RESEARCH PAPER

Optimization of a Self-MicroemulsifyingDrug Delivery System (SMEDDS) of Ziprasidone using a Quality by Design (QbD) Approach

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ABSTRACT

Ziprasidone hydrochloride is a poorly water-soluble atypical antipsychotic exhibiting dissolution-limited oral absorption. The present study aimed to develop and optimize a Self-Microemulsifying Drug Delivery System (SMEDDS) of Ziprasidone using a Quality by Design (QbD) approach to enhance its solubility and dissolution performance. Preformulation studies identified Labrafac WL1349, Cremophor RH40, and PEG 400 as suitable oil, surfactant, and co-surfactant, respectively. A Box–Behnken Design was employed to optimize the effects of oil concentration, surfactant concentration, and Smix ratio on droplet size, self-emulsification time, cumulative drug release, polydispersity index, and percent transmittance. The optimized formulation consisted of 20% oil, 50% surfactant, and a 3:1 Smix ratio. It exhibited a droplet size of 129 nm, self-emulsification time of 25 sec, drug release of 95.7%, and transmittance of 98.6%. The optimized SMEDDS demonstrated rapid emulsification, excellent clarity, nanosized droplets, and improved dissolution, indicating its potential for enhancing the oral bioavailability of Ziprasidone.

Keywords: Ziprasidone hydrochloride, Self-Microemulsifying Drug Delivery System (SMEDDS), Quality by Design (QbD), Box–Behnken Design, Lipid-based drug delivery, Solubility enhancement, Dissolution, Oral bioavailability

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INTRODUCTION

The oral route remains the most widely accepted and preferred method of drug administration due to its convenience, patient compliance, non-invasive nature, cost-effectiveness, and suitability for large-scale manufacturing.1 Oral dosage forms such as tablets, capsules, and suspensions continue to dominate pharmaceutical markets and are extensively used in the management of chronic and acute diseases.[2] However, the effectiveness of oral drug delivery is often limited by poor aqueous solubility and inadequate dissolution of many drug molecules within the gastrointestinal tract, resulting in low and variable bioavailability .3

The Biopharmaceutics Classification System (BCS) provides an important framework for understanding the relationship between drug solubility, permeability, and oral absorption. According to the BCS, drugs are categorized into four classes based on their aqueous solubility and intestinal permeability characteristics.4 BCS Class II drugs possess low aqueous solubility but high permeability, making dissolution the rate-limiting step for absorption. Consequently, these drugs frequently exhibit poor and inconsistent bioavailability despite their favorable membrane permeability. 5The growing number of poorly water-soluble drug candidates in modern drug discovery programs has intensified the need for formulation approaches capable of enhancing dissolution and improving oral absorption.6

Various conventional strategies such as particle size reduction, salt formation, solid dispersions, inclusion complexes, and the use of surfactants and cosolvents have been investigated to improve the solubility of poorly water-soluble drugs. 7Although these techniques can enhance dissolution, they often suffer from limitations including physical instability, recrystallization, precipitation upon dilution, manufacturing complexity, and inconsistent in vivo performance . Consequently, lipid-based drug delivery systems have emerged as promising alternatives for improving the oral delivery of lipophilic compounds.8,9

Lipid-based drug delivery systems improve bioavailability by maintaining the drug in a solubilized state throughout gastrointestinal transit.10 Upon administration, these systems interact with gastrointestinal fluids and bile salts to form colloidal structures that facilitate drug transport across the intestinal membrane. Furthermore, lipid formulations may promote lymphatic transport, reduce first-pass metabolism, and decrease food-dependent variability in absorption 11. Among the various lipid-based approaches, Self-Microemulsifying Drug Delivery Systems (SMEDDS) have gained considerable attention because of their ability to significantly enhance the oral bioavailability of poorly soluble drugs.12

SMEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water microemulsions upon gentle agitation in gastrointestinal fluids. 13The resulting microemulsions generally possess droplet sizes below 100 nm, providing a large interfacial surface area for rapid drug release and absorption.14 By maintaining the drug in a

solubilized state, SMEDDS effectively bypass the dissolution step that limits the absorption of many BCS Class II drugs.15 In addition, SMEDDS offer advantages such as improved solubility, enhanced dissolution rate, reduced food-effect variability, increased bioavailability, ease of manufacturing, and improved formulation stability .16,17

Ziprasidone is a second-generation atypical antipsychotic indicated for the treatment of schizophrenia and bipolar disorder.18 It exhibits antagonistic activity at dopamine D_2 and serotonin 5-HT_2A receptors, along with partial agonistic activity at serotonin 5-HT_1A receptors, contributing to its efficacy in managing psychotic symptoms while maintaining a relatively favorable metabolic profile compared with other atypical antipsychotics.19 Despite these therapeutic advantages, the clinical effectiveness of Ziprasidone is restricted by its poor aqueous solubility and dissolution-limited absorption.20

SMEDDS represent a rational strategy for overcoming the formulation challenges associated with Ziprasidone. By incorporating the drug into an optimized lipid-based system, SMEDDS can maintain the drug in a pre-solubilized form and facilitate rapid formation of nano-sized droplets upon dilution in gastrointestinal fluids. This approach is expected to enhance dissolution, improve absorption, reduce pharmacokinetic variability, and ultimately increase oral bioavailability. Therefore, the present study was undertaken to formulate and evaluate a Self-Microemulsifying Drug Delivery System (SMEDDS) of Ziprasidone with the aim of enhancing its solubility, dissolution behavior, and oral bioavailability.

MATERIAL AND METHOD

MATERIAL

Ziprasidone hydrochloride was obtained from Taj Pharma India Ltd., Vapi, Gujarat, India. Capryol 90, Labrafac WL 1349, oleic acid, Tween 80, polyethylene glycol 400 (PEG 400), and propylene glycol were procured from Merck Pvt. Ltd., Mumbai, India.

PREFORMULATION STUDIES

Preformulation studies were conducted to evaluate the physicochemical properties of Ziprasidone hydrochloride prior to formulation development. Organoleptic characteristics including color, odor, and physical appearance were assessed by visual inspection. The melting point was determined using the capillary method to confirm drug identity and purity. Solubility studies were performed by the shake-flask method in various oils, surfactants, and co-surfactants to identify suitable excipients for SMEDDS development. Drug–excipient compatibility was investigated using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to assess potential physicochemical interactions and ensure formulation stability.

CONSTRUCTION OF PSEUDO-TERNARY PHASE DIAGRAM

A pseudo-ternary phase diagram was constructed using the aqueous titration method to identify the concentration range of oil, surfactant, and co-surfactant capable of forming stable microemulsions. Based on solubility studies, suitable oil, surfactant, and co-surfactant were selected and mixed to prepare Smix ratios of 1:1, 2:1, and 3:1. Oil and Smix were combined in various proportions and titrated with distilled water under continuous stirring. The resulting systems were visually evaluated for transparency, turbidity, and phase separation. The microemulsion region was identified and plotted on a ternary phase diagram, and the Smix ratio producing the largest microemulsion region was selected for further SMEDDS formulation development.

QUALITY BY DESIGN–BASED OPTIMIZATION OF ZIPRASIDONE SMEDDS

A Quality by Design (QbD) approach was employed for the systematic development and optimization of Ziprasidone hydrochloride SMEDDS. The Quality Target Product Profile (QTPP) was established to define the desired product characteristics, including rapid self-emulsification, droplet size below 200 nm, high transmittance, physical stability, and enhanced drug release. Critical Quality Attributes (CQAs) such as droplet size, polydispersity index, self-emulsification time, percent transmittance, and drug release were identified. Risk assessment using Failure Mode and Effects Analysis (FMEA) was performed to determine Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). The concentration of oil, surfactant, and surfactant/co-surfactant ratio were identified as key variables and optimized using Design of Experiments (DoE) to obtain a robust and stable SMEDDS formulation.21

PREPARATION AND OPTIMIZATION OF SMEDDS FORMULATION

The present study aimed to develop and optimize a Ziprasidone hydrochloride-loaded Self-Microemulsifying Drug Delivery System (SMEDDS) using a Box–Behnken Design (BBD). Three formulation variables, namely oil concentration (X_1), surfactant concentration (X_2), and surfactant/co-surfactant ratio (Smix) (X_3), were evaluated for their effects on critical quality attributes including droplet size, self-emulsification time, cumulative drug release, polydispersity index, and percent transmittance. The statistical design facilitated systematic optimization of the formulation and identification of the optimal composition exhibiting rapid self-emulsification, high clarity, and enhanced drug release.

