RESEARCH ARTICLE Int J Life Sci Pharma Res., Vol: 16, Issue: 3, 2026; 29-39

IJLPR

International Journal of Life science and Pharma Research

Content Available at www.ijlpr.com ISSN: 2250-0480



STATISTICAL DEVELOPMENT OF POSACONAZOLE SMEDDS VIA D-OPTIMAL MIXTURE DESIGN UNDER A QBD PARADIGM

JUPALLY POOJA[1], SAGARLA USHARANI[2], VASAVI DEVIREDDY[3], MALLADIJAYA LAKSHMI[4], SHAIK NASEEB BASHA[5], PRASANTHI DOMARAJU[6]*

[1,2,4,5,6]Department of Pharmaceutics, G. Pulla Reddy college of Pharmacy, Mehdipatnam Hyderabad,Telangana, India.
[3]Department of Pharmaceutics, St.Mary,s College of Pharmacy, Secunderabad, Hyderabad,Telangana, India.

***CORRESPONDING AUTHOR**
Dr. D. Prasanthi, M. Pharm, PhD.
Professor, Department of Regulatory Affairs,
G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, India-500028.

DOI: https://doi.org/10.22376/ijlpr.v16i3.2038

ARTICLE HISTORY: Received: 09.07.2026 Revised: 27.08.2026 Accepted: 14.09.2026

Abstract

Introduction: Posaconazole is a class II BCS (Biopharmaceutical Classification System) antifungal drug. Current study objective is to enhance solubility by formulating SMEDDS guided by QbD via experimental design. **Methods:** Solubility studies in surfactants, oils, and co-surfactants were conducted. Critical quality attributes (CQA), emulsification time (R1) and drug release (R2) were taken as dependent factors. Formulations were prepared as per d-optimal mixture design and evaluated for physico-chemical parameters and dissolution studies. **Results:** Maximum solubility 6.953mg/ml in Tween 40, 1.630mg/ml in Transcutol & 0.187mg/ml in Capmul MCM were selected as surfactant, co-surfactant and oil phases. Excipient compatibility was confirmed by FTIR studies. Soluplus was used as Precipitation Inhibitor. Independent factors and dependent factors were mathematically co-related by Linear model and cubic model. From Overlay plots OF1 formulation (43.30ml Capmul MCM, 20ml Tween 40, 36.69ml Transcutol) with desirability co-efficient 0.991 was optimised. This formulation Globule size is 62.7nm, PDI 0.08 and Zeta-potential -0.19 mV. **Discussion:** Quality target product profile was postulated and CQA assessed by experimental design. Oil, Capmul MCM influenced rate of emulsification positively but decreased drug release. Surfactant and co-surfactant increased drug release but slowed emulsification time. D-Optimal mixture design was validated by correlation co-efficient of approx. 0.9 between predicted and actual responses. Formulations followed Fickian diffusion mechanism and were stable for one month at 40°C/75% RH. **Conclusion:** Posaconazole solubility as SMEDDS has been enhanced.

Keywords: *self-micro emulsifying drug delivery system (SMEDDS), QBD (quality by design), FTIR (Fourier Transform Infrared Spectroscopy), Solubility.*

This article is under the CC BY- NC-ND Licence (https://creativecommons.org/licenses/by-nc-nd/4.0)
Copyright @International Journal of Life Science and Pharma Research, available at www.ijlpr.com

1. INTRODUCTION

SMEDDS is an isotropic blend of hydrophilic cosolvents and cosurfactants, able to create fine o/w microemulsions over gentle agitation in aqueous media, used to administer hydrophobic medications with limited bioavailability and low water solubility [1,2,3]. Posaconazole is BCS class-II antifungal drug, an all-purpose triazole antifungal medication for oropharyngeal candidiasis [4,5] in patients at high risk of itraconazole and/or fluconazole refractories and/or as prevention of invasive aspergillus and candida infections which is formulated as SMEDDS to enhance its solubility and bioavailability [6,7].The ratio of oil to surfactant, amount of surfactant present, and temperature at which self-emulsification takes place all have an impact on the self-emulsification process [8,9,10]. The manufacturing and development approach that is strategy-based is known as quality by design. Considering the efficacy and purity of the drug, QBD is viewed as the guarantee for the performance that is intended to be developed for the finished product [11]. This strategy also emphasises the processes unpredictability and improves identification and controls[12].D-optimal mixture design is employed for optimisation [13].Use a simplex lattice mixture design if there are two or three mixture components involved and their ranges are all the same.Use a simplex centroid design if there are three or five

components and their ranges are all the same.Use limited mixture design, also known as D-Optimal design, if there are 2-4 components involved and the ranges of all the components vary[14, 15].As there are several oil and surfactant formulations in the current investigation, the D-optimal design was chosen as the optimisation strategy. Selecting a liquid self-micro emulsifying dosage form method that is lipid-based to help increase the oral bioavailability and solubility of medications with low bioavailability [16,17, 18]. By using the phase titration method (also known as the water titration method), the extended onset of action causes poorly soluble medicines to become more soluble [18,19,20]. In the current study, SMEDDS for posaconazole are being produced utilising QBD design to that extent optimised using D-optimal mixture design.

2. MATERIALS AND METHODS

2.1. Materials: Posaconazole is gift sample from Suven life sciences, Oleic acid is procured from Moly Chem manufacturer. Castor oil,Olive oil and sunflower oil is being procured from Local market. Capmul MCM and Captex is gifted from 200 ABITEC Corporation. Tweens and Spansof different grades are procured from Sisco research laboratories Pvt. Ltd. PEG of grades 400, 600, Methanol and Hydrochloric acid are obtained from S.D fine chemicals Ltd. Transcutol P is procured from Research-Lab Fine Chem Industries. Soluplus is gifted from BASF, The chemical company. Distilled water in house source.

2.2. Methods

2.2.1. Drug-excipient compatibility study Interactions by FTIR: Small quantity of sample with potassium bromide was combined to create potassium bromide (KBr) discs, which were subsequently compacted in a hydraulic press while under vacuum with 6–8 tonnes of pressure. Appropriate holder was used to hold the produced disc in an IR spectrophotometer, and scanned for 12 minutes to record IR spectra from 4000 cm^{-1} to 500^{-1} cm. We compared the resulting spectrum to look for any spectra alterations. They were noted for their presence in the corresponding function's defining peaks [21].

2.2.2. Solubility studies: The method involves adding drugs in excess to 2ml eppendroff tubes with excipients of volume. The eppendroff tubes were shaken in an orbital shaker for 48-72 hours then centrifugedfor 10 minutes at 4500 rpm. The filtrate sampled with syringe filter was diluted appropriately to analyze by Ultraviolet-Visible(UV) spectrophotometer for drug content [22,23].

2.2.3. QBD (Quality by Design):

2.2.3.1. Target product quality profile(TPQP): By "planning with the end in mind," the TPQP lays the strategic groundwork for medication development. The target product profile (TPP) consists of the full pharma product development strategy outlining the main quality characteristics of the therapeutic product, which are firmly connected to patient safety and efficacy. TPP was described as a target liquid SMEDDS formulation of posaconazole that was designed to increase the medication's oral bioavailability. Typical TPP components include the formulation type, dosage strength, mode of administration, timing of drug release, stability and Closure systems [11, 12].

