droplet size and Transcutol P concentration. Reduced droplet sizes promote surface tension decrease and interfacial tension between oil-in-water droplets.[57] Figure 2 depicts the droplet size dispersion (∼10−200 nm), corresponding with optimal SNEDDS composition. Table 7 provides these observations, proving the consistency and stability of the formulations. The effect of dilution on droplet size and zeta potential in S-SNEDDS of BT11 shown in Figure S2.

3.7.3. Drug Release at 15 min (CPR_{15}). Optimized batches demonstrated drug release percentages of 91.5 to 93.5% for BD and 91.6 to 92.9% for TEL at 15 min. Equations 3 and 4 demonstrate that variations in oil phase, surfactant, and cosurfactant concentrations significantly influence drug release kinetics. X_1 (oil concentration): exhibits a positive effect, where higher oil content enhances BD and TEL release, likely due to improved solubilization and diffusion. X_2 (surfactant concentration): shows a negligible effect, suggesting that surfactant concentration does not significantly impact BD and TEL release. X_3 (cosurfactant concentration): displays a negative effect, indicating that higher cosurfactant levels hinder BD and TEL release, possibly by altering interfacial properties and drug partitioning. Efficient drug release at 15 min is important for ensuring optimal bioavailability, highlighting that rapid drug release enhances absorption and bioavailability, ensuring quick therapeutic action. The high (>90%) release within 15 min is attributed to optimized self-emulsification properties and high

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Table 8. Key Characteristics of Optimized Formulation BT11 of Benidipine with TEL

parameter	result	interpretation
cloud point temperature	79.6 ± 1.7 °C	higher than physiological temperature (37 °C), ensuring stability *invivo* without phase separation[45]
refractive index (RI)	1.742 ± 0.14	indicates isotropic nanoemulsion with chemical and physical stability.
entrapment efficiency	99.10 ± 0.29% (BD), 99.25 ± 0.35% (TEL)	high entrapment due to lipophilic nature, enhancing dissolution in the oil phase[45]
viscosity	87 ± 3.2 cP	modest viscosity is attributed to the optimized oil and Smix content, supporting system stability.
conductivity	0.0150 μS/cm	confirms oil-in-water emulsion and phase inversion resistance.
robustness to dilution	stable at 10−900× dilution at pH 6.8, 7.4	no phase separation, maintaining stability across gastrointestinal pH ranges and dilution factors[44,47]

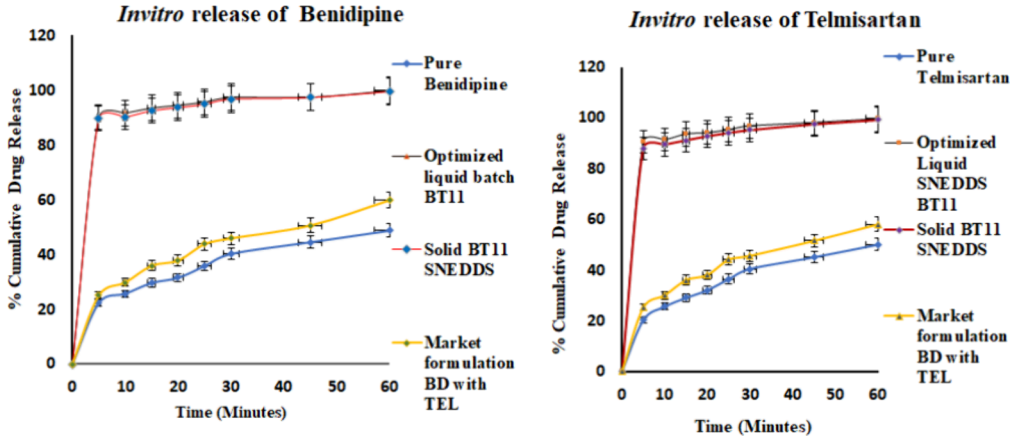

Figure 3. Comparative *in vitro* drug release studies of Benidipine with TEL aqueous suspension, Benidipine with TEL liquid SNEDDS, BT11, S-SNEDDS of BT11, and market formulation (Benidip T 4 mg/40 mg Tab).

solubility of the formulation.[58] Table 4 consolidates the findings on drug release efficiency, validating the improved formulations' quickly dissolving properties.

