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Formulation and Evaluation of Nicardipine Hydrochloride Nanospheres

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Abstract: Nicardipine hydrochloride is a calcium channel blocker used in the treatment of hypertension and angina. However, its clinical efficacy is limited by poor aqueous solubility, low oral bioavailability, and a short half-life. To address these challenges, polymeric nanospheres were developed to enhance the stability of nicardipine and provide controlled drug release. Nicardipine-loaded nanospheres were prepared using the solvent evaporation method, employing the carrier polymer, stabilizer, and the emulsifier. The drug and polymer were dissolved in an organic solvent and emulsified in an aqueous phase under constant stirring. The solvent was then evaporated to form nanospheres. The prepared nanospheres were characterized for particle size, surface morphology, entrapment efficiency, and *in vitro* drug release. The resulting nanospheres exhibited a mean particle size of 1295 nm with a narrow size distribution. Scanning electron microscopy revealed smooth and spherical morphology. Drug entrapment efficiency was found to be 99%, and *in vitro* release studies showed a sustained release of nicardipine of over 99% at the end of 24 h. The optimized formulation followed zero-order kinetics. Nicardipine-loaded nanospheres prepared via the solvent evaporation method demonstrated favorable physicochemical properties and sustained drug release, indicating their potential as an effective delivery system to improve the bioavailability and therapeutic performance of nicardipine.

Keywords: Nicardipine, Nanospheres, Calcium channel blocker, *In vitro* drug release, Drug entrapment efficiency

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Introduction

Nicardipine hydrochloride is a dihydropyridine calcium channel blocker widely used for the treatment of hypertension and angina pectoris. Despite its therapeutic effectiveness, its clinical application is limited by poor aqueous solubility, extensive first-pass metabolism, and a short biological half-life. (Ghosh *et al.*, 2008; Quan *et al.*, 2022; Shanmugasundaram *et al.*, 2023). These pharmacokinetic limitations result in low oral bioavailability and necessitate frequent administration, which can lead to suboptimal therapeutic outcomes and reduced patient compliance.

To overcome these drawbacks, advanced drug delivery systems have been developed to improve the solubility, stability, and controlled release of poorly water-soluble drugs like nicardipine. Among these, polymeric nanospheres have emerged as a promising platform due to their ability to encapsulate hydrophobic drugs, protect them from degradation, and modulate the kinetics of drug release. (Mounika and Kumar 2021) Such systems can enhance bioavailability, reduce dosing frequency, and potentially enable targeted delivery (Pachpute, 2019; Buraphacheep and Boontida, 2025).

The solvent evaporation method is one of the most widely used techniques for the preparation of polymeric nanospheres (Sushma *et al.*, 2023). This method offers several advantages, including simplicity, scalability, and the ability to encapsulate lipophilic drugs efficiently. In this approach, the drug and polymer are dissolved in an organic solvent, which is then emulsified in an aqueous phase containing a stabilizer (Darji *et al.*, 2024). Upon evaporation of the organic solvent, solid nanospheres are formed with the drug entrapped within the polymer matrix (Rao and Gekeler, 2013).

In this study, nicardipine-loaded nanospheres were formulated using the solvent evaporation method to improve drug encapsulation, stability, and release characteristics. Biodegradable polymers were employed as carriers, and the resulting formulations were characterized in terms of particle size, morphology, entrapment efficiency, and *in vitro* drug release profiles. This research contributes to the development of an effective nanocarrier system for enhancing the delivery and therapeutic performance of nicardipine.

Materials and Methods

All the ingredients and chemicals (analytical grade) were obtained from Active Pharma Labs, Hyderabad, India.

UV Calibration Curve

Accurately weighed 10 mg nicardipine was solubilized by 10 ml of ethanol in a 100 ml volumetric flask with distilled water to make up the volume so as to give stock solution 100 µg/ml. The standard solutions are again diluted with water and ethanol to obtain various dilutions in standard volumetric flask. The dilutions were scanned in the wavelength of 200-400 nm.

Fourier Transform Infrared Spectroscopy (*FTIR*)

The infrared spectral matching tests were used to identify any potential drug interaction with the polymers or excipients.

