Drug Delivery

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/idrd20

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To cite this article: Sheetal S. Buddhadev, Kevinkumar C. Garala, Saisivam S, Mohamed Rahamathulla, Mohammed Muqtader Ahmed, Syeda Ayesha Farhana & Ismail Pasha (2024) Quality by design aided self-nano emulsifying drug delivery systems development for the oral delivery of Benidipine: Improvement of biopharmaceutical performance, Drug Delivery, 31:1, 2288801, DOI: 10.1080/10717544.2023.2288801

To link to this article: https://doi.org/10.1080/10717544.2023.2288801

DRUG DELIVERY
2024, VOL. 31, NO. 1, 2288801
https://doi.org/10.1080/10717544.2023.2288801

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RESEARCH ARTICLE

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Quality by design aided self-nano emulsifying drug delivery systems development for the oral delivery of Benidipine: Improvement of biopharmaceutical performance

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ABSTRACT

The primary objective of the research effort is to establish efficient solid self-nanoemulsifying drug delivery systems (S-SNEDDS) for benidipine (BD) through the systematic application of a quality-by-design (QbD)-based paradigm. Utilizing Labrafil M 2125 CS, Kolliphor EL, and Transcutol P, the BD-S-SNEDDS were created. The central composite design was adopted to optimize numerous components. Zeta potential, drug concentration, resistance to dilution, pH, refractive index, viscosity, thermodynamic stability, and cloud point were further investigated in the most efficient formulation, BD14, which had a globule size of 156.20 ± 2.40 nm, PDI of 0.25, zeta potential of −17.36 ± 0.18 mV, self-emulsification time of 65.21 ± 1.95 s, % transmittance of 99.80 ± 0.70%, and drug release of 92.65 ± 1.70% at 15 min. S-SNEDDS were formulated using the adsorption process and investigated via Fourier transform infrared spectroscopy, Differential scanning calorimeter, Scanning electron microscopy, and powder X-ray diffraction. Optimized S-SNEDDS batch BD14 dramatically decreased blood pressure in rats in contrast to the pure drug and the commercial product, according to a pharmacodynamics investigation. Accelerated stability tests validated the product's stability. Therefore, the development of oral S-SNEDDS of BD may be advantageous for raising BD's water solubility and expanding their releasing capabilities, thereby boosting oral absorption.

ARTICLE HISTORY
Received 6 September 2023
Revised 31 October 2023
Accepted 12 November 2023

KEYWORDS
Benidipine; solid self-nanoemulsifying drug delivery systems; S-SNEDDS; ternary phase diagram; central composite design; CCD; quality by design: QBD

1. Introduction

For noninvasive administration, the oral route tends to be practical and accessible. However, inadequate water solubility affects 35–40% of newly approved drugs, resulting in poor dissolution as well as lower bioavailability, increased intra- and inter-subject variability, and hampering dosage uniformity. This poses a considerable challenge for the pharmaceutical sector (Jain et al. 2015). The great majority of medications' solubilization in a given solvent to form a homogeneous arrangement is dependent on solubility, which is a vital interaction. Traditional methods for improving solubility—solid dispersions, inclusion complexes, micronization, co-crystals, supersaturable systems, and complexation with hydrophilic polymers—are all kinds of oral bioavailability; however, these strategies often only address the issue of low solubility (Jain et al. 2015; Bhalani et al. 2022). Lipid-based nanostructured drug delivery systems have demonstrated tremendous potential for enhancing these drugs' oral bioavailability. These techniques enhance bioavailability by facilitating solubilization through the dispersion of fine globules and promoting intestinal absorption while bypassing initial metabolism (Amidon et al. 1995; Dokania and Joshi 2015).

One of the most widely explored formulation options for administering biopharmaceutical classification system (BCS) class II and IV drugs is self-nano emulsifying drug delivery systems (SNEDDS), which has attracted the attention of researchers (Shakeel et al. 2016; Alshahrani et al. 2018; Abushal et al. 2022). SNEDDS, isotropic systems used in drug delivery, contain a cosolvent or surfactant acting as a co-surfactant, along with a hydrophilic solvent. The presence of the co-surfactant enables the formation of fine oil-in-water nanoemulsion when gently mixed with aqueous media. This co-surfactant plays a crucial role in stabilizing the nanoemulsion, aiding in solubilizing lipophilic components and facilitating their dispersion in a hydrophilic environment. By

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/10717544.2023.2288801.

reducing interfacial tension, the co-surfactant helps to form a stable nanoemulsion, enhancing solubilization and delivery of lipophilic drugs or bioactive compounds (Shakeel et al. 2016; Kalam et al. 2017; Buya et al. 2020; Kazi et al. 2020; Shakeel et al. 2021). In the GI tract, due to the stomach's motility and intestinal agitation, SNEDDS formulations disperse rapidly. SNEDDS are widely utilized to make emulsions with droplet sizes less than 200 nm (Buya et al. 2020; Shakeel et al. 2021). The produced emulsion then absorbs into the lymphatic pathway. As a result, it would enhance drug oral bioavailability in SNEDDS by bypassing the liver's first-pass influence. As a result, SNEDDS has become an essential method for improving the oral bioavailability of poorly water-soluble medicines (Buya et al. 2020; Kazi et al. 2020; Shakeel et al. 2021). Moreover, liquid-SNEDDS (L-SNEDDS) is a homogeneous framework without either a liquid or solid phase, making it more stable than a normal emulsion and suited for enormous manufacturing. These systems may enhance the amount and percentage of absorption, as well as produce a more exact plasma time profile. Additionally, SNEDDS provide considerable benefits for efficiency of preparation, scale-up, and long-term stability. The creation of SNEDDS demands a low dosage, a high log *P* value for the medication, and a low melting point (Shakeel et al. 2016; Kumar et al. 2018; Buya et al. 2020; Rathore et al. 2023).

Benidipine (BD), a dihydropyridine with a calcium channel blocker to reduce blood pressure, was chosen for the present experiment. As an anti-anginal and hypertension drug, it is taken orally. Attributed to its large quantity of hepatic first-pass metabolism and high lipophilicity (log *P* of 4.28), it is a drug of BCS class II with poor oral bioavailability (Kumar et al. 2018). BD bioavailability has been boosted using a number of approaches, such as employing solid dispersions and Nano suspension, but regrettably, they have had little effectiveness (Suzuki et al. 1996; Patel and Patel 2021). Solid-SNEDDS (S-SNEDDS) have been studied for successful delivery of various poorly soluble drugs, such as glibenclamide, talinolol, and rifampicin [13, 18, and 19]. Fortunately, there is no study report on BD's S-SNEDDS that may boost its oral bioavailability.

Quality by design (QbD) and Design of experiment (DoE) are vital for formulation by design (FbD), a systematic approach to formulation design. Originally developed for manufacturing planning, QbD is now widely used in various industries, including pharmaceuticals, to ensure product quality (Karasaka 2015; Beg et al. 2019). Applying QbD principles helps optimize complex drug delivery systems by understanding formulation and process parameters.

The intention of this research was to create a formulation of BD-L-SNEDDS utilizing the QbD design with the objective of increasing the drug's bioavailability and solubility considerably. A central composite design (CCD), a DoE, was utilized to create and optimize formulations of L-SNEDDS that were loaded with BD. The Design Expert® CCD was developed using the Stat-Ease Inc. 13 programed (M/s Stat-Ease Inc., Minneapolis, USA). The oil (Labrafil M2125 CS), surfactant (Kolliphor EL), and co-surfactant (Transcutol P), along with other prevalent product characteristics such as globule size, self-emulsification time, and percentage of the drug released in 15 min, and % of transmission, were designated as the examination's critical material attributes (CMAs). Employing a porous adsorbent like Neusilin US2, BD's optimized L-SNEDDS were converted into flow powders by employing an adsorption technique. The research seeks to evaluate the performance of the suggested S-SNEDDS for rats in vivo compared to the pure drug based on pharmacodynamics investigations and in vitro drug release tests.

2. Materials and methods

2.1. Materials

BD was acquired as a free sample from Nikishan Pharmaceutical (Ankleshwar, Gujarat, India). Cremophor® RH 40 and Solutol® HS 15 were provided by BASF (Mumbai, India). A free sample of Labrafil® M 2125 CS and Transcutol P was offered by Gattefose (Mumbai, India). Tween® 20, Tween® 80, Span® 20, Span® 80, polyethylene glycol 400 (PEG 400), polyethylene glycol 200 (PEG 200), propylene glycol (PG), oleic acid, sunflower oil, sesame oil, olive oil, castor oil, peanut oil, eucalyptus oil, cottonseed oil and sodium lauryl sulfate (SLS) were obtained from SD Fine Chemicals (Mumbai, India). Water that had been repeatedly distilled was the solvent for the entire experiment. All of the additional chemicals employed in this investigation were of the analytical kind. Torrent Research Center (Ahmedabad, India) voluntarily provided empty hard gelatin capsules. Fuji Chemical Industries (Burlington, NJ, USA) provided Neusilin US2, Vardhman Healthcare (Ahmedabad, India) offered Aerosil 200, and Evonik Industries (Mumbai, India) provided Aeroperl 300.

2.2. Setting quality target product profile (QTPP) and critical quality attributes (CQAs)

The QTPP was initially set out to include a probable overview of the medicinal product's superior qualities that may increase benidipine oral bioavailability for the maximum suitable pharmaceutical advantages. This was done by applying FbD-based technology to the manufacturing of solid self-nano emulsifying devices. The QTPP is one of the conditions stated by the product development team via the QbD approach for developing therapeutic effects in compliance with the label claim. To be compatible with the QTPP, medications must exhibit visible qualities, such as globule size and flocculation, burst times (which suggest quicker solubilization of the drug in the gastrointestinal fluid), and other patient-focused quality attributes (QAs). The QTPP-established CQAs were linked to providing the product with important features, safety, and efficacy, demonstrating substantial changes when QTPP is altered (Beg et al. 2015; Vohra et al. 2017).

2.3. Risk assessment

The evaluation of components and process features that have a more substantial influence on the efficacy of the medicine is taken into consideration when generating dosage forms within the framework of quality by design. To

investigate the potential interactions between drugs and assimilating excipients, multiple unit operations were employed. Furthermore, a risk assessment technique was utilized to predict any potential hazards or failures that may arise. Using Minitab 16, The Ishikawa fish-bone diagram, as mentioned in supplementary Figure S1, was devised to expedite the risk assessment process and discover the major probable reasons and small details that have an effect on the CQAs of pharmaceutical items (Katamreddy et al. 2018).

2.4. Screening of oil, surfactants, and co-surfactants

2.4.1. Screening of oils

In the shake flask technique, several modified oils, surfactants, and co-surfactants have been proven to have transparency and rapid emulsification, and these qualities were employed in choosing the oils. Excess BD was transferred to screw-capped vials and mixed (Vortex mixer, Remi, Mumbai, India) for 30 s with 2 mL of each excipient. The container was shaken for 72 h at 120 rpm in a water bath shaker at 37 ± 0.5 °C (Rivotek, Mumbai, India). After 72 h, each container was centrifuged in a lab centrifuge (Remi Equipment, Mumbai, India) for 15 min at 3000 rpm. The supernatant was separated using membrane filtration and filter paper with a 0.45 µm particle size. Methanol had been used to dilute the particular component. The total amount of the solubilized drug was determined using an established equation. The research was performed three times, and the average results were provided (Patel et al. 2019; Jaydip et al. 2020). The excipients chosen were all generally regarded as safe (GRAS) and human-safe.

