Ind. J. Pharm. Edu. Res., 2026; 60(2):532-538.
https://www.ijper.org

Original Article

Formulation and Evaluation of Cilnidipine Loaded Nanoparticles for Enhanced Solubility

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ABSTRACT

Introduction: Poorly water-soluble drugs present challenges in development of formulation using conventional methods and are resulting in poor drug performance. Formulating these molecules into nanoparticles based drug delivery, enhances the drug solubility and efficacy. **Objectives:** The objective of this study is to prepare and evaluate cilnidipine loaded nanoparticles to improve the solubility. **Materials and Methods:** Nanoparticles loaded with cilnidipine was prepared by solvent evaporation method and characterized for particle size, polydispersity index, zeta potential, drug content, entrapment efficiency, morphological characteristics, *in vitro* drug release and stability studies. **Results:** The particle size of cilnidipine loaded polymeric nanoparticle was found to be in nanometer range and zeta potential was in negative value indicates that preventing aggregation and improves stability and shelf life. Drug entrapment efficiency was within prescribed range and the drug release studies indicate that the drug release increases when the polymer concentration decreases and possibility of releasing the drug for longer period of time. The correlation coefficient value of Higuchi's model was near one which indicates that the nanoparticles follow diffusion rate-controlled mechanism with non-fickian diffusion. **Conclusion:** The characteristics studies show that cilnidipine nanoparticle can improve the solubility and dissolution rate and also prolong the drug release, thereby increasing the therapeutic activity.

Keywords: Nanoparticulate Drug Delivery, Nanoparticles, Cilnidipine, Solvent Evaporation Method, Dissolution Study.

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Received: 12-04-2025;
Revised: 05-07-2025;
Accepted: 18-08-2025.

INTRODUCTION

The oral drug delivery system is the most popular and practical way to administer drugs because it is easy to produce, is cost effective, allows for versatility in dosage form design and has high patient compliance rate. Oral medicine administration faces number of difficulties systems are poor solubility, dissolution and membrane permeability.[1] Poor water solubility is a problem for between 25 and 40% of all currently available drugs and newly created active medicinal components. Drugs that are poorly soluble in water, large dose are required to achieve an effective plasma concentration, which causes toxicity at aggregation accumulations because of the high concentration of the drug.[2]

Fourth-generation calcium channel blockers like cilnidipine have slow-onset, long-lasting vasodilating impact by blocking the L type Ca^{2+} channels in vascular smooth muscle cells and the N type Ca^{2+} channels in sympathetic neurons. Due to its low water solubility and dissolution rate (≤2 mg/mL), cilnidipine has a low bioavailability and restricted oral absorption.[3] Bioavailability of cilnidipine was of reported approximately 13% due to its low aqueous solubility. Hence, efforts have been made to get innovative formulation like polymeric nanoparticles which significantly improves the bioavailability of this drug by 2.5 to 3 folds.[4]

Nanoparticles are colloidal structures that have been nanonized and range in size from 10 to 1000 nm. The medicine will be dissolved, trapped, encapsulated, or connected to the nanoparticle matrix, which will distribute the drug uniformly.[5] Nanoparticles have several advantages like the increasing aqueous solubility of less soluble drugs, it improves bioavailability which helps in achieving maximum therapeutic response with less side effects and it releases the drug sustained and controlled manner over the period of time and by delivering the drugs to the specific sites to increasing the therapeutic activity and reduce the toxicity.[6,7] Moreover, these particles facilitate high drug loading capacities, enabling the incorporation of substantial amounts of both hydrophilic and lipophilic drugs.[8]

DOI: 10.5530/ijper.20263140

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MATERIALS AND METHODS

Materials

Cilnidipine was procured from Bangalore fine chemicals, PVP K30 was procured from Balaji Drugs, Bangalore, Pleuronic F68 from Sigma Chemicals, Mumbai, India.

Preparation of Cilnidipine Nanoparticles

Solvent evaporation method was employed to prepare Nanoparticles of Cilnidipine by using PVP K-30, and Pleuronic F68. Accurately weighed cilnidipine was dissolved in ethanol and added into the aqueous solution containing, different ratio (1:1, 1:2, 1:3 and 1:4) of PVP K-30, Pleuronic F68 (0.03%) and 40 mL water by using syringe needle positioned directly into surfactant solution. To evaporate the solvent, a magnetic stirrer was used to agitate the solution combination for 2 hr at 1000 rpm. The mixture was centrifuged for 30 min at 10,000 rpm in order to separate the precipitants from the supernatant and was dried andpulverized.[9] Seven such formulations were prepared and labeled as CNPF1 to CNPF7.