Preparation of nicardipine nanospheres

The nanospheres were fabricated by using the solvent evaporation method.The calculated quantities of Hydroxy propyl cellulose and Chitosan were dissolved in Dichloro Methane (DCM) and prepared as aqueous phase, Polyvinyl alcohol and water were mixed and as organic phase. To the aqueous phase, the drug Nicardipine hydrochloride was added with continuous stirring. Finally, both phases were mixed slowly and homogenized for 30 min. The nanosponges were formed and are filtered, and dried. The nanospheres were stored in a desiccator for further use (Mansouri *et al.,* 2008). The composition is shown in Table 1.

Drug entrapment efficiency (*EE%*)

Nanospheres were centrifuged, washed, re-centrifuged and subsequently filtered. An aliquot from the supernatant is taken and diluted (Lingui *et al*., 2013). The free drug can be estimated from the filtrate using a UV-Visible spectrophotometer. The amount of entrapped drug was calculated by subtracting the amount of free drug from the total amount of drug added in the formulation (Fernandes *et al.*, 2002). Drug entrapment efficiency (EE) was calculated by using following formula:

$$EE\ \% = \frac{\text{Amount of entrapped drug}}{\text{Total amount of the drug added}} \times 100$$

In Vitro Release studies

The prepared nanospheres were placed in the

Table 1: Composition of nicardipine nanospheres

Formulation	F1	F2	F3	F4	F5	F6
Nicardipine	20 mg	20 mg	**20 mg**	20 mg	20 mg	20 mg
Ethyl Cellulose	100 mg	75 mg	**-**	75 mg	-	-
HPMC	-	25 mg	**100 mg**	-	-	75 mg
Chitosan	-	-	**-**	25 mg	100 mg	25 mg
PVA	10 mg	10mg	**10 mg**	10 mg	10mg	10 mg
DCM	10 ml	10 ml	**10 ml**	10 ml	10ml	10ml
Water	Q.S.	Q.S.	**Q.S.**	Q.S.	Q.S.	Q.S.

dialysis bag and immersed in 100 ml phosphate buffer saline (PBS) at pH 6.8. The entire system was kept at with continuous magnetic stirring. Samples were withdrawn from the receptor compartment at predetermined intervals (10, 20, 30, 40, 50, 60 min, and 24 h) and replaced by fresh medium. The samples were withdrawn and diluted to 10 ml with phosphate buffered saline, and the amount of drug dissolved was analysed by UV-spectrophotometer at 237 nm (Pachpute, 2019).

Particle size determination and Zeta Potential analysis

The average particle size and zeta potential of the nicardipine-loaded nanospheres were measured using a dynamic light scattering (DLS) technique with a Zetasizer Nano ZS (Malvern Instruments, UK). A diluted suspension of the nanospheres was prepared using double-distilled water and placed in a disposable cuvette for particle size analysis (Nishita and Kumar, 2021). Zeta potential measurements were carried out using folded capillary cells at 25 °C.

Scanning Electron Microscopy scanning (SEM)

The surface morphology and shape of the nanospheres were examined using scanning electron microscopy (SEM) (Kumar *et al.*, 2017; Betala *et al*., 2018)**.**

In Vitro drug release kinetics

The drug release kinetics data of the optimized formulation were fitted with zero-order kinetics, First-order kinetics, Higuchi's model, and Korsmeyer-Peppas model (Solunke *et al*., 2019).

Stability studies

The stability study was conducted as per ICH Guidelines and the percentage entrapment efficacy, percentage CDR were determined (Solunke *et al*., 2019).

Results and Discussion

Construction of the Calibration Curve of Nicardipine Hydrochloride

The correlation coefficient values were 0.9994, indicating excellent linearity of the data. The calibration curve obtained is shown in Table 2 and Figure 1.

