Chapter 2

Literature Review

The information on the literature of SNEDDS was obtained from various search engines such as Pubmed, Scopus, Science Direct, PMC, Google Scholar, Web of Sciences, ChemWeb, and so on. Highly reputed and peer review Journals/Publications were reviewed for data collection. Extensive literature search was done on SNEDDS using SNEDDS, SMEDDS, self-emulsifying formulations, LBDDS, in vitro lipolysis and many others as keywords. Following is a brief review of various approaches by researchers for increasing solubility and bioavailability of drugs by employing SNEDDS approach.

2.1. Review of Work done on Benidipine

Objective	Description	Conclusion	Reference
To design a mucoadhesive tablet of Benidipine to control the release of Benidipine employing Carbopol 934P and HPMC K4M.	The method of preparation is direct compression by employing a simplex lattice design.	The formulation (F4) that is made up of the drug carbopol 934P and HPMC in a ratio of 1:6.5:18.5 exhibited a strong Bucco adhesive force and maximal drug release of 99.0219% in 8 hours.	Mishra, V. V. B. K., Sethy, S., & Rath, A. K. , 2015 [100]
The purpose of the investigation was to create a simple and quick first-order derivative spectrophotometric method for the measurement of	Using the first derivative spectrophotometric method, the difference between two extremum values (peak-to-peak amplitudes) is 230.2/241.5 nm. The suggested method was	The linearity of the method that was used was in the range of 0.2–2.0 μg/mL. The limits of detection and quantification were 0.58 and 1.73 μg/mL, respectively.	Karasaka, A., 2015 [101]

benidipine hydrochloride in pure form and pharmaceutical products.	verified in accordance with the ICH guidelines.		
To develop an extended-release matrix tablet of benidipine hydrochloride (BH) by employing hydrophilic polymers, hypromellose (hydroxyl propyl methyl cellulose [HPMC] K100M), polyacrylate polymers, eudragit RL100 and eudragit RS100, and also chitosan.	The tablets were made using the direct compression technique and the agglomerative phase of comminution (APOC).	Formulation F5, which includes HPMC polymer along with eudragit RS 100, demonstrates prolonged drug release because of the swelling of HPMC polymer, and the release pattern could continue for more than 18 h. The APOC approach keeps the formulation stable and enhances the aqueous solubility of drugs.	Prusty, A., Mishra, A. K., & Kumar Gupta, B., 2018 [102]
To create an easy, quick, accurate, robust, and economical spectrophotometric technique for the quantification of benidipine hydrochloride by implementing quality	The UV spectrophotometric method was designed using methanol as a solvent, and a wavelength of 236 nm was selected as the absorbance maximum (max).	The linearity of the procedure was shown to be good for the concentration range of 3 to 18 µg/ml, with a high correlation coefficient value of 0.9999. The limits of detection and quantification were determined to be 0.20	Manish Kumar, Ajay Kumar Shukla, Ram Singh Bishnoi,

by design (QbD)" approach.		µg/ml and 0.60 µg/ml, respectively. The overall average recovery was determined to be 100% with a low percentage relative standard deviation (% RSD) value.	C. P. Jain 2018 [103]
To prepare and develop gastroretentive microballoons to extend the floating duration as well as sustain the drug content in the blood for a prolonged period of time.	Microballoons of benidipine hydrochloride were produced by emulsion solvent diffusion utilizing Eudragit RS100 and Eudragit S100 as the coating polymers.	The produced batches of the microballoons exhibited an excellent drug entrapment value of 77.28%; the buoyancy was determined to be 84.25%; and the yield was reported to be 90.41. The cumulative drug release profile demonstrated sustained drug release actions for greater than 24 hours because the drug release percentage remained at 83.51% in 24 hours.	Satao, J., Pallavi Wadaskar , Aman Bais, Sushant Bhamburkar, 2020 [104]
The purpose of the present research was the application of quality by design (QbD) methodology to the development and validation of an	Process was verified based on International Conference on Harmonization (ICH) Q2 (R1) requirements for linearity, precision, range, accuracy, and	The linearity of the developed method was demonstrated throughout the concentration range of 50–150 µg/mL for benedipine hydrochloride, with a correlation value of 0.998.	Savkare A. D., Kauthale Jayshri D., Khomane Pankaj

analytical RP HPLC technique for benedipine hydrochloride.	robustness. The separation was conducted on Chemsil ODS C18 and detection was done using a UV detector at 237 nm. The described technique uses mobile-phase methanol, ammonium acetate buffer (85:15), pH 3, and a flow rate of 1.2 ml/min.	The percentage RSD for precision and accuracy of the approach was determined to be less than 2%. The peak was recorded at a retention time of 3.47 minutes. The recommended method may be conveniently applied to evaluate the drug contents in commercialized formulations.	H., Sapkal Prasanna M., 2020, [105]
The purpose of the research was to increase the solubility and dissolution rate of the drug Benidipine (BEN) by solid dispersion utilizing PEG 6000 and Poloxamer 188 carriers in various ratios and applying different methods such as physical mixture and microwave-induced fusion.	Solid dispersion was created by applying multiple methods, including a physical mixture and the microwave-induced fusion method. FTIR was utilized to characterize the samples of SDs and BEN.	The highest improvements in solubility and in-vitro drug release have been observed in solid dispersion produced with Poloxamer 188 (F18) in 1:3 by the microwave-induced fusion technique. The enhanced dissolution rate of BEN from solid dispersion may be attributed to improved wettability and dispersibility of BEN.	Vyas Sanket, Patel Dhaval & Kasota Priya, 2022 [106]

