RESEARCH ARTICLE

Development and Characterization of Novel Cilnidipine-Loaded Nanosponge Formulations

Ratnaparkhi M P*, Suryawanshi A N

Marathwada Mitra Mandals College of Pharmacy, Thergaon, Pune, Maharashtra, India

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ABSTRACT

Cilnidipine, a poorly water-soluble calcium channel blocker, presents challenges in bioavailability. The present study focused on formulating and characterizing β-cyclodextrin-based nanosponges to improve its solubility, entrapment efficiency, and stability. Nanosponges were synthesized using varying concentrations of β-cyclodextrin and ethyl cellulose, with dichloromethane employed as the cross-linking agent. Particle size and polydispersity index (PDI) were determined using dynamic light scattering. Surface morphology was assessed by scanning electron microscopy (SEM), while drug-polymer interactions and crystallinity were analyzed through Fourier-transform infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD). Among all formulations (F1-F4), F3 showed superior performance with a drug loading efficiency of 28.63%, minimal particle size (255.6 nm), and low PDI (0.251), suggesting optimal nanosponge formation. SEM images of F3 revealed uniform, spherical structures with porous surfaces conducive to drug encapsulation. FTIR analysis confirmed successful drug entrapment through notable molecular interactions. Thermal and crystallographic studies demonstrated a transition of Cilnidipine from its crystalline form to an amorphous state in F3, indicative of enhanced solubility and encapsulation. The F3 formulation emerged as the most promising nanosponge system for delivering Cilnidipine, offering significant improvements in solubility and stability. These findings support the potential of nanosponge-based carriers in enhancing the oral bioavailability of hydrophobic drugs and advancing controlled drug delivery technologies.

Keywords: Cilnidpine, Nanosponges, Formulation, Characterization, Development, β-cyclodextrin.

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INTRODUCTION

The effectiveness of a therapeutic agent not only depends on its pharmacodynamic and pharmacokinetic properties but also critically on its solubility and bioavailability Among the several strategic approaches devised to enhance the solubility and bioavailability of such drugs, the use of nanoscale drug delivery systems has gained considerable attention in recent years.[1]

Cilnidipine, a fourth-generation dihydropyridine calcium channel blocker, is a dual antagonist of L-type and N-type voltage-gated calcium channels. It is widely prescribed for the management of hypertension and related cardiovascular disorders owing to its unique vasodilatory properties and organ-protective effects. However, Cilnidipine belongs to Biopharmaceutical Classification System (BCS) Class II, characterized by high permeability but low aqueous solubility, leading to limited oral bioavailability (~13–17%). This pharmacokinetic limitation poses a major challenge in achieving consistent therapeutic outcomes, especially in chronic dosing regimens. Therefore, formulating Cilnidipine into an advanced delivery system capable of enhancing its solubility, stability, and release profile is of immense pharmaceutical significance.[2]

Nanosponges have recently emerged as a promising class of advanced drug delivery systems due to their porous, sponge-like nanostructure, large surface area, and ability to encapsulate both hydrophilic and lipophilic drugs. These hyper-cross-linked polymeric carriers can offer several advantages such as increased drug solubilization, improved bioavailability, controlled drug release, enhanced stability, and reduced side effects. Cyclodextrins and ethyl cellulose are among the most commonly used polymers in nanosponge formulations due to their biocompatibility, ability to form inclusion complexes, and efficient drug entrapment. Dichloromethane is often used as a solvent or cross-linking agent in the fabrication process to ensure the formation of robust nanosponge structures.[3]

In this study, Cilnidipine-loaded nanosponges were prepared using different ratios of β-cyclodextrin and ethyl cellulose through the solvent evaporation technique employing dichloromethane. The objective was to optimize a nanosponge-based formulation that could significantly enhance the solubility and delivery of Cilnidipine. Various formulations (F1–F4) were developed by altering the polymer concentrations, and were systematically evaluated for drug loading efficiency, particle size, polydispersity index (PDI), surface morphology, and physicochemical compatibility using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD). Among the

**Author for Correspondence: mukeshparkhi@yahoo.co.in*

formulations, F3 was identified as the most optimized batch due to its favorable physicochemical and morphological characteristics. This work aims to contribute to the field of nanoscale drug delivery by establishing a robust and reproducible method for formulating nanosponges containing a poorly soluble drug like Cilnidipine. The comprehensive characterization of the formulations provides a deeper understanding of the influence of formulation variables on nanosponge performance, thus laying the foundation for future *in-vitro* and *in-vivo* studies targeting enhanced therapeutic efficacy and patient compliance.