Excipient compatibility studies

Fourier Transform Infrared (FTIR) Analysis

A drug-excipient compatibility study was carried

Table 2: UV Calibration graph of nicardipine

S. No.	Concentration µg/ml	Absorbance nm
1	10	0.1276
2	20	0.2514
3	30	0.3597
4	40	0.4917
5	50	0.6202

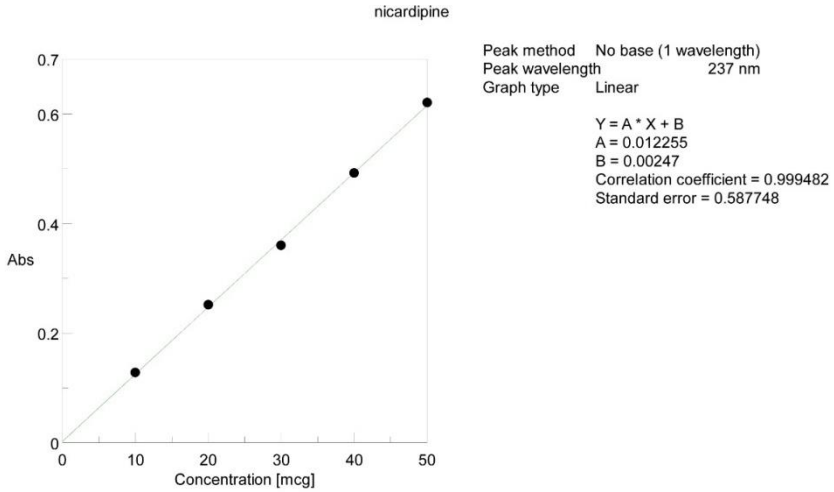

Fig. 1: UV Calibration graph of nicardipine.

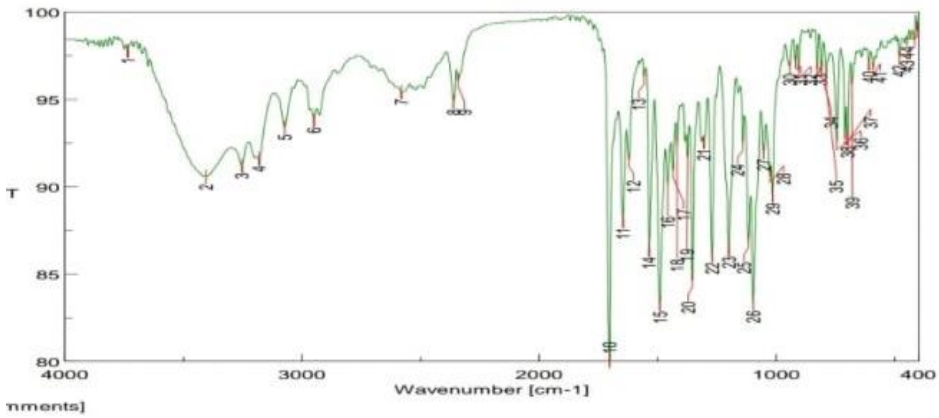

Fig. 2: FTIR spectrum of nicardipine hydrochloride.

out by FTIR analysis. The Pure drug of Nicardipine, physical mixture, and formulation were subjected to FTIR spectroscopy.

From the FTIR, various functional groups pure drug and the optimized formulation of nicardipine hydrochloride were identified (Figs. 2, 3). FTIR spectrum of optimized nicardipine hydrochloride formulation exhibited characteristic bands at 1353.78 cm $^{-1}$ represents NO_2, 1636.30 cm^{-1} represents C=C, 2975.32 cm^{-1}representing N-H, 1703.84 cm^{-1} represents C=O, 3070.41 cm^{-1}representing C-H, and showed that the characteristic peaks of nicardipine hydrochloride were not altered by the addition of excipients and