2.2.3.2. Critical quality attributes (CQAs): Finding the relevant CQAs is the next step after quality target product profile (QTPP) has been connected. CQA is described as “a physiological, pharmacological, or microbial property or feature that should be within an appropriate limit, range, or distribution”. This shows that CQAs are QTTP subgroups that might be affected by modifications to the formulation or process factors. We designated viz. for the objective SMEDDS formulation.The stability of a drug's formulations and its ability for absorbing via the gastrointestinal system (essential for drug release from the formulation) are influenced by the particle size (PS) and time for emulsification (ET)[24,25, 26].

2.2.3.3. Optimization using D-Optimal mixture design

With various weight ratios of the co-surfactant and surfactant as Smix, pseudo-ternary phase diagrams were generated (1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1) ratios of oil:Smix. From the pseudo ternary phase diagram better formulations ratios were consideredfor design [27]. Preparation was done by Phase Titration Method [28], where oil was taken in a beaker and heated at 60°C on continuous stirring, mixture of surfactant, cosurfactant, drug and precipitation inhibitor were added slowly dropwise with gradual stirring, it results in formation of L-SMEDDS [29]. D-Optimal Mixture Design was used to analyse and construct quadratic response surfaces, with levels minimum 20,20,10 and maximum 67.5,60,40 respectively. R1, Self-emulsification time (seconds) and R2, Percentage Drug release in 8 hours was set as dependent factors [30].

Table 01: Formulation Table

Formulation code	Posaconazole (mg)	Capmul MCM (ml)	Tween 40 (ml)	Transcutol (ml)	Soluplus (mg)	Total Formulation (ml)
F1	1000	67.50	20	12.5	400	100
F2	1000	41.25	34.03	24.70	400	100
F3	1000	41.25	20	38.75	400	100
F4	1000	41.25	34.03	24.70	400	100

F5	1000	20	60	20	400	100
F6	1000	20	41.25	38.75	400	100
F7	1000	41.25	34.03	24.70	400	100
F8	1000	67.50	20	12.5	400	100
F9	1000	53.97	20.25	25.77	400	100
F10	1000	20	41.25	38.75	400	100
F11	1000	41.07	48.92	10	400	100
F12	1000	53.87	35.22	10.89	400	100
F13	1000	29.45	46.67	23.86	400	100
F14	1000	20	60	20	400	100
F15	1000	30.92	59.07	10	400	100
F16	1000	30.10	29.89	40	400	100

In the given table, F1,F8 are similar; F2,F4,F7 are similar;F5,F14 are similar and F6, F10 are similar.

2.2.4. Evaluation parameters of liquid smedds

2.2.4.1. Thermodynamic stability studies: L-SMEDDS formulations diluted with water were centrifuged for 15 minutes at 3500 rpm, visually checked for any phase separation. Additionally, the formulations were heated and cooled six times for a total of 48 hours (4°C and 45°C)[31].

2.2.4.2. Visual observation and phase separations: This was carried out by stirring mixture magnetically at 100 rpm at room temperature.After 24 hours, the generated emulsion was visually inspected for precipitation [32].

2.2.4.3. Robustness to dilution: L-SMEDDS were diluted to 50, 100, and 1000 times with 0.1N HCl solution and water. It was checked over for any separation of phases and drug precipitation [31].

2.2.4.4. Self-emulsification time: Sample of formulation was added to media (0.1N HCl/water)dropwise, in Type II USP dissolution apparatus, 50rpm paddle rotation, 37±0.5°C temperature, visually observed for emulsification [33,34].

2.2.4.5. Dispersibility test: 500 ml of distilled water (37°C±0.5°C) with a paddle moving at 50 rpm provided mild agitation when each formulation (0.5 ml) was added. Using the grading method described below, the compounds' in vitro efficacy was assessed visually [31,35].

Grade A is for rapid-forming clear and transparent emulsion, B is for rapid forming slightly less clear emulsion, bluish-white appearance, C for slow emulsifying bright white emulsion or greyish white emulsion with slightly oily appearance, D for emulsion with large oil droplets on the surface with minimal emulsification.

2.2.4.6. Determination of drug content Posaconazole formulation equivalent to one dose (10mg) was added to methanol (10 mL) and sonicated. The solution was appropriately diluted and filtered with Whatman filter paper. The drug content was analysed by UV spectrophotometric analysis at 260 nm [32, 36, 37].

2.2.4.7. *In-vitro* drug dissolution: L-SMEDDS formulation or pure drug sample of one dose were placed inside the pre-soaked dialysis bag, which had both ends shut tightly to prevent leaks. This dialysis bag was placed in 0.1N HCL dissolution media (900ml) at 37°C and 50 rpm in USP Type II dissolution appratus. Samples (5ml) were withdrawn at sampling intervals of 30mins, 1 hour, 2 hrs, 3 hrs, 4 hrs, 5hrs, 6 hrs, 7 hrs, 8 hrs. Sink condition was maintained by fresh media replacement and samples were analysed for drug concentration by UV-spectrophotometer at 260nm [34, 35, 36, 37].

2.2.4.8. Drug kinetics: The data was analysed for zero order, first order, Higuchi release, korsmeyer Peppas equation [37].

2.2.4.9. Droplet size measurement: Optimized liquid SMEDDS formulations mean globule size, poly dispersibility index (PDI) were performed using Dynamic light scattering method by zetasizer Delsa Max analytics run at temperature of 25˚c given in size (d. nm) with 100% intensity [38, 39].

2.2.4.10. Zeta Potential (ZP): Zeta potential of optimized formulation was analysedbyDynamic light scattering method by Delsa Max at the temperature of 25˚c and conductivity of mS/cm at 39.7 [39,40].

2.2.4.11. Stability: Following ICH recommendations, the optimised formulation underwent a one-month stability study. The mixture was taken in glass bottles and kept at 40°C±2°C, 75%±5% RH in the humidity chamber. Samples were analysed weekly for emulsification, drug concentration and level of dissolution [32, 37].

3. RESULTS

3.1. FTIR compatibility studies

Interpretation of OF1FTIRscan: The region1690-1640 shows C=N stretching Imine/oxime functional group, 1400-1000 shows C-F stretching Fluro Compound, 1342-1266 shows C-N stretching, Aromaticamine,

1200-1275 shows C-Ostretching, Alkylarylether, 1450 shows C-H stretching, Methyl group. The interpretation of the Posaconazole FTIR scan and thepeaks in IR spectra of the OF1 (figure 1) show the drug peaks, suggesting no interaction present in the drug and the excipients used to formulate SMEDDS. This also infers drugstability and compatibility with the excipients chosen [36].