2.2. Review of Work done on Telmisartan

Objective	Description	Conclusion	Reference
Research conducted upon the formulation of a self-nanoemulsifying drug delivery system for telmisartan with improved dissolution and oral bioavailability.	Safsol-218, Tween-20, and Transcutol P have been chosen as oils, surfactants, and cosurfactants, respectively, since they demonstrate the greatest solubility for telmisartan. The solubility of drugs was further raised by adding sodium hydroxide (0.67%).	The droplet size of the optimized emulsion was in the nano range. The results of the study demonstrated a 4.34-fold improvement in the oral bioavailability of drugs in comparison with a tablet. It revealed an extensively significant reduction ($p < 0.001$) in the mean blood pressure of hypertensive rats over 48 hours.	Ahmad, J., Kohli, K., Mir, S. R., & Amin, S. , 2011 [107]
The study target is to build a self-nanoemulsifying drug delivery system (SNEDDS) to improve the oral bioavailability of slightly water-soluble telmisartan (TEL).	The solubility of TEL in various oils was investigated to identify the oil phase of SNEDDS. The designed SNEDDS formulation consists of TEL (20 mg), Tween® 20 (43.33% w/w), Carbitol® (21.67% w/w), and Acrysol® EL 135 (32% w/w).	The optimized formulation of the TEL-loaded SNEDDS demonstrated extensive in vitro drug release in 15 min in comparison with the plain drugs, which had a limited dissolving rate. The in vivo investigation demonstrated a 7.5-fold improvement in the oral bioavailability of TEL from the SNEDDS compared with the pure drug suspension.	Jaydeep Patel, Garala Kevin, Anjali Patel, Mihir Raval, Navin Sheth 2011, [108]
To create solid dispersions of	Telmisartan solid dispersions were created	Formulation having a 1:2 ratio of drug: PEG-4000	Lakshmi K, Pranav

telmisartan utilizing polyvinyl pyrrolidone (PVP), polyethylene glycol-1500 (PEG-1500), and polyethylene glycol-4000 (PEG-4000) to enhance its water solubility.	in 1:1, 1:2, and 1:4 ratios of the drug to polymer ratio (by weight) employing the solvent evaporation technique. The formulations were assessed for solubility parameters, drug content studies, drug release studies, and drug-polymer interactions by utilizing the FTIR spectrum.	demonstrated the best release with a cumulative release of 99.49% as compared with 35.82% for the pure drug. The interaction investigations found no interaction between the drugs and polymers. It has been found that PEG-4000 as a carrier could potentially be extremely good to increase the solubility of poorly soluble drugs.	Kumar Reddy M, Rajesh Kaza., 2012, [109]
To generate a self-microemulsifying drug delivery system (SMEDDS) and solid SMEDDS of telmisartan to deal with the difficulties of low solubility and bioavailability.	SMEDDS is generated from castor oil, tween 20, and propylene glycol as oil, surfactant, and co-surfactant.	The formulation, which includes telmisartan (20 mg), castor oil (30% w/w), tween 20 (55% w/w), and propylene glycol (15% w/w), was found to be optimal. The optimized SMEDDS and solid-SMEDDS demonstrated 100% in vitro drug release up to 120 min. Solid-SMEDDS may be seen as a superior solid dose form because solidified formulations are more effective than liquid forms in terms of their stability.	Parul Jaiswal, Geeta Aggarwal, Sasidharan Leela kumari Harikumar, Kashmir Singh 2014, [110]

To design a self-microemulsifying drug delivery system (SMEDDS) and to boost the oral bioavailability of poor water-soluble telmisartan.	Telmisartan SMEDDS is composed of oil, surfactant, and cosurfactant. Psuedoternary phase diagrams were built to find the effective self-emulsifying zone.	The prepared liquid SMEDDS had globule sizes in the nanometric range. The optimal formulation is composed of telmisartan (20mg), Capmul MCM (14.40% w/w), Tween 80 (27.20% w/w), and propylene glycol (54.40% w/w). The exposure (Cmax and AUClast) of the designed SMEDDS was found to be relatively greater (1.54 times) than the reference commercially available product.	Nirali Padia, Arunkumar Shukla, Pragna Shelat 2015, [111]
Research plan to work on the dissolution rate enhancement of telmisartan by modified MCC pellets, utilizing 3^2 complete factorial designs.	In this study, camphor, cross-carmellose sodium (CCS), and spray-dried lactose (SDL) were utilized to create MCC pellets. A complete factorial design 3^2 was utilized in the investigation. Conc. of camphor and CCS have been chosen as independent factors, while % porosity and % drug release in 60 min	Pellet compositions showed satisfactory morphological, flow, and mechanical qualities. Compared to 38.54% drug release after 60 min with MCC pellets, pellets developed with an optimal composition, consisting of a suitable mix of MCC, SDL, camphor, and CCS, released 100% drug throughout 60 min.	Patel, Hetal, Patel, H., Gohel, M., & Tiwari, S. 2016, [112]