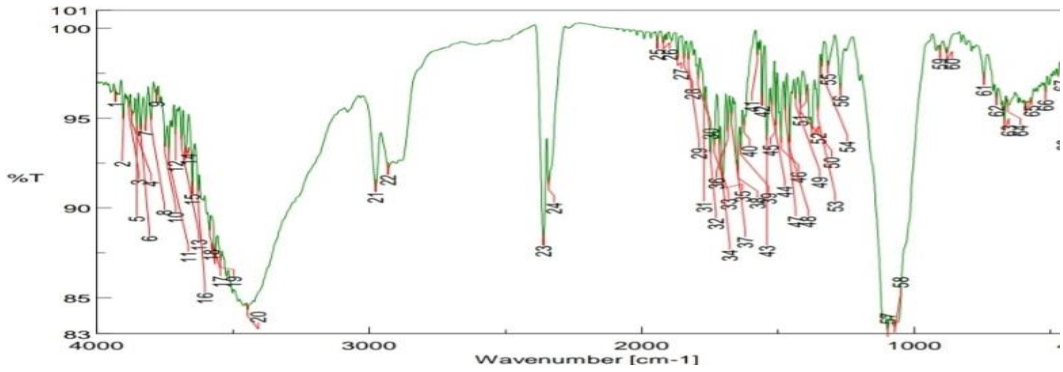

Fig. 3: FTIR spectrum of formulation.

Table 3: Drug Entrapment Efficacy

S. No.	Formulation	Drug entrapment efficacy
1	F1	74%
2	F2	83%
3	F3	99%
4	F4	80%
5	F5	78%
6	F6	84%

after formulation. From the spectra it was clear that there was no interaction between the drug and excipients.

Drug entrapment efficacy

The drug entrapment efficacy of F1 to F6 formulation were determined. It is found that in F3 formulation, (F3) has high entrapment efficacy than other formulation (Table 3).

Particle size determination

The particle size is one of the most important parameters for the characterization of nanoparticles. Nanoparticles are well-dispersed with a narrow size distribution. The average particle size of the formulated nanoparticles was measured using Malvern Zeta sizer. Particle size analysis showed that the average particle size of the nanoparticles was found to be 1295 nm. The results are shown in Figure 4.

Zeta potential determination

The Zeta potential of the synthesized Nanoparticles was recorded by Malven Zeta sizer. Nanoparticles, endowed with zeta potential values greater than +25mV or more negative than –25mV, repel each other and show no tendency to aggregate, thus affording high stability in water. The Zeta potential of the nanoparticles was found to be -5.86 and has good stability. The results are shown in Figure 5.

Scanning Electron Microscopy (SEM)

The prepared nanospheres were spherical and had a smooth surface as shown in Figure 6.

In-vitro Drug release profile

In-vitro drug release of Nicardipine nanospheres

The *in vitro* drug release study was conducted for all 6 formulations. From this study, the formulation (F3) showed increased drug release at the end of 24th h, due to the optimum concentration of polymer. The results are shown

Size Distribution Report by Intensity
v2.1

Malvern

Sample Details

Sample Name:	SAMPLE NICA SIZE 1		
SOP Name:	mansettings.nano		
General Notes:			
File Name:	ZETA AND PSA.dts	**Dispersant Name:**	Water
Record Number:	37	**Dispersant RI:**	1.330
Material RI:	1.59	**Viscosity (cP):**	0.8872
Material Absorbtion:	0.010	**Measurement Date and Time:**	Wednesday, February 19, 202...

System

Temperature (°C):	25.0	**Duration Used (s):**	60
Count Rate (kcps):	249.8	**Measurement Position (mm):**	4.65
Cell Description:	Disposable sizing cuvette	**Attenuator:**	11

Results

			Size (r.nm):	% Intensity	Width (r.nm):
Z-Average (r.nm):	1295	**Peak 1:**	322.1	77.0	45.66
PdI:	1.000	**Peak 2:**	35.26	23.0	4.578
Intercept:	0.888	**Peak 3:**	0.000	0.0	0.000
Result quality :	Refer to quality report				

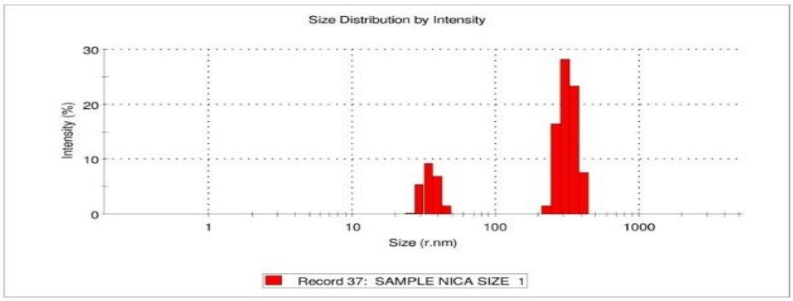

Fig. 4: Particle size determination.