Characterization of nanoparticles

Percentage Yield

Nanoparticle yield was assessed by quantitatively comparing total mass of nanoparticles produced with cumulative mass of copolymer and drug components, below equation was used to find percentage yield of nanoparticles that were made.[10]

$$\% \text{ Yield} = \frac{\text{Weight of obtained nanoparticles}}{\text{Weight of drug and polymer together}} \times 100$$

Drug content

10 mg equivalent of prepared nanoparticles of Cilnidipine was dissolved in ethanol to extract drug from nanoparticles for each formulation. Spectrophotometer reading at 240 nm was taken from filtered solution after 2 hr and % drug content was calculated.[10]

$$\text{Drug content} = \frac{\text{Analysed drug weight}}{\text{Theoretical drug weight}} \times 100$$

Entrapment Efficiency

10 mg equivalent of Cilnidipine nanoparticles was centrifuged at 10000 rpm for 1 hr. Drug concentration in supernatant solution was measured at 240 nm using UV spectrophotometer following centrifugation. Quantification of Cilnidipine nanoparticles encapsulation was calculated by subtracting unbound quantity from overall amount present in dispersion.[11]

$$\text{EE (\%)} = \frac{\text{Total quantity of Cilnidipine} - \text{quantity of free Cilnidipine}}{\text{Total quantity of Cilnidipine}} \times 100$$

In vitro drug release

Drug release studies were conducted using USP Type II dissolving equipment. The study was conducted with nanoparticles carrying 10 mg of equivalent cilnidipine in 900 mL of dissolution fluid, a paddle rotating at 50 rpm, and a constant temperature of 37±0.5°C. 5 mL samples were withdrawn at designated time intervals and equivalent volume of media was then introduced to ensure consistent volume. Samples withdrawn were filtered by using whatman filter paper and 1 mL was taken out from the filtrate and subsequently made to final volume of 10 mL using buffer solution and analysed spectrophotometrically at 240 nm.[12]

Release kinetics

The collected data on drug release was subjected to release kinetics to find the drug release mechanism. It is utilized to characterize the release pattern of pharmaceutical substances from dosage forms. To explain overall drug release, kinetic models such as Zero order, First order, Higuchi, and Korsmeyer Peppas are applied. The results of *in vitro* release profile obtained for optimized formulation was plotted in kinetic models.

Particle size and Poly Dispersity Index (PDI)

Evaluation of size and distribution of particle is crucial when assessing nanoparticle systems.[13] Poly Dispersity Index (PDI) is used to report particle size distribution. Zeta sizernano ZS (Malvern Instruments Ltd., Malvern, UK) is utilized to evaluate particle size and Polydispersity index of cilnidipine nanoparticles.[14] The analyzer chamber is filled with samples, and values are taken while oblique to the incident beam at a 90° angle. For all measurements, disposable cuvettes with a 0.75 mL volume are utilized.[15]

Zeta potential

In order to describe the surface charge characteristics of nanoparticles, zeta potential is used.[11] Formulation CNPF4 was evaluated by measuring the zeta potential at 25±0.5°C by utilizing Zeta sizernano ZS (Malvern Instruments Ltd., Malvern, UK). Instrument is configured with potential of ±150 mV. All the measurements are conducted using disposable curettes with volume of 0.75 mL.[16,17]

Shape and morphology of surface

Scanning Electron Microscope (SEM) is widely employed for analysing morphology andsurface topography of drug delivery systems owing to its simple to use operation and simple sample handling. The surface's morphology and shape were done by SEM (JSM-T330A, JEOL). Small quantity of nanoparticulate solution was applied onto the brass stub used for electron microscopy. Stubs were temporarily subjected to drying and subsequently coated with gold using an ion sputtering technique. Nanoparticle photographs were taken by scanning stub at random. Shape and surface morphology were established based on photomicrographs.[18]

Transmission Electron Microscopy analysis (TEM)