2.4.2. Surfactant and co-surfactant screening

In order to figure out the most suitable surfactant system for the given oily phase, the emulsification capabilities of different surfactants were examined. In a nutshell, 300 mg of the selected oil phase was mixed with 300 mg of the approved surfactant. To promote the mixing of the oil and surfactant, the liquid was then vortexed for 60 s. This isotropic system was weighed properly at 100 mg and diluted with 25 mL of distilled water to generate a fine emulsion. The number of volumetric flasks required to make a homogenous emulsion has been computed as a measure of the emulsification method's efficiency. After settling for two hours, the emulsions' % transmittance was measured at 638.2 nm using a UV-VIS Spectrophotometer (UV-1800, Shimadzu, Japan). Many surfactants have been evaluated for their capacity to emulsify using double-distilled water as a control in order to discover the optimum surfactant for the specified purpose. Co-surfactants may boost the capacity of nano-emulsification (Rao et al. 2015). By adding 200 mg of surfactant to 100 mg of co-surfactant, a total of 300 mg of Labrafil M2125 CS was added, and the mixture was vortexed to establish homogeneity in order to evaluate the relative effectiveness of surfactants. To make a fine emulsion, the isotropic system was weighed properly and diluted with double distilled water. For measuring emulsification ease, the number of volumetric flask inversions required to achieve a homogenous emulsion was determined. The emulsions were then assessed for transparency at 638.2 nm using double-distilled water as a blank on a UV spectrophotometer. As a result of assessments of solubility, surfactants, and co-surfactants have been employed to emulsify the oil (AboulFotouh et al. 2017).

2.5. Building of a ternary phase diagram

Several lipid-to-emulgent ratios ranging from 1:9 to 9:1 were used to determine the boundaries of the nanoemulsion region. Ternary phase diagrams were constructed at 37 °C, employing chosen surfactants and co-surfactants in varied weight ratios in the oil phase and surfactant to co-surfactant mixer (S_{mix}) (1:1, 2:1, and 3:1). The oil phase and each S_{mix} ratio were correctly incorporated using a vortexing process. The mixtures were vortexed for two to 3 min before even being incubated at 37 °C with constant shaking to establish equilibrium. The transparency of the mixture was tested visually. The nanoemulsion was generated utilizing the sample, which was clear or slightly blue. The clear and isotropic properties of the ternary diagrams were highlighted using oil, surfactant, and co-surfactant (Mendes et al. 2017). Each trial was done three times.

2.6. Preparation of BD-loaded SNEDDS

A preset quantity of oil was poured into a screw-capped glass vial carrying 4 mg of properly weighed BD, which was then heated in a water bath at 37 °C. This oily mixture was mixed with the appropriate surfactant and co-surfactant before being homogenized in a rotating motion. The formulations were then kept at room temperature after one additional 15 min of continuous sonication (Mendes et al. 2017).

2.7. Factor screening studies

A few variables among the countless are revealed in screening tests to explain the majority of the experimental variation, resulting in a phenomenon known as the "sparsity effect." These factor screening tests were done as a resource for building the test to find the core few CMAs and/or critical process parameters (CPPs) that have a major effect on the response variable or CQA. To assess independent variables' influence on major quality features, the impacts of the oil (Labrafil M2125 CS), the surfactant (Kolliphor EL), and the cosurfactant (Transcutol P) were studied (Zhu et al. 2020).

2.7.1. CCD design

To strengthen the formulation, a central composite screening strategy was employed to assess the main impacts of the interaction term of different components on the various SNEDDS characteristics. An SYSTAT version 13 experimental design component is in development for a five-level, three-factor rotating CCD ($\alpha = 1.68$) (SYSTAT Software Inc., Chicago, USA). Eight factorial points and six axial points constituted the design (Abd-Elhakeem et al. 2019; Swain et al. 2019). Table 1 shows the coded value and converted

Table 1. Three-factor CCD experiment design grid with variable coded and experimental values.

S. N.	Independent variables	Dependent variables	Goals for dependent variables
1	Quantity of oil (X_1)	Emulsification time	Minimize
2	Quantity of surfactant (X_2)	Droplet size	Minimize
3	Quantity of co-surfactant (X_3)	%Drug release at 15 min	Maximize
4		% Transmittance	Maximize

value for the planned matrix according to the CCD design batches.

According to Table 2, the extremely important features for investigation in the highly influential formulation have included globule size (D_{nm}), percentage transmittance (%T), self-emulsification time (T_{emul}), and percentage of drug release in 15 min (R_{el15}). Fifteen experimental runs were carried out based on the finalized CCD, with the component factors such as oil ((X_1), surfactant (X_2), and co-surfactant (X_3) as shown in Table 3.

The maximization of drug release within a 15-min time frame in the context of S-SNEDDS of Benidipine is driven by several factors. First, it aligns with the desired pharmacokinetic profile and therapeutic window of Benidipine, ensuring prompt therapeutic effects. Second, it supports the formulation's design objectives of enhancing drug solubility, dissolution, and absorption. Third, it may be influenced by in vitro dissolution testing standards and regulatory requirements for assessing drug release characteristics and bioequivalence. Overall, achieving rapid drug release within 15 min improves therapeutic efficacy, meets formulation objectives, and fulfills regulatory expectations.

These SNEDDS formulations were further evaluated for the previously mentioned important properties. The coefficients for every single component of the primary quality parameters have been calculated as follows after eliminating the interaction effects between the variables using the design's constructed non-linear quadratic model.

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (1)$$

Y_i is the dependent variable, b_0 is the average answer over 15 runs, and b_i is the predicted coefficient for factor X_i. The primary affects (X_1, X_2 and X_3) represent the average outcome of collectively modifying each element from its minimal to its maximum value. When two or more factors undergo modification at the same time, the composition changes, as indicated by the interaction terms (X_1 X_2, X_2 X_3 and X_1 X_3). The inclusion of quadratic factors (X_{12}, X_{22} and X_{32}) is intended to analyze the model's non-linearity.

Also, by developing an overlay plot, the component of the optimum (checkpoint) batch was evaluated. The following formula was employed in determining the percentage of relative accuracy of each answer to assess how effective the model was (Inugala et al. 2015).

$$\%\text{Relative Error} = \frac{\text{Predicted value} - \text{Experimental value} \times 100}{\text{Predicted value}} \quad (2)$$

2.7.2. Assessment of SNEDDS for selected responses

The responses that have been taken into consideration include D_{nm}, %T, T_{emul}, and R_{el15}. Each formulation was diluted with water in a ratio of 1:100 while being gently stirred to ensure uniform distribution of the formulation in the aqueous medium. Using the L-SNEDDS Malvern zeta sizer, the average droplet size in nanometers of all 15 generated formulas was identified. Using a UV–visible spectrophotometer, the transmittance of these solutions was tested at 638.2 nm.

The study was carried out on three separate occasions. The L-SNEDDS self-emulsification efficacy was determined by adding 0.1 mL of each formulation to 100 mL of distilled water maintained at 37 ± 0.5 °C. The formulations were evaluated while the solution was being stirred with a stainless steel paddle at an average speed of 50 rpm. Using USP Equipment II (paddle type) at 50 rpm with 0.1 N HCl as the dissolving media, the in vitro solubility of L-SNEDDS and pure drugs were measured. After suitable dilution and analysis on a UV spectrophotometer at 237 nm, an aliquot of the 5 mL sample was collected at various times. After 15 min, the drug release through various formulations had been assessed (Swain et al. 2019).

2.8. Characterization of L-SNEDDS formulations

2.8.1. Visual characterization

The L-SNEDDS formulation, consisting of BD, has been diluted with 100 mL of distilled water and carefully stirred. The spontaneously generated nanoemulsion was examined for homogeneity, clarity, and drug precipitation (Zhu et al. 2020).

2.8.2. Emulsification time determination

Upon diluting the BD-loaded L-SNEDDS formulations with distilled water, the amount of time required for nanoemulsion formation was observed (Abd-Elhakeem et al. 2019).

2.8.3. Calculating the liquefaction time

Each BD-containing L-SNEDDS mixture was put in an opaque polythene bag, which was then affixed to the thermometer's bulb. The melt time was determined using a thermo-regulated heating mantle to maintain the thermometer with the accompanying formula at 37 °C. For this experiment, a round-bottomed flask containing 250 mL of 2.0% SLS has been employed (Swain et al. 2019).

2.8.4. Cloud point temperature measurement

The temperature at which a clear nanoemulsion becomes cloudy is referred to as the cloud point temperature. This was accomplished by repeatedly increasing the temperature of BD-loaded SNEDDS (1 mL) while stirring them on a hot plate magnetic stirrer until they became a hazy emulsion (AboulFotouh et al. 2017).

2.8.5. In vitro dissolution

The present research employed the USP dissolution test equipment-II paddle technique (Electrolab, test apparatus, USA) to assess in vitro drug dissolution for BD-loaded SNEDDS

Table 2. Variables in CCD for SNEDDS of BD.

Composition and limits of the experimental domain						
		Values				
Factor	Role	−α	−1	0	1	+ α
Labrafil M2125 CS	Oil	13.18	20	30	40	46.82
Kolliphor EL	Surfactant	36.59	40	45	50	53.41
Transcutol P	Cosurfactant	16.59	20	25	30	33.41

Table 3. Design plan of CCD batches for the prepared SNEDDS.

	Coded level			X_1	X_2	X_3
Batch	X_1	X_2	X_3	Labrafil M2125 CS (%)	Kolliphor EL (%)	Transcutol P (%)
BD1	−1	−1	−1	20	40	20
BD2	1	−1	−1	40	40	20
BD3	−1	1	−1	20	50	20
BD4	1	1	−1	40	50	20
BD5	−1	−1	1	20	40	30
BD6	1	−1	1	40	40	30
BD7	−1	1	1	20	50	30
BD8	1	1	1	40	50	30
BD9	−1.682	0	0	13.18	45	25
BD10	1.682	0	0	46.82	45	25
BD11	0	−1.682	0	30	36.59	25
BD12	0	1.682	0	30	53.41	25
BD13	0	0	−1.682	30	45	16.59
BD14	0	0	1.682	30	45	33.4
BD15	0	0	0	30	45	25

formulations. The following conditions were utilized in the dissolution study: 900 cc of the dissolving medium, a 50 rpm paddle speed, and a 37 ± 0.5 °C average temperature. The experiment was done utilizing three separate dissolving mediums, namely simulated gastric fluid (SGF), simulated intestinal fluid (SIF), and distilled water. At specified time intervals of 5, 10, 15, 20, 25, 30, 45, and 60 min, the test solution of 5 mL was calculated and replenished using the same amount of the dissolving medium. Following that, the mixtures were put through a 0.45 µm Whatman filter paper (Whatman, NJ, USA). Before being spectrophotometrically examined at 237 nm using a UV–visible spectrophotometer, the resulting samples were properly diluted. Every sample has been collected three times (Goo et al. 2022).

2.9. Evaluation of optimized formulation of BD

2.9.1. Droplet size and zeta potential measurement

With the help of a Zetasizer Nano, dynamic light scattering (DLS) was used to assess the mean droplet diameter (Z-average) of the modified SNEDDS. For this method, 1 mL of BD-loaded SNEDDS was produced from the stock formulation. It was centrifuged for 15 min at 10,000 rpm. This centrifuged SNEDDS formulation's supernatant solution was extracted and diluted with 5 mL of distilled water. To achieve maximal dispersion, moderate agitation was also used. The polydispersity index, particle size, and zeta potential were all assessed (Garg et al. 2016).

2.9.2. pH

A digital pH meter (Systronics, India Ltd., Ahmedabad, India) was used to test the nanoemulsion pH (Naseef et al. 2018).