Zeta Potential Report
v2.2

Malvern

Sample Details

Sample Name:	NICA ZETA 1		
SOP Name:	mansettings.nano		
General Notes:			
File Name:	ZETA AND PSA.dts	**Dispersant Name:**	Water
Record Number:	57	**Dispersant RI:**	1.330
Date and Time:	Wednesday, February 19, 2025 ...	**Viscosity (cP):**	0.8872
		Dispersant Dielectric Constant:	78.5

System

Temperature (°C):	25.0	**Zeta Runs:**	12
Count Rate (kcps):	541.2	**Measurement Position (mm):**	2.00
Cell Description:	Clear disposable zeta cell	**Attenuator:**	9

Results

			Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-5.68	**Peak 1:**	-5.68	100.0	4.95
Zeta Deviation (mV):	4.95	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm):	0.126	**Peak 3:**	0.00	0.0	0.00
Result quality :	Good				

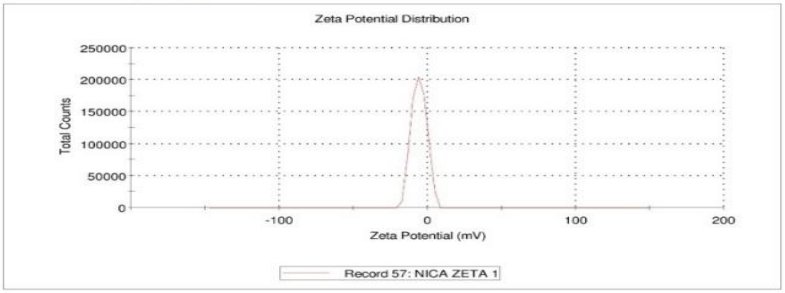

Fig. 5: Zeta Potential report.

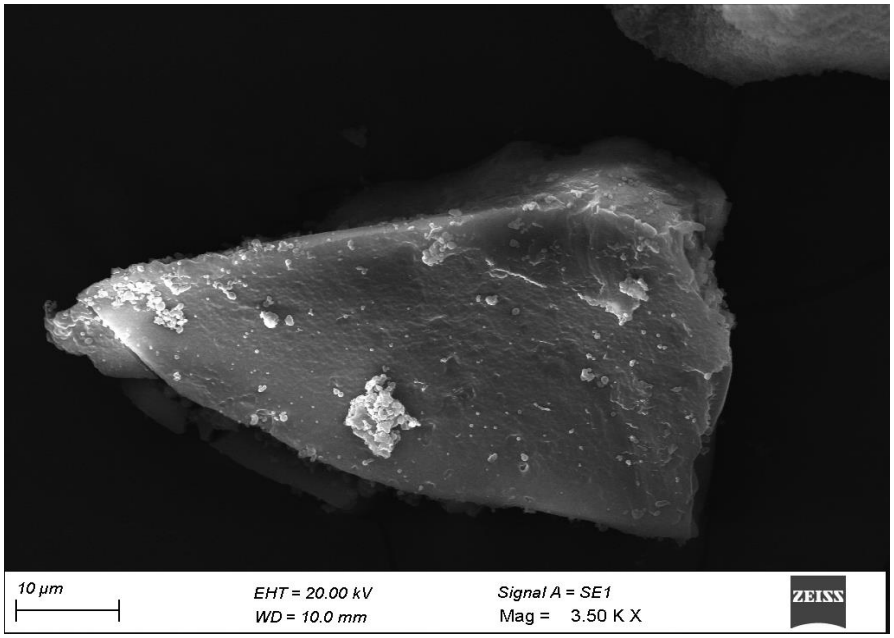

Fig. 6: Scanning Electron Microscope of prepared nanosperes.