TEM analysis is extensively used for characterization of materials, providing detailed information on shape, crystalline structure and elemental composition. This method employs quantitative techniques to ascertain shape, dimensions, morphology, crystalline structure, and elemental composition of formulation.[19]

X-ray Diffraction analysis (XRD)

This method is used to examine arrangement of atoms in materials, particularly those that are crystalline or partially crystalline, by using interference pattern of X-ray. XRD analyses were conducted to investigate solid-state properties and determine crystallographic arrangement of both drug and nanoparticles. X-ray diffraction pattern of drug and nanoparticles was examined employing powder X-ray diffractometer (PAN analytical). X-rays used were CuKα1 radiation filtered using Nickel filter, with energy of 40 kilovolts and scanning rate employed was maintained at $1°min^{-1}$ over 30mA over 0-90°/2θ range.[20]

RESULTS

The physicochemical characteristics of each produced nanoparticle formulation were examined, and the results of *in vitro* drug release tests are listed below.

Percentage yield

Practical yield percentage ranged from 61.6% to 70.2%. This variation is due to differences in concentration of polymer, losses during washing and centrifugation.

Drug content

Drug concentration of produced nanoparticles was assessed and discovered to fall within the specified range of 85.4% to 94.1%. CNPF4 formulation, made with 1:3 ratio of drug to polymer, exhibited greater drug content (94.1%) compared to other formulations.

Drug Entrapment efficiency

Nanoparticles that were prepared underwent evaluation for encapsulation efficiency across all seven formulations. It was determined that the EE ranged from 64.5% to 90.4%. The CNP F7 formulation exhibited greater encapsulation efficiency, specifically 90.4%, compared to the other formulations.

In vitro drug release

Study was done for the nanoparticle and the drug release from the CNPF1 formulation was 99.23% in 6 hr, CNPF2 was 98.02% in 8 hr, CNPF3was 99.48% in 10 hr, CNPF4 was 98.85% in 12 hr, CNPF5 was 83.74% in 12 hr, CNPF6 was 89.64% in 12 hr, CNPF7 was 87.31% in 12 hr and the results are shown in the Figure 1. Release of drug (98.85%) from the CNPF4 formulation was sustained over the period of 12 hr, may be due to high concentration of polymer (1:4). Dissolution release profile indicates that initial rapid drug release could be related to small size of nanoparticles with increased effective surface area, thus increase the solubility of the drug and due to the higher in the polymer concentration, drug release was sustained over the period of 12 hr.

Release Kinetics

Several kinetics models, including zero order kinetics, first order kinetics, Higuchi models, and Korsmeyer Peppas, were used to the *in vitro* dissolution data of the CNPF4 formulation. By using regression analysis, coefficient of correlation values for liner curves were determined from the plots. The r^2 value of Higuchi model was highest (0.9921), therefore, the prepared CNPF4

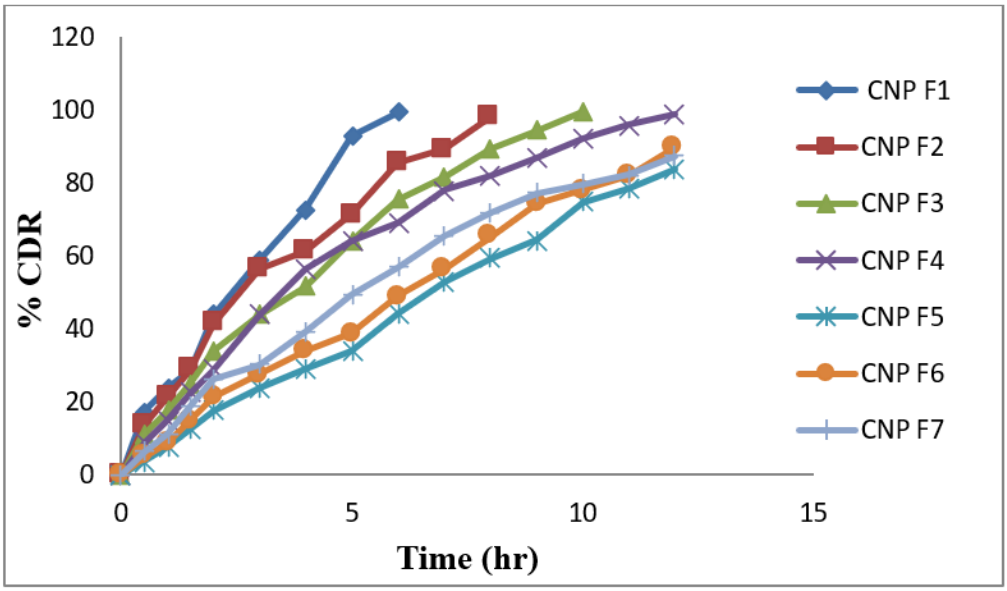

Figure 1: Dissolution Studies.

formulation followed diffusion model release kinetics with non-Fickian diffusion.