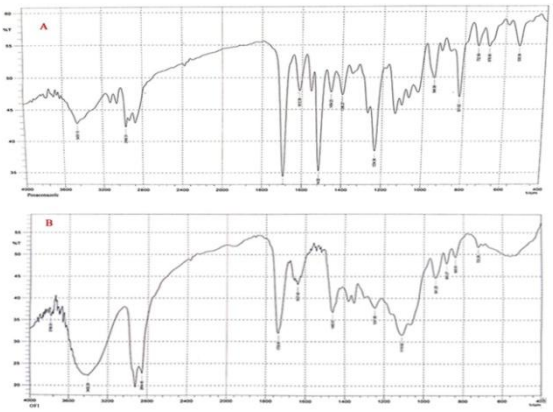


Figure 01: Compatibility studies by FTIR, A, Posaconazole and B, Optimized formula (OF1)

3.2. Solubility studies

The drug in which it is solubilized more which is used to prepare SMEDDS is selected. Posaconazole concentration in different oils, surfactants, and co-surfactants analysed byUV spectroscopy [41, 42] are shown in figure 02.

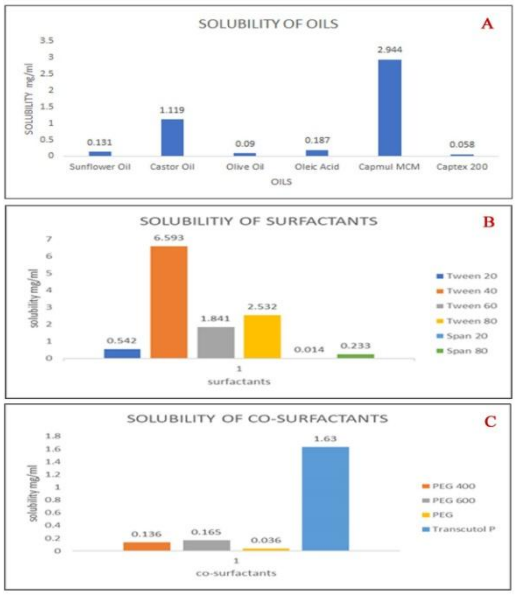


Figure 02: Solubility of Posaconazole in A, oils, B, surfactants and C, co-surfactants.

Posaconazole was better soluble in Transcutol P (co-surfactant), Capmul MCM (oil), and Tween 40 (surfactant) as shown in Figure 02. Hence, they were selected for SMEDDS formulation with improved drug loading capabilities [39].

3.3. QBD (Quality by Design)

In the process of optimization by QbD, first QTPP needs to be postulated. For Posaconazole to improve bioavailability by enhancing solubility, L-SMEDDS dosage form is chosen, as lipids can be chosen for solubility enhancement. According to literature, posaconazole is prescribed for oropharyngeal candidiasis, so oral route of administration is chosen. It is available in the market as 100mg unit dose and dosage regimen is based on infection. Sustained release with unit dose of 100mg per 10ml of L-SMEDDS, packed in air-tight glass bottle and stable at room temperature were set as TPP. Based on QTPP specifications, the CQAs were analysed based on level of risk in Table 2. Attributes globule size, emulsification time and percentage drug release were based on formulation of L-SMEDDS [11,43].

Table 02: Critical quality attributes (CQAs) for L-SMEDDS of Posaconazole and their justifications.

Quality attributes	Target	Is it a CQA?	Level	Justification(s)
Physical attributes Colour, Odour, Appearance	Acceptable to patients. No unpleasant odour.	No	Low	Color, smell, and look were not thought to be important factors since they are not related to efficacy and safety.

Globule size (Dnm)	< 100 nm	Yes	Medium	Nano size is simpler to penetrate through GI lining and paracellular routes. So considered as important.
Emulsification time (Temul)	< 5 min	Yes	High	Lower values of emulsification time facilitate the formation of the emulsion; hence was taken up as highly critical.
Percentage Drug release	100%	Yes	Medium	It gives information on the dosage form's in vitro dissolving performance during the dissolution phase; for this reason, it was regarded as crucial.

From preliminary, Pseudo ternary phase diagram L-SMEDDS with a Smix value of 4:1, and ratios of oil:Smix, 1:9 and 2:8 ratio's showed good results in formation of SMEDDS [44]. In the formulations they were not clear with precipitation. So, soluplus the precipitation inhibitor was added and its concentration was also optimized from 1-4%. Out of which 4% shows the linear drug release and no sign of precipitation was selected. Formulations based on D-Optimal mixture design were formulated and evaluated (Table 3).

Table 03: Evaluation tests for 16 formulations

Formulation code	Thermodynamic stability studies		Robustness	Dispersibility Test	Emulsification Time(sec)	Inference	Drug Content
	Heating/cooling	centriguation					
F1	Fail	x	x	D	50±0.01	Failed	97.31±0.45
F2	Fail	x	x	C	39±0.04	Failed	100±0.11
F3	Fail	x	x	C	41±0.01	Failed	94.46±0.29
F4	Fail	x	x	C	39±0.04	Failed	93.75±0.25
F5	Pass	✓	✓	A	75±0.06	Passed	98.69±0.10
F6	Pass	✓	✓	B	45±0.01	Passed	99.6±0.18
F7	Fail	x	x	C	39±0.04	Failed	93.75±0.25
F8	Fail	x	x	D	50±0.01	Failed	95.79±0.23
F9	Fail	x	x	D	56±0.05	Failed	99.6±0.18
F10	Pass	✓	✓	B	45±0.01	Passed	98.69±0.10
F11	Fail	x	x	C	60±0.02	Failed	100±0.11
F12	Fail	x	x	D	70±0.04	Failed	99.89±0.12
F13	Fail	x	x	C	90±0.02	Failed	96.25±0.26
F14	Pass	✓	✓	A	75±0.06	Passed	95±0.25
F15	Pass	✓	✓	B	75±0.02	Passed	94.62±0.23
F16	Fail	x	x	C	35±0.02	Failed	99.89±0.12

Note: X- indicates failed, ✓-passed.

Table 03. represents all the evaluation parameters performed for 16 formulations in which F5, F6, F10, F14, F15 were passed in all evaluations whereas the remaining formulations failed.

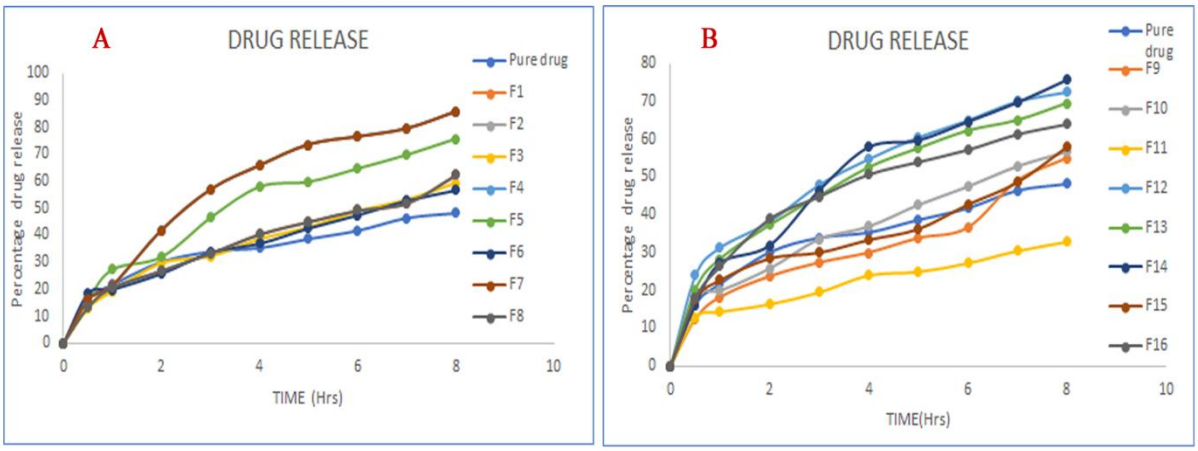


Figure 03: In-vitro dissolution studies of Formulations A, F1 to F8 and B, F9 to F16. Formulations F1 & F8; F2, F4 &F7; F5&F14; F6& F10 are similar.