	were selected as dependent variables.		
The aim of the research is to study comparison work on the enhanced solubility and dissolution rate of telmisartan (TEL) using quasi-emulsion solvent diffusion (QESD) and spherical agglomeration methods.	Based on drug solubility, N, N dimethyl formamide (DMF), chloroform, and water were selected as outstanding solvents, bridging liquids, and bad solvents in accordance with spherical agglomeration.	Agglomerates generated by the QESD approach displayed higher improvements in solubility (2.89 in 0.1N HCl and dissolution rate (2.81 fold) compared with pure drugs. QESD technology is an affordable and easy approach for enhancing the solubility and dissolving rate of TEL.	Praveen Srikumar and Sai Krishna Putta 2017, [113]
To construct a self-microemulsifying drug delivery system (SMEDDS) for augmentation of oral bioavailability of the weakly water-soluble drug Telmisartan (TLS), a BCS class II medicine, by enhancing its dissolution rate.	SMEDDS were created utilizing cinnamon essential oil as the oil phase, Gelucire 44/14 as the surfactant, and Transcutol HP as the co-surfactant. Selected compositions were evaluated in terms of droplet size distribution, zeta potential, and cloud point and then subjected to in vitro drug release tests. The bioavailability	The SEDDS formulations were produced utilizing different quantities of cinnamon oil (20–70%), gelucire 44/14 (20–69%), and transcutol HP (4–27%). The in vitro drug release study and in vivo experiments demonstrated that the release from SMEDDS was more efficient when compared with the drug suspension. The relative bioavailability of SMEDDS to the suspension	Suvendu Kumar Sahoo, Padilam Suresh, Usharani Acharya 2018, [114]

	of the optimized formulation was examined in New Zealand white rabbits.	formulation (20 mg/ml) was 238%.	
The research target is to build a super-saturable self-microemulsifying drug delivery system (Su-SMEDDS) to increase the dissolution and oral bioavailability of telmisartan (TMS).	Amorphous alkalinized Telmisartan was formed into a SMEDDS, comprised of Capmul® MCM (oil), Cremophor® RH40 (surfactant), and tetraglycol (co-surfactant). Su-SMEDDS-SOL was produced by admixing Soluplus® with the SMEDDS at a 5:100 (w/w) ratio.	SuSMEDDS-SOL was more effective in terms of dissolving efficiency (> 90% over 2 h) and dissolution-retaining time (no precipitation over 2 h). An in vivo pharmacokinetic investigation in rats found that the oral bioavailability of Su-SMEDDS-SOL was 4.8-, 1.3-, and 1.2-fold greater than that of the Telmisartan solution.	Park, S. Y., Jin, C. H., Goo, Y. T., Chae, B. R., Yoon, H. Y., Kim, C. H., Song, S. H 2020, [115]
Research intended to increase the solubility and dissolution of BCS class II drugs, telmisartan (TEM), via nano formulation technique.	Bottom-up techniques such as anti-solvent precipitation and emulsification solvent evaporation techniques used to minimize the size of the drugs in micron-sized particles by HPMC E15 and PVP K-25 at 1500–2000 rpm.	The nanosuspensions with a particle size of 338.1 nm, a PDI of 0.146 and zeta potential − 16.2 mV. In vitro drug diffusion studies demonstrated a drug release of 82.6% at the end of 3 h, whereas plain drug suspension displayed only 42.8% release, using nano suspension.	Bhargav, E., Chaithanya Barghav, G., Padmanabha Reddy, Y. 2020, [116]

2.3. Review of work done on combination of Benidipine with Telmisartan

Objective	Description	Conclusion	Reference
The purpose of the study is the development and validation of a stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) technique for simultaneous determination of telmisartan (TEL) and benidipine hydrochloride (BND) in pharmaceutical dosage form.	Reverse-phase chromatography was selected. A C18 column, a 250×4.6 mm column with 5.0 µm particle packing, was utilized for the separation of TEL and BND. TEL (40 µg/ml) and BND (4 µg/ml) in buffer, pH 4.0: Methanol (50:50) was employed as the mobile phase.	The technique was found linear from 20 to 60 µg/ml and 2–6 µg/ml for TEL and BND individually. The suggested method may be employed for regular evaluation of benidipine HCl and TEL in combination dosage form and quality control in bulk manufacture.	Naim, M., Ahmed, A., & G Khan. 2018, [117]
Research aims to create a dual-wavelength spectrophotometric method for the simultaneous measurement of benidipine HCl (BEN) and telmisartan (TEL) in combination tablet dosage form.	The technique was based on measurements of benedipine HCl at the absorption difference between 228.36nm and 245.39nm and telmisartan at the absorption difference between 280.21 nm and 315.39 nm.	The linearity has been achieved in the concentration range of 1–5 µg/ml for Benidipine HCl and 10–50 µg/ml with Telmisartan. The approach showed high repeatability and recovery, with a RSD of less than 2.	Patel, K., Shah, D., & Maheshwari, D.2018, [118]
The study objective is to create an RP-HPLC	The separation of the samples was carried	The retention times of benidipine hydrochloride	Payal G. Jain, Ankit

technique for the simultaneous quantification of benidipine hydrochloride and telmisartan in tablets.	out employing an Inertsil ODS C18 column and a mixture of 0.05M potassium dihydrogen phosphate buffer and acetonitrile as a mobile phase. The flow rate was regulated to 1 mL/min, and effluent was measured at 267 nm by utilizing a PDA detector.	and telmisartan were determined to be 2.977 and 5.167, respectively. The approach was linear across the range of 2–6 µg/mL and 20–60 µg/mL for benedipine hydrochloride and telmisartan. The recovery rates of benedipine hydrochloride and telmisartan have been found to be 100.46%–101.17% and 100.20%–100.38%, respectively.	B. Chaudhary and Shweta M. Bhadani 2018, [119]

