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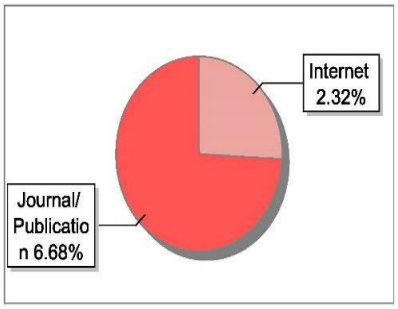


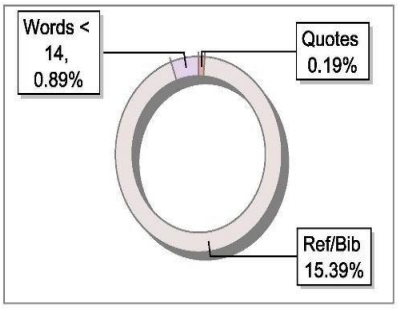


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# Publications

**International Journals**

[1] Buddhadev, S. S., Garala, K. C., Nariya, M., & Rahamathulla, M. (2022). Solid Self Nanoemulsifying Drug Delivery System as a carrier for the enhancement of bioavailability of Benidipine with Telmisartan. European chemical bulletin, 11(11). DOI:10.48047/ecb/2022.11.11.41

[2] Buddhadev, S. S., & Garala, K. C. (2023). Self-nano emulsifying drug delivery system: a potential solution to the challenges of oral delivery of poorly water-soluble drugs. Research Journal of Pharmacy and Technology, 16(10), 4943-1. DOI:10.52711/0974-360X.2023.00801.

[3] Buddhadev, S. S., Garala, K. C., Saisivam, S., Rahamathulla, M., Ahmed, M. M., Farhana, S. A., & Pasha, I. (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). https://doi.org/10.1080/10717544.2023.2288801

**International Conferences**

[1] Buddhadev, S. S., & Garala, K. C. (2020). Pharmaceutical Cocrystals-A Review. In Sciforum. The 2nd International Online Conference on Crystals arranged by MDPI. Retrieved from https://sciforum.net/paper/view/7331 10.3390/IOCC_2020-07331

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# Solid Self Nanoemulsifying Drug Delivery System as carrier for the enhancement of bioavailability of Benidipine with Telmisartan.

**Sheetal S. Buddhadev[1*], Kevinkumar C. Garala[2], Mukeshkumar Nariya[3], Mohamed Rahamathulla[4]**

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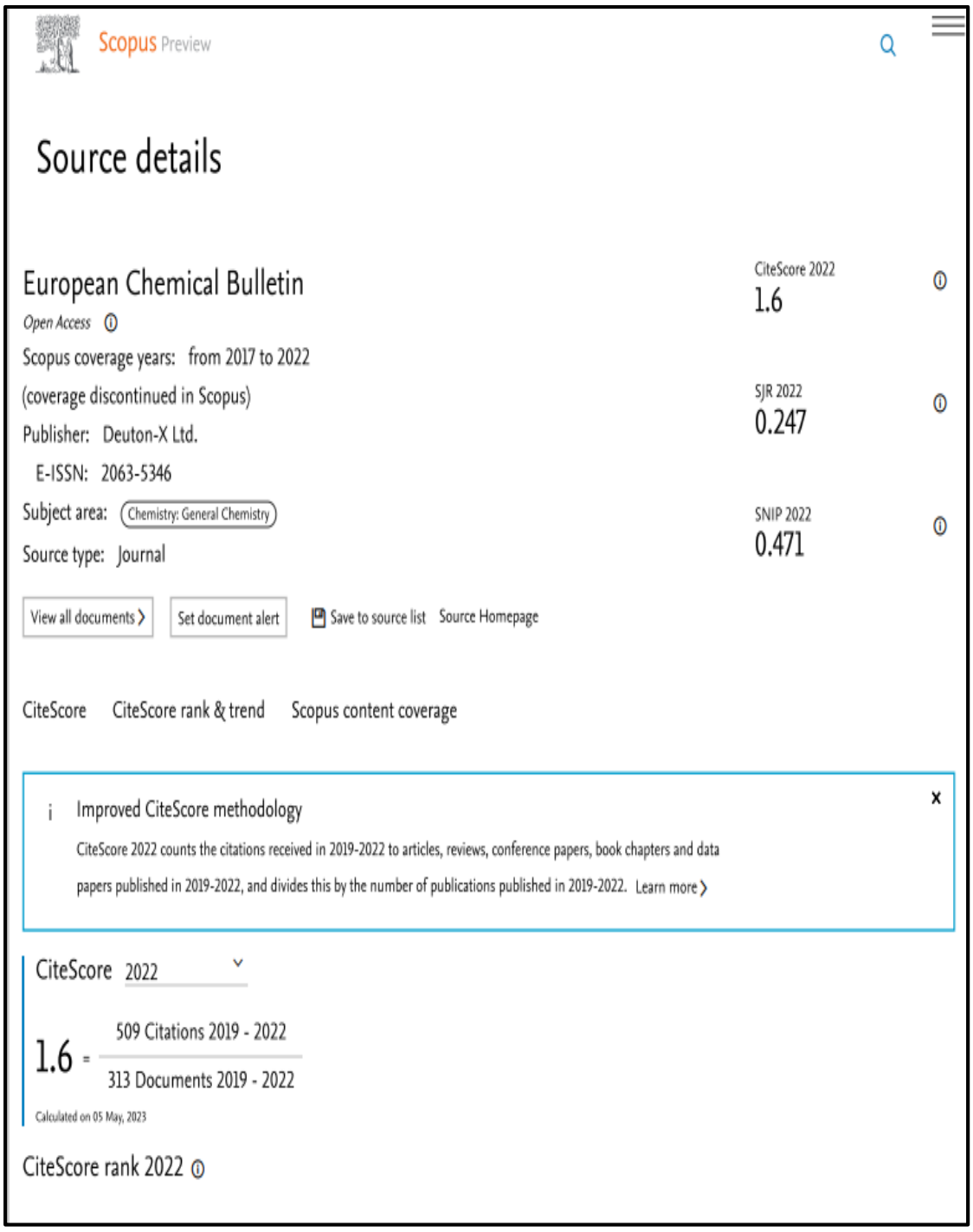
**Abstract**

**Background**: Benidipine (BD) and Telmisartan (TEL), co-administered antihypertensive medicines in the BCS class II group, are characterized by inadequate bioavailability due to restricted water solubility. Self-nano emulsifying drug delivery systems (SNEDDS) offer efficient solubilization for weakly water-soluble medicines due to their ternary ingredients' solubilization and nanonization activity, driven by surfactant and cosolvent. SNEDDS formulations comprise surfactants and cosolvents that facilitate nano droplet dispersion.