In Figure 03, release of drug from formulations is compared against pure drug, where formulations F1, F8; F2, F4, F7; F5, F14 and F6, F10 are similar which are overlapped. Percentage drug release of formulations, reveals F2, F4, F7 release more than 80% compared to other formulations which results less than 80% in 8hours. Model-dependent kinetics: 16 formulations in which all the formulations show an "n-value" <0.5. So, all the formulations show Fickian diffusion transport mechanism.

3.4. OPTIMIZATION: D-OPTIMAL MIXTURE DESIGN

In experimental design optimization, independent factors and dependent factors are related by mathematical relationship in the form of model. In model selection, parameters to be considered are F value greater than 1, p value less than 0.005, difference between adjusted R2 and predicted R2 not more than 0.2, adequate precision ratio of 4, lack of fit greater than 0.01 considered as insignificant and pure error zero [45]. Table 04, represents linear model for response R1 and Cubic model for response R2, where all required parameters are satisfied to navigate the design space except for response R2, negative value for predicted R2.

Table 04: Design summary and statistics for R1 and R2

Response	Self-emulsification time (R1)	Drug release at 8hrs (R2)
Model	Linear model	Cubic model
Sum of square	2434.74	2934.88
Degree of freedom	2	9
Mean squares	1217.3	326.10
F- values	8.53	118.90
p-value	0.0043(significant)	0.0001(significant)
Adjusted R2	0.5012	0.9861
Predicted R2	0.4486	-0.0179
Adeq precision	8.4558	39.5117
Lack of fit	Insignificant	Insignificant
Pure error	0.0000	0.0000

The three-dimensional graphs of Response Surface Model graphs (RSM) are generated by plotting the response model against three of the factors, in which the interaction between the variables and their mutual dependence is observed [46,47]. Figure 4, A for response R1, shows that the Posaconazole solubility increases with amount of oil [48] up to a certain extent and decreases with amount of surfactant & co-surfactant. It depicts the linear relationship between factors A, B, and C. Self -emulsification time increases with more amount of oil and decreases with increase in amount of surfactant & co-surfactant. This shows that several independent factors which are oil component (A), surfactant (B), and co-surfactant (C) show significant effect on the dependent factor which is Self-emulsification time (R1). Quadratic equation of response R1 infers lone interaction term has strong significant effect when compared to interaction terms. According to the attractiveness criterion, the best variables found by the numerical analysis are predicted values. The subsequent graphs predicted vs actual responses in excel were created by graphing the data to get the value of r2 which controls the linearity. For R1 is a self-emulsification system r2 is 0.9641 infers validation of design [46, 47, 49].

Figure 4, B for response R2, shows more amount of oil may lead decrease percent of drug release whereas with greater quantity of surfactant and co-surfactant, the percentage of drug release is also enhanced. Interaction terms AB, AC, BC, ABC, and AB (A-B) have a non-significant effect on drug release. The interaction term AB has a significant

positive synergistic effect on drug release and AC(A-C) has a significant antagonistic effect on drug release. r2 is 0.9997 for percentage Drug Release system [50].

Quadratic equation for self-emulsification time = +51.99A+84.90B+20.67C

Quadratic equation for % drug release = +126.71A+202.24B-1704.53C- 479.28AB+3541.51AC+3431.83BC-4264.45ABC+488.40AB(A-B)-3288.94AC(A-C)- 3061.65BC(B-C).

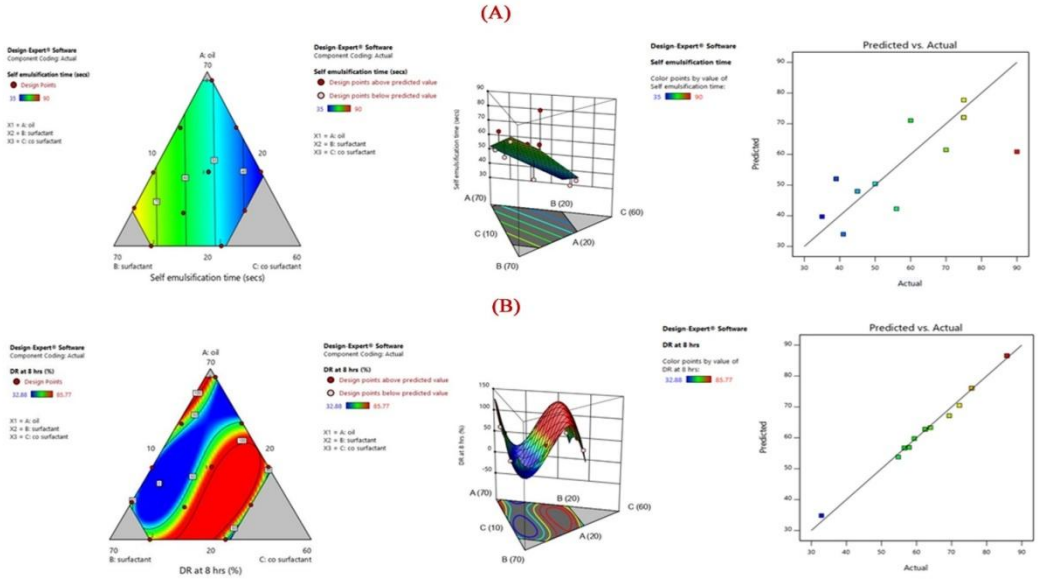


Figure 04 (a): Effect on Self Emulsification Time (b) Effect on Percentage Drug Release showing contour plot, response surface plot and Predicted vs. Actual response.