Particle size and polydispersity index

Sizes of particles have substantial impact on the physical, chemical and biological characteristics of nanoparticles. The average particle diameter and particle dispersion were used to characterize CNPF4 formulation. The measured particle size was determined to be 105.2 nm, while the Polydispersity index was recorded as 0.899. The particle size and polydispersity index of CNPF4 is displayed in Figure 2.

Zeta potential

Characterization of CNPF4 was done to determine how different concentrations of polymer and stabilizer influenced the surface charge of the nanoparticles. Zeta potential of formulation CNPF4 showed negative zeta potential (-13.8 mV) was shown in the Figure 3.

Shape and surface morphology

The surface morphology and shape of the CNPF4 formulation are examined using SEM analysis. Photographs of cilnidipine drug revealed that crystals with needle shaped, confirming the substance's crystalline composition. Nanoparticles showed a

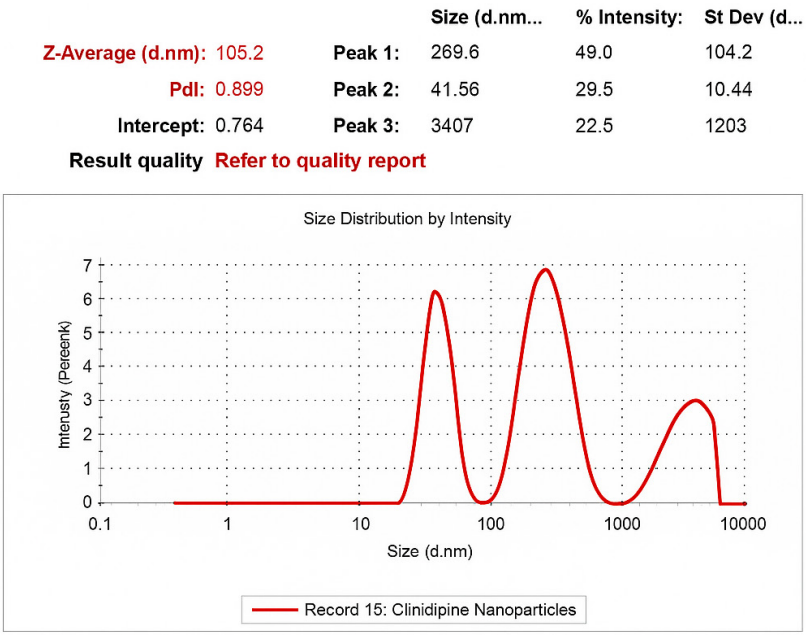

Figure 2: Particle size and size distribution of CNPF4.