**Objective**: This study seeks to investigate the antihypertensive activity of solidified self-nanoemulsifying drug delivery systems (S-SNEDDS) comprising BD and TEL.

**Methods**: Hypertension was produced in rats with oral 10% glucose treatment for three weeks. Animals were grouped: Group 1 as Normal control, Group 2 as Hypertensive control, Group 3 as Hypertensive treated with S-SNEDDS formulation of BD with TEL, and Group 4 as Hypertensive treated with conventional BD-TEL suspension. Rats with a mean blood pressure ≥150 mm Hg were selected. After baseline blood pressure measurement, Group 3 and 4 animals received oral doses of 4 mg BD and 40 mg TEL/kg from optimized S-SNEDDS and pure drug, respectively. Blood pressure was non-invasively monitored using a tail-cuff sensor and Biopack MP36 data gathering system at intervals of 0, 2, 6, 12, and 24 hours.

**Results and Discussion**: In contrast to the hypertensive control group, S-SNEDDS treatment contributed to a progressive blood pressure reduction, peaking at 45 minutes and persisting for 75 minutes. This reduction was statistically different from the control group, demonstrating superior hypertension control compared to BD-TEL suspension. The improved water solubility of BD and TEL due to surfactant presence, together with fast globule dispersion, absolutely contributes to the observed antihypertensive benefits of the SNEDDS formulation.



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***REVIEW ARTICLE***

# Self-Nano Emulsifying Drug Delivery System: A Potential Solution to the Challenges of Oral Delivery of Poorly Water-Soluble Drugs

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**ABSTRACT:**

Lipid-based drug delivery systems (LBDDS) are the most promising technique to formulate the poorly water soluble drugs. Nanotechnology strongly influences the therapeutic performance of hydrophobic drugs and has become an essential approach in drug delivery research. Self-Nanoemulsifying drug delivery systems (SNEDDS) are a vital strategy that combines benefits of LBDDS and nanotechnology. SNEDDS are now preferred to improve the formulation of drugs with poor aqueous solubility. SNEDDS are isotropic mixtures composed of oils, surfactants, and occasionally cosolvents. The ability of these formulations and methods to produce nanoemulsions or fine oil-in-water (o/w) emulsions after moderate stirring and dilution by water phase along the GI tract. SNEDDS has garnered attention during recent years as it improves oral bioavailability, reduces drug dose, and increases drug protection from unsuitable environment in the gastrointestinal tract. It can solve the problems related to the dissolution and bioavailability of the Biopharmaceutics Classifcation System Class II and IV drugs. This review shortly describes the ambiguity between nanoemulsions and microemulsions, mechanism of self-emulsifications, composition and function of various excipients of SNEDDS. This review discusses characterization of SNEDDS, advantage of SNEEDS over other emulsion, biopharmaceutical aspects, and limitation as well as future views. The SNEDDS is a potential formulation for drug delivery. Owing to its small particle size, large surface area, high encapsulation efficiency, and high drug loading, the SNEDDS can improve the rate and extent of oral absorption by maximizing drug solubility in the intestinal absorption site. Moreover, because of the lipid-based formulation of SNEDDS, it can stimulate and enhance lymphatic transport of drugs to avoid hepatic first-pass metabolism, and thus improve their bioavailability.

**KEYWORDS:** Oral bioavailability, Solubility, Self-Nano Emulsifying Drug Delivery Systems (SNEDDS), Lipid-based drug delivery systems (LBDDS), Biopharmaceutical aspect.

## INTRODUCTION:

Because of its safety patient compliance and ability to self-administer the oral administration route is the recommended method of medicine delivery. Oral delivery has been restricted due to severalbarriers present in the gastrointestinal (GI) tract in addition to being the most convenient form of administration. The solubilization of the medicine inside the GI tract is a necessity for drug absorption as insufficient drug dissolution may eventually lead to partial absorption restricted bio-availability, and significant variability following oral administration[1].

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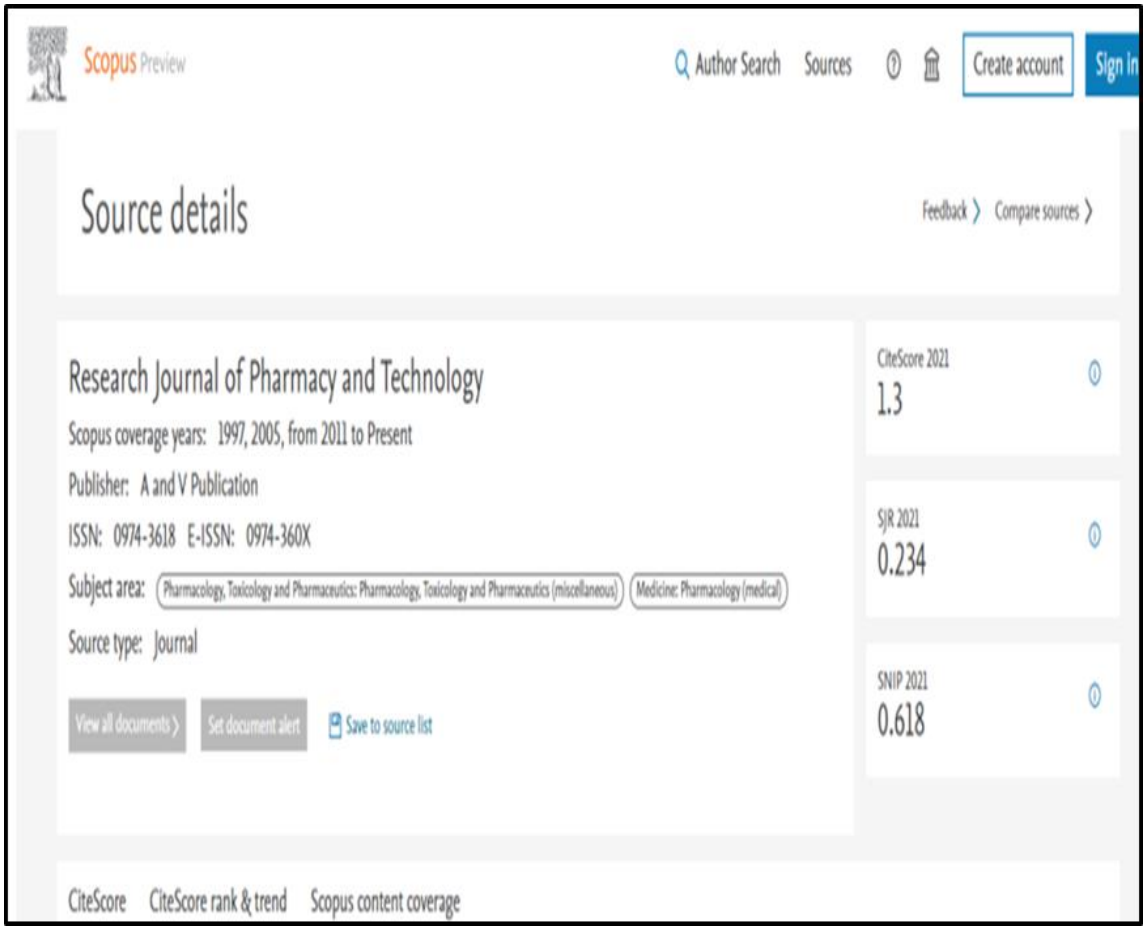
Various attempts are still being made to raise the oral bioavailability of lipophilic medications to improve their therapeutic efficacy. Various lipid-based formulations have been investigated in recent decades to improve the oral administration of lipophilic medications. In recent years there has been an increase in their integration into self-emulsifying drug delivery systems (SEDDS) with a particular focus on self-nano emulsifying drug delivery systems (SNEDDS). SNEDDS on the other hand, are characterized as isotropic mixtures of natural or synthetic oils solid or liquid surfactants, or alternatively one or more hydrophilic solvents and co-solvents/ surfactants.