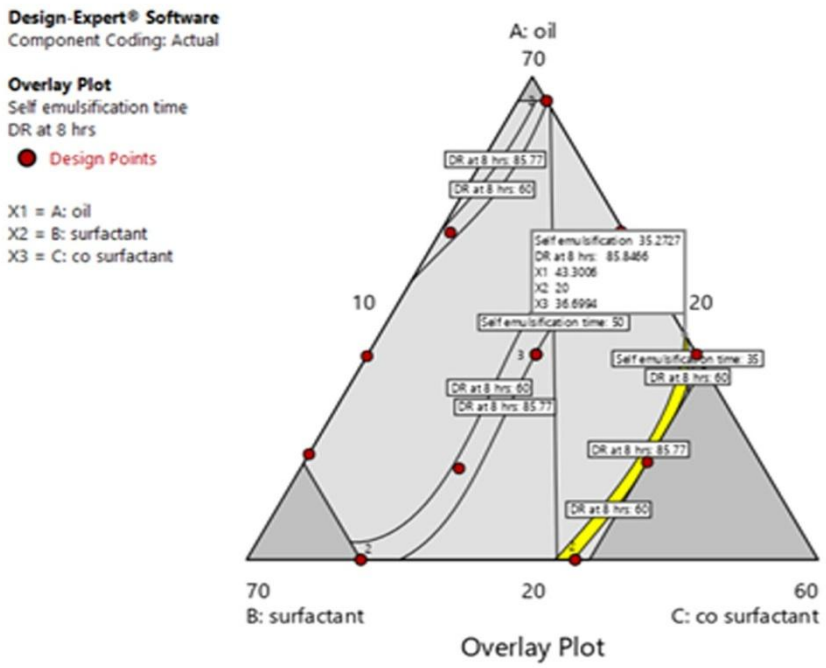


Figure 05: Overlay plot

From overlay plots (Figure 5) and counter-plots for numerical optimization, an optimized formulation is produced, Desirability co-efficient for the optimized formulation was found to be 0.991 [45]. Optimized formulation (OF1) is prepared by taking Capmul MCM, 43.30ml, Tween 40, 20ml and Transcutol, 36.69ml, soluplus (4%) which resulted in self-emulsification time R1, 35.05±0.02 seconds and percentage drug release R2, 84.50±0.01%. The optimized formulation OF1 passed all physicochemical parameters of L-SMEDDS like thermodynamic stability, robustness to dilution and had drug content 100.5±0.1%.

Figure 6A, OF1 showed a Particle size of 66.8nm and a Poly dispersibility index (PDI) of 0.08 (Figure 6B). The formulation has shown a Zeta potential of -0.19 mV (Figure 6C) [51].

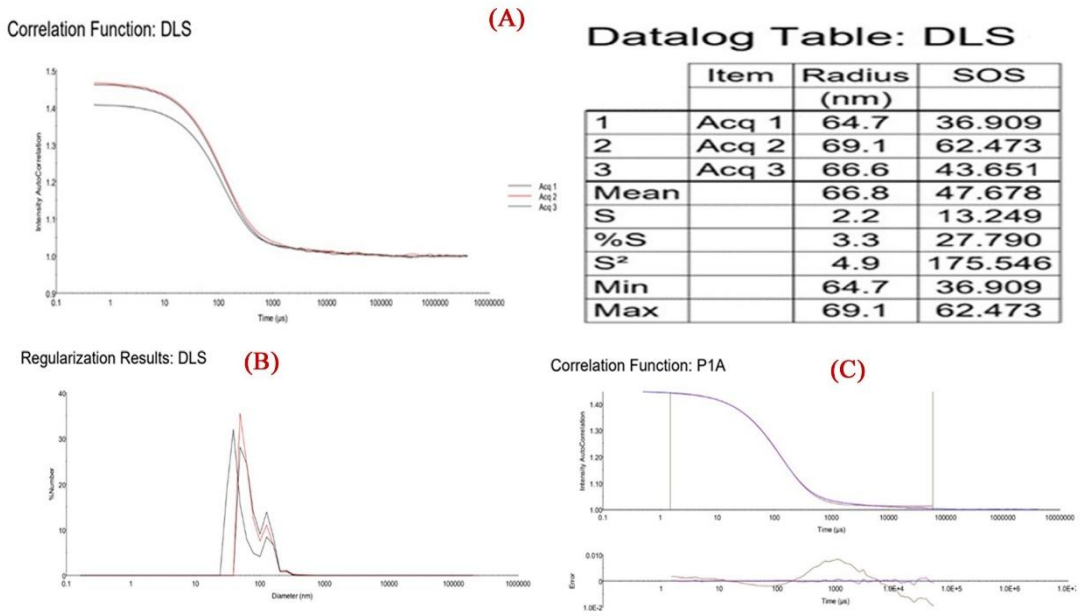


Figure 06: Optimized Formulation OF1, A, Size Plot of particles B, Poly Dispersibility Index (PDI) C, Zeta-potential value.

3.5. Stability Study

OF1 was tested in ambered colored bottle containers. It was carried out at (40°C±2°C/75%±5%RH) accelerated conditions as per ICH guidelines for up to 1 month in a humidity chamber and in between the OF1 were assessed for physical appearance, self- emulsification time, drug content, and percentage drug release every week. After 1 month, the OF1 is stable, with insignificant change in the physical appearance, self-emulsification time, drug content, and percentage drug release (Table 05).

Table 05: Stability studies for optimized formulation

Parameters	Initial	1stweek	2ndweek	1 month
Self-emulsification time (secs)	35.87	35.61	35.54	35.41
Drug content	100.5±0.1	100.04±0.2	100.03±0.3	100.2±0.41
% Drug release	84.75±0.1	84.74±0.21	84.75±0.37	84.77±0.36

4. DISCUSSION

Posaconazole, antifungal for oropharyngeal candidiasis is available in market as tablets, suspension dosage forms, but has less bioavailability due to low solubility. Research on different carriers like novasomes [4], microemulsion [5], nanosuspension [7], phospholipid based nanoformulation [50], nanoemulsion [52], nanocrystalline solid dispersion [53] for oral delivery of posaconazole, revealed enhancement of solubility and bioavailability by in-vivo studies. SMEDDS of posaconazole were not formulated and SMEDDS as carriers of simvastatin [13], ibuprofen [29,35], aripiprazole [37], paclitaxel [39], erlotinib [42], clozapine [49], valsartan [51] and eprosartan [54] increased solubility and bioavailability. SMEDDS of antifungal drugs itraconazole [6] and voriconazole [31] were efficient in solving bioavailability by enhancing solubility and permeability by paracellular transport. Statistical approach of SMEDDS of flutamide & piperine by QbD [19] was appreciable for research in present era of AI tools. In present study, posaconazole SMEDDS formulation by QbD approach was studied. In QbD paradigm, QTPP was selected as L-SMEDDS dosage form for oral delivery with 100mg per 10ml dose. Components of L-SMEDDS are oil, surfactant and co-surfactant. Based on TPQP, CQA attributes and their risk were analysed. Self-emulsification time, globule size and percentage drug release were high risk attributes. For posaconazole the components of L-SMEDDS were selected from solubility studies. Capmul MCM was chosen for the oil phase as it has shown a solubility of 0.187mg/ml which was higher when compared to other oils used namely castor oil, olive oil, and sunflower oil. Tween 40 surfactant has shown a solubility of 6.953mg/ml. Transcutol P, co-surfactant which has shown a solubility of 1.630mg/ml. The drug and excipients were compatible, according to FTIR research on drug excipient compatibility. From ternary phase diagrams, unequal proportions of mixture instead of equal proportions of mixture were inferred. Hence D-Optimal mixture design, where different proportions of each component in mixture can be taken, was selected as design. The ratio of surfactant and co-surfactant ranges taken are from 2:1 to 6:1 and 1:2 to 3:2 (Smix). Then the ratio of oil to Smix taken are from 1:5, 2:3, 7:3 to 7:10 ratio.