2.9.3. Drug encapsulation efficiency

To assess drug entrapment effectiveness, one mL of BD-loaded SNEDDS mixture was prepared and dispersed into 10 mL of methanol. This was rotated at 3000 rpm for ten min. The resulting solution was vortexed, filtered, and diluted with methanol. Using a UV–visible spectrophotometer (UV 1800 Shimadzu, Mumbai, India), the drug's content was analyzed at 237 nm (Naseef et al. 2018).

2.9.4. Rheological study

The viscosity of the developing nanoemulsion was measured using a Brookfield viscometer (Brookfield Engineering Labs, St. Louis, MO, USA) with spindle no. 61 beginning at 20 rpm at 25 °C after the BD-loaded optimized L-SNEDDS formulation was diluted with water in a ratio of 1:250 (Naseef et al. 2018).

2.9.5. Conductivity measurement

A deluxe conductivity meter from MS Electronics (Haryana, India), operating at 50 Hz, was used to test the conductivity. Thermostatic control was employed to keep the temperature at 30 °C with a limit of 0.5 °C (Garg et al. 2016). After dilution with water, SNEDDS were tested for conductivity after dilution with water (1:50).

2.9.6. Thermodynamic stability investigations

Numerous thermodynamic stability tests have been performed using BD-loaded L-SNEDDS formulations, including centrifugation stress testing and heating-cooling cycles (Naseef et al. 2018). For the cooling and heating cycle, the SNEDDS formulation was kept at ambient temperature for no longer than 48 h, and it was additionally kept in a refrigerator between 4 and 8 °C. Each of these setups, all of which are constant at this temperature, was further investigated using centrifugation. After completing the heating-cooling cycle, the formulations underwent a 30 min centrifugation at 3500 rpm. Three freeze-thaw cycles at −21 °C and +25 °C have been carried out for the BD-loaded L-SNEDDS formulations, with storage at each setting lasting at least 48 h.

2.9.7. Robustness to dilution and pH change

To investigate the ways the composition responded when exposed to higher volumes of fluids in the stomach, a dilution analysis of BD-loaded SNEDDS of BD14 in 0.1 N HCL, a phosphate buffer pH 6.8, and water was carried out (Goo et al. 2022). So each sample was routinely screened for purity or precipitation instantly, after 1, 2, and 3 h.

2.10. Preparation of S-SNEDDS

Issues with L-SNEDDS, such as utilizing solid carriers with large surface areas may assist with poor stability, drug

leakage, SNEDDS interactions with capsule shells, etc. This S-SNEDDS combines the advantages of a solid dose form with L-SNEDDS. L-SNEDDS is adsorbable and may be transformed to a combining carriers like Aerosil 200, Aeroperl 300, and Neusilin US2 to develop a free-flowing powder in varying weight ratios of 1:1, 1:1.5, and 1:2 as per Table 4.

L-SNEDDS were introduced gradually to an adsorbent-filled mortar and pestle, mixed for adsorption onto a solid carrier, and then passed through a # BSS 30 sieve to create a consistent, fluid powder (Renugopal et al. 2020; Gausuzzaman et al. 2022). The powder was formed and then put inside of hard Hydroxypropyl methylcellulose (HPMC) capsules for further analysis.

A micromeritic investigation of the powders' bulk density, tapped density, Hausner's ratio (HR), Carr's index (CI), and angle of repose (AR) were conducted as well. As per the literature, bulk density has been employed to determine HR and CI. AR was assessed using the static funnel technique. The flow ability of the porous carriers was examined utilizing the flow property analysis of the micromeritic data. Ultimately, based on these answers, the best solid carrier: L-SNEDDS ratio was selected (Gausuzzaman et al. 2022).

2.11. Characterization of S-SNEDDS

2.11.1. Fourier transform infrared spectroscopy (FTIR) study

The peaks from a FTIR analysis were evaluated to identify compatibility studies between BD, oil, S_{mix}, and Neusilin US2. The FTIR for BD, Neusilin US2, and S-SNEDDS of BD14 were generated as a physical combination using the FTIR-6100 (JASCO, Tokyo, Japan). Using an FTIR spectrophotometer, the substances were scanned from 4000 to 400/cm (Inugala et al. 2015).

2.11.2. Differential scanning calorimeter (DSC)

The metal containers used to keep the samples had crimped lids. The sample and reference pans were constantly heated in the heating chamber from 100 to 400 °C at a scanning rate of 10 °C/min using a stream of nitrogen gas (Goo et al. 2022).

2.11.3. Morphology analysis of S-SNEDDS

Scanning electron microscopy (SEM) was used for evaluating the S-SNEDDS of BD's exterior features. The single-sided tape was used to adhere the S-SNEDDS of BD-14 powder and pure drug samples to aluminum stubs. With such an 8 mm working distance and a 15 kV activating voltage, the gold-coated sample was examined (Gausuzzaman et al. 2022).

2.11.4. Powder X-ray diffraction (PXRD)

Utilizing particle diffraction with X-rays methodologies, the crystalline phase of the pure drug and the S-SNEDDS of BD 14 were studied (Reaven et al. 1988). Using a powder X-ray diffractometer with Ni-filtered C_uK radiation at a voltage of 40 kV and an electrical current of 25 mA, the X-ray diffraction patterns of pure drug and powder S-SNEDDS of BD 14 have been generated. With a scanning rate of 1°/min, the diffraction pattern was examined throughout a 20° range from 10° to 80°.

2.12. In vitro dissolution of S-SNEDDS

In order to evaluate in vitro drug dissolving aspects, S-SNEDDS of BD14 were put in hard HPMC capsules. The loaded capsules were put in a beaker that dissolves in 900 mL of dissolving medium (0.1 N HCl, pH 1.2). For this approach, the regulating strategies were 50 rpm and 37 ± 0.5 °C. Five mL samples were collected, filtered, and, at various intervals, an equivalent volume of the entire medium was added. With the assistance of an UV–visible spectrophotometer, each specimen was studied. Experiments were conducted three times in order to achieve a systematic and consistent mean result (Inugala et al. 2015). The S-SNEDDS of BD14 formulation's drug release profile was derived using a pure drug, the L-SNEDDS of BD14, and the marketed brand Z-Bene, Corazon (A Division Of Arlak Biotech Private Limited), Punjab, India (Inugala et al. 2015).

2.13. Optimization of S-SNEDDS of BD

The quadratic model, encompassing the linear mixture and interactions between two components, was created for all

Table 4. An overview of the CQAs observed for formulations of BD created by the CCD design.

	Average ± SD (n = 3)				
Formulation	T_{emul} (s)	D_{nm} (nm)	$R_{el15min}$ (%)	T (%)	Polydispersity index
BD1	75.67 ± 2.10	186.01 ± 3.10	82.17 ± 1.90	95.67 ± 0.90	0.454
BD2	87.71 ± 2.40	195.23 ± 3.25	83.14 ± 1.95	93.10 ± 0.70	0.258
BD3	68.58 ± 2.25	183.14 ± 3.00	86.11 ± 2.10	98.25 ± 0.50	0.264
BD4	82.12 ± 2.20	191.32 ± 3.30	87.12 ± 1.95	88.00 ± 0.40	0.425
BD5	69.31 ± 2.05	184.23 ± 3.20	84.12 ± 1.90	98.05 ± 0.10	0.331
BD6	83.11 ± 2.80	192.23 ± 3.10	85.65 ± 2.15	85.65 ± 0.90	0.256
BD7	67.37 ± 2.25	184.03 ± 2.90	82.59 ± 1.95	99.10 ± 0.30	0.260
BD8	79.31 ± 2.15	189.10 ± 2.80	86.45 ± 2.10	90.00 ± 0.25	0.265
BD9	67.36 ± 1.90	182.43 ± 2.75	67.25 ± 1.80	91.10 ± 0.50	0.454
BD10	104.21 ± 3.10	199.75 ± 2.90	69.12 ± 1.85	90.10 ± 0.60	0.464
BD11	75.17 ± 2.15	170.12 ± 2.70	81.21 ± 1.75	95.25 ± 0.20	0.421
BD12	70.31 ± 2.80	199.12 ± 2.60	78.74 ± 1.65	87.20 ± 0.30	0.325
BD13	71.14 ± 2.30	164.50 ± 2.50	90.21 ± 1.65	97.67 ± 0.90	0.299
BD14	65.21 ± 1.95	156.20 ± 2.40	92.65 ± 1.70	99.80 ± 0.70	0.250
BD15	69.12 ± 2.05	161.21 ± 2.50	91.32 ± 1.80	98.25 ± 0.50	0.415

the responses using an MLRA approach. Each model was graded based on various statistical criteria, including R^2, Adj. R^2, Pred. R^2 and AP. The significant effect ANOVA's F test, which was done using the Development tool and had a 95% confidence level of P .05, was used to assess the response. Depending on the models for each response, a contour map was constructed. The contour plots of each model were blended to generate an overlay contour plot that was used to find the most appropriate location based on product efficacy (Inugala et al. 2015).

2.14. Pharmacodynamics research

The antihypertensive efficacy of an optimized S-SNEDDS of BD14 and pure BD medicine was tested in adult Wistar albino rats of either sex with weights ranging from 220 to 240 g. The animal center of Accuprec Research Labs Pvt. Ltd. (Ahmedabad, India) provided the animals. The animals were housed in a controlled environment with a 12-h light/dark cycle, a relative humidity of 50–60%, and temperatures of 23 ± 2 °C. Six rats were allocated to each of the four groups: hypertension control, normal control, hypertensive treated with the SNEDDS formulation, and hypertensive treated with normal BD. The method was authorized by Ahmedabad's 20th Institutional Animal Ethics Committee (IAEC) of Accuprec Research Labs Pvt. Ltd. (protocol number: ARI/PT/712/2022). The IAEC approved the requirement for animals, and all research was carried out in conformity with the standards provided by the Council for Supervision of Experiments on Animals, India (Reaven et al. 1988).

The research employed 10% fructose dissolved in the water and administered to Wistar rats to produce hypertension (the equivalent of ingesting a meal with 48–57% fructose) for two weeks, and that was related to higher plasma levels of insulin, glucose, and triglycerides. All of the animals had free access to food and 1 percent NaCl. A tail cuff sensor technique was applied to noninvasively monitor blood pressure after two weeks with a Biopack MP36 data gathering device, the NIBP200A—small animal tail noninvasive blood pressure system (BIOPAC System Inc., USA). Following 2 weeks, systolic and diastolic blood pressure were gathered by employing the Biopack data collection equipment, which represented the hypertension stage in rats except for the control group. All rats having a systolic blood pressure of 150 mm Hg were selected. The species were split into four groups:

Group 1: normal control group
Group 2: Hypertensive control (disease control)
Group 3: Treatment for hypertension formulation (S-SNEDDS of BD)
Group 4: Treatment for hypertension with standard BD suspension

Groups 3 and 4 animals got 2 mg/kg of S-SNEDDS of BD and regular BD suspension (Young and Landsberg 1981; Prajapat et al. 2017). Following administration of test medicines to respective groups, the decline of blood pressure was recorded at separate times (0, 2, 4, 6, and 8 h)

2.15. Accelerated stability research

The optimized S-SNEDDS of BD-14 formulation was submitted to a six-month accelerated stability test in a stability chamber (Nova Instruments Private Limited, Mumbai, India) at 40 ± 2 °C temperature and 75 ± 5% RH. S-SNEDDS BD-14 was packed in HPMC capsules, sealed, and preserved in the stability chamber in a glass container with a cotton stopper. After 0, 1, 2, 3, and 6 months, the specimens were removed from the stability chamber and examined in 15 min for emulsification efficiency, globule size, percent transmittance, and release of drugs (Prajapat et al. 2017).