When SNEDDS formulations are launched into the gastrointestinal tract's lumen they come into touch with GI fluid and create a fine emulsion (micro/nano) which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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.

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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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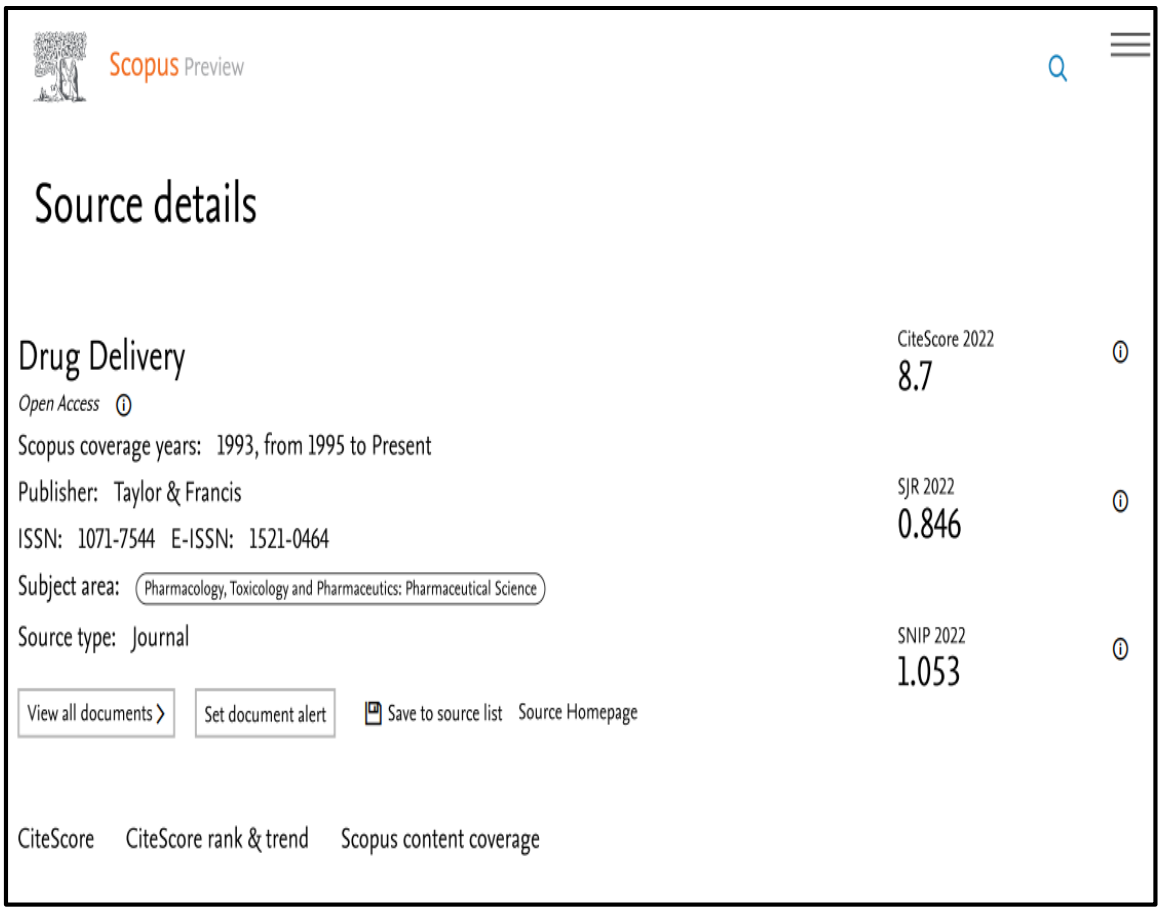
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## Certificate

This is to certify that that the project proposal no. ARL/PT/712/2022 entitled **Formulation and Development of Solid Self-Emulsifying Drug Delivery Systems of Antihypertensive Drugs** submitted by **Mrs.Sheetal Buddhadev** has been approved by IAEC of Accuprec Research Labs Pvt. Ltd., Ahmedabad in its meeting held on 07/10/2022 and Rats (36) have been sanctioned under this protocol for duration of next 12 months.

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# Summary

## Introduction

The oral route is often promoted for drug delivery owing to its cost-effectiveness and possibility for self-medication, leading to high patient compliance. However, medicines in BCS classes II and IV frequently suffer challenges in oral administration due to their poor water solubility, resulting in lower and unpredictable bioavailability. Lipid-based nanostructured drug delivery systems increase oral bioavailability by enhancing solubilization and bypassing first-pass metabolism. Among these, self-nano emulsifying drug delivery systems (SNEDDS) gain interest. SNEDDS are isotropic mixes forming fine oil-in-water nanoemulsions in GI fluids. They quickly disperse in the GI system, generating minute droplet-sized emulsions that are absorbed through the lymphatic pathway, improving drugs bioavailability. SNEDDS offer uniformity and stability, making them suitable for large-scale production.