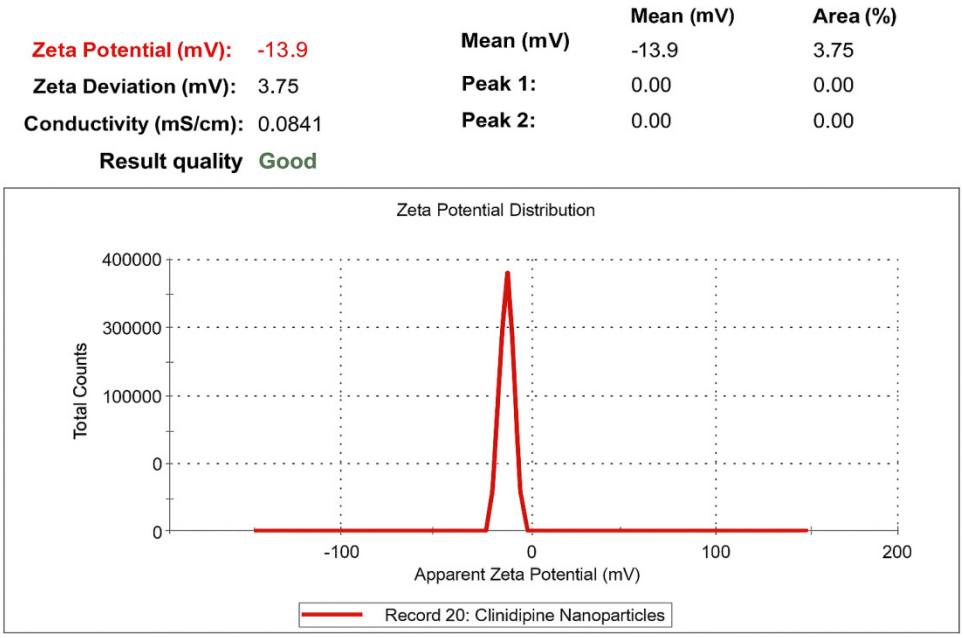

Figure 3: Zeta potential of CNPF4.

distance change in the shape and morphology, spherical form with generally consistent sizeand no crystals of drug were present. Nanoparticles of formulation CNPF4 has smooth and spherical shape with different sizes without aggregation was seen from the photographs shown in the Figure 4.

X-ray diffractometery

The X-ray diffractogram of the drug showed distinct peaks at 2θ angles of 12, 13, 18, 19, 23, 27 and 35°, indicating high degree of crystallinity for the medication (Figure 5a). Absence of distinct peaks in the nanoparticles CLN spectrum (Figure 5b) indicates that the drug was evenly distributed at a molecular level and maintained its structural integrity.

Transmission Electron Microscopic (TEM) study

TEM image revealed the presence of polymeric nanoparticles with a uniformly distributed smooth spherical surface. The outcome confirmed the particle size measurements obtained using light scattering. Morphology of nanoparticles was found to have a spherical shape and consistent size, as depicted in Figure 6.

DISCUSSION

Nanoparticle of cilnidipine is aimed to prepare by solvent evaporation method using different concentration of PVP K 30 and Pleuronic F68. Physico-chemical parameters, including particle size, polydispersible index, zeta potential, drug content, entrapment efficiency, shape and surface morphology, and drug release were assessed for the developed nanoparticles. Particle size was measured by using Malvern Zeta sizer and average size of the particle was discovered to be 105.2 nm. The zeta potential of cilnidipine nanoparticles showed a surface charge of -13.6 mV. The drug content of nanoparticles for all formulation ranges from 85.4% to 94.1%. The entrapment efficiencies varied from 85.4% to 94.1% and it was observed from the findings that increasing the concentration of both polymer and surfactant results with high entrapment efficiency. Shape and surface morphology was studied by SEM analysis and observed that the particles are spherical shape and showed smooth morphology. The drug release from the formulation CNPF1 was 99.23% in 6 hr, CNPF2 was 98.02% in 8 hr, CNPF3 was 99.48% in 10 hr, CNPF4 was 98.85%, CNPF5 was 83.74%, CNPF6 was 89.64% and CNPF7 was 87.31% in 12 hr indicates that decrease in the drug release due to increase in

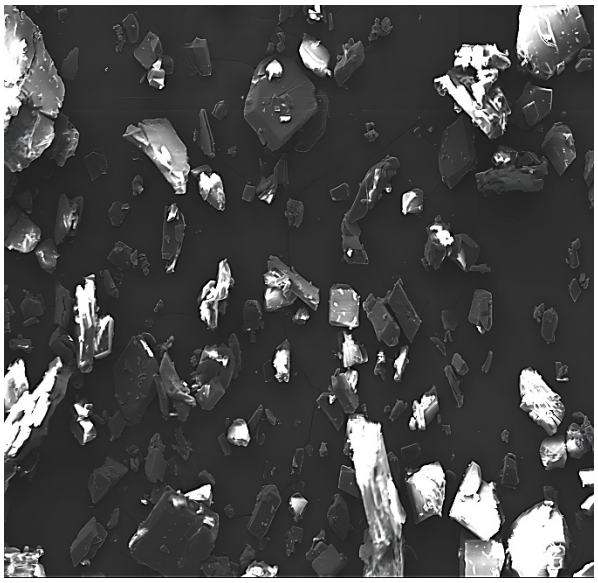

Figure 4: SEM Photomicrograph of CLN.