2.16. Statistical evaluation

The results from multiple formulations were compared for statistical significance by utilizing a non-parametric Kruskal–Wallis test. Each analysis of variance (ANOVA) for the derived parameters had a relevance level of P at 0.05. Every piece of information was presented as a mean ± SD.

3. Results and discussion

3.1. Target product profile

The main characteristics of the L-SNEDDS of BD are laid out, including the preparation type, therapeutic dose and strength, action processes and mechanisms, pharmacokinetics, packaging, and storage requirements.

3.2. Critical quality attributes

The primary formulation features for the L-SNEDDS of BD were found as the CQAs from TPP components examined in the formulation. Further, the rationale behind using CQAs and their influence on the medicinal efficacy of the L-SNEDDS of BD was examined. Fishbone illustration was developed to illustrate how key material characteristics, and manufacturing process variables, influenced the manufacture of S-SNEDDS for BD. Also, a sequential exercise was conducted to select the components that presented a high risk by creating a risk evaluation.

3.3. Risk evaluation

The Ishikawa fishbone depiction for the S-SNEDDS was designed to depict a cause-and-effect relationship between the potential factors that impact drug CQAs. The CQAs for BD-S-SNEDDS, along with a synopsis of each one, were examined for early risk assessment studies. Due to the severe risks that they encounter from CQAs, three factors—the amount of lipid, surfactant, and co-surfactant—were discovered to be highly relevant. In contrast, process factors including the kind of stirrer being used, the length of stirring, and the agitation speed were determined to be part of a medium level of risk. Using the above methodologies, early risk estimation tests revealed that these three factors were significantly essential

3.4. Preliminary investigations

3.4.1. Excipients screening

The solubility of the drugs in the oil is the major element controlling the degree to which the SNEDDS formulation preserves the drug in the solubilized condition during storage. Oil has been proven to boost the medicine's intestinal permeability while also delivering the greatest medication solubility achievable. Figure 1(a) illustrates the bar chart describing the solubility of BD in various oils, which was determined to be in the following order: eucalyptus oil < sunflower oil < sesame oil < castor oil < peanut oil < olive oil < soybean oil < oleic acid < Labrafil M 2125 CS. Labrafil M 2125 CS was chosen as the oil having the maximum solubility for the drug being used. Nonionic surfactants are frequently chosen for oral consumption since they have been considered to be safer than ionic surfactants. They are also expected to increase the nanoemulsion stability across a larger pH and ionic strength range. Additionally, they may reversibly change the gut mucosa to enhance the absorption of any co-administered drug. In the objective of finding which nonionic surfactants had the optimal hydrophilic lipophilic balance (HLB) for emulsifying the chosen oil and solubilizing the medication (Patel et al. 2019), the bar chart in Figure 1(b) depicts the drug's solubility in surfactants, which were discovered to be in the following sequence: Tween 20< Span 20 < Tween 80 < Span 80 < Solutol HS 15< Chromophore RH 40< Kolliphor EL. BD solubility studies done in different excipients and buffers at 37 °C. The capability of the surfactant to spontaneously emulsify oil when diluted with distilled water served as one of the selection criteria. The number of inversions and the % transmission utilized to establish the emulsification abilities of different surfactants and co-surfactants had been written down.

Thus, based on the outcomes of the emulsification and solubility studies, Kolliphor EL was selected as a surfactant for further evaluation. The co-presence of surfactants provides the surfactant layer with the proper flexibility and assists in the development of the different curvatures essential for the synthesis of nanoemulsion in a range of compositions. The co-surfactant enhances the region accessible for the production of nanoemulsion by reducing surface tension even more and fluidizing the surfactant layer (Reaven et al. 1988). Figure 1(c) exhibits a bar graph demonstrating a drug's solubility in co-surfactants, of all of the co-surfactants that were investigated had the drug's solubility in the following order: PEG-400< PEG-200< PG < Transcutol P. Transcutol P was identified as a co-surfactant based on its solubility and the percentage of transparency of the generated emulsions. Finally, Labrafil M 2125 CS, Kolliphor EL, and Transcutol P were selected as the oil, surfactant, and co-surfactant, respectively, based on the findings of the tests of solubilization capacity and emulsification efficiency.

3.4.2. Ternary phase diagrams

In the beginning, ternary phase diagrams were produced using Labrafil M 2125 CS (oil), Kolliphor EL (surfactants), and Transcutol P (co-surfactant) at 1:1, 2:1, and 3:1 ratios for determining the largest area for the production of thermodynamically stable nanoemulsion, as shown in Figure 2. The oil and S_{mix} were combined in different quantities ranging from 9:1 to 1:9. An outstanding nanoemulsion region was observed between Labrafil M 2125 CS, Kolliphor EL, and Transcutol P, which may be attributed to the emulsification of oil by a sole surfactant and a co-surfactant. After being diluted with 100 mL of water and 0.1 mL of SNEDDS, they received a score based on their calculated opacity and percent transmittance. For further testing and drug loading, only clear and transparent mixtures were selected. The ratio of 3:1 between the three combinations was proved to be the best region for nanoemulsion. The self-nano emulsifying system's clarity increased when the concentration of S_{mix} was elevated while the concentration of oil was dropped. Additionally, the surfactant decreased the interaction between the oil and the water, allowing SNEDDS to disperse more rapidly in an aqueous medium and reduce particle size when diluted with water (Rao et al. 2015).

3.4.3. Effect of BD on the phase diagram

Figure 2 depicts the way different amounts were taken into account when assessing the quantity of oil, surfactant,

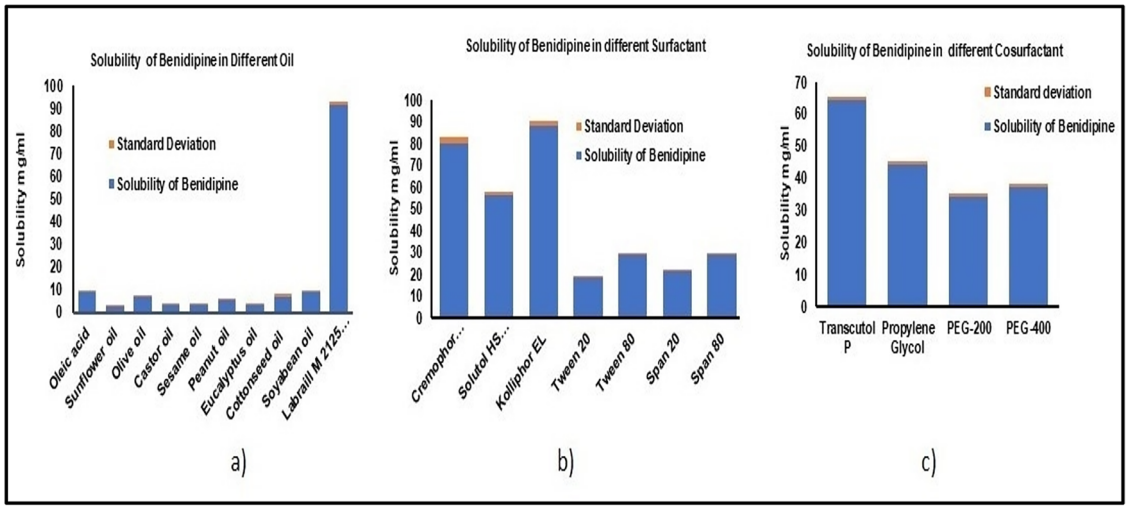

Figure 1. (a): Solubility of BD in various oil, (b) solubility of BD in different surfactants and (c) solubility of BD in different co-surfactants.

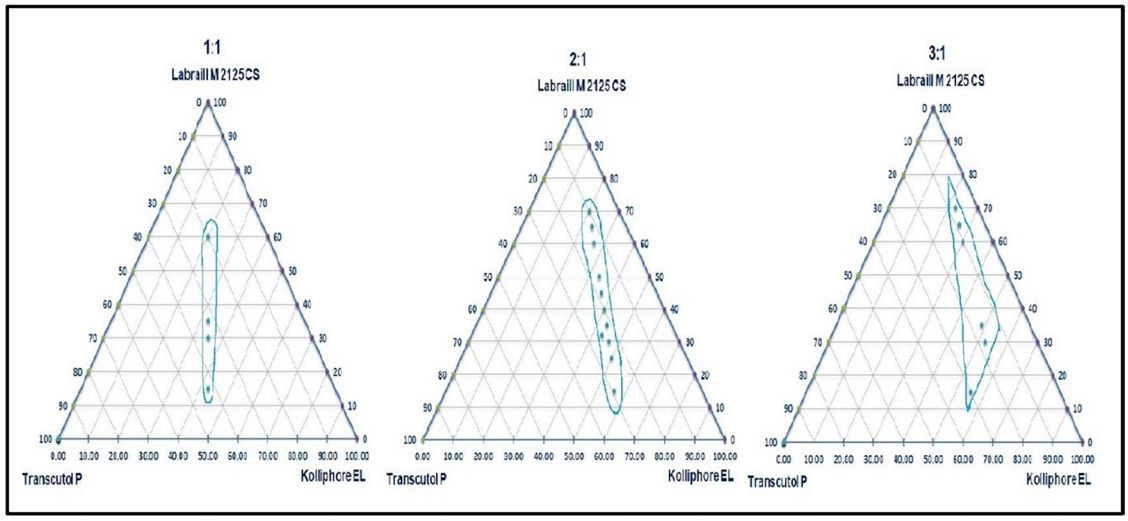

Figure 2. Ternary phase diagrams of the o/w emulsified regions of 1:1, 2:1, and 3:1 ratios of Labrafil M 2125 CS, Kolliphor EL, and Transcutol P.

Table 5. Regression assessment of batches of BD-loaded SNEDDS from CCD.

Model	df[c]	SS[d]	MS[e]	R^2
T_{emul} (s) ($Y_{1)}$				
Regression				
FM[a]	9	1426.438	158.4931	0.9509
RM[b]	2	1298.969	649.4844	0.8659
Residual				
FM	5	73.7113	14.7423	$F_{cal}=1.2352$
RM	12	201.1803	16.7650	$F_{critical}=4.88$ df= (7,5)
D_{nm} (μ) ($Y_{2)}$				
Regression				
FM	9	2028.2927	225.3659	0.9025
RM	2	855.0392	427.5196	0.8648
Residual				
FM	5	563.7756	112.7551	$F_{cal}=1.4865$
RM	13	1737.0292	144.7524	$F_{critical}=4.88$ df = (7,5)
$\%Rel_{15\,min}$ ($Y3$)				
Regression				
FM	9	616.350	68.483	0.9229
RM	3	463.466	154.488	0.9201
Residual				
FM	5	107.208	21.441	$F_{cal}=1.1884$
RM	11	260.092	23.645	$F_{critical}=8.94$ df = (6,3)
%T ($Y4$)				
Regression				
FM	9	225.910	25.102	0.9255
RM	1	94.906	94.907	0.8378
Residual				
FM	5	95.953	19.190	$F_{cal}=0.05202$
RM	13	226.956	17.458	$F_{critical}=3.73$ df = (8,7)

[a]FM, Full model;
[b]RM, Reduced model;
[c]Non-significant ($P>.05$) coefficients.

and co-surfactant that should be included in the BD nanoemulsion system. The key three formulation constituents of the nanoemulsion were Transcutol P, Kolliphor EL, and Labrafil M 2125 CS. When a hydrophobic drug (BD) is entrapped in the SNEDDS, the self-emulsifying performance diminishes.

In addition, the drug may precipitate in a 1:1 ratio. In the present experiment, integration with BD in the 1:1 ratio dropped the efficient self-emulsifying efficiency, although there was no change in the 3:1 ratio.