3.7.4. Percentage Transmittance (%T). The emulsification of liquid SNEDDS preconcentrates created dispersions with high transmittance percentages (86.50 ± 0.95 to 99.60 ± 0.70%). High transmittance (∼100%) suggested nanoscale droplet dispersion and a quick emulsification process. Experimental results (eq 5) demonstrated that increasing oil content lowered transmission owing to greater lipophilicity and diminished transparency.[29] Table 4 emphasizes the link between oil content and transmittance values, indicating formulation efficacy.

3.7.5. Polydispersity Index (PDI). Increased oil concentrations resulted in larger droplet sizes and higher PDI values. Polynomial equation analysis showed the substantial interaction between oil ratio and surfactant concentration, with negative coefficient values showing their synergistic effect on lowering droplet size. An essential component of the self-emulsification method is the nanoscale size of the nanosized droplets (∼175.12 ± 2.70 nm), which produced larger interfacial areas, ensuring rapid drug release, stability, and enhanced bioavailability. Table 7 reveals a PDI range of 0.226 to 0.354, highlighting homogeneous particle dispersion. Reduced droplet size promotes bioavailability by enabling efficient penetration across biological membranes.[49−53] Figure 2 further represents these results, showing the optimal droplet size range within the nanoemulsion formulations.

3.7.6. Zeta Potential. Zeta potential measurements varied from −17.20 to −28.39 mV, showing formulation stability. Negative zeta potential showed the existence of negatively charged molecules at the o/w interface, leading to droplet repulsion and inhibiting phase separation. This characteristic ensured the physical stability and transparency of the nanoemulsion.[54] Table 6 confirms this finding, offering similar zeta potential values across all formulations.

3.8. Assessment of Drug-Loaded Optimum Formulation. BT11 exhibits excellent stability and performance across critical parameters, as observed in Table 6. The high cloud point ensures stability at physiological temperatures, while an RI of 1.742 ± 0.14 confirms isotropic nanoemulsions. Near 99% drug entrapment reflects efficient drug incorporation, supported by optimal viscosity (87 ± 3.2 cP). Conductivity and robustness to dilution confirm phase stability and adaptability, making BT11 suitable for oral administration.[44,45,47] The optimized SNEDDS formulation remained stable due to the self-emulsification efficiency and surfactant−*co*-surfactant interactions, regardless of variations in pH and dilution. The key characteristics of optimized formulation BT11 of Benidipine with TEL are shown in Table 8.

3.9. *In Vitro* Drug Release Assessment of DoE-Optimized Batches. The *in vitro* drug release characteristics of Benidipine with TEL-SNEDDS, Benidipine and TEL pure drug, and the commercially available formulation are shown in Figure 3. The findings indicate that Benidipine with TEL-SNEDDS demonstrated greater drug release rates in the first hours of the experiment compared to Benidipine with TEL pure medicine, as well as the commercially available formulation. Throughout the first hour of the study, all batches of Benidipine with TEL-SNEDDS exhibited a release of Benidipine and TEL above 95% of the drug. Conversely, the Benidipine with TEL pure drugs released only 48.7% of the Benidipine and 50.1% for TEL. A similar approach to market formulation demonstrated a release of 59.8% for Benidipine and 58.1% for TEL. Solidification of optimized liquid SNEDDS of Benidipine with TEL BT11 is shown in Table S4.