Quality by design (QbD) and Design of experiment (DoE) are essential for formulation by design (FbD), a systematic approach to formulation design. Developed initially for factory planning, QbD is now extensively utilized in other sectors, including medicines, to assure product quality. Applying QbD concepts helps improve complex drug delivery systems by understanding formulation and process characteristics.

Hypertension plays a significant function in developing cardiovascular diseases (CVDs) including myocardial infarction and stroke globally. Hypertension is the leading risk factor for mortality and disability in India, according to study published in The Lancet on regional health (South-East Asia), 2022. Antihypertensive are a range of drugs that are applied to treat hypertension (high blood pressure). Antihypertensive drugs is designed to prevent consequences of high blood pressure, including strokes and myocardial infarction.

Different studies have proved that combination treatment with pharmaceuticals with a particular mechanism of action assists in effective and speedy management of blood pressure. The combination of an angiotensin-converting enzyme (ACE) inhibitor with a calcium channel blocker (CCB) has several benefits over monotherapy such as substantially better BP control and reduced CCB-induced pedal edema. This combination is recognized as a good treatment for lowering both systemic and intra-renal hypertension, hence protecting the kidneys.

Benidipine (BD), a dihydropyridine with a calcium channel blocker to lower blood pressure, was used for the current investigation. As an anti-anginal and hypertension drugs, it is given orally. Attributed to its considerable amount of hepatic first-pass metabolism and high lipophilicity (log P of 4.28), it is a drug of BCS class II with low oral bioavailability. Similarly, telmisartan (TEL), an angiotensin II receptor antagonist for hypertension, possesses challenges in oral bioavailability due to its BCS class II classification with poor solubility and high permeability. It is commonly administered combined with other antihypertensive medicines, such as calcium channel blockers, in the treatment of hypertension with renal failure. Thus, the need for the investigation is to resolve the issues associated to the administration of medicines with limited water solubility and bioavailability.

Thus, in order to get the major therapeutic benefits from the combination of BD and TEL in a single carrier, the lipid-based drug delivery system, such SNEDDS was employed to boost the solubility of both and ultimately improve the bioavailability of both drugs at the site action. Dual medicines loaded SNEDDS produces smaller droplets of nanoemulsion with significant surface area for the increased bioavailability and better absorption. Solidification of liquid SNEDDS into solid SNEDDS was also done to produce the stable dose form with higher patient compliance.

Thus, the main rationale of this study was to develop a Benidipine and Benidipine with Telmisartan-S-SNEDDS formulation employing the QbD framework with the objective of increasing the drug's bioavailability and solubility considerably, as well as identify all hazards, critical material attributes, and process factors whose variability has a vital

influence on the intended product quality. The graphical depiction of summary is provided in picture 7.1 and 7.2. The following were the outcomes acquired from the current investigation.

## Literature Review

BD and TEL finds challenges in oral bioavailability due to its BCS class II classification with poor solubility and high permeability. Several researcher has been employed multiple approaches to boost bioavailability of BD has been reported such utilizing solid dispersions, nano suspension, mucoadhesive tablet, extended release tablet, and gastro retentive micro balloons for benidipine.

Whereas several research work has been reported to enhance solubility and bioavailability of TEL like self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), solid dispersions, super-saturable self-microemulsifying drug delivery system (Su-SMEDDS), modified MCC pellets, and nanosuspensions. This review help to know BD and TEL property like solubility in different component of SNEDDS and very much useful for selection of different component of SNEDDS.

Various estimation methodology are published for measurement of telmisartan (TEL) and benidipine hydrochloride (BD) in pharmaceutical dosage form such reverse-phase high-performance liquid chromatography (RP-HPLC) and dual-wavelength spectrophotometric approach. This review help in this work for estimation of BD and TEL in BD with TEL SNEDDS.

Multiple literature reviews were conducted on self-nano-emulsifying drug delivery systems (SNEDDS) to investigate the selection of crucial components in the development of a self-nano-emulsifying drug delivery system (SNEDDS). Various factorial designs were employed to examine the impact of different components on various responses, such as self-emulsification time, droplet size, in-vitro release, and percentage of transmittance. These reviews aid in research on the selection of various

components and the effect of these components on different elements of SNEDDS, as well as the assessment of SNEDDS.

Similarly, a literature study was done on a self-nanoemulsifying drug delivery system (SNEDDS) of different drugs such as lovastatin, valsartan, bosentan, ritonavir, olmesartan, medoxomil, ritonavir, and voxelotor, applying the quality by design (QBD) approach. This review aims to establish the quality target product profile (QTPP) and identify the significant quality characteristics of quality (CQAs) in order to deliver a comprehensive understanding of the outstanding attributes of the drug that can enhance its bioavailability when administered orally, leading to optimal pharmaceutical benefits.

Various literature reviews were carried out on pharmacological studies that would investigate the suitable dosage and amount of fructose administration for creating hypertension in Wistar rats, as well as a review of the link between the plasma concentration of benidipine and its cardiovascular effects to examine the effectiveness of pharmacokinetic-pharmacodynamics (PK-PD) models. A research study was conducted to review antihypertensive and antihyperlipidemic effects of Moringa stenopetala in rats with fructose-induced hypertension. Review work has taken place on the nimodipine and clinidipine SNEDDS for pharmacodynamics experiments carried out on Wistar rats.

## Materials and Methods

A detailed investigation of BD, TEL, and excipients is carried out. BD and TEL were described for their numerous physiochemical qualities, including nature, color, odor, and solubility. BD and TEL were identified by different spectral analyses, such as UV spectroscopy, FTIR spectroscopy, and DSC. The UV spectrophotometric method of analysis was developed and validated for the estimation of BD and BD with TEL. Performance studies have been conducted to determine the compatibility between BD and TEL in a solid state. The solid-state compatibility was evaluated using DSC, XRD, and FTIR studies.

The use of QbD provides an interaction between critical quality attributes (CQA), the quality target of the product profile (QTPP), critical material attributes (CMA), and critical process parameters (CPP). The main agenda of using QbD in the pharmaceutical industry is to develop a robust pharmaceutical product which can achieve the best therapeutic efficacy, quality attributes and long shelf life over storage.