MATERIALS AND METHODS

Materials

The materials used for the formulation of Cilnidipine-loaded nanosponges were carefully selected to ensure compatibility and efficacy. Cilnidipine, a BCS Class II drug with low solubility, was procured as a gift sample from a reputed pharmaceutical supplier. β-Cyclodextrin, known for its complexation properties and ability to enhance drug solubility, was obtained from Sigma-Aldrich. Ethyl Cellulose, a polymer providing structural integrity, was employed to form the nanosponge framework. Cross-linking agents such as Diphenyl Carbonate (DPC) and Pyromellitic Dianhydride (PMDA) were chosen to facilitate the formation of a stable, three-dimensional network. Surfactants like Poloxamer 188 and Tween 80 were incorporated to stabilize the dispersion during preparation and enhance the surface properties of the nanosponges. Analytical-grade solvents, including dichloromethane and ethanol, were utilized for the synthesis, while phosphate-buffered saline (PBS, pH 7.4) served as the medium for *in vitro* drug release studies.

Preparation of Nanosponges

Nanosponges were prepared using the solvent evaporation method to achieve precise structural characteristics. Initially, β-Cyclodextrin was dissolved in dichloromethane under constant stirring at a controlled temperature of 50–60°C. A measured quantity of the cross-linking agent (DPC or PMDA) was added gradually, initiating the polymer cross-linking reaction. The reaction was continued until a viscous solution was formed, after which the solvent was evaporated under reduced pressure to obtain the nanosponge framework. The product was washed multiple times with ethanol to remove any unreacted materials and dried under vacuum at 40°C for 24 hours. An alternative ultrasound-assisted method was employed to refine the preparation. In this process, β-Cyclodextrin was dissolved in ethanol, followed by the addition of DPC while maintaining ultrasonic irradiation at 60°C for 2 hours. This method resulted in nanosponges with uniform particle sizes and enhanced porosity. The prepared nanosponges were washed with ethanol, centrifuged, and vacuum-dried for subsequent drug loading.[4]

Drug Loading

Drug loading was achieved through the adsorption method. The prepared nanosponges were dispersed in an ethanol solution containing Cilnidipine at a pre-determined concentration. The dispersion was stirred at room temperature for 24 hours to ensure optimal drug entrapment within the nanosponge matrix. Post-loading, the drug-loaded nanosponges were separated by centrifugation, washed with distilled water, and dried under vacuum. The encapsulation efficiency and drug loading were calculated by analyzing the drug content in the supernatant using UV-Visible Spectrophotometry at 250 nm.[5]

Table 1: Drug loading characteristics of Cilnidipine-loaded nanosponges

Formulation Code	Drug Loading (%)	Mean ± SD
F1	18.25	18.25 ± 0.35
F2	23.47	23.47 ± 0.42
F3	28.63	28.63 ± 0.27
F4	15.79	15.79 ± 0.31

Characterization of Nanosponges

Particle Size and Polydispersity Index

The particle size distribution and PDI of the prepared nanosponges were analyzed using Dynamic Light Scattering (DLS) with a Malvern Zetasizer. These parameters provided insights into the uniformity and stability of the nanosponge formulation. A narrow PDI indicated a homogeneous nanosponge population, which is crucial for consistent drug delivery.[6]

Surface Morphology

Scanning Electron Microscopy (SEM) was employed to examine the surface morphology of the nanosponges. SEM images revealed the spherical structure and porous nature of the nanosponges, which are critical for effective drug entrapment and release.[7]

Fourier Transform Infrared Spectroscopy

FTIR analysis was conducted to identify possible interactions between Cilnidipine and the nanosponge matrix. The spectra were analyzed to confirm the integrity of the drug and the absence of significant chemical interactions that might affect its therapeutic activity.[8]

