Research Article

J. innov.appl. pharm. Sci, 11[3] 2026, 68-73

Journal of Innovations in Applied Pharmaceutical Science [JIAPS]

Content available at: www.saap.org.in ISSN: 2455-5177

DESIGN, DEVELOPMENT, AND EVALUATION OF NANOSUSPENSIONS FOR ENHANCING THE ORAL BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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Article History

Received: 06-07-2026
Revised: 15-08-2026
Accepted: 11-09-2026

Keywords: *Ziprasidone hydrochloride, Nanosuspension, Bioavailability enhancement, Plackett–Burman design, Factorial design,Dissolution enhancement.*

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Abstract

Bioavailability enhancement is nowadays a great challenge to the pharmaceutical industries. The drug specifically from BCS class II and IV are always considered to have a dissolution rate limited bioavailability. Various approaches have been used to enhance the rate of dissolution of such types of drugs in order to get better bioavailability. Plackett - Burman Design was effectively employed to identify formulating and processing key parameters that are affecting the quality of the ziprasidone hydrochloride nanosuspension. 3^2 factorial design was employed for optimization of the formulation of nanosuspension. All the predetermined independent variables were found to affect the dependent variables from the resultant nanosuspension. The optimum formulation prepared by response optimizer by desirability function provided a final formulation with D = 0.9035 which released 96.61% of ziprasidone hydrochloride within 15 mins. The *in-vivo* studies confirmed that nanosuspension loaded ziprasidone hydrochloride showed asignificantly better AUC as compared to marketed formulation and dose of ziprasidone hydrochloride was reduced about 33.0 % to reach plasma concentration of marketed formulation. The improved formulation could offer improved drug delivery strategy which might allow concomitant use of ziprasidone hydrochloride in nanosuspension form. The nanosuspension of drug exhibited 33% improvement in bioavailability.

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INTRODUCTION

Bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action [1]. From a pharmacokinetic perspective, bioavailability data for a given formulation provide an estimate of the relative fraction of an orally administered dose that is absorbed into the systemic circulation when compared with the bioavailability data obtained from a solution, suspension, or intravenous dosage form. In addition, bioavailability studies provide other useful pharmacokinetic information related to drug distribution and elimination, the effects of nutrients on drug absorption, dose proportionality, and the linearity of the pharmacokinetics of the active and inactive moieties.

Bioavailability data can also provide indirect information about the properties of a drug substance before it enters the systemic circulation, such as permeability and the influence of presystemic enzymes and/or transporters. The bioavailability of a drug is largely determined by the properties of the dosage form, in addition to the physicochemical properties of the drug that determine its absorption potential. Differences in bioavailability among formulations of a given drug can have clinical significance; therefore, determining whether drug formulations are equivalent is essential.

Poorly water-soluble drugs are increasingly becoming a challenge because of their inadequate dissolution in the gastrointestinal tract, which is necessary for achieving satisfactory oral bioavailability.

MATERIALS AND METHODS

The drugs used in the study were Candesartan Cilexetil (CC), Telmisartan (TM), and Ziprasidone Hydrochloride Monohydrate (ZH). Candesartan Cilexetil (USP grade) was obtained as a gift sample. Telmisartan (USP grade) was also obtained as a gift sample. Ziprasidone Hydrochloride Monohydrate (USP grade) was received as a gift sample.

Poloxamer 188 and Poloxamer 407, used as stabilizers, were of AR grade and were obtained as gift samples. Polyvinyl alcohol (AR grade) was procured, while PVP K30 (AR grade) was obtained. Sodium Lauryl Sulphate (AR grade) was also procured.

The solvents used in the study were Dichloromethane (AR grade), Ethanol (AR grade), Methanol (AR grade), 2-Propanol (AR grade), Butanol (AR grade), Ethyl Acetate (AR grade), and Dimethyl Sulfoxide (AR grade). Mannitol (AR grade), used as a cryoprotectant, was also obtained.

METHODOLOGY

Scanning and Preparation of Calibration Curves of the Drugs

Scanning and Preparation of the Calibration Curve for Candesartan Cilexetil

For the estimation of drug content in the Candesartan Cilexetil nanosuspension, a calibration curve was prepared using methanol as the solvent, as Candesartan Cilexetil exhibits solubility in methanol.