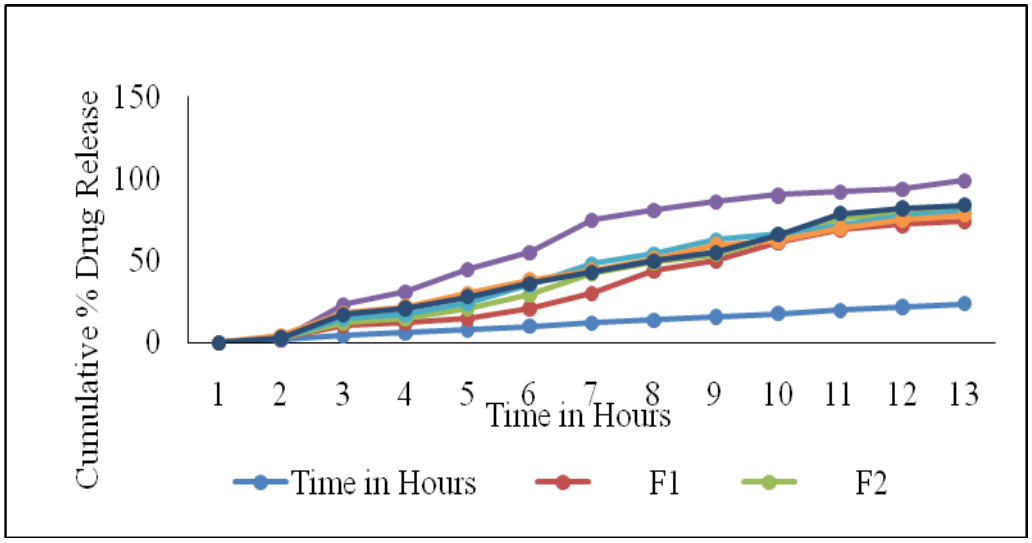

Fig. 7: *In vitro* drug release of nicardipine hydrochloride nanosphere**.**

in Figure 7.

In-vitro Drug release kinetics

Formulation

Zero Order

Time Vs Cumulative % drug release was plotted and is shown in Figure 8. From the graph R^2value was found to be 0.9328.

First Order

Time Vs Log Cumulative % drug release were plotted and is shown in Figure 9 From the graph R^2value was found to be 0.9058.

Higuchi's Model

The square root of time Vs Cumulative % drug release was plotted and is shown in Figure 10. From the graph R^2value was found to be 0.9369.

Korsmeyerpeppas

Log time Vs Log Cumulative % drug release were plotted and is shown in Figure11. From the graph R^2value was found 0.8632.

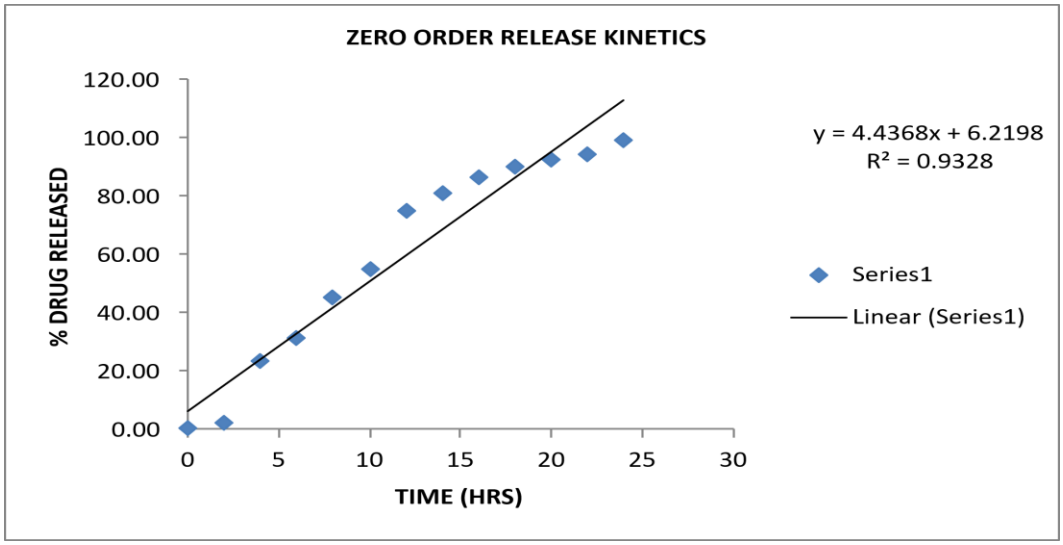

Fig. 8: Zero order.