Each SNEDDS formulation was produced sequentially, releasing the drug until it reached a steady state after 1 h. Subsequently, the combined drug release for formulations BT4,

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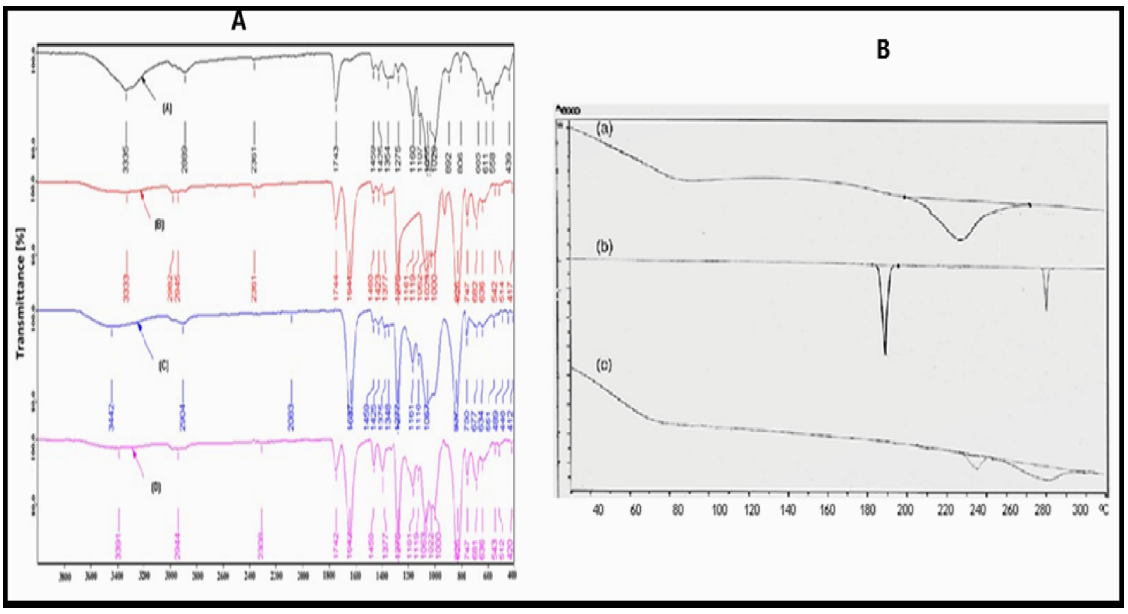

Figure 4. (A) FTIR spectra of (A) Neusilin US2. (B) Physical mixture of Benidipine, TEL, and Neusilin US2. (C) Benidipine with TEL. (D) S-SNEDDS of Benidipine with TEL. 4B:DSC Thermogram of (a) Neusilin US2, (b) Benidipine with TEL, and (c) optimized S-SNEDDS of Benidipine with TEL.

BT7, BT9, BT11, BT13, and BT15 exceeded 99%, whereas for formulations BT1, BT2, BT3, BT5, BT8, BT10, BT12, and BT14, it was above 98%. These results led to the selection of BT11 for optimization and further investigation, owing to its smaller droplet size, quicker emulsification time, more effective drug release, and enhanced transmittance.

Previous research suggested that the nanopores of solid carriers might be able to hold liquid SNEDDS. Even so, the size, configuration, and extent of these openings, along with their total surface area, significantly influence the dissolution of these systems.[50] Neusilin US2, the solid carrier employed in this study, exhibits a high specific surface area characterized by well-defined porosity. Based on this structural feature, it was hypothesized that the liquid self-nanoemulsifying drug delivery system (SNEDDS) was adsorbed into the intraparticulate pores of the carrier. The findings suggest that the liquid SNEDDS is encapsulated within the porous matrix of the solid carrier, thereby maintaining its interfacial interaction with the dissolution medium.[59]

The drug release in liquid SNEDDS in 0.1 N hydrochloric acid (HCl) is much higher during the first 5 min compared to the solid SNEDDS formulation. Possibly, the extended delay in the drug release for S-SNEDDS might be ascribed to the desorption process from the adsorbed carriers. The S-SNEDDS batches produced for Benidipine with TEL exhibited a drug release rate of about 85% during a time frame of around 15 min ($f2 < 50$). The enhanced drug release from the optimized batches may have resulted in the effective release of the therapeutic agent in its solubilized condition in a dissolving medium by the SNEDDS formulation.[48] L-SNEDDS and S-SNEDDS in BT11 exhibit first-order kinetics, indicating that the amount of drug released from the porous matrix is directly proportional to the amount of drug present in its inner layers.[49]

3.10. Flow Property of Various Pore Carriers. The optimized liquid SNEDDS BT11 formulation was effectively converted into a solid SNEDDS by adsorption onto porous solid carriers, yielding a free-flowing powder. The alteration is characterized by significant lipid consumption, with levels of up to 80%.[50,51] Consequently, the choice of an appropriate solid carrier material is essential for formulating an efficient solid SNEDDS composition.