For the production of BD and BD with TEL-loaded SNEDDS, oil was chosen on the basis of the highest solubility of both drugs by utilizing the shake flask technique. A variety of oils were included in this research, such as synthetic oils, natural oils, synthetic monoglycerides, synthetic diglycerides, and synthetic triglycerides. For the purpose of emulsifying the chosen oil, the surfactant and co-surfactant were also selected on the basis of their emulsification capacities. For the generation of oil in water nanoemulsions, several surfactants with different HLB values ranging from 8–16 having cation, ionic, and non-ionic natures may be utilized. The selection of co-surfactant was based on its emulsification capabilities with the assigned oil and surfactant. The ternary phase diagram was used to determine the surfactant-co-surfactant ratios. These diagrams were constructed on the basis of the greatest isotropic nanoemulsion zone, and they assisted in determining the largest area for the manufacture of thermodynamically stable nanoemulsion.

Out of various response surface methodologies CCD was selected for formulation optimization of BD-SNEDDS as it considers a total system of SNEDDS as 100%. CCD design with three-factors was employed for studying the effect of formulation variables on the selected responses. Initial experiments and literature survey revealed that these three factors % of the oil (Labrafil M2125 CS), % of the surfactant (Kolliphor EL), and % of the cosurfactant (Transcutol P) were critical for the BD-SNEDDS performance. Design expert® program to investigate the influence of process factors on the predicted responses. The 15 formulations were produced and analyzed for the influence of independent factors like self-emulsification time ($Y_1$), droplet size ($Y_2$), percentage of drug release in 15 minutes ($Y_3$), and transmittance ($Y_4$).

Similarly, BD with TEL-SNEDDS has been optimized using BBD and response surface methodology (RSM), a design expert® program to investigate the influence of process factors on the predicted responses. The 15 formulations were produced and tested for the influence of independent factors, such as self-emulsification time ($Y_1$), droplet size Dnm ($Y_2$), percentage of BD release in 15 minutes ($Y_3$), percentage of TEL release in 15 minutes ($Y_4$), and % transmittance ($Y_5$). Then, the produced SNEDDS were assessed for several characteristics, such as droplet size and PDI, percentage of transmittance, zeta potential, robustness to dilution, and analysis of drug content. A thermodynamic stability analysis was carried out to assess the effects of fluctuations in temperature on SNEDDS formulations and discover any signs of phase separation.

The optimized liquid SNEDDS was transformed into solid SNEDDS by adsorption on the solid carrier, i.e., Neusilin US2. Solid-state characterization of the obtained S-SNEDDS of BD and BD with TEL was done by FTIR, DSC, XRD, and SEM. The shape and size of droplets created upon the reconstitution of s-SNEDDS were evaluated using transmission electron microscopy (TEM). The S-SNEDDS of BD14 formulation's drug release profile was compared with a pure drug, the L-SNEDDS of BD14, and the marketed brand Z-Bene, Corazon. Similarly, drug release examinations of the pure drug (BD with TEL), liquid SNEDDS of BT11, S-SNEDDS of BT11 formulations, and commercially available tablet Benidip T 4 mg/40 mg Tab (Precia Pharma Pvt. Ltd.) have been carried out.

The quadratic model, covering the linear mixture and interactions between two components, was generated for all the responses using an MLRA technique. Statistical analysis was done using one-way analysis of variance, with the threshold of statistical significance set at $p < 0.05$. The significant effect ANOVA's F test, which was done using the development tool and had a 95% confidence level of $P < 0.05$, was used to evaluate the response. Depending on the models for each answer, a contour map was produced. Based on the desired functions and response characteristics, an appropriate formulation was produced for both BD loaded SNEDDS and BD with TEL loaded SENDDS.

A pharmacodynamic investigation has been authorized by the Institutional Animal Ethics Committee at the 20th IAEC Meeting at Accuprec Research Labs Pvt. Ltd., Ahmedabad (ARL/PT/712/2022). The research employed 10% fructose dissolved in the water and administered to Wistar rats to generate hypertension (the equivalent of taking in a meal containing 48–57% fructose) over two weeks. The antihypertensive effects of pure BD medicines, BD along with TEL medicines, and the optimum S-SNEDDS of BD14 and BT11 were investigated in adult Wistar albino rats. After two weeks, a tail cuff sensor technology was employed to non-invasively measure blood pressure using the Biopack MP36 collecting device.

As per the ICH recommendations, the accelerated stability experiments for optimized S-SNEDDS of BD14 and BT11 were carried out in a stability chamber maintained at 40 ± 2°C with 75% ± 5% relative humidity for a period of 6 months.

## Results and Discussion

There is a demand for increasing the pharmacodynamic potential of benidipine and telmisartan, which are thus selected as drug candidates in the current investigation. For the current experiment, SNEDDS formulations were employed to increase the solubility of both and ultimately enhance the bioavailability of both drugs at the site of action.

The method of analysis was established and tested for the estimation of BD and BD with TEL using UV spectroscopy. UV-visible spectroscopy testing was done at 237 nm wavelength for both 0.1N HCl and methanol. The correlation coefficient (R2) for BD was found to be 0.9986 in methanol and 0.9991 in 0.1N HCl. So, this equation was utilized for the measurement of the solubility of the BD in various solvents, drug content, and drug release. For BD with TEL, overlain spectra have been carried out, and four wavelengths—229.30 nm and 246.32 nm for BD and 280.10 nm and 315.29 nm for TEL—were chosen for the measurement of both drugs using the dual wavelength spectrophotometric methods. The linearity of BD and TEL was discovered to be in the range of 1–5 µg/ml and 10–50 µg/ml, respectively. The accuracy of the method was confirmed by recovery tests of marketed formulations at three levels (80%,

100%, and 120%). The percentage recovery for BD and TEL was found to be 98.25–101.30% for both medications.

After a duration of 12 hours, the color and texture of the combination, including BD and TEL, remained unaltered, demonstrating that there was no sign of interaction between the two distinct compounds. This compatibility was further confirmed by the use of DSC, XRD, and FTIR spectrum analysis.

The key features of the L-SNEDDS of BD and BD with TEL have been produced utilizing the QBD approach, including manufacturing technique, therapeutic dosage and strength, action mechanisms and processes, pharmacokinetics, packaging, and storage specification. The critical quality of the L-SNEDDS of BD and BD with TEL was identified as the CQAs obtained from the QTPP components explored in the formulation. In addition, the reasons for adopting CQAs and their effect on the therapeutic efficacy of the L-SNEDDS of BD and BD with TEL were investigated.

