World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579

SJIF Impact Factor: 6.916

Year - 2026

Volume: 5; Issue: 5

Page: 377-391

CANDESARTAN, A POORLY SOLUBLE DRUG, WAS FORMULATED AND EVALUATED AS NANOSUSPENSION

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Article Received: 4 March 2026 | | Article Revised: 26 March 2026 | | Article Accepted: 15 April 2026

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DOI: https://doi.org/10.5281/zenodo.19917396

How to cite this Article: J. Praveen Kumar, Sathish M., Dr. D. Jothieswari (2026) CANDESARTAN, A POORLY SOLUBLE DRUG, WAS FORMULATED AND EVALUATED AS NANOSUSPENSION. World Journal of Pharmaceutical Science and Research, 5(5), 377-391.

ABSTRACT

Formulating medications with low solubility presents significant hurdles for the pharmaceutical business, as it reduces the drugs' therapeutic efficacy and bioavailability. A workable remedy is offered by nanosuspensions, a consequence of nanotechnology that dramatically improves drug dissolving and saturation solubility by reducing particle size to the submicron range. By creating, synthesizing, and carefully characterizing nanosuspensions, this extensive study seeks to improve the effectiveness and delivery of medication in a variety of medicinal applications, especially for poorly soluble drugs. A Spectroscopy (FTIR), and Scanning Electron Microscopy (SEM). These studies contribute to the further improvement and optimization of the formulations by providing a thorough understanding of the thermal and structural characteristics of the thorough Preformulation study covering essential components, such as drug- excipient compatibility tests, is the first stage of the research process. Comprehending these essential connections is vital for effective formulation. The next step involves creating nanosuspensions by an ultrasonication-antisolvent precipitation method. The careful selection of stabilizers and solvents is necessary to ensure stability and efficacy while optimizing the formulation process. Deep insights into the physicochemical properties of the nanosuspension can be gained by physicochemical and analytical characterization using cutting-edge methods like Differential Scanning Calorimetry (DSC), Fourier Transform Infrared drug particles at the nanoscale. A detailed analysis of important factors, such as drug and stabiliser concentrations, the volume ratio of solvent to antisolvent, the speed of stirring, and the length of sonication, is necessary to optimize the properties of nanosuspension. In vitro drug release experiments employ the resultant nanosuspensions, enabling a comprehensive comparison with unmilled suspensions and commercially available formulations. This paper also examines the fabrication technique of lyophilized nanosuspensions, which improves the formulations' stability and convenience of use over storage and provides a useful solid unit dosage form for medications with low water solubility. This talk focuses on the structural configurations and diverse applications of polaxemer (188and457), sodium lauryl sulfate, povidone (PVP K-30), and polyvinyl alcohol.

KEYWORDS: Nanosuspensions, Poorly soluble drugs, Ultrasonication method, Drug characterization.

INTRODUCTION

Attempts are being made to incorporate medications having a water solvency higher than 40% into conventional measurement systems (Joshi *et al.,* 2019). Class II prescriptions are known to dissolve ineffectively in both natural and fluid solvents, making them a significantly more challenging challenge. When it comes to thesekinds of high log P synthetic compounds that are insoluble in water, the nanosuspension structure is desired. Low bioavailability and solubility issues can be addressed in a number of ways, including co-dissolvability, micronization, salt generation, and tasteful arrangement. a variety of techniques, including solid dispersion, ß-cyclodextrin inclusion structures, liposomes, nanoparticles, nanogels, nanoemulsions, nanosuspension, emulsions, particle size reduction, and co-solvent applications (Kumari *et al.,* 2023). Not without justification: not every prescription can benefit from the use of every one of these strategies. In these circumstances, nanosuspensions are the recommended method. Rather than using lipidic frameworks as a treatment approach, nanosuspensions are being used for drugs that are insoluble in both fluid and inorganic environments.

For the process of insoluble drug nanozation, these techniques are recommended.With this technique, one can work autonomously, in an unfamiliar setting, and with little equipment, reducing molecules' size to two or three hundred nanometers. Therefore, regardless of the delivery mechanism used, careful consideration of the kind and stabiliser emphasis is necessary for the effective assembly of nanosuspension. With this arrangement, stabilizers that are polymeric or surfactant- based can be utilized. Different from carpet lipidic transporters, strong lipid nanoparticles called nanosuspensions are polymeric colloidal floor covering transporters.

Sometimes the oral dosage forms of water-soluble drugs that are slowly absorbed and inefficient show insufficient bioavailability. For solid drugs to be absorbed, they must dissolve. The amount of time the medicine spends at the absorption site may not be sufficient if it is difficult to dissolve or cannot cross the epithelial barrier (for example, if it is highly polar and ionized). Bioavailability is frequently very varied and low in these circumstances (Russell *et al.,* 1994). The bioavailability of a medicine can be impacted by a variety of factors, including age,sex,physical activity, genetic genotype, stress, disorders (such achlorhydria, malabsorption syndromes), or prior GI surgery (like bariatric surgery).

Reducing the water solubility of drugs to increase their bioavailability remains one of the hardest problems in medicine. According to estimates, the pharmaceutical sector discovers up to 40% of novel chemical entities with restricted water solubility every year (Bhalani *et al.,* 2022).

A drug's permeability and solubility have a significant impact on how bioavailable it is. Certain drugs have never been easy to prepare for oral administration due to their solubility. Other examples are phenytoin, digoxin, griseofulvin, and sulphathiazole. Since high throughput screening of possible therapeutic agents was introduced, the quantity of poorly soluble drug candidates has increased dramatically. One of the most frequent and challenging problems facing formulation scientists in the pharmaceutical sector today is the formulation of poorly soluble compounds for delivery.