3.5. SNEDDS optimization using experimental design

Design Expert 13 was hired to develop the experimental pattern. Table 4 provides a summary of the CQAs observed for formulations of BD prepared in accordance with the CCD design for the response variables (Y_1), transmittance percentage (Y_2), self-emulsification time (Y_3), and percentage of drug release in 15 min (Y_4). Other characteristics, such as the use of multiple regression analysis, are utilized to examine the generated SNEDDS, and the CCD model has been designed to fit the 2nd-order polynomial model. The outcomes of a regression analysis of the CCD categories of BD-loaded SNEDDS are provided in Table 5.

The mathematical link between the evident replies and a polynomial equation was identified. Quadratic polynomial equation-according to the following equation:

$$Y_1(\text{Emulsification time}) = 68.987 + 8.295X_1 - 1.947X_2 - 1.827X_3 - 0.045X_1X_2 + 0.867X_2X_3 + 0.02X_1X_3 + 6.075X_1^2 + 1.463X_2^2 - 0.150X_3^2 \quad (3)$$

$$Y_2(\text{Droplet size}) = 159.595 + 4.364X_1 + 2.830X_2 - 1.469X_3 - 0.496X_1X_2 + 0.431X_2X_3 - 0.541X_1X_3 - 0.541X_1X_3 + 12.798X_1^2 + 10.510X_2^2 + 1.930X_3^2 \quad (4)$$

$$Y_3(\%\text{Drugreleaseat15min}) = 90.264 + 0.769X_1 + 0.222X_2 + 0.320X_3 + 0.296X_1X_2 - 1.081X_2X_3 + 0.426X_1X_3 - 6.719X_1^2 - 2.550X_2^2 + 1.499X_3^2 \quad (5)$$

$$Y_4(\%\text{Transmittance}) = 98.203 - 2.636X_1 - 0.780X_2 + 0.099X_3 - 0.547X_1X_2 + 0.99X_2X_3 - 1.085X_1X_3 - 2.639X_1^2 - 2.418X_2^2 + 0.236X_3^2 \quad (6)$$

In opposition to a negative symbol, which indicates an antagonistic influence, a positive sign indicates a synergistic

Table 6. Outcomes of the ANOVA test for the BD-loaded SNEDDS.

	T_{emul} (s)(Y_1)		D_{nm} (Y_2)		%$R_{el15\,min}$ (Y_3)		%T (Y_4)	
Coefficients	FM[a]	RM[b]	FM	RM	FM	RM	FM	RM
b_0	68.987	70.604	159.595	175.26	90.264	88.940	98.203	93.812
b_1	8.295	8.295	4.364	–	0.769	–	−2.636	−2.636
b_2	−1.947	–	2.830	2.8301	0.222	0.222	−0.780	–
b_3	−1.827	–	−1.469	–	0.320	0.320	0.099	–
b_4[c]	−0.045	–	−0.496	–	0.296	–	−0.547	–
b_5[c]	0.867	–	0.431	–	−1.081	–	0.99	–
b_6[c]	0.02	–	−0.541	–	0.426	–	−1.085	–
b_7	6.075	5.572	12.798	8.028	−6.719	−6.316	−2.639	–
b_8[c]	1.463	–	10.510	–	−2.550	–	−2.418	–
b_9[c]	−0.150	–	1.930	–	1.499	–	0.236	–

[a]FM, full model;
[b]RM, reduced model;
[c]df, degree of freedom;
[d]SS, sum of squares;
[e]MS, mean of squares.

effect. Table 6 summarizes the results of the ANOVA analysis for BD-loaded SNEDDS. Using contour plots and response surface plots, the connection between the dependent and independent variables has been further examined.

3.5.1. Composition elements' impact on responses

According to the results of the regression analysis, X_1 (oil) showed a positive sign, while X_2 (surfactant) and X_3 (co-surfactant) showed negative signs. Investigations revealed that, among all independent parameters, variations in the quantity of oil and surfactant greatly impacted drop size. The emulsification process presumably slowed and decreased as the formulation's amount of oil increased, the size of the drops increased, and it became more lipophilic (Reaven et al. 1988). The modified R^2 and the projected R^2 show that they are effective is released. There is a tremendous quantity of surface area accessible for drug and GIT absorption because of the wide range of nanoscale sizes in the droplets (Reaven et al. 1988). Droplet sizes in the emulsion ranged from 156.20 ± 2.40 to 199.75 ± 2.90 nm. The quadratic polynomial equation previously stated is used to figure out droplet size. Contrarily, the amount of Transcutol P has an adverse effect on drop size, which indicates that as the amount of Transcutol P increases, the drop size decreases (Inugala et al. 2015). The model's importance was established by its F value of 1.4865, and the importance of each model parameter was emphasized by its p values of less than 0.05. The projected R^2 is in a considerable amount of agreement with the modified R^2, demonstrating their practical consistency with the standard as experimentally coded.

For planned batches, a range of 78.74% to 92.65% of the drug was released at the scheduled 15-min interval. The only independent variable whose modification dramatically impacted CPR_{15} was the oil content. To create a nanoemulsion, the compositions needed to be blended properly; changing the quantity of any one composition would have an impact on the system's overall balance, which was essential to keeping the drug solubilized (Garg et al. 2016). The quadratic polynomial equation stated earlier can be used to determine the drug release percentage after 15 min. The model's F value of 1.1884 was examined using an ANOVA and found to be significant. If the p-value is less than 0.05, the model terms (independent variables) are presumably useful in predicting the outcome. It was evident that the independent factors significantly affected outcome prediction, with an R^2 of 0.9229. There is a fair degree of agreement between the estimated R^2 and the adjusted R^2.

The outcomes for percent transmittance varied from 85.65 ± 0.90 to 99.80 ± 0.70%. The SNEDDS dispersion was transparent and clear, with a broad range of nanometer-sized droplets and a transmittance score based on a percentage of around 100%. Clear solutions have higher transmittance values than turbid solutions due to increased scattering of the incoming radiation. The influence of factors on the response rate of transmittance is shown in the cubic polynomial equation for determining transmittance. The findings of the regression analysis revealed that while the quantity of co-surfactant had little influence on transmission, the proportion of oil to surfactants was affected. The oil amount exhibited a weak correlation with the outcome measure, as demonstrated by the oil amount's (X_1) negative coefficient. The transmission percentage dropped as the quantity of oil increased in the constant weight formulation. This was made possible because as the composition changed, the oil level increased, becoming less transparent and more lipophilic (Rani and Radha 2023).

3.5.2. Response surface and contour plot analysis

To demonstrate the connection between the dependent and independent elements and to explore their interactions, two-dimensional contour plots and three-dimensional surface response plots were constructed. Figures 3 and 4 represent the results of the response surface and contour diagram, respectively. The corresponding fall in globule size with a decrease in oil concentration may be explained by an immediate increase in surfactant concentration, which may swiftly emulsify the oil phase and lower the globule size. The lack of surfactant may have contributed to the prolongation of the emulsification process as the oil concentration grew. To minimize the amount of free interfacial energy and function as a mechanical barrier that hampers emulsion coalescence, surfactant molecules cling to the outermost emulsion droplets. As a consequence, an arbitrary thermodynamic dispersion evolved (Zafar et al. 2022). As a consequence, increased concentration enhances emulsification and drug absorption.

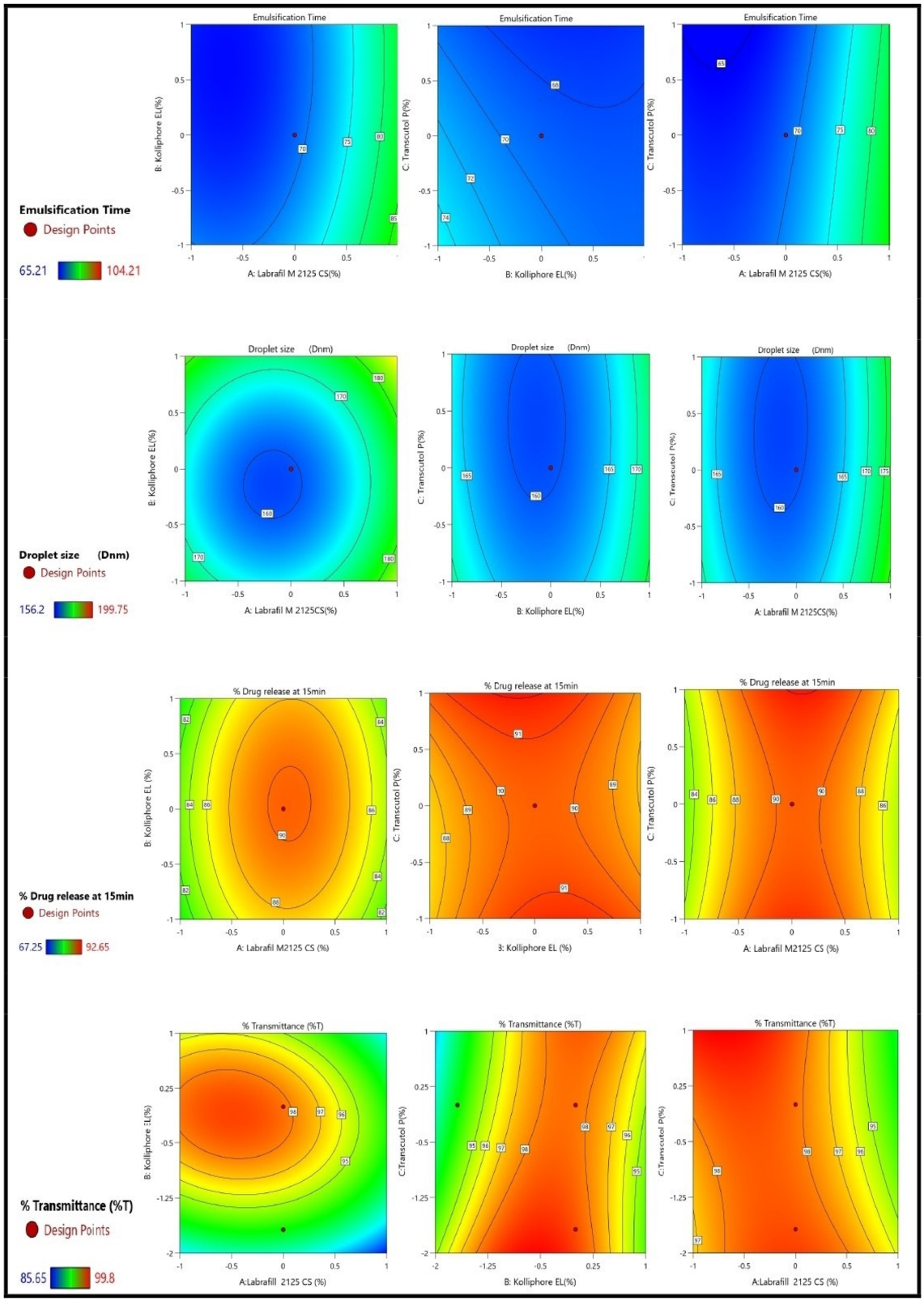

Figure 3. 2D model graphs extracted from the DoE software displaying the influences of selected in dependent variables on the dependent responses throughout preparation of self-emulsifying drug delivery systems.

3.5.3. Identification and evaluation of optimum formulation using desirability function

All of the responses in the present investigation were subject to restrictions, and a method of desired functionality was adopted. An optimal formulation was constructed based on the desired functions, and response characteristics. Globule size, % transmittance, self-emulsification duration, and % drugs dissolved in 15 min were measured. The relationship between the expected and actual variable components was studied (Figure 5).