Labrafil M 2125 CS, Kolliphor EL, and Transcutol P were chosen as the oil, surfactant, and co-surfactant, respectively, based on the results of the tests of solubilization capacity and emulsification efficiency for BD-SNEDDS. While eucalyptus oil, Kolliphor EL, and Transcutol P have been selected as the oil, surfactant, and co-surfactant, respectively, for BD with TEL-SNEDDS, on the basis of findings of solubilization capacity and emulsification effectiveness, Transcutol P was chosen as a co-surfactant as it emulsified both the selected oil and the surfactant and resulted in the creation of a clear emulsion with a transmittance higher than 98%.

In the ternary phase diagram for BD, a ratio of 3:1 amongst the three combinations has been proven to be the most efficient area for nanoemulsion. When the concentration of Smix increased while the concentration of oil decreased, dropped. A nanoemulsion area was created owing to an increase in self-emulsification, lower interfacial tension, and fast dispersion of oil in the aqueous phase. While for BD with TEL, the phase diagram with the (3:1) ratio has been confirmed to be the most efficient area for nanoemulsion.

The extra phase diagrams with (1:2) and (1:3) ratios showed broad nano-emulsification areas as compared to the least emulsified sections (2:1).

The optimized formulation for Benidipine-formulation BD14 consisted of Benidipine (4mg), Labrafil M2125 Cs (30%), Kolliphor EL (45%), and Transcutol P (50%) with a globule size of 162.25nm, drug release of drug within 15 minutes, 90.15%, self-emulsification duration of 67.25 sec, and %transmittance (99.50). While optimized formulation for BD with TEL-formulation BT11 contained Benidipine (4mg), Telmisartan (40 mg), Eucalyptus oil (60%), Kolliphor EL (35%), Transcutol P (10%) with a globule size of 175.12 nm, release of drugs (BD and Tel) within 15 minutes (more than 90%), self-emulsification time of 53 sec, and %transmittance (99.60%).

The regression analysis findings reveal that $X_1$ (oil) had a positive coefficient, but $X_2$ (surfactant) and $X_3$ (co-surfactant) exhibited negative coefficients. Research is showing that differences in the amount of oil and surfactant have a substantial influence on the size of the drops compared to other independent factors.

The emulsification process certainly experienced a decrease in speed as well as efficacy as the amount of oil in the formulation increased, resulting in larger droplet sizes and a higher level of lipophilicity. Increased oil content resulted in larger and more lipophilic droplets, possibly accelerating the emulsification process.

The droplet sizes in the emulsion ranged from 156.20±2.40 to 199.75±2.90 nm for BD-SNEDDS and 176.24±1.90 to 194.20±2.10 nm for BD with TEL –SNEDDS. Droplet size increased with an increase in the concentration of oil, while it decreased with an increase in the concentration of Smix. On the other hand, increasing the quantity of Transcutol P has a negative influence on drop size, resulting in a reduction in drop size.

The oil concentration was the only independent variable whose change significantly influenced CPR15. To form a nanoemulsion, the compositions needed to be mixed effectively; increasing the amount of any one composition would have an effect on the system's overall balance, which was essential to maintaining the drugs solubilized. For

the intended batches of BD loaded SNEDDS, a range of 78.74% to 92.65% of the drugs were released at the stipulated 15-minute interval. Whereas, different batches for BD with TEL resulted in drug percentages of 91.5% to 93.5% for BD and 91.6% to 92.9% for TEL at the 15-minute interval. The different patterns of drug release displayed in different formulations might be achievable because of the presence of varying quantities of oil phase, surfactant, and cosurfactant.

The findings for percent transmittance ranged from 85.65±0.90 to 99.80±0.70% for BD SNEDDS while, 86.50±0.95% to 99.60±0.70% for BD with TEL-SNEDDS. The SNEDDS dispersion was transparent and clear, with a comprehensive range of nanometer-sized droplets and a transmittance score based on a percentage of about 100%. The results of the regression analysis indicated that while the quantity of co-surfactant had no influence on transmission, the proportion of oil to surfactants changed. Higher oil content resulted in decreased transmission as a consequence of greater lipophilicity along with decreased transparency.

Based on the desirability index, formulation BD14 was found to be an optimized batch with a desirability index of 0.987. Similarly, based on the desirability index, formulation BT11 was found to be an optimized batch for BD with TEL with a desirability index of 0.975. The predicted batch demonstrates significant reproducibility within the percentage deviation. From the result, it shows that the prediction value is close to the experimental value, therefore the design is significant.

When the optimum liquid SNEDDS BD14 and BT11 had been diluted 10, 100, 250, 500, and 900 times by volume in 0.1N HCl and phosphate buffer pH 6.8, there was no evidence for phase separation in any of the formulations studied. When the transmission of the generated nanoemulsion was diluted with 0.1N HCl, phosphate buffer pH 6.8, and saline phosphate buffer pH 7.4. This determined the ability of the boosted SNEDDS formulation to generate nanoemulsions at different physiological pH levels.

BD SNEDDS showed a zeta potential ranging from −15.21 mV to -21.45 mV. While BD with TEL shows zeta potential ranging from -17.20 mV to -28.39 mV, zeta potential

values were constantly negative across all formulations. This may be attributed to the composition of the oil-in-water (o/w) emulsion. The presence of negative charges resulted in repulsive interactions between the nanoemulsion droplets, indicating the physical stability of the formulations.

The reported cloud point temperature for BD SNEDDS is 69.9±1.5 °C and for BD with TEL is 79.6±1.7 °C, while the normal body temperature is 37 °C. In light of this, it can be said that the newly developed formulation remains stable in vivo at physiological temperature and did not exhibit phase separation while kept at room temperature or when given via the digestive system.

The mean refractive index of the optimal formulations BD14 was shown to be 1.752±0.1, while for BD with the TEL-optimized formulation BT11, it was found to be 1.742 ± 0.14, which suggests that the nanoemulsion is isotropic.

The effects of heating and cooling, centrifugation, and freeze-thaw cycling on the phase separation of nanoemulsions and the precipitation of drugs have been studied, and it has been found that the optimized formulations BD14 and BT11 and almost all batches of SNEDDS have been stable without any signs of drug precipitation, phase separation, creaming, or breaking. So we ultimately conclude that developed SNEDDS is thermodynamically stable.