For the estimation of cumulative percentage drug release from the Candesartan Cilexetil nanosuspension, 0.05 M phosphate buffer (pH 6.5) containing 0.7% v/v Polysorbate 20 was used as the dissolution medium.

Selection of Solvent and Antisolvent

The solubility of the selected drugs was studied in different solvents and their combinations. The selection of a good solvent and an antisolvent was based on the solubility of the drug in the respective solvents. Approximately 10 mg of the drug was added to 10 mL of each solvent in specific-gravity bottles. This quantity was sufficient to obtain a saturated solution.

Preparation of Nanosuspension by the Antisolvent Precipitation–Ultrasonication Method

The selected drug was dissolved in the appropriate solvent to prepare the drug solution. The drug solution was then added to the selected antisolvent containing the appropriate stabilizer under controlled conditions. The resulting dispersion was subjected to ultrasonication to reduce the particle size and obtain a stable nanosuspension.

Lyophilization of Nanosuspension of the Optimized Batch

The optimized nanosuspension was converted into a dry powder using mannitol as a cryoprotectant at a total solid-to-cryoprotectant ratio of 1:1. The nanosuspension was subjected to lyophilization using a laboratory lyophilizer. Before lyophilization, the sample was maintained at −80°C for 8 h for freezing. The frozen sample was then subjected to the lyophilization process for approximately 6–8 h until a dry powder was obtained. The dried product was removed from the chamber and stored in an airtight container for further studies.

Selection of Stabilizer

Different stabilizers, including Polyvinyl Alcohol, PVP K30, Sodium Lauryl Sulphate, Poloxamer 188, and Poloxamer 407, were screened by preparing nanosuspensions. The prepared nanosuspensions were evaluated for saturation solubility, mean particle size, polydispersity index (PDI), and zeta potential. Based on these evaluation parameters, the most suitable stabilizer was selected for further studies.

Drug–Excipient Compatibility Study

Drug–excipient compatibility studies represent an important stage in the preformulation development of pharmaceutical dosage forms. Potential physical and chemical interactions between the drug and excipients may affect the chemical, physical, and therapeutic properties, as well as the stability, of the dosage form. Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) were selected to evaluate drug–excipient compatibility.

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was performed using a Shimadzu FTIR-8400 spectrophotometer (Shimadzu, Tokyo, Japan). The spectra were recorded over the wavelength range of 4000–400 cm^{-1}. The samples, including the pure drug, stabilizer, and physical mixture, were analyzed using the KBr pellet method. The prepared pellet was placed in the light path, and the spectrum was recorded.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using a DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of the samples, including the pure drug, stabilizer, physical mixture, and lyophilized nanosuspension. The instrument consisted of a DSC-60 calorimeter, flow controller (FCL-60), thermal analyzer (TA-60WS), and operating software (TA-60). The samples were placed in hermetically sealed aluminum pans and heated at a scanning rate of 10°C/min over a temperature range of 30°C to 330°C under an air atmosphere. An empty aluminum pan was used as the reference.

Plackett–Burman Design

The Plackett–Burman design is suitably used for screening a large number of factors that are believed to affect important product characteristics or quality attributes. It is generally employed during the initial phase of a study. Based on a review of the literature, five factors were selected as potential factors affecting the quality characteristics of the nanosuspension.

Checkpoint Analysis

Checkpoint analysis was performed to confirm the utility of the established response surface and contour plots in the preparation of the nanosuspension. The values of the independent variables (X_1 and X_2) were selected, and the corresponding values of the dependent variables were calculated by substituting the selected values into the reduced polynomial equation. Nanosuspensions were then prepared experimentally using the selected levels of the independent variables (X_1 and X_2) at the same checkpoint values. The experimentally obtained responses were evaluated and compared with the predicted values to validate the adequacy of the established model.

Evaluation of Nanosuspensions

The prepared nanosuspensions were evaluated for various physicochemical and pharmaceutical parameters, including particle size, polydispersity index (PDI), zeta potential, saturation solubility, drug content, and in vitro drug release, as applicable.

RESULTS AND DISCUSSION

Scanning and Preparation of Calibration Curves

Scanning and Preparation of the Calibration Curve of Candesartan Cilexetil in Methanol

A standard stock solution of Candesartan Cilexetil was prepared in methanol according to the method described in the experimental section. The prepared solution was scanned using a UV–Visible spectrophotometer over the wavelength range of 200–400 nm. The UV absorption spectrum of Candesartan Cilexetil exhibited a maximum absorption (λmax) at 254 nm, as shown in Figure 01.