Therefore, vast range of components of mixture was studied using D- Optimal mixture design. Sixteen formulations were chosen based on the optimization design. When trials were done with Capmul MCM, Castor oil, PEG600, Tween 40, Transcutol P precipitation was observed. Soluplus was used along with Capmul MCM, Transcutol P, Tween 40 the formulation was clear without phase separation or precipitation. Hence soluplus was used in further study as Precipitation Inhibitor. The three components of the three-component system used to design the mixed experimental investigation were the oil A (Capmul MCM), the surfactant B (Tween 40), and the co-surfactant C (Transcutol P). The responses used were the emulsification time (R1) and the total amount of medication released after 8 hours (R2) which were identified by CQA as high risk. For all the formulations, evaluation studies comparing them to pure drugs included thermodynamic stability, visual observation, emulsification time, dispersibility test, robustness to dilution, drug content, and in-vitro dissolution. The percent drug release was found to increase with a decrease in A (Oil phase), was found to increase with an increase in B (surfactant), and was found to increase with an increase in C (co-surfactant). It was also observed that an increase in A (Oil phase) shows more emulsification time, and that an increase in B surfactant and C co-surfactant shows less time for self-emulsification time. For these formulations predicted vs. Actual responses showed a correlation coefficient which indicates the validation of the D-Optimal mixture design. By using design expert software version 11. From overlay plots and counter-plots for numerical optimization, an optimized formulation is produced, Desirability co-efficient for the optimized formulation was found to be 0.991. Optimized formulation (OF1) is prepared by taking Oil Capmul MCM, 43.30ml, surfactant Tween 40, 20ml and co-surfactant Transcutol, 36.69ml, soluplus (4%) which showed self-emulsification time R1, 35.05±0.02 seconds and percentage drug release R2, 84.50±0.01%. Particle size for OF1 was 66.8 nm, size less than 100nm gives better permeability, which is CQA. PDI of formulation less than 0.3, indicates uniformity of particles. PDI of OF1 was 0.08 inferring uniformity of particles. Zeta potential for the formulation was -0.19 mV. Higher positive or negative zeta potential indicates like charges and repulsion between particles, better stability. In the study, charge inducers were not added, so only slight negative charge which could be induced by stirring of formulation in its preparation is observed. For the optimised formulation, accelerated stability investigations were conducted for one month, and the formulation's stability was confirmed.

5. CONCLUSION

With the help of SMEDDS, the current study aimed to increase the bioavailability and solubility of the antifungal medication Posaconazole. And it was examined that the solubility and bioavailability of Posaconazole can be enhanced with optimization technique by D-Optimal mixture design using the QBD approach.

6. CONSENT FOR PUBLICATION

Not applicable.

7. FUNDING

The authors received no specific funding or financial support for this work.

8. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

9. ACKNOWLEDGEMENTS

The authors are thankful to G. Pulla Reddy College of Pharmacy, Hyderabad for providing facilities for the project.

10. AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as follows: J. P.: Design of methodology, conducting research and investigation process; S.U.: Conducting research and investigation process, Preparation of draft manuscript; V.D.: Formal analysis of data; M. J. L.: Preparation, creation and/or presentation of the published work; N. B. S.: Reviewing and editing; P.D.: Conceptualization, project administration, overall supervision, Final editing the manuscript and citation.

11. REFERENCES

4 Badhei L, Mishra D, Nandi P, Samal HB. Self-Micro-Emulsifying Drug Delivery Systems: In-Depth Review on Enhancing Solubility and Therapeutic Efficacy of BCS Class II Drugs. Current Drug Safety. 2025;20(3):345-362. https://doi.org/10.2174/0115748863354153250225074632.

5 Panigrahi KC, Patra C, Rao MEB, Jena G, Sahoo L. SEDDS Basic Design and Recent Formulation Advancement: A Concurrent Review. Pharmaceutical Nanotechnology. 2022:10(5):335–350. https://doi.org/10.2174/2211738510666220817124744.

6 Prasanthi D and Meghana G. Self emulsifying drug delivery system: an approach to enhance solubility and permeability. International Journal of Current Advanced Research, 2019. 8(1); 16931-16938. http://dx.doi.org/10.24327/ijcar.2019.16938.3150

7 Rukari, T., Pingale, P. L., & Upasani, C. D. (2024). Optimizing novasomes: impact of oleic acid and co-surfactant ratio on posaconazole delivery: In vitro & Ex vivo pharmacokinetic study. Journal of Applied Pharmaceutical Research, 12(3), 88-98. https://doi.org/10.69857/joapr.v12i3.536.

8 Sanaei Oskouei S, Araman A, Erginer Y. Preparation, optimization, and in vitro drug release study of microemulsions of posaconazole. Journal of Drug Delivery Science and Technology.