The current study typically employs porous solid carriers such as Aerosil 200, Aeroperl 300, and Neusilin US2. In the first stages of the study, the main emphasis was on testing these solid carriers in order to determine their oil adsorption capacity. Taking into account the SNEDDS ratio and oil adsorption properties, this evaluation was necessary to find the best carrier. It has also been emphasized how important it is to look at the flow characteristics of the final product because these directly affect how uniform and consistent the dosage form is during formulation.

The results, as shown in Tables S6, indicate that the solid SNEDDS formulation employing Neusilin US2 as the carrier—particularly at a 1:1.5 L-SNEDDS-to-adsorbent ratio—demonstrates enhanced efficiency. This particular combination demonstrated superior flow characteristics, including a higher flow rate, compared to other ratios and adsorbents. Moreover, micromeritic statistics, including Hausner's ratio and % compressibility, demonstrated that the adsorption of L-SNEDDS onto the Neusilin US2 surface significantly enhanced free-flowing properties. These results indicate Neusilin US2 as an extremely effective carrier for achieving excellent flow characteristics in solid SNEDDS formulations.

3.11. Characterization of S-SNEDDS. *3.11.1. FTIR.* FTIR is an analytical technique used for assessing the interaction between drugs and excipients in formulations through the comparison of their spectra. The chemical interaction among the substances under investigation may account for unexpected deviations, such as the absence or decrease in spectra. Figure 4 displays the FTIR spectra of Neusilin US2, a composite material consisting of Neusilin US2, BD, and TEL, along with the S-SNEDDS of BT11. Pure BD exhibits characteristic bands at 3401 cm^{-1} (N−H stretching), 1708 cm^{-1} (C═O stretching), 1574 cm^{-1} (C═C stretching), 2852 cm^{-1} (N═O stretching), 1165 cm^{-1} (N═O stretching), 1018 cm^{-1} (N═C stretching), and 777 cm^{-1} (C═C stretching) while TEL exhibits character-

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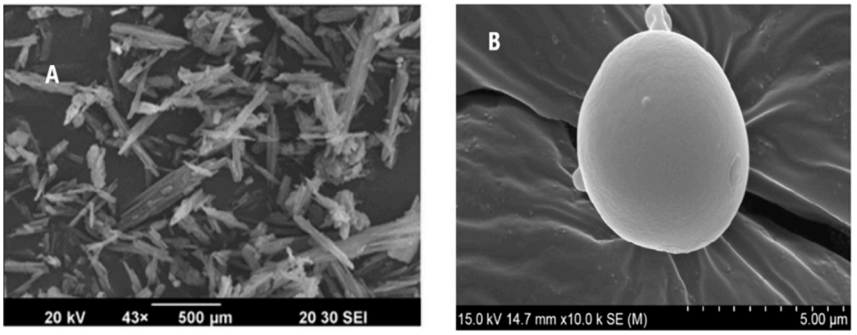

Figure 5. SEM image of (A) pure Benidipine with TEL (B) S-SNEDDS of BT11.