Comparative in vitro drug release studies of BD pure drug, BD-L-SNEDDS, and BD marketed product demonstrate that, in contrast to the pure drug's release profile of 42.40% and the marketed product's dissolution rate of 49.12%, all produced SNEDDS batches had a drug release rate of about 90% within 60 minutes. Likewise, comparative in vitro drug release studies of Benidipine with Telmisartan pure drug, Benidipine with Telmisartan liquid SNEDDS, BT11, and market formulation (Benidip T 4 mg/40 mg Tab) show that during the first hour of the investigation, all the BD with TEL SNEDDS batches released BD and TEL more than 95% of the drug, compared to the BD with TEL pure drug, which released just 48.7% of the BD and 50.1% for TEL. A similar approach to market formulation showed a release of 59.8% for BD and 58.1% for TEL.

The optimized liquid SNEDDS was transformed into solid-SNEDDS (S-SNEDDS) by adsorption over the solid carrier, i.e., Neusilin US2. Data showed that for BD and BD with TEL, the medication formulation L-SNEDDS: adsorbent (1:1.5) had the smoothest and driest look. It was reported to have good flow properties and flow rate in Neusilin US2, in contrast to the L-SNEDDS adsorbent formulations with ratios of 1:1 and 1:2. Based on the micromeritic characteristics, including bulk density, tapped density, Hausner's ratio (HR), Carr's index (CI), angle of repose (AR), and flow rate, in addition to self-emulsification efficacy, BD and BD with TEL and powder (S-SNEDDS) flow may be considered acceptable.

Characterization of SSNEDDS of BD and BD with TEL was done by FTIR, DSC, SEM, and PXRD. In FTIR research, the S-SNEDDS of BD14 revealed the characteristic peaks of both BD and Neusilin US2, demonstrating that the drug was still present in the combination and had not undergone any molecular changes or interactions with carriers (Labrafil M2125 CS, Kolliphor EL, Transcutol P, and Neusilin US2). Similarly, for BD with TEL, the S-SNEDDS of BT11 displayed the typical peaks of both BD, TEL, and Neusilin US2, demonstrating that the drug continued to exist in the combination and had not suffered any molecular modifications or interactions with carriers (Eucalyptus oil, Kolliphor EL, Transcutol P, and Neusilin US2).

In the DSC investigation, a substantial endothermic peak was discovered in the pure BD thermogram at precisely 220.02°C, which is associated with the melting temperature of BD. In this specific case of S-SNEDDS BD14, the drug's endothermic peak was 106.21°C. It may then appear to change from a crystalline to an amorphous state. Similarly for BD with TEL, the prominent melting endotherm peak shows the crystalline form of benidipine and telmisartan at 189.08 and 278.10 °C, respectively, while the physical mixture demonstrated an evident drug peak at 237.22 and 273.37 °C, respectively, which can be interpreted as shifting from crystalline to amorphous form. The lack of any new peaks in S-SNEDDS demonstrates the compatibility between BD and excipients, as well as BD with TEL and excipients in the present formulation.

A SEM photograph of S-SNEDDS of BD shows smooth surface particles that aggregated to generate bigger particles without crystalline morphology. The drug

showed up in SEM images as small, irregularly shaped particles with a rough outer surface. Whereas S-SNEDDS of BD with TEL developed as irregular rod-form crystals. Liquid SNEDDS was adsorbed on the surface of Neusilin US 2. This suggested that L-SNEDDS might have caused considerable impacts on the Neusilin US2 surface.

X-ray diffraction patterns of benidipine and telmisartan revealed significant and strong peaks at the diffraction angles, indicating the drug's crystalline structure of the drugs. The drug's transition from its original crystalline state to an amorphous or molecularly dispersed state in the S-SNEDDS formulation. It has been confirmed by the lack of prominent peak representations of such a crystalline form in the S-SNEDDS diffractogram of BD and BD with TEL.

According to in vitro release studies on L-SNEDDS and S-SNEDDS of BD14 and BT11, BD and TEL released more than 85% of their contents after 15 minutes and 100% after 60 minutes ($f2 < 50$). Within the first 5 minutes, the amount of drug released in liquid SNEDDS in 0.1 N HCl within the first 5 minutes was greater than from the S-SNEDDS formulation. The delay in drug release for S-SNEDDS may be attributed to the desorption process from the adsorbed carriers.

Pharmacodynamics studies reveal that S-SNEDDS of BD and BD with TEL displayed greater bioavailability when compared to both pure BD and BD with TEL drugs. This improved bioavailability could be due to the higher solubility of BD and BD with TEL achieved with the S-SNEDDS formulation. This difference in hypertensive response suggests that the S-SNEDDS formulation has better drug solubility and absorption kinetics achieved by the S-SNEDDS formulation.

After six months of storage at 40±2°C and 75±5% relative humidity, the BD-loaded S-SNEDDS of BD14 samples and the BD with TEL-loaded S-SNEDDS of BT11 displayed no noticeable changes in emulsification efficacy, size of the globules, percentage of transmission, or release of the drug over a period of fifteen minutes. These findings suggest that BD14 and BT11 in the augmented S-SNEDDS exhibit chemical and structural stability.

# Conclusion

Using QbD, BD-S-SNEDDS, and BD with TEL-S-SNEDDS formulations have shown the potential for creating an effective formulation with increased oral bioavailability, solubility, and dissolution rate. Based on pre-formulation and risk assessment studies, the maximum drug solubility in each oil, surfactant, and co-surfactant was selected. The ternary components that were used in BD as the oil phase, surfactant, and co-surfactant have been identified as Labrafil M 2125 CS, Kolliphor EL, and Transcutol P. Whereas, Eucalyptus oil, Kolliphor EL, and Transcutol P have been identified as the ternary components for BD, with TEL utilized as the oil phase, surfactant, and co-surfactant. The oil phase, the screened surfactant, and the co-surfactant have been utilized to construct phase diagrams in varying weight ratios of 1:1, 2:1, and 3:1 for BD and 1:1, 2:1, 3:1, 1:2, and 1:3 for BD with TEL. The component concentration employed in the SNEDDS formulation has been optimized by a central composite design for BD and a Box-Behnken design for BD with TEL. The DoE approach enables formulation scientists to rapidly discover component interactions and reduce the number of tests necessary for improving formulations.

Further benefits associated with converting to S-SNEDDS include increased formulation stability and ease of handling. Neusilin US2 has developed excellent SNEDDS that have outstanding flow properties. The optimized formulation S-SNEDDS of BD14 and BT11 exhibited significant antihypertensive efficacy above the control at both doses ($p<0.001$). Hence, the resulting S-SNEDDS has been proven to be an effective carrier for BD and BD with TEL for the control and treatment of hypertension. The novel formulation may be scaled up and evaluated for safety and effectiveness in preclinical research. The application of the QbD approach during development restored various diverse views and helped analyze interactions between material and process factors on important quality characteristics of the formulation. It was believed that the QbD-guided building of SNEDDSs carrying biopharmaceuticals, along with the establishment of accurate and predictive in vitro analysis methods, could reduce the distance between academia and the pharmaceutical industry in this area and, consequently, successfully satisfy therapeutic needs.