EXPERIMENTAL DESIGN

Ziprasidone hydrochloride-loaded SMEDDS formulations were developed using a Box–Behnken Design (BBD) generated through Design-Expert® software. A total of 15 experimental runs were performed to evaluate the influence of three independent variables at three levels (-1, 0, and +1).

Table 1. Independent variable Design

Factor	Level used, actual (coded)	Level used, actual (coded)	Level used, actual (coded)
Independent Variables	Low (-1)	Medium (0)	High (+1)
X1 = Oil concentration (% w/w)	10	20	30
X2 = Surfactant concentration (% w/w)	30	40	50
X3 =Smix ratio (Surfactant : Co-surfactant)	1:1	2:1	3:1

The selected levels were based on preformulation studies, pseudo-ternary phase diagram analysis, and QbD-based risk assessment. These variables were chosen because of their significant influence on microemulsion formation, droplet size distribution, emulsification efficiency, and drug release behavior.

PROCEDURE

SMEDDS formulations were prepared according to the Box–Behnken Design matrix by dissolving Ziprasidone hydrochloride in the selected oil phase, followed by the addition of the

surfactant and co-surfactant mixture (Smix) under continuous stirring to obtain a clear and homogeneous system. The prepared formulations were evaluated for droplet size, self-emulsification time, polydispersity index, percent transmittance, and drug release. The experimental data were analyzed using Design-Expert® software to identify the optimized formulation. The dependent variables selected for optimization were droplet size (Y_1), self-emulsification time (Y_2), cumulative drug release (Y_3), polydispersity index (Y_4), and percent transmittance (Y_5).

Table 2. Experimental Design Model for Box–Behnken Design

Run	A: Oil Concentration (% w/w)	B: Surfactant Concentration(% w/w)	C: Smix Ratio
1	10	30	2
2	30	30	2
3	20	40	2
4	20	50	3
5	20	50	1
6	20	40	2
7	20	30	3
8	10	40	3
9	30	40	1
10	30	40	3
11	30	50	2
12	10	50	2
13	20	40	2
14	20	30	1
15	10	40	1

EVALUATION OF SMEDDS

SELF-EMULSIFICATION TIME

Self-emulsification time was determined by introducing 1 mL of SMEDDS into 500 mL of distilled water maintained at 37 ± 0.5 °C under gentle stirring (50 rpm). The time required to form a clear microemulsion was recorded.

VISUAL ASSESSMENT AND CLARITY

The diluted SMEDDS (100 µL in 10 mL distilled water) was visually examined against black and white backgrounds for transparency, turbidity, precipitation, and phase separation.

PERCENT TRANSMITTANCE

Percent transmittance was measured by diluting 100 µL of SMEDDS with 10 mL distilled water and analyzing the dispersion at 638 nm using a UV–Visible spectrophotometer.

DROPLET SIZE AND POLYDISPERSITY INDEX (PDI)

Droplet size and PDI were determined using dynamic light scattering (DLS) after diluting 100 µL of formulation with 10 mL distilled water. Measurements were performed at 25 °C.

ZETA POTENTIAL

Zeta potential of the diluted microemulsion was measured using a zeta potential analyzer at 25 °C to evaluate the surface charge and stability of the droplets.

VISCOSITY MEASUREMENT

Viscosity was measured using a Brookfield viscometer at 25 ± 1 °C and 100 rpm to assess the flow behavior of the formulations.