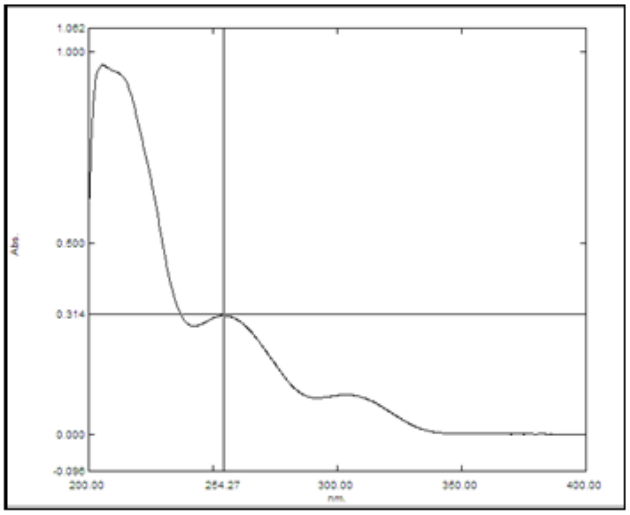


Figure01: Scanning of candesartan cilexetil in methanol

A calibration curve was prepared in methanol over the concentration range of 5–30 µg/mL using a UV–Visible spectrophotometer. The absorbance of the prepared solutions was measured at 254 nm. The procedure was performed in triplicate to validate the calibration curve. The results are presented in Table 01.

Table 01: Calibration Curve Data of Candesartan Cilexetil in Methanol

Sr. No.	Concentration (µg/mL)	Absorbance at 254 nm* (Mean ± SD)
1	0	0.000 ± 0.000
2	5	0.164 ± 0.012
3	10	0.309 ± 0.015
4	15	0.463 ± 0.015
5	20	0.596 ± 0.015
6	25	0.751 ± 0.010
7	30	0.889 ± 0.018

*Indicates the average of three determinations.

A calibration curve was constructed by plotting absorbance against concentration (µg/mL), as shown in Figure 4.2. The regression equation was found to be **Y = 0.0295X + 0.0109**, with a regression coefficient ($\mathbf{R^2}$) of **0.9995**.

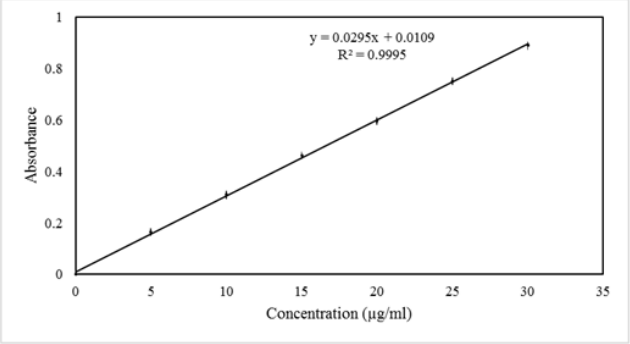


Figure 02: Calibration Curve of Candesartan Cilexetil in Methanol

Scanning and Preparation of the Calibration Curve of Candesartan Cilexetil in 0.05 M Phosphate Buffer (pH 6.5) Containing 0.7% v/v Polysorbate 20

A standard stock solution of Candesartan Cilexetil (10 µg/mL) was prepared in 0.05 M phosphate buffer (pH 6.5) containing 0.7% v/v Polysorbate 20. The prepared solution was scanned using a UV–Visible spectrophotometer over the wavelength range of 200–400 nm. The UV absorption spectrum of Candesartan Cilexetil exhibited a maximum absorption (λmax) at 259 nm [183], as shown in Figure 03.