Nanosuspensions ‘Advantages

The following are the main benefits of nanosuspension technology :(Padma*etal.*,2010)

a) Stabilizers facilitate the development of large-scale production and ensure long-term physical stability.
b) The advantages of administering nanosuspensions orally include improved absorption, a lowered fed/fasted ratio,

and a faster onset.

c) The administration method known as intravenous (IV) can rapidly target and degrade tissue.

d) Medication administered intramuscularly or subcutaneously may reduce tissue irritation.

e) Enhanced bioavailability when administered intravenously and inhaled,

f) To improve their bioavailability, drugs having high log Pvalues can be synthesized as nanosuspensions.

g) Increased biological efficacy due to the medication's rapid rate of solubility and saturation

Nanosuspension Formulation (Patravale*etal.,* 2004)

Accelerants	Function	Examples
Stabilizers	Completely moisten the drug particles, halt Ostwald's ripening and agglomeration of nanosuspensions, and provide a steric or ionic barrier.	In addition to soy lecithins, poloxamers 188, 407, Polysorbate 80, HPMC E-15, HPMC E-50, PVP K-25, and PVP K-30
Co- surfactants	Influence phase behavior when making nanosuspensions with microemulsions.	Bile salts, dipotassium glycyrrhizinate, transcutol, ethanol, and isopropanol
Organic solvent	A solvent that is safer and authorized by pharmaceuticals for use in formulation manufacture.	Ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, methanol, ethanol, and chloroform.
Other toppings	Depending on the medication moiety's properties or the delivery route's needs	buffers, polyols, osmogens, salts, and cryoprotectants, among others.

AIM AND OBJECTIVES

The purpose and goals of the medication that was chosen for nanosuspension;

1. The Pre-formulation study of selected drugs.
2. To Scanning and calibration curve preparation of selected drugs.
3. Selection of solvents and stabilizer for the formulation of nanosuspension.
4. Preparation of nanosuspension by antisolvent precipitation followed by ultrasonication technique from selected drugs.
5. Characterization of developed nanosuspension formulation by various physicochemical parameters as well as analytical techniques.
6. Study of in-vitro drug release profile of optimized formulation and comparison of it with un-milled suspension and marketed formulation.
7. To create lyophilized nanosuspensions of pharmaceuticals that is not easily soluble in water using the antisolvent precipitation-ultrasonication approach. The lyophilized substance must be transformed into a solid unit dosage form for ease of handling.

USE OF NANOSUSPENSIONS IN MEDICATION DELIVERY

From a formulation perspective, nanosuspensions are practically ideal drug delivery vehicles for the parenteral route. Almost all drugs can be produced for parenteral administration since the drug particles are directly nanosized, which simplifies the process. Consequently, nanosuspensions have the potential to greatly increase the drug's parenterally tolerated dose, thereby reducing therapy costs and enhancing therapeutic efficacy. The maximum amount of paclitaxel nanosuspension that can be used is three times greater than the amount of Taxol that is currently on the market; Taxol solubilizes the drug with ethanol and CremophoreEL (Maand Mumper, 2013).

Nanosuspensionscanbeadministeredusingavarietyofparenteralmethods, including intra-articular, intra-peritoneal, and intravenous injection. A medicine administered parenterally must be soluble or include particles/globules less than 5

μm in order to avoid capillary obstruction. In this regard, liposomes are significantly more versatile and ideal for parenteral dispersion. Nevertheless, they often encounter problems such as excessive manufacturing expenses, difficulties in expanding, and physical unreliability. Nanosuspensions may be able to address the aforementioned problems. Furthermore, it has been found that parenterally administered drugs function better when administered as nanosuspensions (Pateland Agrawal, 2011).

List of materials and equipment used in the manufacture and investigation of nanosuspension

Make use of	Content	Level	Producing
Medication	Candesartan Cilexetil	USP.	Gift sample from Alembic Research the Vadodara Centre,
Stabilizer	Poloxamer188,	Grade of AR	Gift Sample of Astron Research Centre,Ahmedabad ,and Aristo Pharmaceutical LTD. Sikkim
	Poloxamer407,	Grade of AR	Gift Sample from Astron Research Centre,Ahmedabad,andAristo pharmaceutical LTD. Sikkim
	Polyvinyl alcohol	Grade of AR	Loba Chemie Pvt. Ltd. Mumbai. And Alkem Laboratories LTD. Sikkim
	PVP K30	Grade of AR	S.D. Fine Chemicals, Mumbai and Alkem Laboratories LTD. Sikkim
	Sodium Lauryl Sulphate	Grade of AR	Himedia Laboratories Pvt.Ltd. Mumbai And Alkem Laboratories LTD .Sikkim
Solvent	Dichloromethane	Grade of AR	Chemdyes Corporation ,Rajkot, and Ajanta pharma Guwahati.

Equipment list

Sr.No.	Equipments/ Instruments	Model/Make
1	Electronic weighing balance	Japan'sShimadzu AUX 220
2	Higher-upstirrer	India’sRemiEquipmentsPvt.Ltd.
3	Bath sonicator	Bransone ultra sonicuorporationUSA.
4	Probe sonicator	FrontlineElectronicsand MachineryPvt. Ltd
5	UV spectrophotometer	Japan's1800ShimadzuUV.
6	Cooling micro centrifuge C24BL	India’sRemiEquipmentsPvt.Ltd.
7	FTIR spectrophotometer	Japan's8400Shimadzu.
8	Particle size analyzer	Zetatrac,microtrac.USA., Malvern Mastersizer3000
9	Magneticstirrer2LH	India’sRemiequipmentsPvt.Ltd.
10	Digital Water bath	India’sBio-tech.
11	Differential scanning calorimeter	Japan'sShimadzuDSC,ta-60wa.