2.4. Review of work done on preparation of Self Emulsifying Drug delivery system

Objective	Description	Conclusion	Reference
The existing study endeavor comprises the creation of liquid self-nano-emulsifying drug delivery systems (SNEDDS) to enhance the bioavailability of carvedilol by enabling its transport through lymphatic circulation.	Formulation was created by using combinations of Capmul PG8, Cremophor EL, and Trancutol HP. The SNEDDS, optimized utilizing a central composite design (CCD), were tested for several response factors, viz., drug release parameters, emulsification time, emulsion droplet size, and mean dissolution time.	SNEDDS formulation demonstrated a 3–4 fold improvement in the bioavailable fraction, absorption number, and wall permeability of carvedilol as in contrast to the pure drug and marketed formulation. 100% release of drug had been identified within 20 minutes in the case of VAL7, but merely 67% and 77% of the drug had been released at the same time in the case of pure drug and marketed composition, respectively.	Bhupinder Singh, Lalit Khurana, Shantanu Bandyopadhyay, Rishi Kapil & O.O.P. Katare 2011, [120]
The purpose of this research is to develop and structurally optimize self-emulsifying drug delivery system formulations incorporating	Formulations were developed utilizing Capryol 90®as oil, two surfactants, Cremophor EL® and Labrasol®, and cosurfactant, transcutol HP. CCRD was utilized for optimization. Oil%, Smix: Cosurfactant ratio, and	Optimize formulation, which involves 10% oil, 1.31 as Smix : Cosurfactant, and 2 as Cremophor EL®: Labrasol®. It demonstrates quicker and more complete dissolution of amisulpride than aqueous drug suspension. Also, it	Ahmed A, Aboelwafa and Amal I. A. Makhlouf 2012, [121]

amisulpride for the enhancement of dissolution as well as oral absorption utilizing a central composite rotatable design (CCRD).	CremophorEL®:Labrasol® were chosen as independent variables, whereas mean droplet size, drug loading, and light absorbance were taken as dependent variables.	indicates a remarkable improvement in the bioavailability of amisulpride in rabbits.	
The purpose of the current investigation was to establish and analyze the self-nanoemulsifying drug delivery system (SNEDDS) of glimepiride (GMP), a poorly soluble medicine.	A three-component, three-level Box-Behnken design (BBD) was implemented to study the main and interaction effects of independent variables, particularly X_1 (amount of Capmul MCM), X_2 (amount of Acrysol K 140), and X_3 (amount of Transcutol P) , where percentage of transmittance value (Y_1), droplet diameter (Y_2), and percent drugs released in 5 minutes (Y_3) as the dependent variables.	The droplet diameter of the optimized formulation has been determined to be 34.10 nm. The most effective formulation produced by the response optimization using the desirability function gave the final formulation with D = 0.9943, which released 79.85% of GMP during 5 minutes. The optimized batch demonstrated a considerably (P <0.001) higher release of medicine as compared to pure GMP.	Sunny R. Shah, Rajesh H. Parikh, Jayant R. Chavda , And Navin R. Sheth. 2013, [122]
The research effort consists of the production of a self-microemulsifying	SMEDDS may be manufactured utilizing Capryol 90 as oil, Labrasol as surfactant, and Captex 500 as cosurfactant,	Developed SMEDDS demonstrating release of drugs for liquid SMEDDS formulation (99.91%), droplet size (9.15 nm), Zeta	Shukla, J. B., Jani, G. K., & Omri, A.

drug delivery system (SMEDDS) of candesartan cilexetil.	containing 32 mg of candesartan cilexetil. Solid SMEDDS compositions (Tablet) have been produced by adsorption to solid carrier technology, employing optimal liquid SMEDDS formulation	potential (-23.2), viscosity (0.8824 cP), and infinite dilution capacity. Optimized formulation converts into S-SMEDDS employing Aeropearl 300 pharma as optimum adsorbents. The oral bioavailability of drugs (15%) has been increased by up to 1.78 fold.	W. 2016, [123]
The present investigations comprise the development and assessment of solid self-nanoemulsifying drug delivery systems (S-SNEDDS) applying porous carriers to increase the oral bioavailability of olmesartan medoxomil.	Equilibrium solubility tests and pseudoternary phase diagrams displayed the suitability of oleic acid, Tween 40, and Transcutol HP as the lipid, surfactant, and cosolvent for the preparation of the liquid SNEDDS. S-SNEDDS formulations were developed by adsorbing L-SNEDDS onto the porous carriers, viz., Aerosil 200, Aeroperl 300, Sylysia 550, Neusilin US2, and Fujicalin SG.	From the several solid carriers employed, Neusilin US2 showed better oil adsorption capacity, micrometric characteristics, outstanding flowability, and compactibility. Approximately 2.6-fold improvement in the drug release rate has been observed from the optimized S-SNEDDS. In vivo pharmacokinetic tests in Wistar rats indicated a 2.32 and 3.27-fold improvement in Cmax and AUC of the drug generated by optimized S-SNEDDS	Beg S, Katare O, Saini S, Garg B, Khurana RK, Singh B. 2016, [124]