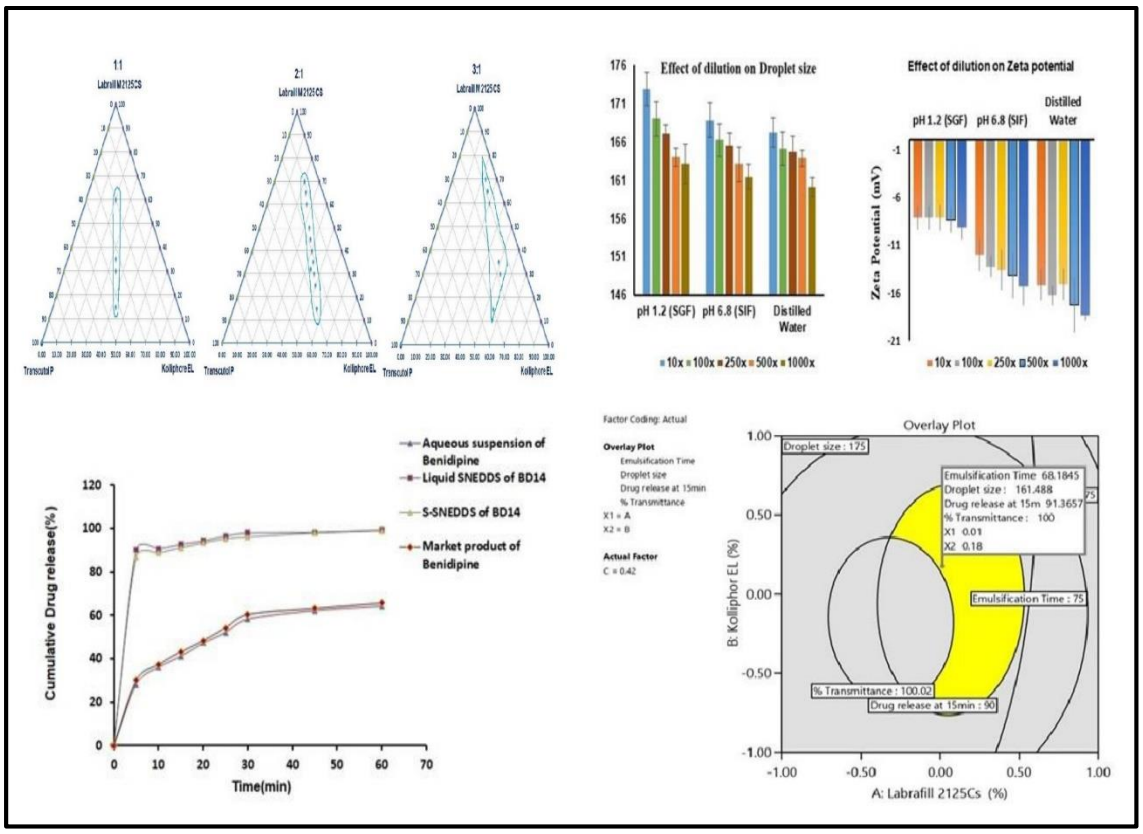


Figure 7.1 Pictorial representation of summary of Benidipine SNEDDS

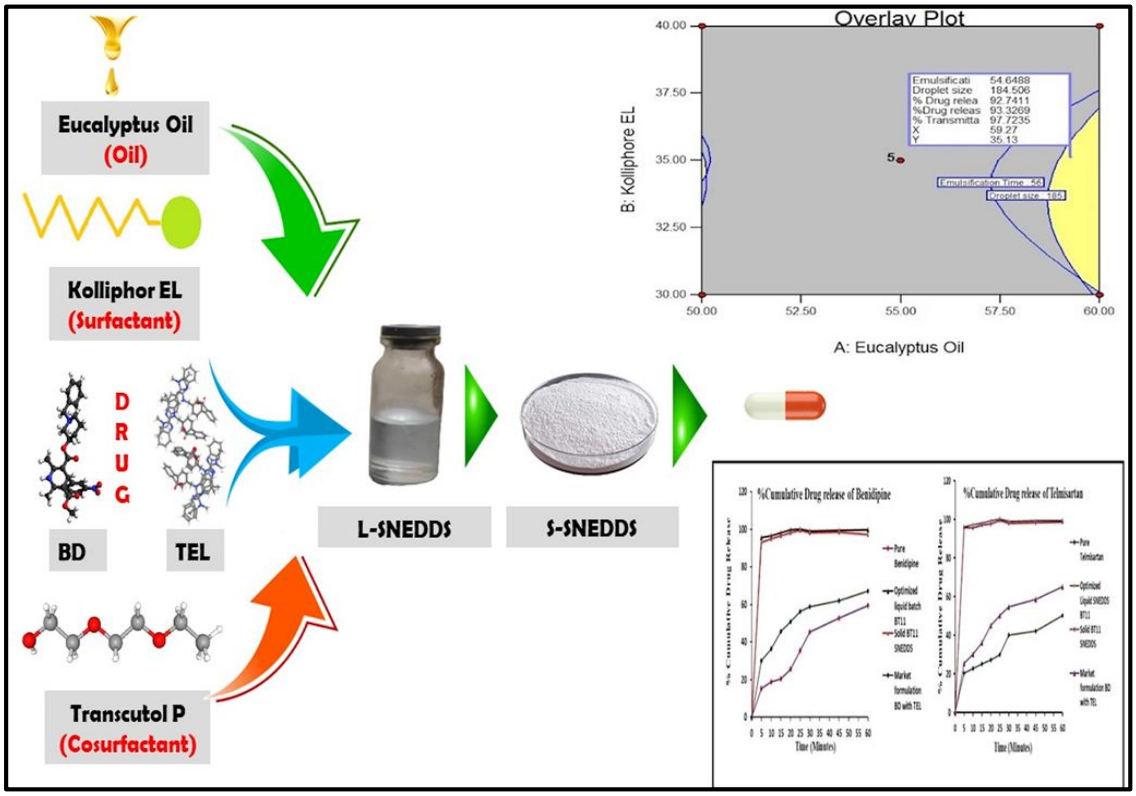


Figure 7.2 Pictorial representation of summary of Benidipine with Telmisartan SNEDDS