ANALYZATION AND ASSESSMENT DRUG CURVE PREPARATIONS

Candesartan cilexetil scanning in methanol and calibration curve preparation

10 milligrams of candesartan cilexetil were carefully weighed and diluted in 5 ml of methanol in volumetric Flask with a capacity of 100 ml to create a standard stock solution (100 μg/ml). After five minutes of sonication, methanol was added to the mixture to get the volume up to 100 ml. Using the usual stock solution, a methanolic solution containing 10 μg/ml of candesartan cilexetil was made. The 200–400 nm wavelength range was examined using a UV light, and the wavelength with the greatest absorption was marked as max (λmax) for additional analytical examination.

To achieve a 5–30 μg/ml concentration, appropriate aliquots were taken from the standard stock solution (100 μg/ml)and placed into different volumetric flasks having a capacity of 10 ml. These flasks were then filled to capacity with methanol. The absorbance of these solutions was measured at a selected max (λmax). The experiment was run three times to guarantee the calibration curve's accuracy. A calibration curve was created by charting the relationship between absorbance and concentration (μg/ml).

Preparing the calibration curve and scanning Candesartan cilexetil in 0.7%v/v polysorbate 20 in 0.05 M phosphate buffer, pH 6.5

Accurately weighing 10 mg of candesartan cilexetil and dissolving it in 5 ml of 0.05 M phosphate buffer,pH6.5,with0.7%v/v polysorbate20 in a100ml volumetric flask yielded a standard stock solution of 100 µg/ml of the medication. After five minutes of sonication, it was diluted to 100 millilitres using 0.05M phosphate buffer (pH 6.5) with 0.7% v/v polysorbate 20. From the usual stock solution, a candesartan cilexetil (10 µg/ml) solution containing 0.7% v/v polysorbate 20 was prepared. The wavelength that showed the maximum absorption during a UV scan between 200 and 400 nm was designated as "max" for additional analytical investigation.

PLACKETT-BURMANDESIGN(Gacula, 1993, **Patel** and **Patel,2020)**

The Plackett-Burman design is frequently employed in the early phases of an investigation because it is well-suited for screening a wide range of variables thought to be influencing significant product features or attributes. After a research of the literature, five criteria were chosen to affect the nanosuspension's calibre. The Plackett-Burman design was used to identify the primary factor influencing the nanosuspension's quality, stability, and efficacy. Eight tests (preliminary screening formulations) were designed to screen for five independent factors: the quantity of drug (X1), stabiliser (X2), solvent to antisolvent volume ratio (X3), stirring speed (X4), and sonication time (X5) in milliseconds for each of the three medicines. The dependent variables that were selected were mean particle size in nm (Y2) and saturation solubility in µg/ml (Y1).

The net effect of a single factor was calculated using the evaluated parameter values from the following equations.

$Effect of X_1=((Y_1+Y_4+Y_6+Y_7)-(Y_2+Y_3+Y_5+Y_8))/8$	Eq…..(3.1)
$Effect of X_2=((Y_1+Y_2+Y_5+Y_7)-(Y_3+Y_4+Y_6+Y_8))/8$	Eq…..(3.2)
$Effect of X_3=((Y_1+Y_2+Y_3+Y_6)-(Y_4+Y_5+Y_7+Y_8))/8$	Eq…..(3.3)
$Effect of X_4=((Y_2+Y_3+Y_4+Y_7)-(Y_1+Y_5+Y_6+Y_8))/8$	Eq…..(3.4)
$Effect of X_5=((Y_1+Y_3+Y_4+Y_5)-(Y_2+Y_6+Y_7+Y_8))/8$	Eq…..(3.5)

3^2 USING FACTORIAL DESIGN TO OPTIMISE CRITICAL PARAMETER

The study employed a 3^2 factorial design to examine the drug quantity in milligrammes of candesartan cilexetil and the solvent to antisolvent volume ratio (Kakran *et al.,* 2010, Das and Suresh, 2011, **Shirsath** *et al.,***2022**), as well as the drug amount in milligrammes of telmisartan and ziprasidone hydrochloride and the stirring speed (Pignatello *et al.*, 2002). Along with CPR at 15 min in ziprasidone hydrochloride nanosuspension.

NANOSUSPENSION EVALUATION

Particle sizes and PDI

The size distribution (poly dispersity index) and mean particle size of the resulting nanosuspension were examined using the Zetasizer (Zetatrac, Microtrac, Japan). This technique utilizes the principle of light diffraction and is commonly referred to as photon correlation spectroscopy (PCS). Before the measurement, the materials were appropriately diluted with water to an acceptable scattering intensity, and they were then shaken to re-disperse (Shinde and Hosmani, 2014).

Zeta Potential

The Zeta potential measures the electric charge at the surface of the particle to ascertain if colloidal systems are physically stable. Aqueous dispersions show long- term electrostatic stability when their zeta potential is greater than

|30mV|. In this work, the electrophoretic mobility of the particles was measured using the Zetasizer (Zetatrac, Microtrac, Japan) to determine the Zeta Potential (Shinde and Hosmani, 2014).