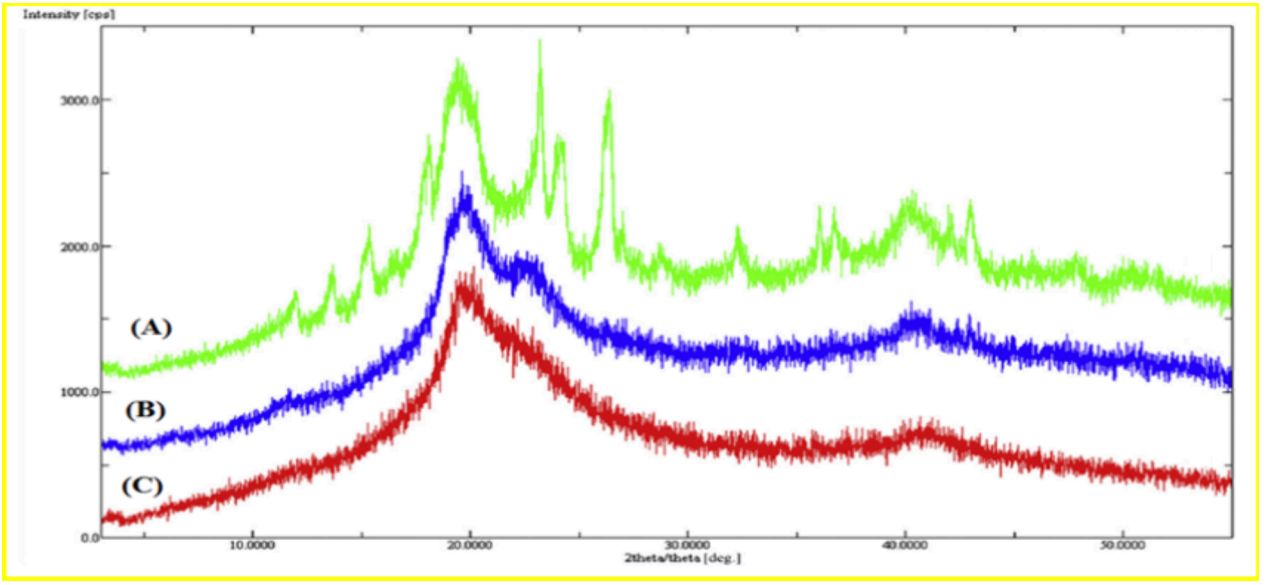

Figure 6. PXRD of (A) drug: Benidipine with TEL, (B) Neusilin US2, and (C) S-SNEDDS of Benidipine with TEL.

istic bands at 1895 cm^{-1} (C−H stretching), 1266 cm^{-1} (C−N stretching), 3134 cm^{-1} (aromatic N−H stretching), 1402 cm^{-1} (C═O stretching), 883 cm^{-1} (C═C stretching), and 741 cm^{-1} (C═O stretching) whereas Neusilin US2 shows characteristic bands at 1743 cm^{-1} (C−H stretching), 1273 cm^{-1} (C−N stretching), 2944 cm^{-1} (aromatic N−H stretching), 1423 cm^{-1} (C═O stretching), 885 cm^{-1} (C═C stretching), and 806 cm^{-1} (C═O stretching).

The S-SNEDDS of BT11 exhibited the distinctive peaks of BD, TEL, and Neusilin US2, showing that the drug was still present in the combination and had not undergone any molecular changes or interactions with carriers such as eucalyptus oil, Kolliphor EL, Transcutol P, and Neusilin US2. The minor shift on certain peaks has been explained by the overlapping of the excipients' peaks. The results reveal that there are no compatibility issues among BD, TEL, and other chemicals that were used for the fabrication of prepared S-SNEDDS.

3.11.2. DSC. A thermolysis procedure using DSC was conducted to ensure the physical characteristics of the medicine resulting from clearly defined phases of molecular transition between crystalline and amorphous components in the powder combination. Figure 4B shows that the important melting endotherm peak shows that benidipine and TEL are crystallized around 189.08 and 278.10 °C, respectively. Similarly, the thermogram of the optimized formulation's physical mixture showed small endothermic drug peaks at 184.22 and 273.37 °C, respectively. However, the absence of an unexpected drug peak in S-SNEDDS suggests a potential transition from a crystalline to an amorphous state, potentially leading to an increase in water solubility.[57]

3.11.3. Morphology Evaluation of S-SNEDDS. SEM images of Benidipine with TEL and S-SNEDDS BT11 are shown in Figure 5A and Figure 5B, respectively. The drug Benidipine and TEL particles first appeared as irregular rod-shaped structures. The surface of Neusilin US 2 exhibited the adsorption of liquid SNEDDS, which is observable in tiny adsorbed particles. The scanning electron micrograph of S-SNEDDS of BT11 revealed the absence of nonlinear crystals of drug Benidipine and TEL. This finding shows that the drug is completely diffused in the S-SNEDDS of the BT11 formulation without any precipitation or crystallization. Furthermore, the outermost structure exhibits scattered tiny openings and pores, which may further facilitate the rapid absorption of water and thus allow rapid dispersion in the stomach environment. In addition, the results indicate thorough adsorption of L-SNEDDS onto the carrier materials, as seen by the absence of oil globules in the S-SNEDDS.