2022;73:104090. https://doi.org/10.1016/j.jddst.2022.104090.
9 Tubtimsri S, Weerapol Y. Enhanced ocular delivery of itraconazole via a self-emulsifying drug delivery system: improved antifungal activity and cellular uptake. AAPS Pharmaceutical Science and Technology. 2025;26:110. https://doi.org/10.1208/s12249-025-03254-w.
10 Tejaswini K, Sen S, Mane SS, Bajad G, Dengale S, Ranjan OP. Development of posaconazole nanosuspension for bioavailability enhancement: formulation optimization, in vitro characterization, and pharmacokinetic study. Journal of Drug Delivery Science and Technology. 2023;78:104434. https://doi.org/10.1016/j.jddst.2023.104434.
11 Deep A, Rimmy, Tahlan S. Novel Approaches of Self Emulsifying Drug Delivery Systems and Recent Patents: A Comprehensive Review. Applied Drug Research Clinical Trials Regulatory Affairs. 2023;10(1):48-63. https://doi.org/10.2174/2667337109666230120095944.
12 Singh DK, Tiwary AK, Bedi N. Self-Microemulsifying Drug Delivery System for Problematic Molecules: An Update. Recent Patents on Nanotechnology. 2020;14(1):15–37. https://doi.org/10.2174/1872210513666190619102521.
13 Nanda A, Kadian R. A Comprehensive Insight on Recent Advancements in Self Emulsifying Drug Delivery Systems. Current Drug Delivery 2023:20(8):1095–1111. https://doi.org/10.2174/1567201819666220914113324.
14 Jupally, Pooja, Srilakshmi Damagundam, and Prasanthi Domaraju. "Quality by Design (QBD) Tool for Quality Control in Pharmaceutical Industry". International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2023; 16 (2): 6480-87. https://doi.org/10.37285/ijpsn.2023.16.2.10.
15 Habib, B.A., Abdertawab, N.F., & Salah Ad-Din, I. D-optimal mixture design for optimisation of topical dapsone niosomes: in vitro characteriation and in vivo activity against Cutibacterium acnes. Drug Delivery, 2022, 29 (1), 821-836. https://doi.org/10.1080/10717544.2022.2048131
16 Kalpana G.P, Apeksha T.P, Jenee R.C, Asha S.P, Purvi A,S and Mukesh C,G. D-Optimal mixture design for optimisation of self micro-emulsifying drug delivery system of simvastatin: characterization and in vitro evaluation. Bulletin Pharmaceutical Research. 2018, 8 (2): 156-168. https://doi.org/10.21276/bpr.2018.8.2.1
17 Jagdish K.A, Rajeshwar V, Birendra S, Vasudha B. Integrated Quality by design approach for developing nanolipidic drug delivery systems of Olmesartan Medoxomil with enhanced antihypertensive action. Advanced Pharmaceutical Bulletin. 2020, 10 (3), 379-388. https://doi.org/10.34172/apb.2020.046
18 Beg, S. (2021). Mixture Designs and Their Applications in Pharmaceutical Product Development. In: Beg, S. (eds) Design of Experiments for Pharmaceutical Product Development. Springer, Singapore.pp 87-96. https://doi.org/10.1007/978-981-33-4717-5_8.
19 Laffleur F, Millotti G, Lagast J. An Overview of Oral Bioavailability Enhancement through Self-Emulsifying Drug Delivery Systems. Expert Opinion on Drug Delivery. 2025;22(3):341–361. https://doi.org/10.1080/17425247.2025.2479759.
20 Maharana RL, Swain S, Mahapatra SK, Jena BR. Self-Emulsifying Drug Delivery Systems: Concept to Applications, Regulatory Issues, Recent Patents, Current Challenges and Future Directions. Current Pharmaceutical Biotechnology. 2024;25(16):2117-2135. https://doi.org/10.2174/0113892010296223240612050639.
21 Uttreja P, Karnik I, Youssef AAA, Narala N, Elkanayati RM, Baisa S, Alshammari N, Banda S, Vemula S, Repka MA. Self-Emulsifying Drug Delivery Systems (SEDDS): Transition from Liquid to Solid — A Comprehensive Review of Formulation, Characterization, Applications, and Future Trends. Pharmaceutics. 2025;17(1):63. https://doi.org/10.3390/pharmaceutics17010063.
22 Saha M, et al. QbD Approach towards Robust Design Space for Flutamide/Piperine Self-Emulsifying Drug Delivery System with Reduced Liver Injury. AAPS PharmSciTech. 2022;23(1):62. https://doi.org/10.1208/s12249-022-02213-z
23 Kadian R, Nanda A. A Comprehensive Insight on Self Emulsifying Drug Delivery Systems. Recent Advances in Drug Delivery and Formulation. 2021;15(3):206-223. https://doi.org/10.2174/2667387815666211207112803.
24 Priani S, Nurhaliza A, Chaerunisaa A, Wilar G, Sopyan I. Solidification of SNEDDS Using Mesoporous Carriers (2020–2025): A Review of Design, Biopharmaceutical Enhancement, and Therapeutic Impact. Drug Design, Development and Therapy. 2025;19:4947-4976. https://doi.org/10.2147/DDDT.S577016.
25 Verma R, Mittal V, Pandey P, Bhatia S, Bhatia M, Karavasili C, Behl T, Al-Harrasi A, Tagde P, Kumar M, Kaushik D. Exploring the Role of Self-Nanoemulsifying Systems in Drug Delivery: Challenges, Issues, Applications and Recent Advances. Current Drug Delivery. 2023:20(9):1241–1261. https://doi.org/10.2174/1567201819666220519125003.
26 Chauhan A, Kamal R, Mishra R, Shekho D, Awasthi A. A Comprehensive Guide to the Development, Evaluation, and Future Prospects of Self-nanoemulsifying Drug Delivery Systems for Poorly Water-soluble Drugs. Current Pharmaceutical Design. 2024;30(24):1889-1925.

https://doi.org/10.2174/0113816128296705240327065131.

27 Panwar J, Ekbbal R, Ali H. Nanoemulsion: A Promising Nanotechnology Tool to Achieve the Unmet Oral Bioavailability Enhancement Needs. Drug Delivery Letters. 2025;15(1):33-52. https://doi.org/10.2174/0122103031340010250116180142.

28 Vaghela S, Chaudhary S, Chaudhary A. A Systemic Review on the Self Micro Emulsifying Drug Delivery System. International Journal of Pharmaceutical Sciences Review and Research 2021;69(1):151–158. https://doi.org/10.47583/ijpsrr.2021.v69i01.027.

29 Tonjan R, Singh DK. Functional excipients and novel drug delivery scenario in self-nanoemulsifying drug delivery system: a critical note. Pharmaceutical Nanotechnology. 2022;10(5):350-370. https://doi.org/10.2174/2211738510666220829085745

30 Wu, L., Qiao, Y., Wang, L., Guo, J., Wang, G., He, W., Yin, L., & Zhao, J. (2015). A Self-microemulsifying Drug Delivery System (SMEDDS) for a Novel Medicative Compound Against Depression: a Preparation and Bioavailability Study in Rats. AAPS PharmSciTech, 16(5), 1051–1058. https://doi.org/10.1208/s12249-014-0280-y.

31 Inugala S, Eedara BB, Sunkavalli S, Dhurke, R, Kandadi P, Jukanti R, Bandari S,(2015). Solid self-nanoemulsifying drug delivery system (S-SNEDDS) of Darunavir for improved dissolution and oral bioavailability: in vitro and in vivo evaluation, European Journal of Pharmaceutical Sciences: official journal of the European Federation for Pharmaceutical Sciences, 74, 1–10. https://doi.org/10.1016/j.ejps.2015.03.024

32 Saritha D, Penjuri Subhash Chandra Bose, and Ravoru Nagaraju. Formulation and evaluation of self-emulsifying drug delivery system (SEDDS) of ibuprofen. IJPSR. 2014; 5 (9):3511- 3519. http://dx.doi.org/10.13040/IJPSR.0975-8232.5(8).3511-19.

33 Jeong JH, Yoon TH, et al. Quality by Design (QbD)-Based Development of a Self-Nanoemulsifying Drug Delivery System for the Ocular Delivery of Flurbiprofen. Pharmaceutics. 2025;17(5):629. https://doi.org/10.3390/pharmaceutics17050629.

34 Dewangan HK, Sharma R, Shah K, Alam P. Development, Analysis, and Determination of Pharmacokinetic Properties of a Solid SMEDDS of Voriconazole for Enhanced Antifungal Therapy. Life (Basel). 2024;14(11):1417. https://doi.org/10.3390/life14111417.

35 Prasanthi D, G. Meghana and V. Navya. Formulation and Evaluation of Solid-self Nano emulsifying drug delivery system of Famotidine. International Journal of Pharmaceutical Sciences and Research, 2021; 12(11): 5785-5799. http://dx.doi.org/10.13040/IJPSR.0975-8232.12(11).5785-99.

36 Singh R, Thagale R. Comparative Study of SNEDDS and SEDDS for Enhancing Oral Delivery of Vildagliptin. Oriental Journal of Chemistry. 2025;41(4):1119-1131. https://doi.org/10.13005/ojc/410440.

37 Ashfaq M, Shah S, Rasul A, Hanif M, Khan HU, Khames A, Abdelgawad MA, Ghoneim MM, Ali MY, Abourehab MAS, Maheen S, Iqbal O, Abbas G, El Sisi AM. Enhancement of the Solubility and Bioavailability of Pitavastatin through a Self-Nanoemulsifying Drug Delivery System (SNEDDS). Pharmaceutics. 2022;14(3):482. https://doi.org/10.3390/pharmaceutics14030482.