Substances Used

Subsequent to preparing a one milliliter aliquot and diluting it with methanol, the nanosuspension underwent filtration with a 0.2 micrometer filter. Using a UV spectrophotometer, the total drug content was calculated at the greatest drug concentration. Symbol: (Shid *et al.*, 2014)

$$\text{CompleteDrugContent} = \frac{(\text{Drug Amountin Aliquot} \times \text{TotalNanosuspension Volume}}{\text{AliquotVolume}} \quad \text{Eq…..(3.9)}$$

Solubility in saturation

The resulting nanosuspension's saturation solubility was checked by placing it in avial and stirring it for 48 hours at 100 RPM using a magnetic stirrer. Subsequently, an eppendorf tube was filled with 2 milliliters of the nanosuspension and centrifuged at 10,000 RPM for 30 minutes. After the appropriate dilution with blank dissolving media, the supernatant was filtered with a 0.2 µm syringe filter and examined with a UV-visible spectrophotometer(UV-1800,Shimadzu,Japan)at the maximum drug concentration. Every sample was subjected to three separate analyses. The calibration curve was used to calculate saturation solubility (Muller *et al.*, 2001).

Invitro dissolution research

For an in-vitro dissolving study,the USP 24 paddle was utilized (ELECTROLAB TDT-06P). dissolving media was used. Carefully pouring the media into the dissolution vessel reduced foaming of the medium during the experiment.At37°C, dissolution was carried out at the paddle speed listed in Table 5.3. The dissolving vessels received a nanosuspension that matched one dosage of the drug. At intervals of 2, 4, 6, 8, 10, 15, 30, 45, and 60 minutes, 5 ml samples were collected. They were quickly filtered through a 0.2 µm syringe filter before being subjected to spectrophotometric analysis. The dissolving vessel was then filled with 5 ml of fresh media. The studies were carried out three times, and the average outcomes were published (Li *et al.*, 2011).

Decomposition Situation	**As in Candesartan, Cilexetil Nanosuspension**
Media for dissolution	pH 6.5 0.05M Phosphate Buffer: consists of 20 Polysorbate0.7% v/v
Amount of Media for dissolution	250
RPM (speed)	50
Intervals of Sampling	2, 4, 6, 8, 10, 15, 30, 45, And 60 minutes

Investigating stability more quickly in compliance with ICH criteria Accelerated stability analysis in line with CCNS ICH criterion

In compliance with ICH guidelines, accelerated stability (temperature 40.0 ± 2°C and 75.0 ± 5% relative humidity) tests on lyophilized nanosuspension were carried out for six months at storage condition, temperature 25.0 ± 2°C and 60.0 ± 5% relative humidity. The lyophilized nanosuspension was enclosed in tight gelatin capsules. Particle size, saturation solubility, percent CPR at 2 minutes for CCNS, and percent weight-to-weight of drug content were measured on the extracted samples at regular intervals (0, 1, 3, and 6 months) (ICH, Q1A (R2)).

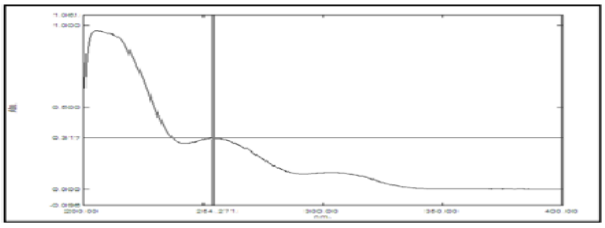
LYOPHILIZATIONOFANOPTIMALBATCH NANOSUSPENSION

Using a lyophilizer, mannitol (1:1, total solid: cryoprotectant) was utilized as a cryoprotectant to transform the nanosuspension into a dry powder. During the lyophilization process, samples were held in a compartment with a temperature controlled at -80°C for eight hours. The nanosuspension was removed from the chamber and stored in an airtight container for subsequent usage after it dried into a powder in six to eight hours.

RESULTS AND DISCUSSION

Preparing the calibration curve and scanning for candesartan cilexetil in methanol

Using the procedure outlined in the experimental section, the candesartan cilexetil standard stock solution was made in methanol and scanned with a UV Visible spectrophotometer between 200 and 400 nm. Figure 6.1 displays the UV absorption spectrum of candesartan cilexetil, which peaks at 254 nm (Pradhan *et al.*, 2011).



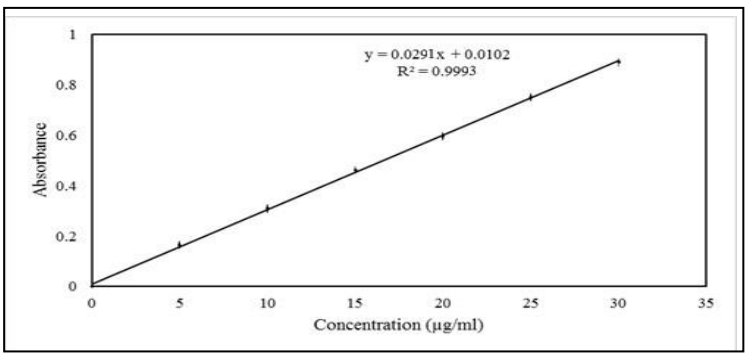
Candesartan cilexetil scanning in methanol isshown

Using a UV-Visible spectrophotometer, a calibration curve for methanol in the range of 5–30 µg/ml was created. The absorbance of these solutions was measured at 254 nm. To ensure that the calibration curve was accurate, this procedure was carried out three times. Table presents the data.

Table Candesartan cilexetil calibration curve data in methanol are shown.