		compared to the pure drug solution.	
The goal of the present investigation was to develop self-nanoemulsifying drug delivery systems (SNEDDS) for polypeptide-K (PPK) with the aim of achieving oral delivery.	Box-Behnken design (BBD) was employed to create and optimize the composition of SNEDDS. Oleoyl polyoxyl-6 glycerides (A), Tween 80 (B), and diethylene glycol monoethyl ether (C) were utilized as oil, surfactant, and co-surfactant, respectively, as independent variables. The influence of changes in their composition was observed on the mean droplet size (y_1), polydispersity index (PDI) (y_2), % drug loading (y_3), and zeta potential (y_4).	The optimal composition of the SNEDDS formulation was 25% v/v oleoyl polyoxyl-6 glycerides, 37% v/v Tween 80, 38% v/v diethylene glycol monoethyl ether, and 3% w/v PPK. The biochemical, hematological, and histological findings from streptozotocin-induced diabetic rats indicated outstanding antidiabetic efficacy of PPK incorporated in SNEDDS at both dosages (i.e., 400 mg/kg and 800 mg/kg) as compared to its pure form in both doses.	Garg, V., Kaur, P., Singh, S. K., Kumar, B., Bawa, P., Gulati, M., & Yadav, A. K. 2017, [125]
To create a self-nanoemulsifying drug delivery system (SNEDDS) for Lovastatin to enhance its solubility and bioavailability.	The optimized Lovastatin SNEDDS formulation (F8) consists of a combination of Acrysol EL 135 as the oil phase, Lauro glycol 90, and Capmul MCM as the surfactant and co-surfactant, respectively.	Formulation F8 was found to be the best formulation on the basis of assessment factors. The particle size of the optimized formulation had been found to be 4.9 nm, and the Z-average was 71.5 nm, indicating all the	Bhikshapathi, D. V. R. N., & Priya, K. 2018, [126]

		particles were in the nanometer range. Pharmacokinetic study in rats demonstrated that, in contrast to the pure drugs, the optimized SMEDDS composition considerably improved the oral bioavailability of Lovastatin.	
The research endeavor was aimed at producing a solid self-nanoemulsifying drug delivery system (S-SNEDDS) for deferasirox (DFX).	Based on solubility tests of DFX in different parts, peceol™, kolliphor® EL, and transcutol were chosen as excipients. Pseudo-ternary phase diagrams were generated, and the selected DFX-SNEDDS formulation was transformed into S-SNEDDS by adsorbing into porous carriers.	The in vitro drug release studies showed that the DFX release (Q5%) from S-SNEDDS stabilized with Neusilin UFL2 was much greater (93.6 ± 0.7% within 5 min) compared with the marketed product (81.65 ± 2.10%). The results in general suggested that the S-SNEDDS formulation of DFX might perhaps have the power to boost the solubility of DFX,that could in turn have the capacity to improve its oral bioavailability.	Alghananim, Alaa, Yıldız Ozalp, Burcu Mesut, Nedime Serakinci and Sevgi Gungor 2020, [127]
The purpose of the current research	Cotton seed oil, tween 80, and transcutol have been	The optimized formulation offers globule sizes of	Yadav, V. K.,

was to design, develop, and evaluate a solid form of liquid self-nanoemulsifying formulation for increasing the oral bioavailability and dissolution of itraconazole.	selected as important components in the development of a self-nanoemulsifying drug delivery system (SNEDDS). These formulations were evaluated by thermodynamic stability, emulsifying rates, robustness to dilution and pH effects, globule size, zeta potential, in vitro investigation, etc.	141.20±0.69 nm, pdi 0.29±0.04, zeta potential 11.2±0.69 mV, and is fast dissolving within 30 min with over 90 percent of the drug released. Employing Neusilin US2 as a solid adsorbent approach for altering the optimal formulations into powder form. In vitro drug releases of solid SNEDDS and liquid SNEDDS are nearly the same.	Balamuralidhara, V., & Hemanth Kumar, S. 2020, [128]
This work aims to create a solid self-nanoemulsified drug delivery system (S-SNEDDS) for lamotrigine (LMG) to increase its solubility and oral bioavailability (BA).	Nineteen liquid SNEDDS were created (R1-R19) utilizing D-optimal design with varied ratios of oil, surfactant (S), and cosurfactant (Cos). The formulations were assessed for robustness to dilution, droplet size, thermodynamic stability tests, self-emulsification time, in-vitro releases in 0.1 N HCl, and phosphate buffer (PB; pH 6.8).	Eight S-SNEDDS were constructed (S1–S8) using 2^3 factorial designs. The optimized S-SNEDDS was S2, adsorbed on Aeroperl® 300 in a ratio of 1:1, with the highest results with regard to in-vitro drug released in 0.1 N HCl at 15 min (100%) in comparison to pure LMG (73.40%) and Lamictal® (79.43%), and in-vitro drug released at PB at 45 min (100%) contrasting to pure LMG	Rehab Abdelmonem, Marian Sobhy Azer, Amna Makky, Abdelazim Zaghloul, Mohamed El-Nabarawia 2020, [129]