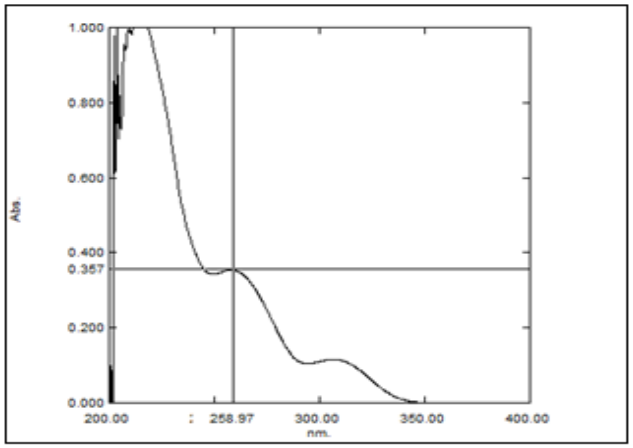


Figure 03: Scanning of candesartan cilexetil in 0.05 M phosphate buffer, pH 6.5containing 0.7% v/v polysorbate 20

A calibration curve was prepared in 0.05 M phosphate buffer, pH 6.5 containing 0.7% v/v polysorbate20[172]intherangeof4-16µg/mlbyUV-Visiblespectrophotometer.The The absorbance of the prepared solutions was measured at 259 nm. The procedure was performed in triplicate to validate the calibration curve. The results are presented in Table 4.2.

Selection of Solvent and Antisolvent

The solvent and antisolvent were selected based on the solubility of Candesartan Cilexetil in different solvents and their combinations [164]. The results indicated that Candesartan Cilexetil exhibited the highest solubility (5.31 mg/mL) in methanol and the lowest solubility (0.00119 mg/mL) in water. Therefore, methanol and water were selected as the solvent and antisolvent, respectively. The results are presented in Table 4.3.

Table 03: Results of Solvent Selection for Candesartan Cilexetil Nanosuspension (CCNS)

Drug	Solvent	Solubility (mg/mL) (Mean ± SD)*
Candesartan Cilexetil	Water	0.00119 ± 0.0001
	Methanol	5.31 ± 0.54
	Alcohol	2.51 ± 0.21
	Isopropanol	0.33 ± 0.012
	N-Butanol	0.13 ± 0.052
	Alcohol:2-Propanol (1:1)	0.55 ± 0.034
	Alcohol:Butanol (1:1)	0.17 ± 0.029
	Ethyl Acetate	0.34 ± 0.038

*Indicates the average of three determinations.

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was performed using a Shimadzu FTIR-8400 spectrophotometer (Shimadzu, Tokyo, Japan). The

spectra were recorded over the wavelength range of 4000–400 cm^{-1}, as shown in Figures 4.5A, 4.5B, and 4.5C.

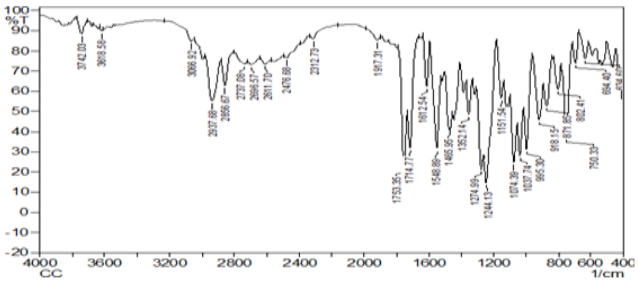


Figure 4A: FT-IR Spectrum of Candesartan Cilexetil

Plackett–Burman Design (PB)

The Plackett–Burman (PB) design is one of the most commonly used screening designs for investigating a large number of factors and identifying the critical factors with a minimal number of experimental runs while maintaining a good degree of accuracy. Generally, the number of experimental runs required to investigate the main effects in a Plackett–Burman design is a multiple of four [189,190]. The design is primarily used during the initial phase of a study to identify the factors that have significant effects on the selected responses. Provided that interaction effects are nil or negligible, the Plackett–Burman design can be used effectively to estimate the main effects of the selected factors.

The Plackett–Burman design was found to be effective for estimating the main effects of the selected independent variables. As shown in Table 4.7, the selected response parameters exhibited considerable variation, suggesting that the independent variables had significant effects on the selected response parameters.