The lot number	Concentration Relative (µg/ml)	Theabsorbance (Mean±SD)at 254 nm*
1.	0.0	0.000± 0.0
2.	5.0	0.175± 0.013
3.	10.0	0.310± 0.016
4.	15.0	0.474± 0.016
5.	20.0	0.597± 0.016
6.	25.0	0.762± 0.011
7.	30.0	0.890± 0.019

Figure illustrate show to plot absorbance against concentration in µg/ml to create a calibration curve. The regression equation was then determined to be Y = 0.0291x +0.0102,and its regression coefficient was 0.9993.



Selectinga stabilizer

A number of stabilizers, including sodium lauryl sulphate, polyvinyl alcohol, poloxamer 407, poloxamer 188, and PVP K-30, were screened by generating nanosuspensions under the following processing and formulation conditions (Pandya *et al.*, 2010).

Table represents Acompilationand analysisof theselection criteriafor aCCNS stabilizers.

Batch No.	Stabilizers	Stabilizers' measurement in milligrams)	Dosage of Candesartan Cilexetil (milligrams)	Shakin g Speed, or RPM	Stirring Time (h)	Sonication Time (min)	Antisolvent Solvent VolumeAs a ratio
CF1.	PolyvinylAlcoho l	30.0	10.0	800.0	4.0	20.0	1:20
CF2.	PVPK30	30.0					
CF3.	SodiumLauryl Sulphate	4.0					
CF4.	Poloxamer188	30.0					
CF5.	Poloxamer407	30.0					

The produced nanosuspensions (CF1. to CF5) were evaluated for their saturation solubility, mean particle size, polydispersity index (PDI),and zeta potential, as shown in Table shows, in order to decide which stabiliser would be best for additional research.

Batch No.	Applyinga Stabiliser	Solubility of Saturation (µg/ml) (Mean±SD)*	Average Particle Size(nm) (Mean ± SD)*	(Mean ± SD)*PDI	Mean ± SD ZetaPotential (mV)*
CF1.	PolyvinylAlcohol	54.37±1.29	512.1±4.3	1.094±0.12	31.33±1.02
CF2.	**PVPK30**	**80.24±2.02**	**243.4±5.5**	**0.299±0.05**	**-32.90±0.89**
CF3.	SodiumLauryl Sulphate(SLS)	51.40±0.99	436.1±9.4	0.743±0.03	-30.80±0.92
CF4.	Poloxamer188	60.92±0.58	320.1±8.9	0.564±0.04	-31.28±1.25
CF5	Poloxamer407	57.32±0.88	598.1±5.9	1.090±0.16	20.64±1.10

Fourier transformed infrared (FTIR) spectroscopy

Shimadzu FTIR8400 spectro photometer (Shimadzu, Tokyo, Japan)was used for the FTIR spectroscopy.

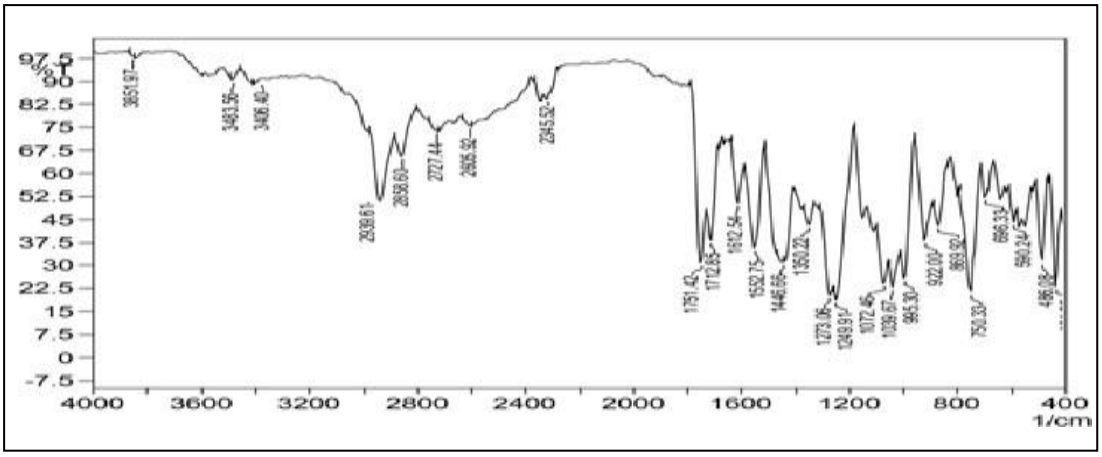


Figure shows Displays the FT-IR spectra of a physical combination of PVPK-30 and Candesartan Cilexetil.

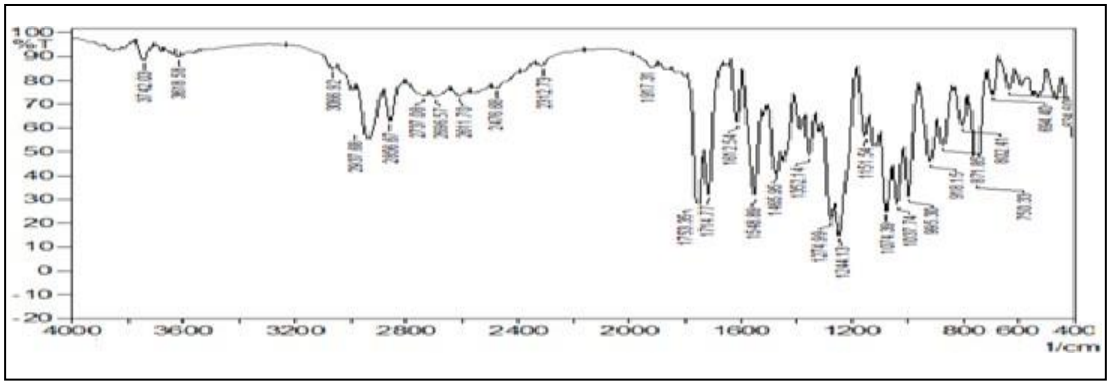


Table Observed responses and Plakett-Burmandesign batch configuration for CCNS (preliminary screening formulations.