38 Darusman F, Amalia F, Priani SE. Development and Characterization of Orally Ibuprofen Self Emulsifying Drug Delivery Systems (SEDDS). Indonesian Journal of Pharmaceutical Science and Technology (IJPST). 2022;9(2):51–63. https://doi.org/10.24198/ijpst.v9i2.31508.

39 Kumar M, Chawla PA, Faruk A, Chawla V. Design and evaluation of solid self-nanoemulsifying drug delivery systems of cyclosporine developed with a superior adsorbent base. RSC Pharmaceutics. 2025;2(1):127-142. https://doi.org/10.1039/D4PM00198B.

40 Amoolya Chennuri and Prasanthi D, (2018). Solubility enhancement of aripiprazole by solid-self emulsifying drug delivery systems. International Journal of Pharmaceutical Sciences and Drug Research, 10(4), 233-245. https://doi.org/10.25004/IJPSDR.2018.100405.

41 Silva I, Castro e Souza MA, Machado R, Barbosa de Oliveira R, Leite EA, da Costa César I. Enhancing oral bioavailability of an antifungal thiazolylhydrazone derivative: development and characterization of a self-emulsifying drug delivery system. International Journal of Pharmaceutics. 2024;665:124011. https://doi.org/10.1016/j.ijpharm.2024.124011.

42 Hea-Young C, Kang JH, Ngo L, Phuong T, yong BL. Preparation and Evaluation of Solid-Self-Emulsifying Drug Delivery System Containing Paclitaxel for Lymphatic Delivery. Journal of Nanomaterials.2016. 3642418, 14 pages. https://doi.org/10.1155/2016/3642418.

43 Chen Y, Wang S, Hu Q, Zhou L. Self-Emulsifying System Coloaded with Paclitaxel and Coix Seed Oil Deeply Penetrated to Enhance Efficacy of Cervical Cancer. Current Drug Delivery 2022:19 (9):979–988. https://doi.org/10.2174/1567201819666220628094239.

44 Balakrishnan, P., Lee, B. J., Oh, D. H., Kim, J. O., Lee, Y. I., Kim, D. D., Jee, J. P., Lee, Y. B., Woo, J. S., Yong, C. S., & Choi, H. G. (2009). Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. International journal of pharmaceutics, 374(1-2), 66–72. https://doi.org/10.1016/j.ijpharm.2009.03.008

45 Truong, D. H., Tran, T. H., Ramasamy, T., Choi, J. Y., Lee, H. H., Moon, C., Choi, H. G., Yong, C. S., & Kim, J. O. (2016). Development of Solid Self-Emulsifying Formulation for Improving the Oral Bioavailability of Erlotinib. AAPS PharmSciTech, 17(2), 466–473. https://doi.org/10.1208/s12249-015-0370-5.

46 Kumar V, Rastogi V. Advancements in Solubility and Bioavailability Enhancement of BCS Class II Drugs: A Comprehensive Review Using Quality by Design Approach for Self-Emulsifying Drug Delivery Systems. Oriental Journal of Chemistry. 2025;41(6). https://doi.org/10.13005/ojc/410631.

47 Gangane P, Singh K, Rabade V. Enhancement of the Solubility of Lipophilic Drug by Self-Micro Emulsifying Drug Delivery System (SMEDDS) For Oral Administration. Indian Journal of Pharmaceutical Education and Research. 2023;57(3s):s511–s519. https://doi.org/10.5530/ijper.57.3s.59

48 Kothamasi P, Bandari V, Babasaheb KS, Naredla B, Shaik NB, Domaraju P. Optimization of favipiravir microsponges for pulmonary drug delivery. J Appl Pharm Sci. 2025;15(03): 112–121. http://doi.org/10.7324/JAPS.2025.206181

49 Rao NJ, Khan Z, Akhtar MS, Ansari MD, Solanki P, Ahmad FJ, Aqil M, Sultana Y. Development of Bedaquiline-Loaded SNEDDS Using Quality by Design (QbD) Approach to Improve Biopharmaceutical Attributes for the Management of Multidrug-Resistant Tuberculosis (MDR-TB). Antibiotics. 2023;12(10):1510. https://doi.org/10.3390/antibiotics12101510.

50 Huang X, Feng L, Lu X, Yang F, Liu S, Wei X, Huang J, Wang Y, Huang D, Huang T. Development and Optimization of a Self Micro-Emulsifying Drug Delivery System (SMEDDS) for Co-Administration of Sorafenib and Curcumin. Drug Delivery and Translational Research. 2024;15(5):1609–1625. https://doi.org/10.1007/s13346-024-01699-3

51 Silva-Neto AF, Amaral ARC, Danda LJ, Chaves LL, Alves LD, Soares MFR, Soares-Sobrinho JL. Decoding excipients in lipid-based self-emulsifying drug delivery systems: Insights into physicochemical properties and therapeutic outcomes. International Journal of Pharmaceutics. 2025;683:126018. https://doi.org/10.1016/j.ijpharm.2025.126018.

52 Pethani R, Dudhat K, Soniwala MM, Shah S, Manek R, Dudhrejiya A, Pethani T, Gadoya A, Mori D. Formulation and statistical optimization of clozapine solid self emulsification system for improving the dissolution properties. Journal Dispersion Science and Technology. 2024:45(12):2451–2463. https://doi.org/10.1080/01932691.2023.2301461.

53 Bayat F, Dadashzadeh S, Aboofazeli R, Torsahbi M, Hashemi Baghi A, Tamiji Z, Haeri A. Oral delivery of posaconazole-loaded phospholipid-based nanoformulation: preparation and optimization using design of experiments, machine learning, and TOPSIS methods. International Journal of Pharmaceutics. 2024;660:123879. https://doi.org/10.1016/j.ijpharm.2024.123879.

54 Dixit, A. R., Rajput, S. J., & Patel, S. G. (2010). Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS PharmSciTech, 11(1), 314–321. https://doi.org/10.1208/s12249-010-9385-0

55 Gorle A, Ahire K, Shende R. Design, Development and Characterization of Nanoemulsion developed by High Pressure Homogenization (HPH) method Containing Antifungal Drug. Journal of Drug Delivery and Therapeutics. 2022;12(2):24–32. https://doi.org/10.22270/jddt.v12i2.5245.

56 Rayapolu R, Yadav B, Apte S, Venuganti VK. Development of posaconazole nanocrystalline solid dispersion: preparation, characterization and in vivo evaluation. Pharmaceutical Development Technology. 2024;29(8):770-784. https://doi.org/10.1080/10837450.2024.2353314.

57 Shirkhedkar AA, et al. Self-microemulsifying Drug Delivery System for Solubility and Bioavailability Enhancement of Eprosartan Mesylate: Preparation, In-vitro, and In-vivo Evaluation. Pharmaceutical Nanotechnology. 2023;11(1):72-80.

58 https://doi.org/10.2174/2211738510666220915100150.