3.11.4. PXRD. The X-ray diffraction patterns of Benidipine and TEL revealed prominent and strong peaks at 2θ diffraction angles of 4.4523, 8.1456, 9.9819, 17.2137, 18.6489, 19.8632, 21.5225, 23.8034, 25.5001, 27.7464, 29.1848, 36.2450, 40.5628, 48.5634, and 54.1674°, confirming the crystalline nature of both drugs. In contrast, Neusilin exhibited no intense diffraction

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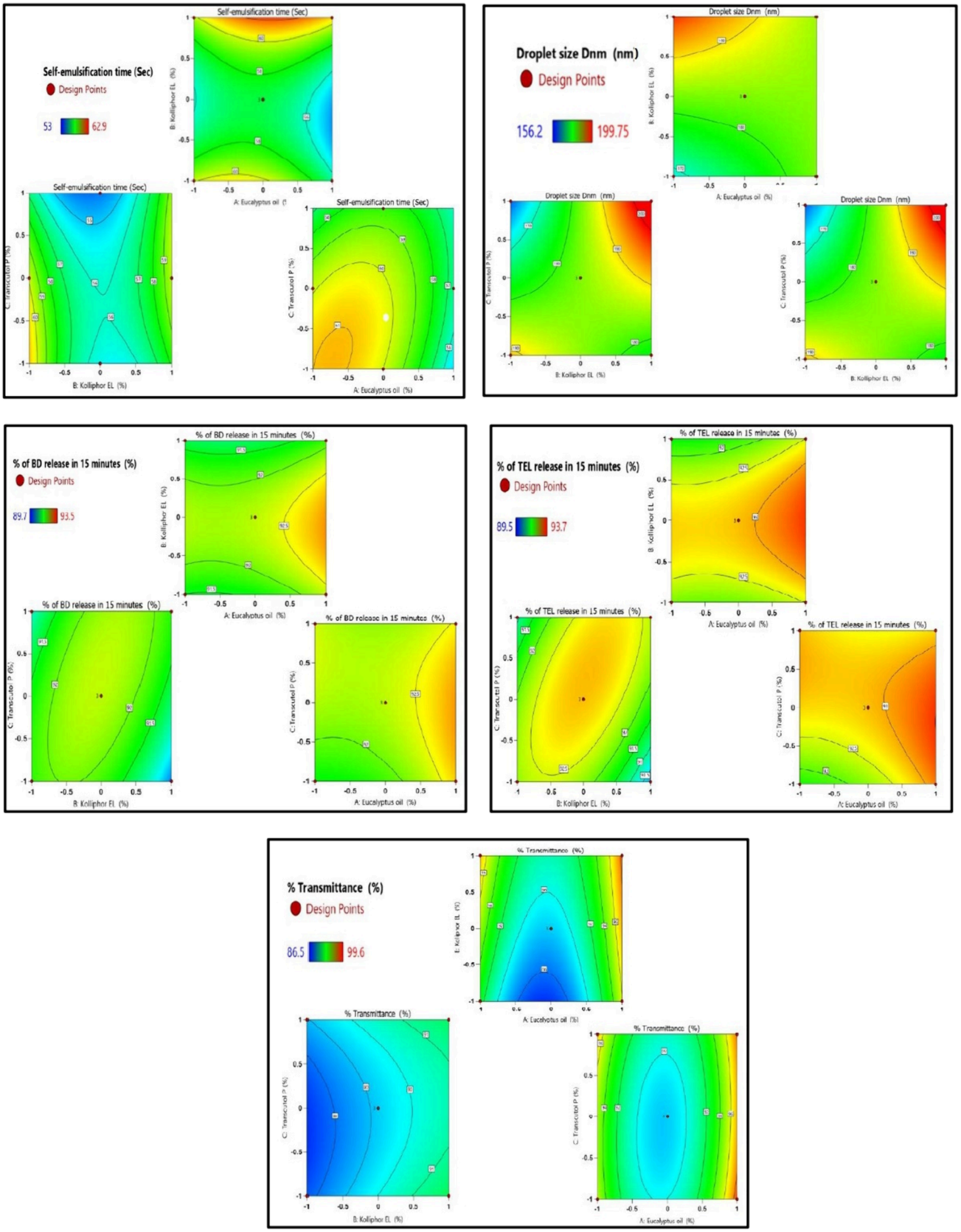