		(30.46%) and Lamictal® (92.08%). The BA of S2 has increased by 2.03 and 1.605 folds in comparison with pure LMG and Lamictal®, respectively.	
This work is intended to design and improve a self-nanoemulsifying drug delivery system (SNEDDS) for bosentan (BOS) to address its poor oral bioavailability owing to low water solubility.	The primary components of the formulation have been selected as glyceryl monolinoleate (lipid), polyoxyl 40 hydrogenated castor oil (surfactant), and caprylocaproyl polyoXyl-8 glycerides (co-surfactant). The composition of BOS-SNEDDS was developed utilizing the BoX-Behnken design (BBD).	The generated SNEDDS were thermodynamically stable, with a droplet size of 17.11 nm, a poly-dispersity index of 0.180, and an emulsification time of <1 min. The BOS-loaded SNEDDS demonstrated 3.0, 7.97, 4.23, and 4.94-fold rises in the % of cumulative dissolution compared to the reference tablets. SNEDDS increased the Cmax and AUC 1.67 and 2.12-fold and 5.15 and 1.84-fold in fasting and fed conditions, respectively, in comparison to the reference.	Duygu Yilmaz Usta., Zeynep Safak Teksin 2022, , [130]
The goal of the current research was to explore the potential of the	The self-nanoemulsifying drug delivery system was created from Capmul MCM (oil), Tween 20 (surfactant),	The droplet size, polydispersity index, self-emulsification duration, and equilibrium solubility	Pavan Ram Kamble, Karimunni

self-nanoemulsifying drug delivery system (SNEDDS) for improving the solubility and oral bioavailability of plumbagin.	and propylene glycol (cosurfactant). The central composite design was applied as a statistical method to optimize the composition variables X_1 (oil) and X_2 (surfactant: co-surfactant mixture ratio) of the SNEDDS. The responses that were evaluated were droplet size, self-emulsification time, % of drug release at 15 min, and equilibrium solubility. Best liquid SNEDDS was adsorbed on Neusilin US2.	of the optimized formulation were 58.500 ± 1.170 nm, 0.228 ± 0.012, 17.660 ± 1.520 s, and 34.180 ± 1.380 mg/mL, respectively. Drug release had been estimated to be 93.320% ± 1.090. In vivo anti-inflammatory investigations have shown higher effectiveness from the SNEDDS than with pure plumbagin. Pharmacokinetic studies in rats demonstrated that a solid SNEDDS exhibited 4.49-fold higher bioavailability compared to pure plumbagin.	Sameer Shaikh 2022, [131]

2.5. Review of work done on preparation of Self Emulsifying Drug delivery system using QBD Approch

Objective	Description	Conclusion	Reference
The present research comprises systematic development, optimization, and assessment (in vitro, in situ, and in vivo) of the solid formulations of SNEDDS lovastatin, applying a rational quality by design (QbD)-based approach to formulation by design (FbD).	Preformulation studies in combination with the initial risk assessment assisted in the selection of lipid (i.e., Capmul MCM), surfactant (i.e., Nikkol HCO-50), and co-surfactant (i.e., Lutrol F127) preferred critical material attributes (CMAs) for the formulation of S-SNEDDS. A face-centered cubic design (FCCD) was applied for optimization utilizing Nikkol-HCO50 (X_1) and Lutrol-F127 (X_2), examining CQAs such as globule size, liquefaction time, emulsification time, mean dissolution time, dissolving efficiency, and permeation parameter.	The optimized formulation displayed excellent globule size in the nanosize range, a significant increase in the dissolving rate and penetration of the drug, and numerous enhancements in the absorption and permeability parameters during in situ SPIP and in vivo pharmacodynamics investigations.	Sarwar Beg, Premjeet Singh Sandhu, Rattandeep Singh Batra, Rajneet Kaur Khurana & Bhupinder Singh 2014, [132]
The aims of the current investigations were to construct the systematic optimized self-	The quality profile target product (QTPP) was established, and key quality characteristics were identified. Preformulation investigations comprising equilibrium	In situ SPIP experiments indicated considerable improvement in the absorptivity and permeability characteristics of SNEDDS attributable to	Bandyopadhyay, Shantanu, Beg, Sarwar, Prakash,

nanoemulsifying drug delivery systems (SNEDDS) of valsartan using the comprehensive QbD technique.	solubility and pseudoternary phase titration examinations enabled the identification of appropriate lipids and emulgents for the formulation of SNEDDS. Risk evaluations and factor screening studies permitted the selection of Lauroglycol FCC and Capmul MCM L8 (i.e., lipid), Tween 40, and Tween 80 (i.e., emulgent) as the critical material attributes (CMAs) for SNEDDS. A central composite design (CCD) was utilized for systematic optimization of SNEDDS, using globule size (Dnm), drug release in 10 min (Q10min), and the amount permeated in 45 min (%Perm45min) as the CQAs.	the suppression of P-gp/MRP2 efflux vis-à-vis the traditional marketed formulation and pure drug. In vivo pharmacokinetic investigations substantiated a considerable elevation in the oral bioavailability of drugs from SNEDDS compared to the marketed formulation. The establishment of varying levels of in vitro and in vivo correlations (IVIVC) displayed excellent goodness of fit between the in vitro drug release data and the in vivo absorption parameters.	Om Sharma, Gajanand & Singh, Bhupinder . 2015, [133]
The purpose of this work was to construct a self-nanoemulsifying drug delivery system (SNEDDS) for bosentan utilizing	The principal component of the formulation, compared to lipid (Capmul MCM), surfactant (LABRASOL), and co-surfactant (PEG 600), has been selected on the basis of saturation solubility. The most suitable blend of Capmul	The improved formulation demonstrated 98.5% drug release in 15 minutes, a globule size of 62.5 nm, an emulsification time of 12 seconds, and a PDI of 0.146. The TEM investigation indicated drug	Kahnu Charan Panigrahi, Jayashree Jena, Goutam Kumar Jena, Ch.