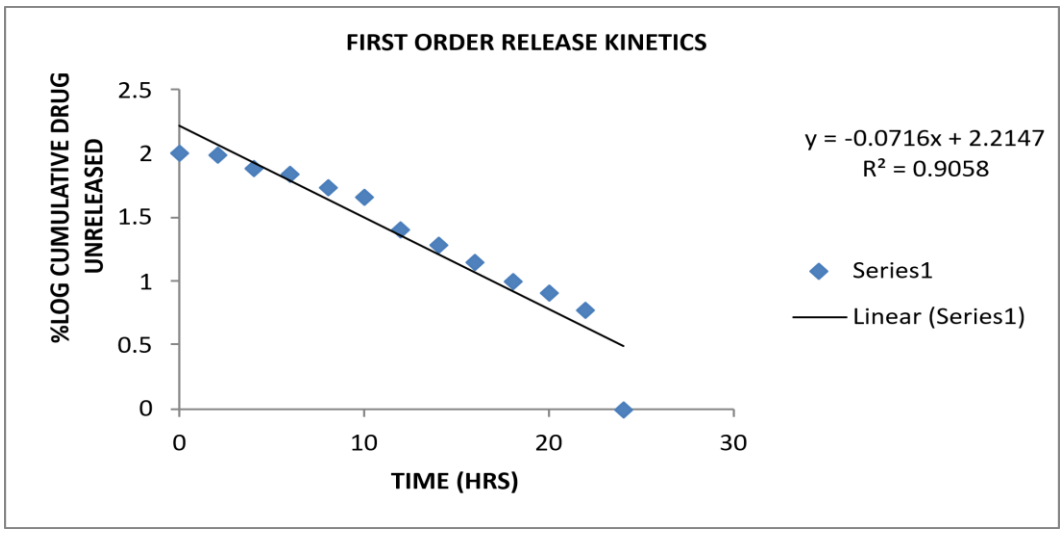

Fig. 9 : First order.

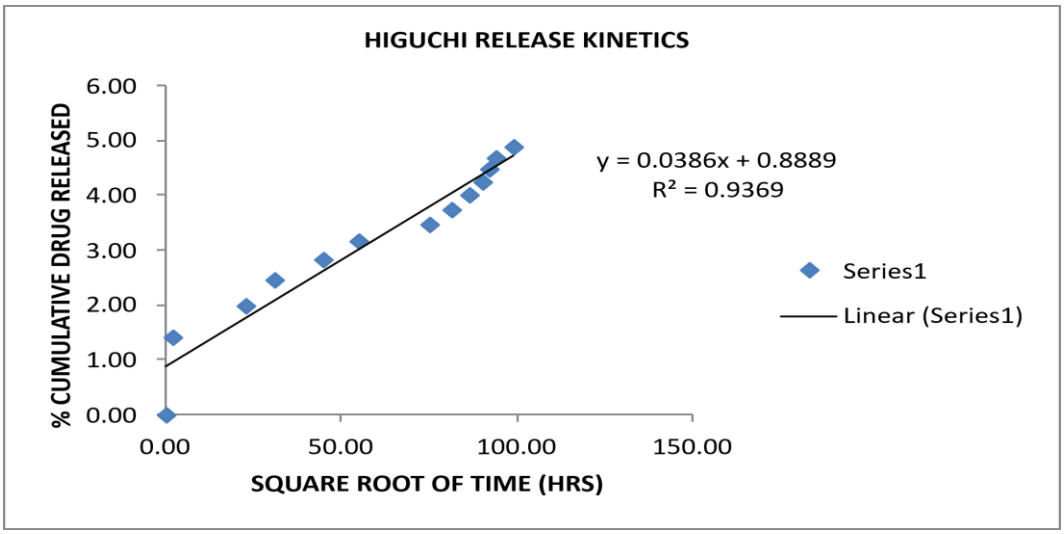

Fig. 10: Higuchi's model.