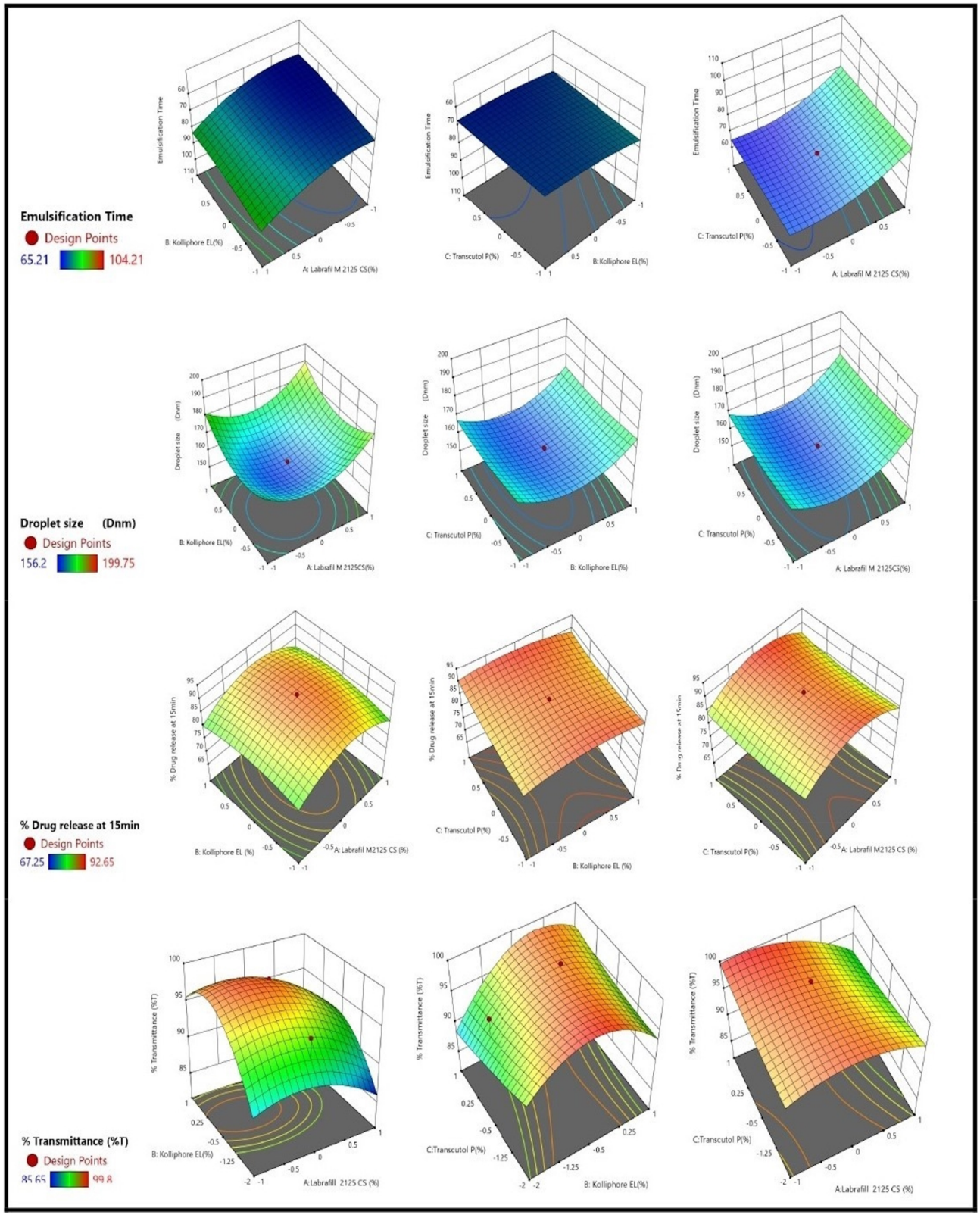

Figure 4. Response surface plots generated from the DoE program exhibiting the impacts of chosen in dependent variables on the dependent responses during construction of self-emulsifying drug delivery systems.

Other features of the altered composition were analyzed. The mean droplet size and emulsification time were decreased in the responses while improving transmittance as well as drug release within 15 min. All of the responses received equal time. The formulation that achieved all of the maximum response variables and offered the optimum desirability function was chosen. X_1 = 30.0%, X_2 = 38.0%, and X_3 = 40% w/w of the selected formulation were assessed to have an overall impact of 0.987. For the responses Y_1, Y_2, Y_3, and Y_4, Table 7 gives both the predicted and actual values.

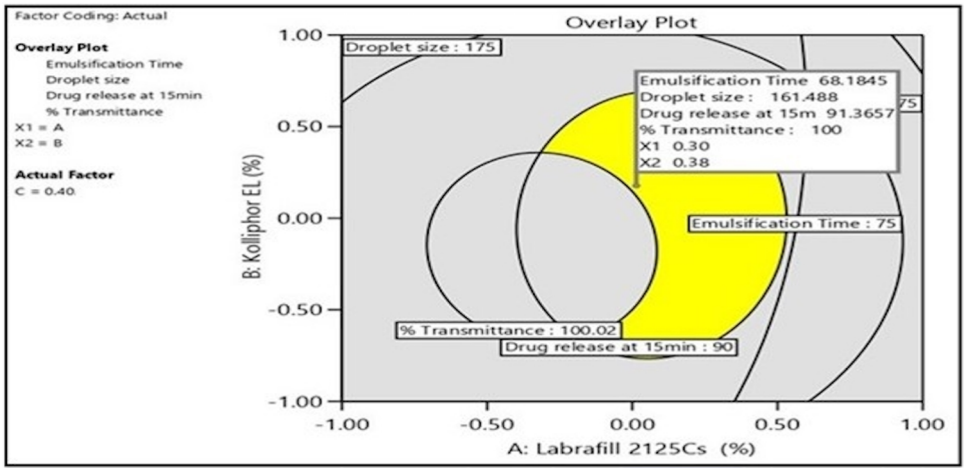

Figure 5. Overlay plot for optimized formulation of BD-loaded-SNEDDS.

Table 7. Predicted and measured values for optimized BD-loaded SNEDD.

Response	Predicted value	Experimental value[a]	% Relative error
T_{emul} (s) ($Y_{1)}$	68.1845	67.25 ± 1.875	1.389
D_{nm} (μ) ($Y_{2)}$	161.488	162.25 ± 3.50	−0.478
$\%Rel_{15\,min}$ (Y_3)	91.3657	90.15 ± 2.15	1.33
%T (Y_4)	100	99.50 ± 1.78	0.5

[a]Values are of mean ± SD ($n = 3$), SD: Standard deviation

3.6. Assessment of drug-loaded optimum formulation

3.6.1. Evaluation and dilution of opposition

The clarity of the drug-loaded, optimized liquid SNEDDS (BD14) was visually appraised. It was proven to be homogeneous and optically clean, with a light yellow color. It did not show any indication of precipitation or production processes.

3.6.2. Robustness to dilution

SNEDDS are pre-concentrates that only produce o/w nanoemulsion after dilution; phase separation issues arise when the formulation is exposed to indefinite dilution in GI fluids. Drugs with pH-dependent solubility may precipitate as a result of these pH shifts (Rani and Radha 2023). In order to prevent this, optimum liquid SNEDDS (BD14) was diluted in 0.1 N HCl and phosphate buffer pH 6.8 10 times, 100 times, 250 times, 500 times, and 900 times by volume. There was no indication of phase separation in any of the formulations examined. Interestingly, droplet size dropped as the pH level and the dilution factor rose from 10 to 500 times. It was obvious in Figure 6 that upon enhancing the availability of surfactants at the oil-water interface, droplet dispersion improved, which dropped the dilution factor to a particular level and resulted in the creation of uniform and smaller droplets. A slight rise in zeta potential has been detected along with the change in pH and after increasing the dilution factor from 10 to 900 times. Despite this, these modifications indicated the integrity of SNEDDS in nano-form when the gastrointestinal tract's volume and pH were varied. This established the potential of increased SNEDDS formulation to create nanoemulsions at different physiological pH.

3.6.3. Self-emulsification time

It is the time needed after dilution with water for the L-SNEDDS to generate uniform dispersion. When exposed to dilution while still being gently stirred, the SNEDDS should scatter totally and swiftly. The enhanced formulation's self-emulsification time was 65.21 ± 1.95 s. Reduced T_{emul} levels in the present studies supported the spontaneity of the L-SNEDDS-generated nanoemulsions' emulsification.

3.6.4. Drop size and zeta potential

The nanoemulsion particle size plays an essential role in the self-emulsification process. The quantity of drug released from the ideal SNEDDS formulation is significantly influenced by the drop size of the developed nanoemulsion. The enlarged interfacial area for drug release is formed by the nanoscale droplets. The range of the allowable nanoemulsion definition (10–200 nm) was substantially within the range of the average drop size of the nanoemulsion formed by the drug loaded optimized SNEDDS formulation, which was around 156.20–199.75 nm as seen in Supplementary Figure S2. According to Table 4, the PDI value was 0.250–0.450, demonstrating the narrow dispersion of declines. The value of the zeta potential of −15.21 to −21.45 mV for the produced nanoemulsion, as given in Table 4, demonstrated excellent stability. Phase separation is maintained as a result of a significant electrostatic repulsive force that precludes droplet coalescence (Panigrahi et al. 2018).

3.6.5. Transmittance test

The clean, transparent, and nanosized globules have been seen, and the percent transmittance was 99.80 ± 0.70%.

3.6.6. Cloud point measurement

The measured cloud point temperature is 69.9 ± 1.5 °C, while the normal body temperature is 37 °C. In considering this, it can be claimed that the newly developed formulation was steady in vivo at physiological temperature and did not show phase separation when stored at room temperature or when given via the digestive system (Mohd et al. 2015).

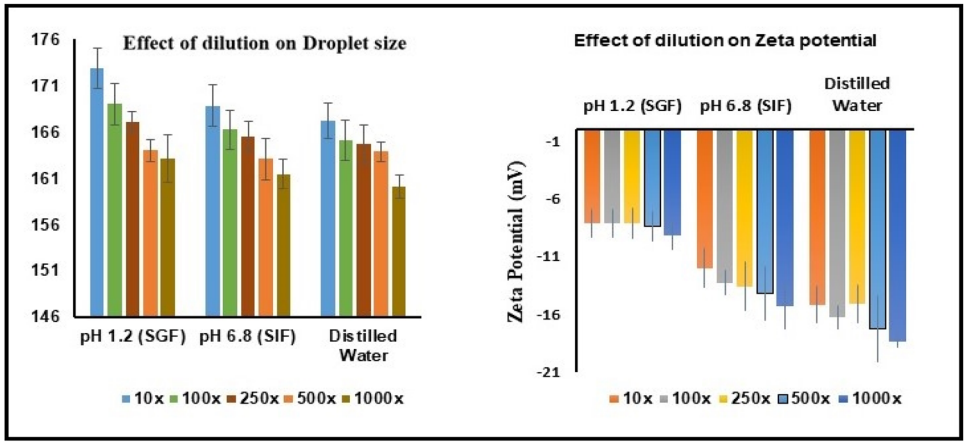

Figure 6. Dilution investigations on droplet size and zeta potential.

Table 8. Evaluation of SNEDDS BD1 to BD15 formulation of design.