the quality by design (QBD) technique with higher bioavailability.	MCM, LABRASOL, and PEG 600 was determined by applying the response surface method (RSM) with a central composite design (CCD). A pharmacokinetic investigation was undertaken to establish several key parameters.	entrapment inside the oil globules in the nanosize range. The pharmacokinetic investigation of the enhanced formulation demonstrated quicker dissolution and absorption, which was confirmed by a significantly higher Cmax, greater AUC, and smaller Tmax than the pure drug bosentan.	Niranjan Patra, M.E. Bhanoji Rao 2018, [134]
The purpose of the study was to create SNEDDS containing the poorly water-soluble drug ritonavir by implementing QbD principles.	Initially, the Plakett-Burman design (PB) was utilized as a screening design to identify the significant effect of six independent variables on the parameters (globule size (nm), self-emulsification time (sec), and percent dissolving efficiency at 15 min) of SNEDDS. Then, central composite design (CCD) is employed to find the best layout space between the amount of oleic acid (X_1), surfactant (X_2), and co-surfactant (X_3).	PB design has been demonstrated to be particularly useful for identifying likely critical material characteristics (CMAs) impacting the production of SNEDDS and CCD, which aided in selecting the optimal design space. The ideal formulations have been created according to the displayed model, investigated for responses, and selected to be equivalent to 118nm for globule size and 135	Narendra Chikkanna ,Ramesh Chandrashekar 2018, [135]

		seconds for self-emulsification time.	
The research attempts to provide a systematic methodology for building the lipidic self-nanoemulsifying formulation of olmesartan medoxomil, utilizing the concepts of quality by design (QbD).	Mixture design was applied for systematic adjustments of the composition of nanolipidic formulations, which were subsequently assessed for reduced globule size, stable zeta potential, and lower values of polydispersity index. The process of solidification of the self-nanoemulsifying drug delivery system (SNEDDS) was carried out utilizing porous carriers and then transformed on the basis of oil adsorption potential, powder flow characteristics, and drug release performance. A pharmacokinetic investigation was done in male Wistar rats to find the drug's absorption properties.	The optimized liquid SNEDDS demonstrated globule size <100 nm, emulsification efficiency <5 minutes, and in vitro drug release >85% over 30 minutes. Additionally, the solid SNEDDS formulation was successfully developed using Neusilin US2, which has the highest oil adsorption capacity and outstanding micromeritic properties. The pharmacokinetic study displayed a 4- to 5-fold increase ($P<0.05$) in the values of Cmax, AUC, and Tmax obtained from the nanoformulations compared to the marketed formulation.	Jagdish Kumar Arun, Rajeshwar Vodeti, Birendra Shrivastava Vasudha Bakshi 2020, [136]
The goal of this work was to create a self-nano-emulsifying drug delivery system	The preparatory preformulation studies and the risk assessment carried out allowed the proper selection of independent factors for the optimization of	The developed ideal Ritonavir-SNEDDS by QbD approach produced a robust and sustainable approach to increasing the	Gowthami K, Kavitha A, Samatha P,

(SNEDDS) for a poorly water-soluble anti-retroviral drug, Ritonavir, through Quality by Design (QbD).	dependent variables. Droplet size (nm), emulsification time (seconds), polydispersity index (PDI), and % transmittance comprised the different responses considered for the investigation. Labrafil® M 1944 CS (oil), Tween 80 (surfactant), and PEG 6000 (cosurfactant) are the independent variables assessed in the design.	oral bioavailability of Ritonavir and was examined by the characteristics investigated: droplet size (264.7 nm), emulsification time (46.1 sec), PDI (0.415), and % transmittance (94.8).	Chandramouli R 2020, [137]
To overcome the restrictions of voxelotor (an antisickling drug), low water solubility and low oral bioavailability, a self-nanoemulsifying drug delivery device was designed.	Various oils, surfactants, and cosurfactants were evaluated for their solubilization ability for the drugs. The region of nanoemulsification has been identified employing a ternary phase diagram. An experimental mixture design and a desirability function had been applied to select SNEDDSs that contain the greatest amount of lipids and the least amount of surfactant and that possess the most effective emulsification properties.	The optimized SNEDDS formulation showed self-emulsifying time (32 s), droplet size (35 nm), and zeta potential (−8 mV). In vitro dissolution investigations demonstrated a 3.1-fold increase in drug solubility from the optimized SNEDDS versus pure drug powder. In comparison with the drug Additionally, the generated SNEDDS raised the oral bioavailability (1.7-fold) of voxelotor in rats.	Buya, A.B., Terrasi, Mbinze, J.K., Muccioli, G.G., Beloqui,A 2021, [138]