Batch No.	Dosage of Candesarta -n Cilexetil (milligrams) X1	Quantity of PVP K-30 (mg) X2	Volume Ratio Between Anti-solvent and Solvent X3	Shakin g Speed, or RPM X4	Soni Catio -n Duration (Min) X5	Solubil- ity of Saturat-ion (µg/ml) (Mean ± SD)*Y1	Particle Size Average (nm) (Mean± SD)*Y2
CF6.	20.0	50.0	1:20	800 RPM	30.0	**95.24 ± 2.2**	**259.1 ± 4.7**
CF7.	10.0	50.0	1:20	1200 RPM	10.0	**89.45 ± 1.9**	**272.2 ± 3.9**
CF8.	10.0	30.0	1:20	1200 RPM	30.0	**88.25 ± 1.8**	**370.1 ± 6.2**
CF9.	20.0	30.0	1:10	1200 RPM	30.0	**100.54 ± 2.1**	**257.1 ± 5.2**
CF10.	10.0	50.0	1:10	800 RPM	30.0	**93.24 ± 0.9**	**337.1 ± 4.2**
CF11.	20.0	30.0	1:20	800 RPM	10.0	**117.30 ± 0.8**	**218.5 ± 4.6**
CF12.	20.0	50.0	1:10	1200 RPM	10.0	**75.30 ± 0.9**	**467.1 ± 5.9**
CF13.	10.0	30.0	1:10	800 RPM	10.0	**45.54 ± 1.4**	**563.1 ± 6.2**

3^2 Factorial configuration

Using different candesartan cilexetil concentrations and the volume ratio of solvent to antisolvent, several formulations were created (Kakran *et al.*, 2010, **Shirsath,** *et al.*, **2022**). A 3^2complete factorial design was employed in order to evaluate the impact of the two independent factors on the predefined dependent variables, namely mean particle size and saturation solubility, as indicated in Table.

BatchNo.	Candesartan Cilexetil Amount Level X1	Volume Ratio of Antisolvents at Solvent Level X2	(Mean±SD)*, Average Particle Size (nm)Y1	Solubility of Saturation (µg/ml), (Mean±SD)*Y2
CFD1.	-1	-1	435.0± 9.3	72.97±2.16
CFD2.	-1	0	343.0± 6.1	95.23±2.04
CFD3.	-1	1	381.0± 8.8	85.88±1.68
CFD4.	0	-1	411.0± 7.1	35.99±0.62
CFD5.	0	0	310.0±11.1	50.05±0.92
CFD6.	0	1	354.8± 6.0	38.94±1.12
CFD7.	1	-1	336.7± 7.7	94.71±1.55
CFD8.	**1**	**0**	**240.8± 8.6**	**114.03±2.53**
CFD9.	1	1	319.0± 9.1	101.35±1.33
ConvertingRealUnitsfrom Coded Levels				
AdjustablesLevel		**Low(-1)**	**Medium(0)**	**High(1)**
X1		10milligrams	15milligrams	20milligrams
X2		1:10	1:15	1:20

*Denotes the mean of three findings

Zeta potential, PDI, percent weighted drug content, and cumulative percentage released (CPR) at two minutes were among the other metrics that were evaluated, as indicated in below Table.

Batch No.	At two minutes, CPR(% w/w)(Mean± SD)*	PDI, (Mean±SD)*	Zeta Potential (mV), (Mean±SD)*	Content of Drugs(%w/w), (Mean±SD)*
CFD1.	**91.46 ± 3.85**	**0.540 ± 0.052**	**18.87 ± 1.53**	**93.27 ± 1.22**
CFD2.	**99.80 ± 1.03**	**0.525 ± 0.050**	**-29.42± 2.13**	**94.83 ± 2.15**
CFD3.	**97.22 ± 1.44**	**0.665 ± 0.072**	**16.54 ± 1.25**	**95.37 ± 1.36**
CFD4.	**95.51 ± 2.02**	**0.745 ± 0.085**	**-24.37± 0.99**	**92.73 ± 0.58**
CFD5.	**98.47 ± 3.88**	**0.866 ± 0.096**	**-10.50± 0.58**	**99.37 ± 0.87**
CFD6.	**98.03 ± 0.84**	**0.877 ± 0.102**	**18.76 ± 1.66**	**99.47 ± 1.53**
CFD7.	**99.74 ± 1.45**	**0.532 ± 0.086**	**17.19 ± 1.89**	**98.23 ± 1.44**
CFD8.	**97.24 ± 1.92**	**0.354 ± 0.043**	**25.99 ± 1.86**	**101.18± 1.59**
CFD9.	**93.01 ± 2.12**	**0.998 ± 0.059**	**22.15 ± 2.13**	**98.94 ± 1.28**

*Denotes the mean of three findings

Statistical analysis

After the regression coefficient values were inserted into the formula (3.8), a complete model was generated. Microsoft Excel® version 2013 (Microsoft Corporation, Washington, USA) was used to perform the regression analysis; Tables 6.11 and 6.12 display the fitting results.