Figure 7. 2D model graphs extracted from the DoE software displaying the influences selected in dependent variables on the dependent responses throughout the preparation of emulsifying drug delivery systems.

peaks, indicating its amorphous nature. However, the sharp peaks characteristic of the crystalline structure of BD and TEL were absent in the diffractogram of the S-SNEDDS containing both drugs, as shown in Figure 6. This affirms the change of BD

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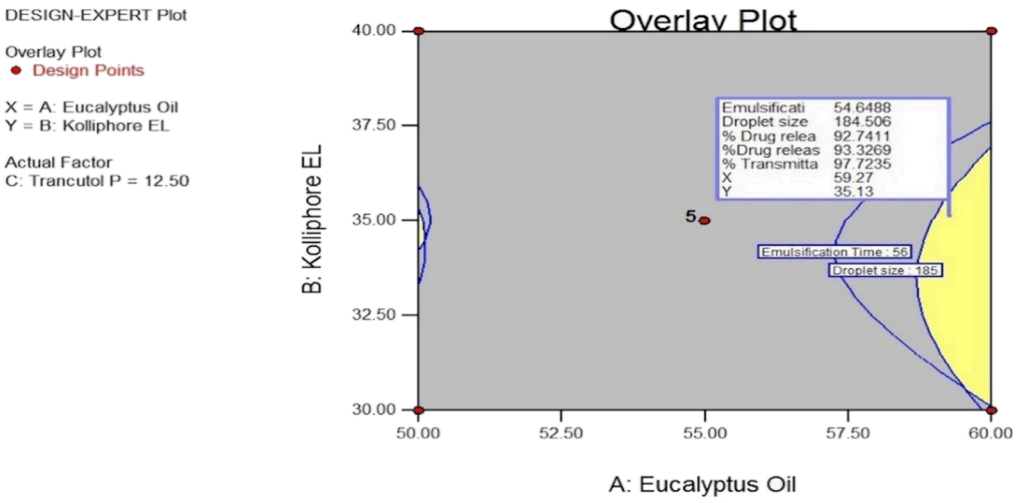

Figure 8. Overlay plot for optimized formulation of Benidipine with TEL-loaded-SNEDDS.

and TEL from crystalline to amorphous or molecularly dispersed states in the S-SNEDDS formulation. These findings indicate that the drugs exist in an amorphous or disordered crystalline phase within the oily core.

3.12. Contour Plot Analysis. In order to highlight the correlation between the dependent and independent variables and to analyze their interactions, two-dimensional contour plots were created. Figure 7 presents the contour plot results. The decrease in droplet size as oil concentration decreases may be attributed to the rapid increase in surfactant concentration, which improves the efficiency of emulsifying the oil phase and reduces droplet size. The time it took to emulsify was prolonged as oil content increased, which may have been caused by the surfactant deficiency. The attachment of surfactant molecules to the outermost emulsion droplets reduces the free interfacial energy and provides a mechanical barrier that prevents emulsion droplets from colliding. A spontaneous thermodynamics distribution was produced as a consequence. Therefore, a larger concentration improves emulsification and medication absorption.[59]