ELECTRICAL CONDUCTIVITY

Electrical conductivity was determined by dispersing 1 mL of SMEDDS in 50 mL distilled water and measuring conductivity using a conductivity meter to confirm the type of microemulsion formed.

REFRACTIVE INDEX

The refractive index of the diluted formulation was measured using a refractometer at 25 ± 1 °C to assess transparency and isotropic characteristics of the microemulsion system.22

IN VITRO DISSOLUTION STUDIES

In vitro dissolution studies of the optimized SMEDDS formulation were performed using a USP Type II (paddle) dissolution apparatus to compare its drug release profile with pure Ziprasidone hydrochloride and a conventional drug suspension. Dissolution testing was conducted in 900 mL of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C with a paddle speed of 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed using a UV–Visible spectrophotometer at 318 nm. The cumulative percentage drug release was calculated and plotted against time to evaluate the dissolution performance of the formulation.

RESULT :

PREFORMUALTION STUDIES

Preformulation studies were carried out to evaluate the physicochemical properties of Ziprasidone hydrochloride prior to the development of the Self-Microemulsifying Drug Delivery System (SMEDDS) and preformulation studies Details are as per table 3.

Table 3. Preformulation studies

Study	Parameter/Excipient	Observation
Organoleptic Evaluation	Appearance	White to off-white crystalline powder, odorless
Melting Point	Melting Point	303 ± 1.0 °C
Oil Solubility	Labrafac WL1349	48.87 ± 0.35 mg/g
Surfactant Solubility	Cremophor RH40	75.10 ± 0.30 mg/g
Co-surfactant Solubility	PEG 400	82.80 ± 0.30 mg/g
Calibration Curve	λmax	318 nm
Calibration Curve	Concentration Range	2–20 µg/mL
Calibration Curve	Regression Equation	y = 0.0374x + 0.0005
Calibration Curve	Correlation Coefficient	R^2 = 0.9991

DRUG-EXCIPIENT COMPATIBILITY STUDIES

FTIR analysis confirmed the retention of characteristic peaks of Ziprasidone hydrochloride in the physical mixture, indicating no significant drug–excipient interaction and demonstrating compatibility with Labrafac WL1349, Cremophor RH40, and PEG 400 for SMEDDS development.

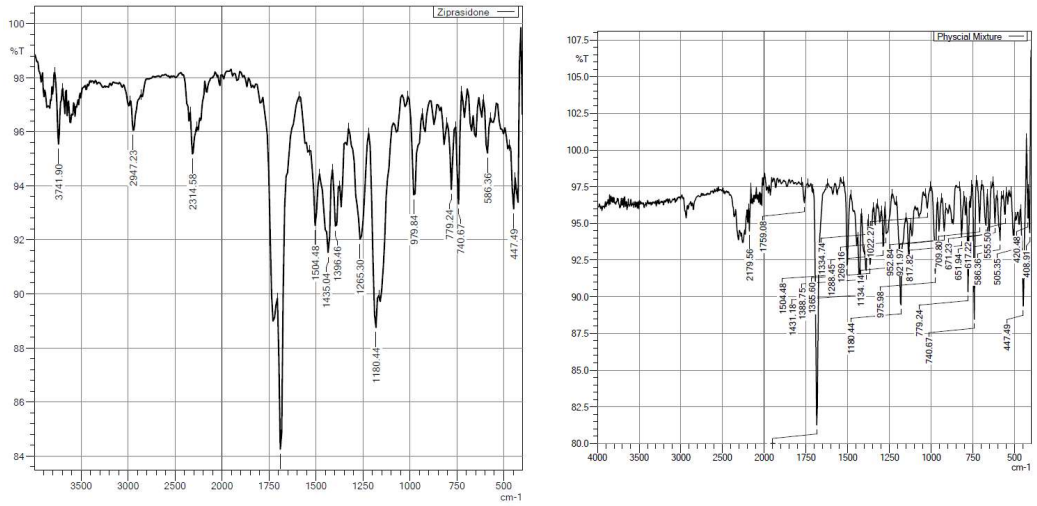

Figure FTIR spectrum of Ziprasidone hydrochloride (A) and physical mixture(B)