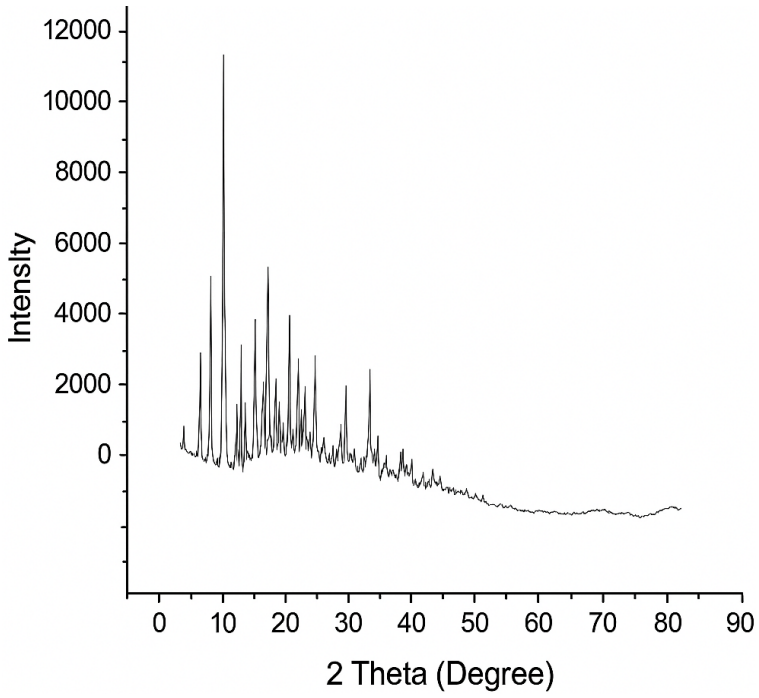

Figure 5a: X-ray diffract gram for CLN.

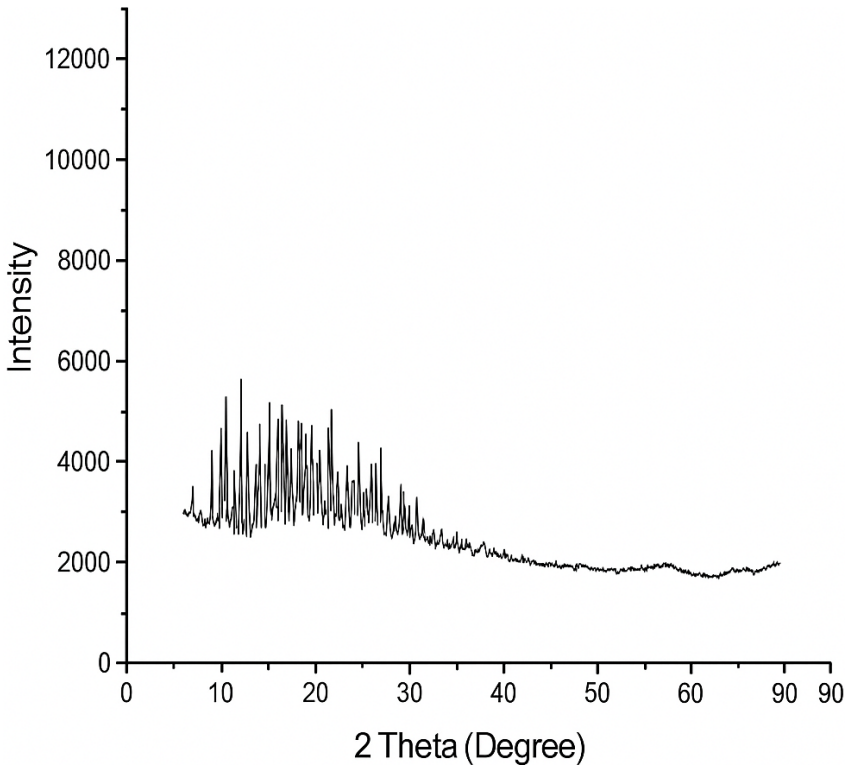

Figure 5b: X-ray diffract gram of CNP.