Table 04: Layout and Observed Responses of Plackett–Burman Design Batches for CCNS (Preliminary Screening Formulations)

Batch Code	Amount of Candesartan Cilexetil (mg) X_1	Amount of PVP K30 (mg) X_2	Solvent:Antisolvent Volume Ratio X_3	Stirring Speed (rpm) X_4	Sonication Time (min) X_5	Saturation Solubility (µg/mL) Y_1 (Mean ± SD)*	Mean Particle Size (nm) Y_2 (Mean ± SD)*
CF6	20	50	1:20	800	30	95.13 ± 2.1	259.0 ± 4.6
CF7	10	50	1:20	1200	10	89.34 ± 1.8	272.1 ± 3.9
CF8	10	30	1:20	1200	30	88.14 ± 1.7	370.0 ± 6.1
CF9	20	30	1:10	1200	30	100.43 ± 2.0	257.0 ± 5.1
CF10	10	50	1:10	800	30	93.13 ± 0.9	337.0 ± 4.1
CF11	20	30	1:20	800	10	117.29 ± 0.7	218.4 ± 4.5
CF12	20	50	1:10	1200	10	75.29 ± 0.8	467.0 ± 5.8
CF13	10	30	1:10	800	10	45.43 ± 1.3	563.0 ± 6.1

*Indicates the average of three determinations.

Optimization of Other Preliminary Parameters [191–193]

Candesartan Cilexetil nanosuspensions were prepared using PVP K30 as the stabilizer. Three different amounts of PVP K30, namely 30, 40, and 50 mg, were selected. Nanosuspensions were prepared according to the procedure described in the experimental section. The prepared nanosuspensions were evaluated for various parameters, including mean particle size and saturation solubility, to select the optimum amount of PVP K30 for further formulation studies.

As shown in Table 4.8, **50 mg of PVP K30** was selected because it produced the lowest mean particle size and the highest saturation solubility among the tested concentrations.

Stirring speed is an important process parameter in the preparation of nanosuspensions. For optimization of the stirring speed, 800, 1000, and 1200 rpm were selected. Nanosuspensions were prepared according to the procedure described in the experimental section. The prepared nanosuspensions were evaluated for mean particle size and saturation solubility to select the optimum stirring speed for further formulation studies. As shown in Table 4.8, **1200 rpm** was selected because it produced the lowest mean particle size and the highest saturation solubility among the tested stirring speeds.

Sonication time is another important process parameter that can influence particle-size reduction during nanosuspension preparation. Sonication times of 10, 20, and 30 min were evaluated. The prepared nanosuspensions were evaluated for mean particle size and saturation solubility. Based on the results presented in Table 4.8, **30 min of sonication** was selected because it produced the lowest mean particle size and the highest saturation solubility.

Table 4.a. Results of Optimization of Other Preliminary Parameters for CCNS

Batch Code	Preliminary Parameter	Level	Mean Particle Size (nm) (Mean ± SD)*	Saturation Solubility (µg/mL) (Mean ± SD)*
CF14	Amount of Stabilizer (mg)	30	328.5 ± 5.1	85.07 ± 1.11
CF15		40	301.1 ± 8.2	92.15 ± 1.21
CF16		50	293.5 ± 7.7	95.67 ± 1.14
CF17	Stirring Speed (rpm)	800	389.8 ± 6.7	88.01 ± 0.98
CF18		1000	342.2 ± 9.8	91.32 ± 1.29
CF19		1200	251.0 ± 4.6	102.22 ± 1.02
CF20	Sonication Time (min)	10	382.8 ± 3.8	79.71 ± 1.19
CF21		20	319.0 ± 9.4	87.24 ± 1.31
CF22		30	244.5 ± 6.2	95.30 ± 1.14

*Indicates the average of three determinations.

Drug Content

An aliquot (1 mL) of the prepared nanosuspension was diluted with methanol and filtered through a 0.2 µm membrane filter. The total drug content was determined using a UV–Visible spectrophotometer at 254 nm. The drug content was found to be **101.01% w/w** of Candesartan Cilexetil.

Saturation Solubility

The saturation solubility of the optimized Candesartan Cilexetil nanosuspension and the pure drug was found to be **109.8 µg/mL** and **1.192 µg/mL**, respectively. The saturation solubility of the nanosuspension was therefore approximately **92-fold higher** than that of the pure drug.

This substantial increase in saturation solubility may be attributed to the reduction in particle size and the consequent increase in surface area. The enhanced saturation solubility may contribute to improved dissolution and, potentially, improved oral bioavailability.

In Vitro Dissolution Study

The dissolution profiles of the Candesartan Cilexetil nanosuspension, unmilled pure drug suspension, and marketed formulation (ATACAND® tablet) are presented in Figure 4.13.