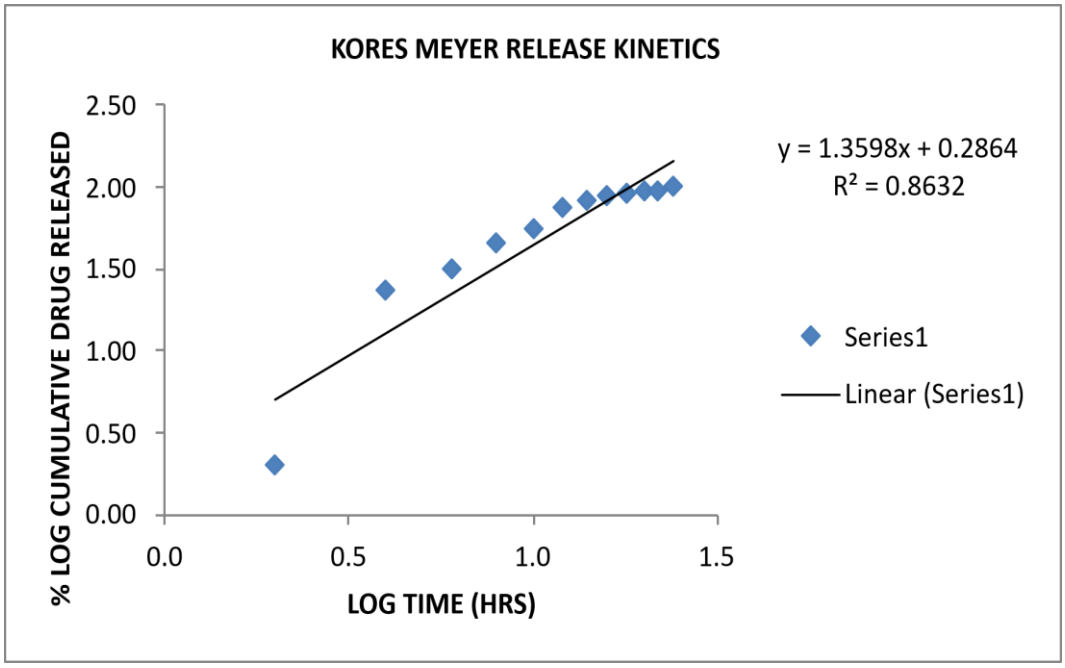

Fig. 11: Korsmeyerpeppas.

Table 4: Stability studies

Formulation	% Entrapment efficacy	%CDR
Before stability studies	98.67	98.70
After stability studies	98.21	98.34

It revealed that the release of the drug from optimized formulation followed zero order kinetics and the release was independent of concentration (Figs. 8-11). Higuchi model showed good linearity r^2= 0.9369, and the Peppas model implies that the formulation followed non-Fickian diffusion

Stability studies

The stability study was conducted percentage entrapment efficiency and percentage CDR were determined, and the results are shown in Table 4. From the results, there was no marked change observed during the stability study period.

Conclusion

In this study, nicardipine-loaded nanospheres were successfully formulated using the solvent evaporation method, employing ethyl cellulose as the carrier material. The method proved effective in producing nanospheres with desirable physico-chemical characteristics, including uniform particle size, high drug entrapment efficiency, and a sustained drug release profile. The encapsulation of nicardipine into polymeric nanospheres offers a promising strategy to overcome its inherent limitations, such as poor aqueous solubility and low oral bioavailability.

The *in vitro* results demonstrated that the nanosphere formulation could potentially maintain therapeutic drug levels over an extended period, which may reduce the frequency of administration and improve patient compliance. Overall, the solvent evaporation method is a simple and scalable technique suitable for the development of controlled-release nicardipine delivery systems.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval

not required.

Author Contributions

Each author has contributed equally in designing the research, conducting thorough analysis, drafting the manuscript, and refining its content. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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