PSEUDO-TERNARY PHASE DIAGRAM

Pseudo-ternary phase diagrams were constructed using Labrafac WL1349, Cremophor RH40, and PEG 400 to identify the self-microemulsifying region. Among the evaluated Smix ratios, 3:1 exhibited the largest and most stable microemulsion region, followed by 2:1 and 1:1, indicating superior emulsification efficiency at higher surfactant concentrations. The 1:2 Smix ratio showed a limited microemulsion region due to inadequate stabilization of oil droplets. The enhanced microemulsion region observed with the 3:1 ratio was attributed to effective interfacial tension reduction and improved droplet stabilization. Therefore, Smix ratios of 1:1, 2:1, and 3:1 were selected for further optimization studies.

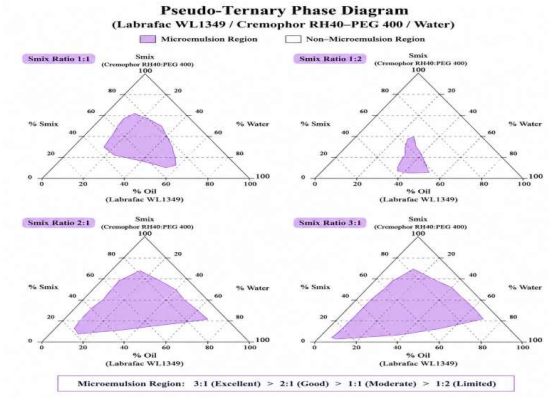

Figure XX

QBD-BASED DOE OPTIMIZATION

A Box–Behnken Design (BBD) was employed under the Quality by Design (QbD) framework to optimize the Ziprasidone SMEDDS formulation. Three independent variables—oil concentration (X_1, 10–30% w/w), surfactant concentration (X_2, 30–50% w/w), and Smix ratio (X_3, 1:1–3:1)—were evaluated for their effects on critical quality attributes, including droplet size (Y_1), self-emulsification time (Y_2), cumulative drug release (Y_3), polydispersity index (Y_4), and percent transmittance (Y_5). The optimization aimed to minimize droplet size, emulsification time, and PDI while maximizing drug release and transmittance to obtain an optimized SMEDDS formulation.

BOX-BEHNKEN DESIGN MATRIX AND EXPERIMENTAL RESPONSES

The Ziprasidone SMEDDS formulations were evaluated for droplet size, self-emulsification time, cumulative drug release, polydispersity index (PDI), and percent transmittance. The formulations produced droplet sizes ranging from 96–219 nm, indicating successful formation of nano-sized emulsions. Self-emulsification time varied between 25–66 sec, demonstrating rapid dispersion upon dilution. Cumulative drug release at 30 min ranged from 78.5–95.7%, while PDI values ranged from 0.210–0.478, indicating acceptable droplet size distribution. Percent transmittance ranged from 86.5–98.6%, confirming the formation of clear and transparent microemulsions. Overall, oil concentration, surfactant concentration, and Smix ratio significantly influenced the performance and quality attributes of Ziprasidone SMEDDS.

Table 4. Box-Behnken Design Matrix with Observed Responses

Run	Oil (%)	Surfactant (%)	Smix	Droplet size (nm)	SET (sec)	CDR at 30 min (%)	PDI	Transmittance (%)
1	10	30	2	100	51	81.4	0.352	92.1
2	30	30	2	212	66	82.3	0.314	90.1
3	20	40	2	135	34	85.1	0.238	94.1
4	20	50	3	129	25	95.7	0.453	98.6
5	20	50	1	118	29	79.8	0.226	87.5
6	20	40	2	132	35	91.7	0.238	97.5
7	20	30	3	128	41	94.7	0.478	98.2
8	10	40	3	98	33	92.6	0.442	97.9
9	30	40	1	202	56	82.3	0.215	88.2
10	30	40	3	217	48	92.5	0.475	97.8
11	30	50	2	219	43	83.5	0.312	96.3
12	10	50	2	97	28	82.1	0.305	95.2
13	20	40	2	144	34	85.2	0.319	95.3
14	20	30	1	141	49	80.7	0.210	89.1
15	10	40	1	96	38	78.5	0.215	86.5