	Average Particle Size(nm) (Y1),		
	The coefficient of	**Std. Error,**	**The value of P,**
b0.	308.3333	5.35183	1.16E-05
b1.	-44.66671	2.931313	0.000613
b2.	-23.16671	2.931313	0.004222
b11.	-17.001	5.077183	0.044113
b22.	71.5001	5.077183	0.000777
b12.	8.7009	3.59013	0.007059
	R^2= 0.994141		

Contour-plottedplots

Two-dimensional contour plots were made to assess the connection between independent and dependent variables using the statistical programme Minitab 17 (Minitab Inc., USA), as shown in Figure.

Figure (A) displays the contour plot for mean particle size (nm) at fixed values between 250 and 400 nm. The nonlinearity of the contour plot was found. As a result, the particle size and the independent factors did not correlate linearly. The minimum (light green zone) is easily visible thanks to the contour map, which also displays the solvent: antisolvent volume ratio and candesartan cilexetil dosage for the lowest mean particle size. The solvent to antisolvent ratio is roughly 1:15 (coded value 0), whilethe amount of candesartan cilexetil is 20 mg (coded value +1).Figure (B) displays the contour plot for saturation solubility (µg/ml)at predetermined values ranging from 40 to 100 µg/ml. The nonlinearity of the contour plot was found. Consequently, the relationship between the independent and dependent variables was nonlinear. The maximum (dark green zone) is clearly visible thanks to the contour map, which also determines the solvent: antisolvent volume ratio and the candesartan cilexetil quantity for maximal saturation solubility.

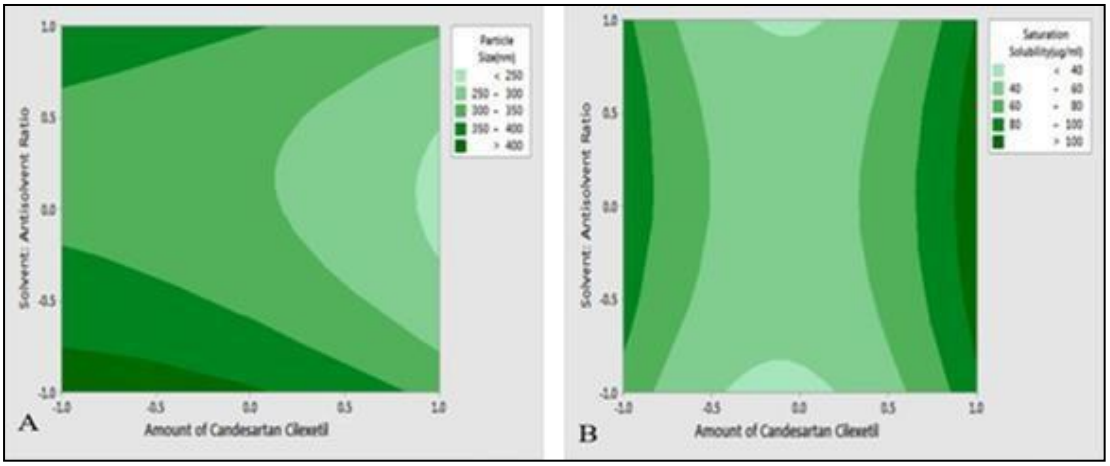


Figure (A) CCNS contour plotshows the impact of meanparticle size.

(B) CCNS contour plot demonstrating the influence of saturation solubility.

Surface diagrams

Plotting response surfaces is a wonderful way to identify the primary and secondary impacts of the independent variables.

The response surface plot of mean particle size as a function of independent parameters is displayed in Figure 6.10 (A). The mean particle size decreases as the plot moves towards the centre. The middle of the plot displays the antisolvent volume ratio (codedvalue0)and candesartan cilexetil (coded value +1) in order to achieve the lowest particle size achievable through the use of an intermediate solvent.

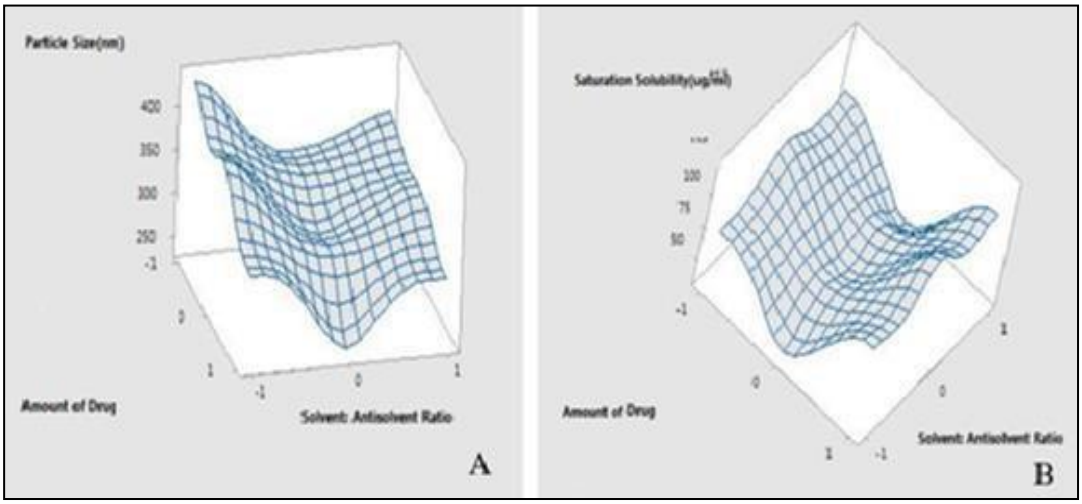


Figure shows (A) the impact of average particle size on the response surface plot of the CCNS. (B) Plot of the CCNS response surface for the effect on solubility at saturation Using Minitab17.0'sdesirability function, candesartan cilexetil nanosuspension is optimized. in vitro dissolution