	Average ± SD (n = 3)				
Formulation	Liquification time[a] (s)	Viscosity[a] (centi poise)	Zeta potential[a] (mV)	Cloud Point[a] (°C)	Refractive index[a]
BD1	70.50 ± 2.50	140 ± 1.63	−15.23 ± 0.84	73.2 ± 1.9	1.762 ± 0.12
BD2	82.25 ± 2.80	158 ± 2.55	−17.51 ± 0.60	73.9 ± 1.7	1.789 ± 0.18
BD3	65.10 ± 2.30	132 ± 2.55	−20.52 ± 0.84	69.7 ± 1.1	1.745 ± 0.14
BD4	79.10 ± 2.85	152 ± 1.40	−19.56 ± 0.85	74.4 ± 1.5	1.752 ± 0.13
BD5	66.15 ± 1.80	137 ± 2.10	−21.21 ± 0.30	75.6 ± 1.7	1.742 ± 0.12
BD6	80.20 ± 2.80	154 ± 2.40	−19.32 ± 0.64	72.8 ± 2.2	1.761 ± 0.12
BD7	65.10 ± 2.10	125 ± 1.30	−18.95 ± 0.56	85.6 ± 2.6	1.757 ± 0.17
BD8	75.20 ± 2.40	148 ± 2.40	−21.45 ± 0.30	83.7 ± 2.8	1.780 ± 0.18
BD9	64.75 ± 1.87	110 ± 1.90	−18.63 ± 0.30	75.8 ± 1.7	1.739 ± 0.14
BD10	95.20 ± 2.70	175 ± 2.20	−19.12 ± 0.20	79.6 ± 1.7	1.773 ± 0.17
BD11	72.20 ± 2.60	141 ± 1.60	−16.12 ± 0.24	64.2 ± 1.5	1.798 ± 0.20
BD12	67.50 ± 1.90	118 ± 1.92	−21.23 ± 0.18	71.5 ± 2.2	1.765 ± 0.19
BD13	69.25 ± 1.95	145 ± 2.15	−15.21 ± 0.20	68.9 ± 1.7	1.761 ± 0.12
BD14	62.20 ± 1.70	125 ± 1.50	−17.36 ± 0.18	69.9 ± 1.5	1.752 ± 0.14
BD15	64.50 ± 1.65	136 ± 1.75	−16.50 ± 0.24	70.5 ± 1.9	1.765 ± 0.18

[a]Values are of mean ± SD (n=3), SD: Standard deviation

3.6.7. Determination of the refractive index

The optimized formulation's refractive index came out to be 1.752 ± 0.14 (Table 8), experiencing the isotropy of the nanoemulsion.

3.6.8. Thermodynamic stability investigations

When evaluated at different temperatures, these cycles revealed that the optimized formulation was stable and did not exhibit any signs of drug precipitation or phase separation.

3.6.9. %Drug content

The optimized formulation's percentage drug content of 99.22 ± 0.29% indicated that the SNEDDS formulation possessed a consistent drug distribution.

3.6.10. Conductivity test

To anticipate the kind of nanoemulsion created during dilution, the electrical conductivity of the optimal BD-loaded SNEDDS formulation was examined. The conductivity of o/w emulsions in BD-loaded systems was reported to be 0.193 µS/cm.

3.7. Evaluation of the DoE batches' in vitro drug release

In-vitro drug released study of aqueous suspension of Benidipine and developed batches of Benidipine, BD1 to BD15 is shown in Supplementary Figure S3. When developing SNEDDS, surfactants, and co-surfactants were used, which may spontaneously emulsify the oil into much thinner droplets (less than 200 nm) while affording a significant surface area for drug release on objects (Panigrahi et al. 2018). In essence, the pure drug and the marketed product could only discharge 45% and 40% of the drug, respectively, compared to the intended batches. All produced SNEDDS formulations proceeded to release the drug progressively until the steady state was achieved at 1 h. By that time, the cumulative drug release for formulations BD13, BD14, and BT15 was >99%, whereas for formulations BD1, BD6, BD7, BD8, BD9, BD10, BD11, and BD12, it was 95. Among the 15 formulations, BD14 exhibits a smaller droplet size, shorter emulsification time, higher transmittance, and greater drug release compared to the other formulations. As a result, BD14 was selected as the optimal formulation for further investigation.

3.8. Flow property of various pores carriers

The study's results were presented utilizing several micromeritic characteristics such as AR, CI, HR, and flow rate. Three characteristics were employed to improve the S-SNEDDS formulation: oil absorption power, in vitro dissolving rate, and flow conditions (Gausuzzaman et al. 2022). In contrast to Aerosil 200 and Aeroperl 300, Neusilin US2 has the greatest oil absorption capability. As can be noted, the drug with the highest content as well as the smoothest and most dry appearance, L-SNEDDS: adsorbent (1:1.5), was determined to have outstanding flow characteristics and flow rate in Neusilin US2 when compared to L-SNEDDS: adsorbent (1:1 and 1:2). As a consequence, Neusilin US2, L-SNEDDS: Adsorbent (1:1.5), had been selected as the pore's carrier in the mixture with the highest percentage of drug content and drug release to facilitate a subsequent investigation.

3.9. In vitro characterization of S-SNEDDS of BD

An investigation was done to find out if the composition of BD as S-SNEDDS could speed up the process of dissolution. When S-SNEDDS are exposed to the dissolving liquid, their solid structure dissolves, and L-SNEDDS are capable of being released from adsorbent gaps. L-SNEDDS were then spontaneously distributed into small globules with large interfacial areas, which demonstrated better solubilization (Renugopal et al. 2020). In contrast to the values of 58.80% and 60.15% that Figure 7 indicates, L-SNEDDS and S-SNEDDS demonstrated that pure drug and a commercial specimen of BD delivered more than 85% of their contents after 15 min and 100% within 60 min. The dissolution profile of Benidipine was assessed by comparing it with a solid dispersion (SD) that was prepared using a fusion method induced by microwave. The SDs created through the microwave method exhibited a maximum cumulative release of 60.67 ± 6.53% after 30 min (Vyas et al. 2022). On the other hand, the Optimized S-SNEDDS of BD14 achieved a release of more than 85% within just 15 min. Therefore, it can be concluded that S-SNEDDS outperformed the solid dispersion of BD in terms of dissolution characteristics.

The drug released from liquid SNEDDS in 0.1 N HCl after the first 5 min was faster than from the S-SNEDDS formulation. This delay in medicine release for S-SNEDDS may be attributed to the desorption process from the adsorbent carrier. The produced batches of S-SNEDDS of BD may release more than 85% of the medication in roughly 15 min ($f2 < 50$). The capacity of the SNEDDS formulation to release the drug directly in its solubilized state in a dissolving fluid may have contributed to the increased release of drug from the optimized batches (Panigrahi et al. 2018).

Since it is predicted that liquid SNEDDSs can be held in the pores of solid carriers, the size, shape, and length of the holes, coupled with a specific surface area, play crucial roles in the dissolving behavior of these systems (Mohd et al. 2015). NeusilinUS2, which was utilized as a solid carrier in this investigation, has a wide surface area and large pores (Sharma et al. 2020); consequently, we believed that liquid SNEDDSs filled the intraparticular holes of the adsorbent.

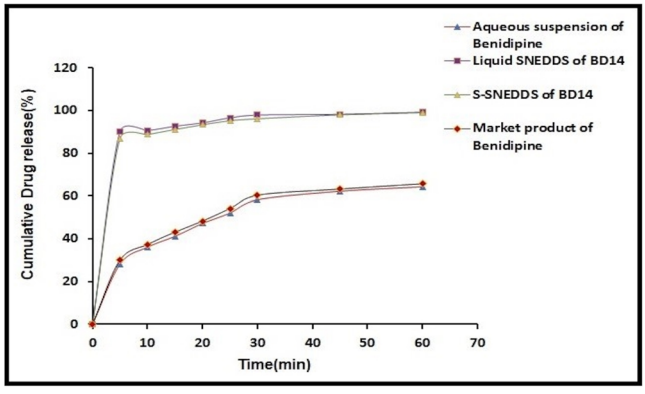

Figure 7. Comparative in vitro drug release studies of BD aqueous suspension, BD-L-SNEDDS, BD14-S-SNEDDS, and BD marketed product.

3.10. Characterization of S-SNEDDS

3.10.1. FTIR

The FTIR spectra of Neusilin US2, BD, a physical mixture of Neusilin US2 and BD, and S-SNEDDS of BD14 are shown in Figure 8. The S-SNEDDS of BD14 showed the characteristic peaks of both BD and Neusilin US2, showing that the drug was still present in the mixture and had not experienced any molecular changes or interactions with carriers (Labrafil M2125 CS, Kolliphor EL, Transcutol P, and Neusilin US2).

3.10.2. DSC

A significant endothermic peak was seen in the pure BD DSC thermogram at exactly 226.02 °C, which correlates to the melting point of the material as illustrated in Figure 9. In the case of S-SNEDDS BD14, the drug's endothermic peak was 106.21 °C. The ability of SNEDDS to suppress BD

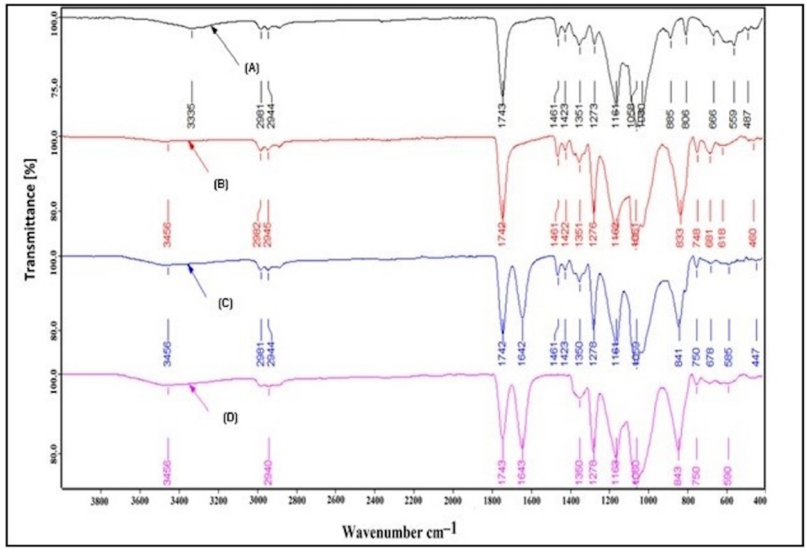

Figure 8. FTIR spectra of (A) Neusilin US2, (B) physical mixture of BD and Neusilin US2, (C) BD, and (D) S-SNEDDS BD14.

crystalline and solubilization may be associated with BD enhanced melting behavior. It may consequently seem to transform from a crystalline to an amorphous form, which might significantly increase water solubility (Young and Landsberg 1981).

3.10.3. Morphology evaluation of S-SNEDDS

SEM images of BD (Figure 10A) and S-SNEDDS BD14 can be seen in Figure 10(B). Since S-SNEDDS of BD had smooth surface particles that aggregated to generate bigger particles without crystalline morphology, the drug showed up in SEM images as tiny, irregularly shaped particles with a rough outside surface. This suggested that L-SNEDDS could have a considerable influence on the Neusilin US2 surface.

3.10.4. PXRD

Figure 11 displays the PXRD trends for S-SNEDDS, Neusilin US2, and BD. S-SNEDDS lacked significant peaks that could be recognized as drug peaks, while BD showed significant, identifiable peaks. The S-SNEDDS Diffractogram suggests that changeover would happen through an amorphous shape.

3.11. Pharmacodynamics research

Fructose administration was successful in inducing hypertension in Groups II, III, and IV rats, as evidenced by the highly substantial ($p < 0.001$) difference in BP recorded when compared to Group I, as shown in Figure 12. This group has been referred to as the control group. The studies show that BD14 and S-SNEDDS have a greater increase in pharmacodynamics effects than BD in suspension form. Table 9 depicts the systolic, mean, and diastolic blood pressure readings with standard error of measurement (SEM) for each group, including the normal control group (G1), hypertensive control (G2), benidipine SNEDDS (G3), and pure BD (G4). However, the S-SNEDDS of BD (BD14) demonstrated a more significant increase in its bioavailability than the drug in suspension form, as seen in Table 9. A comparable difference may be observed in systolic and diastolic activity reductions compared with the control. The difference in hypersensitive activity between the optimized formulation and control ($p < 0.001$) at both levels can be observed on the basis of the increased sol-ubility of BD in SNEDDS formulations. The possible reason could be increased benidipine water solubility and dissolution rate due to the surfactant's presence as well as the quick dispersion of globules (Prajapat et al. 2017).