OPTIMIZED FORMULATION SELECTION

Statistical optimization identified Run 4 as the optimized Ziprasidone SMEDDS formulation. The formulation contained 20% w/w oil, 50% w/w surfactant, and a 3:1 Smix ratio, producing a droplet size of 129 nm, self-emulsification time of 25 sec, cumulative drug release of 95.7%, PDI of 0.453, and percent transmittance of 98.6%. The optimized formulation demonstrated rapid emulsification, nano-sized droplet formation, high clarity, and enhanced drug release, making it suitable for further characterization and stability studies.

Table 5. Composition and Response Profile of Optimized Formulation

Parameter	Optimized Formulation Result
Optimized batch	Run 4
Oil concentration	20% w/w
Surfactant concentration	50% w/w
Smix ratio	3:1
Droplet size	129 nm
Self-emulsification time	25 sec
Cumulative drug release at 30 min	95.7%
Polydispersity Index	0.453
Percent transmittance	98.6%

VALIDATION OF OPTIMIZED FORMULATION

The optimized formulation showed less than 6% prediction error, confirming the accuracy, reliability, and predictive capability of the Box–Behnken optimization model.

Table 6. Predicted and Observed Responses of Optimized Formulation

Response Parameter	Predicted Value	Observed Value
Droplet Size (nm)	136.64	129.00
Self-emulsification Time (sec)	23.62	25.00
Cumulative Drug Release (%)	94.98	95.70
Polydispersity Index	0.446	0.453
Percent Transmittance (%)	100.01	98.60

EVALUATION OF OPTIMIZED ZIPRASIDONE SMEDDS

The optimized Ziprasidone SMEDDS showed rapid emulsification, nanosized droplets, high clarity, good stability, suitable viscosity, and enhanced performance.

Table 7. Evaluation of Optimized Ziprasidone SMEDDS

Parameter	Result
Appearance before dilution	Clear, homogeneous, isotropic system
Drug precipitation	Not observed
Phase separation	Not observed
Appearance after dilution	Clear to slightly bluish microemulsion
Self-emulsification time	25 sec
Emulsification grade	Rapid and complete emulsification
Droplet size	129 nm
Polydispersity Index (PDI)	0.453
Zeta potential	−23.15 mV
Percent transmittance	98.6%
Electrical conductivity	185.4 µS/cm
Viscosity	126.8 cP
Refractive index	1.341

CONCLUSION

The present study successfully developed and optimized a Self-Microemulsifying Drug Delivery System (SMEDDS) of Ziprasidone hydrochloride to improve its physicochemical

performance and dissolution characteristics. A systematic formulation approach combined with Box–Behnken Design enabled the identification of critical formulation variables influencing the quality attributes of the SMEDDS. The optimized formulation exhibited a clear, homogeneous, and isotropic appearance with no evidence of drug precipitation or phase separation, indicating excellent formulation stability and drug solubilization.

Upon aqueous dilution, the formulation rapidly formed a clear to slightly bluish microemulsion with a self-emulsification time of 25 seconds, demonstrating efficient spontaneous emulsification. The optimized SMEDDS produced nanosized droplets (129 nm) with a PDI of 0.453, indicating acceptable droplet size distribution. The zeta potential value of −23.15 mV suggested adequate electrostatic stability of the dispersed droplets. High percent transmittance (98.6%) confirmed the optical clarity of the microemulsion, while conductivity studies verified the formation of an oil-in-water system. Suitable viscosity (126.8 cP) and refractive index (1.341) further supported the desirable physicochemical characteristics of the formulation.

Overall, the optimized Ziprasidone SMEDDS demonstrated rapid self-emulsification, nanosized droplet formation, excellent clarity, and favorable stability characteristics, indicating its potential as an effective lipid-based delivery system for enhancing the oral performance and therapeutic efficacy of Ziprasidone hydrochloride.

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