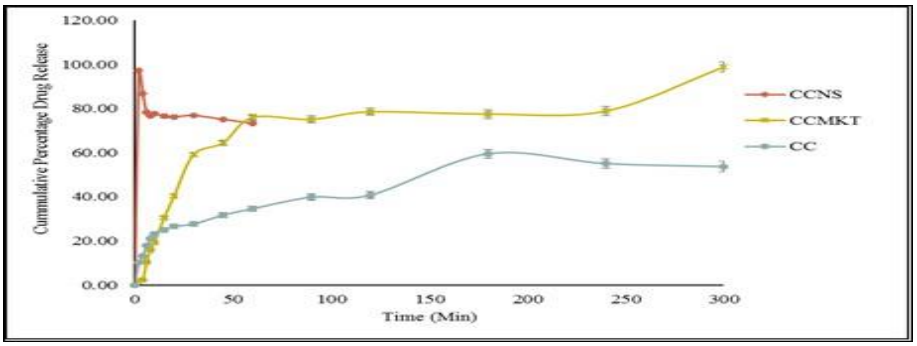


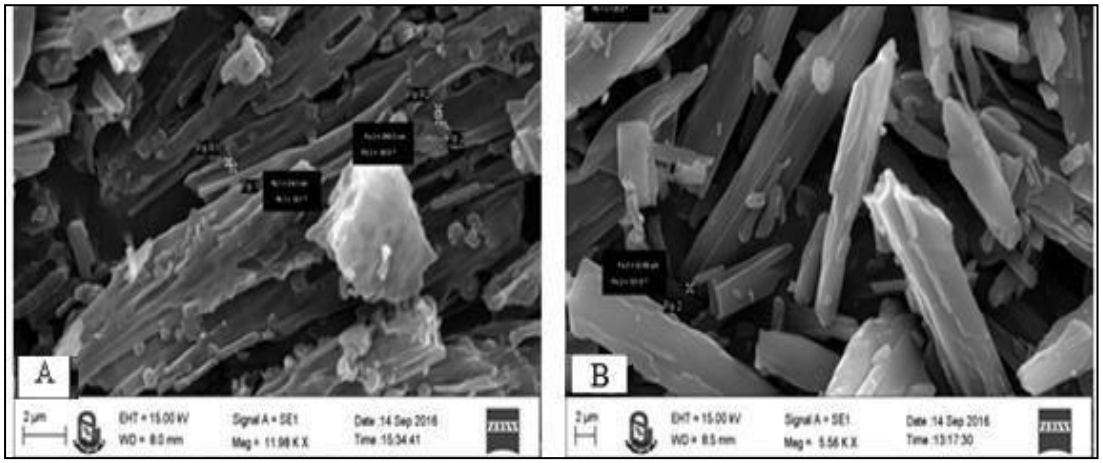
Figure represents Contrasting the in-vitro dissolution of Candesartan Cilexetil nanosuspension with its commercial formulation and un-milled suspension.

Table represents Assessment criteria of a refined batch of CCNS.

Assessing Factors	Outcomes
Particle Size Average,	242.8 nm
PDI,	0.342
Potential Zeta,	25.97 mV
ContentofDrug	101.02 %w/w
Solubility atSaturation	109.7µg/ml
AtTwo Minutes, CPR	97.14%w/w

Scanning electron microscopy (SEM)

Figure represents (A) Candesartan Cilexetil: An investigation using scanning electron microscopy and (B) Electron microscopy with CCNS.



Results of CCNS's Accelerated Stability Research

Serial No.	Conditions of storage for a stability analysis	Time frame (months)	EvaluatingElements			
			Particle Size Average (nm) (Mean± SD)*	Solubility of Saturation (µg/ml) (Mean ± SD)*	At two minutes, CPR (%w/w) (Mean± SD)*	Content of Drugs (%w/w) (Mean ± SD)*
1	25°C ±	0.0	242.6±4.6	111.86±1.6	97.14±0.62	101.02±0.36
	2°C					
2		1.0	259.2±5.2	110.51±0.8	96.86±2.96	100.86±0.53
	and60%					
3	±5%	3.0	265.2±8.2	109.8±0.9	95.93±1.13	99.86±0.48
4	RH	6.0	281.1±7.8	109.08±1.8	95.14±1.82	97.17±0.88

SUMMARY AND CONCLUSION

One method that exhibits the vapor pressure effect and significantly enhances the effective surface area of medication particles is nanosuspension. Additionally, by quickening the rate of dissolution, this method increases bioavailability candesartan cilexetil, are poorly soluble in water. For medications, dissolution is thus a rate-limiting step.

Candesartan cilexetil nanosuspension is made by first utilizing antisolvent precipitation and then ultrasonication technology to improve the in-vitro drug release profile. PVP K-30 was discovered to be the most efficient candesartan cilexetil stabilizer. A compatibility study using FTIR and DSC testing demonstrated drug-excipient compatibility. The quality of the candesartan cilexetil nanosuspension was effectively affected by crucial processing and formulation variables that were identified by Burman –Plackett Design. Usinga 3^2 factorial design, the formulation of the nanosuspension was assessed for its main effects, interaction effects, and quadratic effects. The final formulation of the response optimizer, obtained from the desirability function, released 97.14% of candesartan cilexetil with a half-life of two minutes and D = 1.001.layer's higher pH causes a weak acid salt form to dissolve and become more soluble more quickly.

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