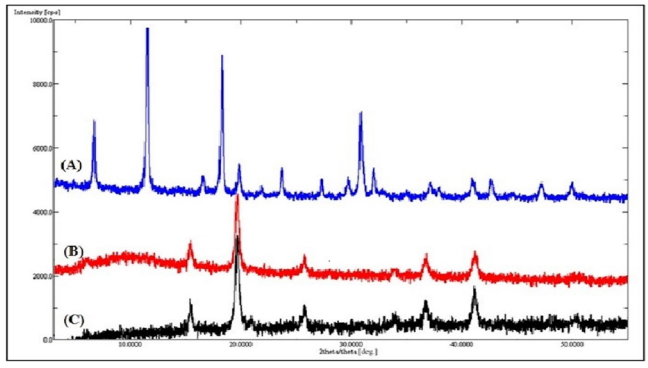

Figure 11. XRD patterns of (A) BD, (B) Neusilin US2, and (C) S-SNEDDS BD14.

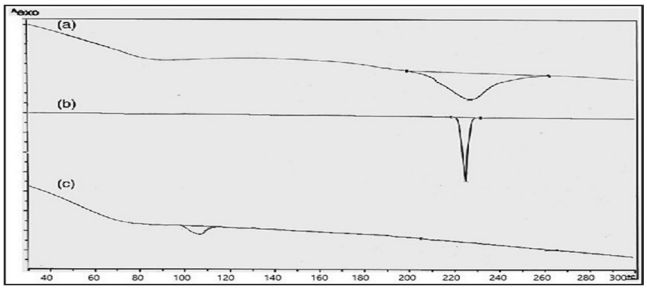

Figure 9. DSC thermogram of (a) Neusilin US2, (b) BD, and (c) optimized S-SNEDDS BD14.

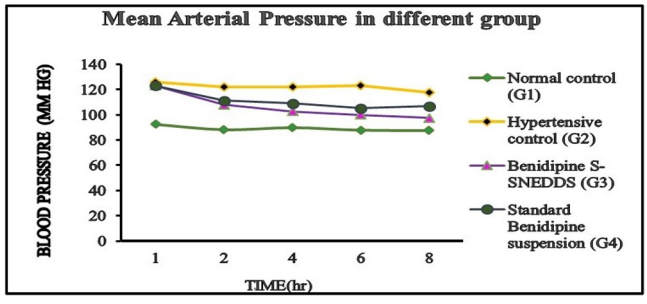

Figure 12. Mean arterial pressure in normal control, hypertensive control, and hypertension treated with BD-S-SNEDDS and pure BD suspension.

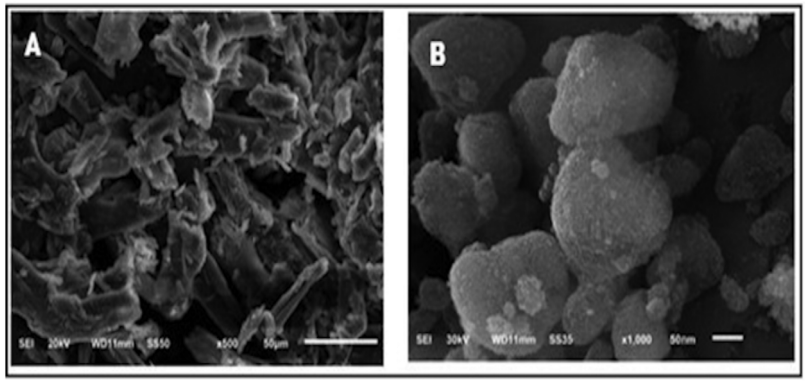

Figure 10. SEM image of (A) pure drug and (B) S-SNEDDS of BD14.

Table 9. Pharmacodynamics investigation of BD-SNEDDS and BD suspension.

Treatments	Types	Blood pressure (mm Hg)					
		0 h	1 h	2 h	4 h	6 h	8 h
Normal control (G1)	Systolic	117.0 ± 1.633	112.83 ± 1.40	110.33 ± 2.201	107.00 ± 1.155	103.83 ± 1.851	106.17 ± 3.070
	Mean	92.67 ± 1.232	88.17 ± 0.864	89.89 ± 0.901	87.78 ± 0.918	87.50 ± 0.576	86.83 ± 0.373
	Diastolic	80.50 ± 1.408	75.83 ± 1.195	79.50 ± 0.885	78.17 ± 1.078	79.33 ± 1.174	77.17 ± 1.078
Hypertensive control (G2)	Systolic	162.67 ± 1.667@	157.83 ± 1.740@	155.50 ± 1.648@	162.667 ± 1.764@	155.50 ± 1.821@	162.83 ± 3.060@
	Mean	126.22 ± 1.655@	121.94 ± 1.543@	121.94 ± 1.703@	123.33 ± 1.167@	117.83 ± 1.659@	121.28 ± 0.218@
	Diastolic	108.00 ± 1.770@	104.00 ± 2.221@	105.17 ± 2.040@	103.67 ± 1.308@	99.00 ± 1.966@	100.50 ± 1.544@
Benidipine S-SNEDDS (G3)	Systolic	158.0 ± 0.856	138.50 ± 1.118*	131.83 ± 0.946*	128.33 ± 1.054*	124.50 ± 1.147*	126.00 ± 1.770*
	Mean	123.11 ± 1.365	107.83 ± 0.864*	102.72 ± 0.777*	99.89 ± 0.991*	97.61 ± 1.013*	99.33 ± 1.029*
	Diastolic	105.67 ± 1.820	92.50 ± 1.648*	88.17 ± 1.515*	85.67 ± 1.282*	84.17 ± 1.078*	86.00 ± 1.033*
Suspension (G4)	Systolic	157.17 ± 2.561	144.50 ± 1.258*	139.167 ± 1.014*	132.50 ± 1.500*	134.50 ± 1.668*	138.83 ± 1.701*
	Mean	123.17 ± 2.506	111.39 ± 1.477*	108.94 ± 1.240*	105.17 ± 0.453*	106.83 ± 1.179*	107.28 ± 1.418*
	Diastolic	106.17 ± 2.522	94.83 ± 2.272*	93.83 ± 1.797*	91.50 ± 1.088*	93.00 ± 1.506$	91.50 ± 1.784*

Note: Each of the values is in Mean ± SEM ($n = 3$) @$P < 0.01$, while compared to the normal control group; $$P < 0.05$, *$P < 0.01$, when contrasted to a hypertensive control group (Annova followed by Dunnett's multiple't' test)

Table 10. Result from the stability investigation of optimized BD-loaded S-SNEDDS.

Parameters	Formulation at 40 ± 2 °C and 75 ± 5% RH.				
Months	0	1	2	3	6
Visual appearance	Transparent	Transparent	Transparent	Transparent	Transparent
Emulsification time T_{emul} (s)	65.21	65.85 ± 1.7	66.20 ± 1.4	67.80 ± 1.2	68.10 ± 0.5
Droplet size (D_{nm})	156.20 ± 2.40	158.10 ± 1.4	158.85 ± 1.3	159.45 ± 1.7	160.15 ± 1.1
% Drug release Benidipie in 15 min	92.65 ± 1.70	91.80 ± 1.35	91.06 ± 1.14	90.20 ± 1.1	90.05 ± 1.22
%Transmittance	99.80 ± 0.70	99.60 ± 0.60	99.20 ± 0.15	98.50 ± 0.25	98.15 ± 0.40

Note: Each of the values is in Mean ± SEM ($n = 6$)

3.12. Accelerated stability investigations

The optimum BD-loaded S-SNEDDS of BD14 samples showed no apparent change in emulsification efficacy, globule size, % transmission, or drug release in 15 min after 6 months of storing at 40 ± 2 °C and 75 ± 5% RH. This shows that BD14 in the improved S-SNEDDS is chemically and structurally stable. Table 10 displays the stability characteristics for the benidipine-loaded S-SNEDDS of BD14.

4. Conclusions

Using QbD, BD-S-SNEDDS formulations have shown the potential to develop an effective formulation with improved oral bioavailability, solubility, and dissolving rate. Based on pre-formulation and risk assessment studies, the maximum drug solubility in each oil, surfactant, and co-surfactant was chosen. The ternary elements used as the oil phase, surfactant, and co-surfactant have been identified as Labrafil M 2125 CS, Kolliphor EL, and Transcutol P. The oil phase, the screened surfactant, and the co-surfactant have been employed to create phase diagrams in varied weight ratios of 1:1, 2:1, and 3:1. The component concentration utilized in the SNEDDS formulation was optimized through a central composite design. The DoE method enables formulation scientists to quickly recognize component interactions and reduce the number of tests required to improve formulations. The thermodynamic stability, pH-based dilution, and dissolve studies successfully showed the efficacy of the SNEDDS architecture to tackle the issues of low water solubility, stomach instability, and BD dissolution rate. Further benefits of switching to S-SNEDDS include improved formulation stability and ease of handling. Neusilin US2 has provided excellent SNEDDS with remarkable flow properties. The optimized formulation S-SNEDDS of BD14 revealed significant antihypertensive efficacy over the control at both dosages ($p < 0.001$). The novel formulation might be scaled up and examined for safety and efficacy in preclinical research.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University, Saudi Arabia, for funding this work through the Large Program (grant number RGP-2/374/44). We are very thankful to Nikishan Pharmaceuticals (India), Gettefosse (India), BASF (India), Fuji Chemical Industries (USA), and Torrent Research Center (India) for providing respective gift samples. We are thankful to Faculty of Pharmacy, Noble University, Junagadh, and School of Pharmaceutical Science, Atmiya University, Rajkot for providing the facilities to carry out the research work.

Ethical approval statement

The animal study protocol was approved by the IAEC of 20th Institutional Animal Ethics Committee, Accuprec Research Labs Pvt. Ltd., Ahmedabad, dated 7/10/2022 (Letter No. ARI/PT/712/2022). Self-emulsifying drug delivery systems (SNEDDS) are recognized for increasing the solubility and bioavailability of hydrophobic drugs like Benidipine, a BCS class II agent with low solubility and high permeability. Benidipine also binds effectively to proteins (98%), causing issues with its solubility during formulation. Our work attempts to explore the pharmacodynamic impact of a newly built self-nanoemulsifying drug delivery system (SNEDDS) for Benidipine. Using animals in this study is an appropriate technique to examine the pharmacodynamics impact of a newly built SNEDDS for delivering Benidipine with solubility and bioavailability challenges.

Animals had been kept in a polypropylene cage with a stainless steel grill on top. The bedding material was dried wheat husk (post-hulled) that was replaced every morning during acclimatization periods. The rats

were given a typical rat pellet diet. The drinking water was given in polypropylene bottles with stainless steel sipper tubes at all times. Animals were subjected to 12 h of day and night cycles with a standard temperature of 23 ± 3 °C and a relative humidity of 50–60%. No use of anesthetics or analgesics was allowed for the performance of the study, and clinical signs and mortality were checked out at least once a day. The authors have adhered to the ARRIVE guidelines.

Author contributions

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

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This project was funded by the Deanship of Scientific Research at King Khalid University, Saudi Arabia, through the Large Program (grant number RGP-2/264/44).

Data availability statement

The data presented in this study are available on request from the corresponding author.

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