3.13. Identification and Evaluation of Optimum Formulation Using Desirability Function. To validate the generated models, checkpoint formulations were developed and evaluated based on droplet size, percentage transmittance, self-emulsification time, and percentage release of medicines (Benidipine and TEL) during a 15 min time frame. All responses submitted in the current study were restricted, and the optimal desirability function was mathematically constructed.[52] Given the essential functions and response characteristics, an appropriate formulation was developed. It emerged that the design had sufficient prediction because of the small variances between the expected results and the average of the results of the experiment observed across both of the responses. As shown in Figure 8, we evaluated X_1, X_2, and X_3 for the selected formulation at percentages of 59.27, 35.13, and 12.50% w/w, respectively, resulting in an overall impact of 0.975. The expected and actual values for the responses Y_1, Y_2, Y_3, Y_4, and Y_5 are displayed in (Table S6).

3.14. Accelerated Stability Investigations. The optimized Benidipine with TEL-loaded S-SNEDDS of BT11 samples did not change significantly in droplet size, emulsification efficiency, percentage transmittance, or drug release (both BD and TEL) within a 15 min period after being stored for 6 months at a temperature of 40 ± 2 °C and a relative humidity of 75 ± 5%. An examination of the optimized S-SNEDDS showed that BT11 has excellent chemical and physical stability. Table S7 presents the stability characteristics of the Benidipine with TEL-loaded S-SNEDDS of BT11.

4. CONCLUSIONS

The present study effectively developed and optimized a solid self-nanoemulsifying drug administration system (S-SNEDDS) for the simultaneous administration of benidipine and TEL using the QbD methodology. The BBD facilitated the systematic optimization of formulation components, identifying eucalyptus oil, Kolliphor EL, and Transcutol P as the most effective combination. The optimized formulation (BT11) exhibited nanosized globule formation (<100 nm), quick emulsification (<30 s), high transmittance (>95%), and improved in vitro drug release, significantly enhancing the dissolution profile compared with pure drugs and commercial formulations. Moreover, stability experiments conducted at 40 ± 2 °C and 75 ± 5% relative humidity over 6 months validated the retention of droplet size, emulsification efficiency, transmittance, and drug release properties, hence confirming the long-term integrity of the formulation. These results demonstrate that S-SNEDDS may serve as a potentially superior oral drug delivery system for improving the bioavailability and therapeutic effectiveness of antihypertensive medications, presenting a promising alternative to conventional dosage forms.

■ ASSOCIATED CONTENT

Data Availability Statement

The data presented in this study are available in Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10838.

(Table S1) Benidipine with TEL S-SNEDDS quality target product profile (QTPP); (Table S2) critical quality attributes (CQAs) for S-SNEDDS of Benidipine with TEL and their justifications; (Table S3) data indicating recovery studies of Benidipine and TEL; (Table S4) solidification of optimized liquid SNEDDS of Benidipine with TEL BT11; (Table S5) micromeritic properties of S-SNEDDS of Benidipine with TEL BT11; (Table S6)

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predicted values and measured values for optimized Benidipine with TEL-loaded S-SNEDDS of BT11; (Table S7) result from the stability investigation of optimized Benidipine with TEL-loaded S-SNEDDS; (Figure S1) bar chart defining the Benidipine with TEL solubility in different oils, surfactants, and cosurfactants; and (Figure S2) effect of dilution on droplet size and zeta potential in S-SNEDDS of BT11 (PDF)

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Conceptualization, K.C.G and M.R.; methodology, S.S.B. and K.C.G.; formal analysis, S.S.B. and K.C.G.; investigation, S.S.B and S.S.; data curation, M.R., U.H., and M.Y.B.; validation, M.M.A. and I.P.; visualization, M.M.A., U.H., and M.R.; writing—original draft preparation, S.S.B., S.S.B., and K.C.G.; writing—review and editing, I.P., A.A., and M.R. Supervision, K.C.G.; project administration, K.C.G; resources, A.A. and M.R.; software, U.H., Y.B., and S.S.B.; funding acquisition, M.R. All authors have read and agreed to the published version of the manuscript.

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Notes

The authors declare no competing financial interest.

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