The nanosuspension exhibited rapid drug release, with more than **97.13%** of the drug released within **2 min**. In comparison, the cumulative percentage drug release from the unmilled pure drug suspension and marketed formulation was **34.63%** and **75.97%**, respectively, at **60 min**.

These results demonstrate that the nanosuspension substantially enhanced the dissolution rate of Candesartan Cilexetil compared with the unmilled pure drug suspension and the marketed formulation.

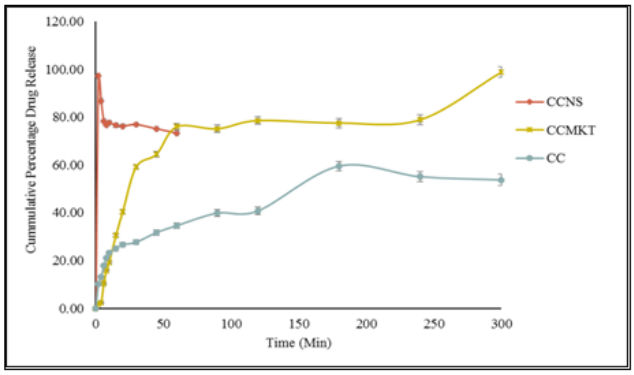


Figure 4.b: Comparison of In Vitro Dissolution of Candesartan Cilexetil Nanosuspension with the Marketed Formulation

Table 4.b: Experimental Results of TFD Batches

Batch Code	Response 1 (Mean ± SD)	Response 2 (Mean ± SD)	Response 3 (Mean ± SD)	Response 4 (Mean ± SD)
TFD1	92.17 ± 1.84	0.529 ± 0.049	17.38 ± 1.82	95.24 ± 1.02
TFD2	101.27 ± 2.25	0.919 ± 0.112	−28.10 ± 2.06	97.52 ± 1.11
TFD3	88.64 ± 1.56	0.784 ± 0.082	−15.33 ± 1.48	100.95 ± 1.84
TFD4	97.92 ±	0.963 ±	−18.08 ±	99.81 ±
	1.91	0.101	1.09	0.54
TFD5	93.32 ± 1.42	0.845 ± 0.062	27.76 ± 2.15	96.00 ± 0.29
TFD6	98.24 ± 1.38	0.459 ± 0.038	−29.96 ± 1.87	99.54 ± 0.81
TFD7	96.25 ± 2.05	0.419 ± 0.051	−18.22 ± 1.55	94.00 ± 0.73
TFD8	93.28 ± 1.09	0.716 ± 0.068	−19.04 ± 1.61	92.10 ± 0.58
TFD9	91.27 ± 1.19	0.645 ± 0.043	19.27 ± 1.72	93.24 ± 0.69

* Indicates average of three determinations

The usual reported dose of Telmisartan for the management of hypertension is 40–80 mg once daily. Lower initial doses may be considered in patients with hepatic or renal impairment. In the present study, a dose of 40 mg/day of Telmisartan nanosuspension was investigated. The results suggested that conversion of Telmisartan into nanosuspension form could potentially allow the dose to be reduced from 40 mg/day to 32.7 mg/day. The reduced dose corresponded to 81.75% of the conventional dose, indicating a calculated dose reduction of 18.25%.

CONCLUSION

Nanosuspension technology is a promising formulation approach for improving the dissolution and potentially

enhancing the oral bioavailability of poorly water-soluble BCS Class II drugs. Candesartan Cilexetil, Telmisartan, and Ziprasidone Hydrochloride nanosuspensions were successfully optimized using experimental designs and suitable stabilizers. The optimized formulations demonstrated rapid drug release and improved bioavailability compared with the respective marketed formulations. Based on the results obtained in the present study, the reported improvement in bioavailability was 38.13% for Candesartan Cilexetil, 33% for Ziprasidone Hydrochloride, and 18.25% for Telmisartan. Overall, the findings suggest that nanosuspension technology may be a useful strategy for enhancing the dissolution characteristics and oral bioavailability of poorly water-soluble drugs.

AUTHOR CONTRIBUTIONS

Both authors contributed to equally.

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMNET

Authors are thankful to the management and principal of SIMS College of Pharmacy, Guntur, and Andhra Pradesh, India

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