2.6. Review of work done on Pharmacology study

Objective	Description	Conclusion	Reference
The current study examined the best acceptable concentration and duration of fructose administration for creating hypertension in Wistar rats. The link between fructose-induced hypertension and hyper insulinemia was also investigated.	The rats were administered with 5%, 10%, or 20% fructose in drinking water. The most significant changes, including increases in blood pressure, fluid consumption, and plasma levels of insulin, glucose, and triglycerides, and a reduction in food intake after fructose therapy, were found with the 10% solution.	Administration with 10% fructose in drinking water (equal to a diet containing 48–57% fructose) over one week or longer is suitable for the rapid production of fructose-induced hypertension in Wistar rats, which is related to higher levels of plasma insulin, glucose, and triglycerides.	Soter Dai and John H. McNeil, 1995, [139]
This research studied the link between the plasma concentration of benidipine and its cardiovascular effects in order to examine the effectiveness of pharmacokinetic-pharmacodynamic (PK-PD) models in defining this relationship.	Two groups of 24 healthy individuals received either a 4- or 8-mg benidipine hydrochloride tablet; 11 extra participants received a placebo. Serial blood samples and PD evaluations were done for 8 hours. Plasma concentrations of benidipine were evaluated employing validated LC/MS/MS equipment, and the effects on blood pressure and heart rate were studied throughout the same period of time.	Benidipine achieved mean peak plasma concentrations of 1.04 and 3.85 ng/mL at 0.5 and 0.75 h following 4 and 8 mg doses, respectively. Peak cardiovascular effects were observed approximately 2 hours after the administration of each dose. Maximum decreases in diastolic blood pressure with 4 and 8 mg of benidipine were	Yun MS, M.-H. Yun MS, W. Kang and K.-I. Kwon, 2005, [140]

		7.79 and 14.75 mmHg, respectively.	
To examine the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of telmisartan in spontaneously hypertensive (SH) rats employing indirect response and effect-compartment link models and comparing two PK-PD models fitting quality.	The SH rats were given a single oral dosage of 2, 4, and 8 mg/kg of telmisartan. The plasma concentrations of telmisartan were measured by the liquid chromatography-mass spectrum technique. The mean arterial blood pressure has been determined in order to explain the pharmacodynamics of telmisartan using tail-cuff manometer. The relationship between telmisartan concentration and hypertension in the SH rats was evaluated using an indirect response model.	The PK characteristics indicated dose proportionality, with an extended half-life of 16 h, a clearance of 0.15 $L•kg^{-1}•h^{-1}$, and a volume of distribution of 5.36 $L•kg^{-1}$ in the research. The hypotensive response to telmisartan may be expected more effectively by utilizing the indirect response model than the effect-compartment link model. The modeling technique utilized here may be effective in enhancing the therapeutic treatment of telmisartan.	Kun HAO, Yuan-cheng Chen, Yan-guang Cao, Dan Yu, Xiao-quan Liu , Guang-Ji Wang .2007, [141]
Moringa stenopetala is an herb that has been utilized in Ethiopian traditional medicine as a therapy for the treatment of hypertension and diabetes. The purpose	Rats were randomly assigned into control and treatment groups (n = 6). Treatment groups were administered daily extracts (250, 500, and 1000 mg/kg) orally with fructose. In contrast, positive, negative, and normal control	The investigation indicated that aqueous and 70% ethanol extracts considerably inhibited blood pressure in a dose-dependent manner equivalent to that of the standard drugs. Similarly,	Geleta, B., Makonnen , E., Debella, A., & Tadele, A. 2016, [142]

of this research was to investigate antihypertensive and antihyperlipidemic effects in fructose-induced hypertensive rats.	groups were given captopril (20 mg/kg/day with fructose) or alone fructose (66% w/v ad libitum) with distilled water ad libitum over 15 days consecutively. The blood pressure was reported every 5th day employing a tail cuff blood pressure analyzer, and on the 16th day, the blood was collected to examine the antihyperlipidemic impact utilizing a laboratory chemistry analyzer.	the extracts prevented increases in the lipid profile (cholesterol, glucose, and triglycerides) in contrast to the negative control. The biochemical test showed that extracts exhibited an increase in liver but no effect on renal function indicators as compared to normal control.	
The research objective is to provide the poorly water-soluble drug nimodipine in a solid self-emulsifying formulation. This research study comprises a systematic strategy for SMEDDS development and its characterization.	Liquid SMEDDS was developed employing a simplex lattice matrix design. The optimized liquid SMEDDS was solidified using adsorbents and transformed into a capsule dosage form. Further, the novel formulation was evaluated by in-vivo pharmacodynamics investigations using a Sprague-Dawley rat, and blood pressure was determined using the non-invasive cuff tail technique.	This research study comprises a systematic strategy for SMEDDS development and its evaluation. Among all the adsorbents, Syliod XDP3 had been selected based on its increased flow properties compared to the other adsorbents. A pharmacodynamic study demonstrated that an optimized solid SMEDDS batch	Manali D. Prajapat , Nilesh J. Patel, Aditi Bariya, Snehal S. Patel, Shital B. Butani. 2017, [143]

		significantly reduced blood pressure in SD rats.	
The research work intends to build a DOE-optimized lipid-based system for Clinidipine to increase oral bioavailability.	Formulations have been developed on the basis of DOE, where data modeling between independent factors (% oil, oil/six ratio, and drug loading) and dependent variables (droplet size, clarity, and drug solubility) under the Box Behnken design has been investigated and optimized. The optimized formulation was examined for pharmacodynamic experiments carried out on Wistar rats at low and high doses and compared with CIL oral suspension as a control.	The optimized formulation consists of 40.4% (w/w) ethyl oleate as oil, 48.6% (w/w) cremophor EL as a surfactant, and 11% (w/w) transcutol as cosurfactant. The average drop size and zeta potential of SNC-7 were 72.10 nm and 1.96±0.045 mv, respectively. DOE optimization confirmed that SNEDDS generated the fast dissolution of CIL despite its suspension. SNC-7 formulation demonstrated significant antihypertensive activity higher than control.	Pankaj Kumar Sharma, Anoop Kumar , Vikesh Kumar Shukla. 2022, [144]