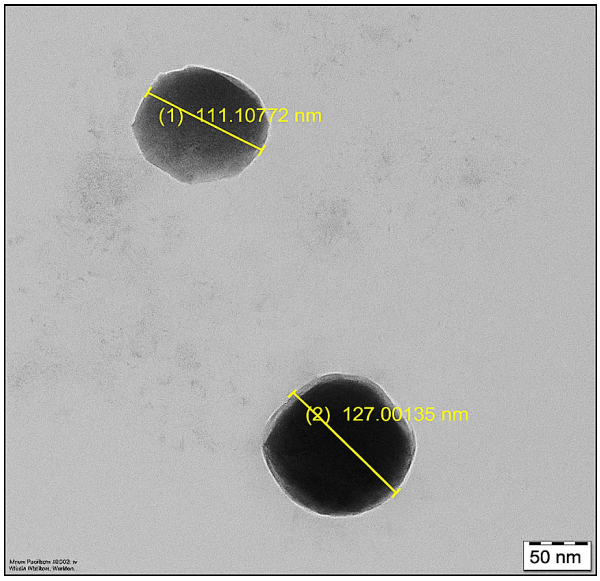

Figure 6: Image's scale bar represents 50 nm.

the amount of the polymer. Based on drug content, entrapment efficiency, particle size, zeta potential, and *in vitro* drug release experiments, CNPF4 was chosen as the optimal formulation. Kinetics of CNPF4 formulation showed diffusion model release kinetics with non-Fickian diffusion mechanism.

CONCLUSION

In the current study nanoparticles of cilnidipine is developed by solvent evaporation method to enhance solubility and dissolution of the drug. Since the nanoparticle's particle size was in the nanometer range, it is possible that the solubility may be improved. SEM analysis shows that the nanoparticles were spherical in shape and no drug crystals were present. The *in vitro* drug release studies showed that possibility of releasing the drug for prolong time period, this is may be due to increase in concentration of both polymer and surfactant. The drug release mechanism indicates that the prepared nanoparticles follows diffusion rate-controlled mechanism with non-Fickian diffusion. Hence, the nanoparticle prepared by solvent evaporation method was a useful for the incorporation of poorly water-soluble drug like cilnidipine. Hence, it was concluded that polymeric nanoparticles drug delivery system can be useful for enhance the solubility and bioavailability of cilnidipine.

ACKNOWLEDGEMENT

We acknowledge Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University and King Faisal University, Al-Ahsa, Saudi Arabiafor providing support to carry out the present work.

ABBREVIATIONS

nm: Nanometer; **mV:** Millivolts; **r^2:** Coefficient correlation; **mg:** Milligram; **mL:** Millilitre; **%:** Percentage; **PVP:** Poly Vinyl Pyrolidone; **rpm:** Rotation per minute; **hr:** Hour; **UV:** Ultra violet; **°C:** Degree Centigrade; **PAN:** Polyacrylonitrile; **min:** Minute.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the deanship of scientific research, vice presidency for graduate studies and scientific research, King Faisal University, Al-Ahsa, Saudi Arabia [Grant No.KFU252965].

SUMMARY

This study aimed to develop and evaluate Cilnidipine nanoparticles using the solvent evaporation method with PVP K30 and Pleuronic F68 in varying quantities. Prepared nanoparticles were evaluated for their size, polydispersity index, zeta potential, drug content, entrapment efficiency, morphology, drug release and stability. Drug content of cilnidipine loaded polymeric nanoparticles ranges from 85.4% to 94.1%, whereas drug entrapment efficiencies vary within similar range. Particle size of CNPF4 formulation was measured to be 105.2 nm and its zeta potential was measured to be -13.6 mV. Drug release has been estimated from all formulations and was found to be 83.74% to 99.48% and it was observed over an extended duration, showing that drug release decreased as the polymer concentration increased. Higuchi model yielded a r^2 value of 0.992, indicating that nanoparticles comply with diffusion rate-controlled process characterized by non-fickian diffusion. This investigation indicates that nanoparticles can extend the release of the drug, leading to increased therapeutic effectiveness and a decrease in dose-dependent side effects.

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Cite this article: Kuppan M, Joshi V, Chohan MS, Sreeharsha N. Formulation and Evaluation of Cilnidipine Loaded Nanoparticles for Enhanced Solubility. Indian J of Pharmaceutical Education and Research. 2026;60(2):532-8.