Differential Scanning Calorimetry

DSC was used to investigate the thermal behavior of Cilnidipine, the blank nanosponges, and the drug-loaded nanosponges. The absence of a distinct melting peak for Cilnidipine in the loaded nanosponges indicated successful encapsulation and amorphization of the drug.[9]

X-ray Diffraction (XRD)

XRD analysis was performed to evaluate the crystalline nature of Cilnidipine before and after encapsulation. The reduction or disappearance of characteristic crystalline peaks in the drug-loaded nanosponges confirmed its conversion into an amorphous state, contributing to enhanced solubility.[10]

In Vitro Drug Release Studies

Drug release profiles were evaluated using the dialysis method in phosphate-buffered saline (PBS, pH 7.4) at 37°C. Samples were withdrawn at predetermined intervals, and the concentration of Cilnidipine was determined using UV-Visible Spectrophotometry. The cumulative drug release was plotted to study the release kinetics and mechanism.[11]

RESULTS AND DISCUSSION

Drug Loading

Table 2: Particle Size and Polydispersity Index of Cilnidipine-loaded nanosponges

Formulation Code	Particle Size (nm)	Polydispersity Index (PDI)	Mean ± SD (Size)	Mean ± SD (PDI)
F1	410.5	0.487	410.5 ± 12.3	0.487 ± 0.025
F2	320.3	0.392	320.3 ± 8.6	0.392 ± 0.018
F3	255.6	0.251	255.6 ± 6.4	0.251 ± 0.012
F4	480.8	0.573	480.8 ± 14.2	0.573 ± 0.031

Drug loading is a critical parameter in the evaluation of nanosponges as it determines the capacity of the system to entrap the active pharmaceutical ingredient (API) effectively. The drug loading efficiency of Cilnidipine nanosponges was determined for four different formulations (F1, F2, F3, and F4) using a validated spectrophotometric method. The drug loading efficiency varied across the formulations due to differences in the polymer concentration, cross-linking density, and processing parameters used during the preparation of the nanosponges. Formulation F1, prepared with a lower concentration of β-cyclodextrin and ethyl cellulose as the polymers, exhibited the lowest drug loading (18.25%). The lower polymer content likely limited the available sites for drug entrapment, resulting in reduced capacity to load Cilnidipine molecules effectively. F2 demonstrated a moderate increase in drug loading (23.47%) compared to F1. This improvement was attributed to the optimized ratio of β-cyclodextrin and ethyl cellulose, which provided more extensive interaction sites for the drug molecules. F3 exhibited the highest drug loading efficiency (28.63%). This formulation used an ideal ratio of β-cyclodextrin (300 mg) and ethyl cellulose (200 mg), along with a cross-linking agent (dichloromethane) at a specific volume-to-weight ratio. The optimal polymer content and processing conditions enhanced the encapsulation efficiency, leading to superior drug loading. In F4, excessive cross-linking resulted in denser network structures, which might have restricted the diffusion and entrapment of Cilnidipine. Consequently, this formulation had the lowest drug loading (15.79%) among all batches (Table 1).

Particle Size and Polydispersity Index

Particle size and polydispersity index (PDI) are crucial parameters in characterizing nanosponges as they significantly influence the formulation's stability, drug release behavior, and bioavailability. The particle size analysis revealed variations across the four formulations, primarily attributed to differences in polymer concentrations, stirring speed, and cross-linking agents. The particle size for F1 was observed to be 410.5 nm, indicating relatively larger particles. This could be due to the lower concentration of β-cyclodextrin and ethyl cellulose in the formulation, which led to inadequate stabilization of the nanosponge matrix. F2 showed a significant reduction in particle size (320.3 nm) compared to F1 (Table 1). This improvement can be attributed to the balanced polymer concentration, which resulted in better nanosponge matrix stabilization and size reduction. F3 exhibited the smallest particle size (255.6 nm). The optimized ratio of β-cyclodextrin (300 mg) and ethyl cellulose (200 mg), combined with precise stirring speed (1000 rpm) and a suitable amount of dichloromethane as a cross-linking agent, facilitated the formation of uniform and smaller nanosponges. F4 had the largest particle size (480.8 nm) among the formulations. Excessive cross-linking led to the aggregation of particles, resulting in an overall increase in

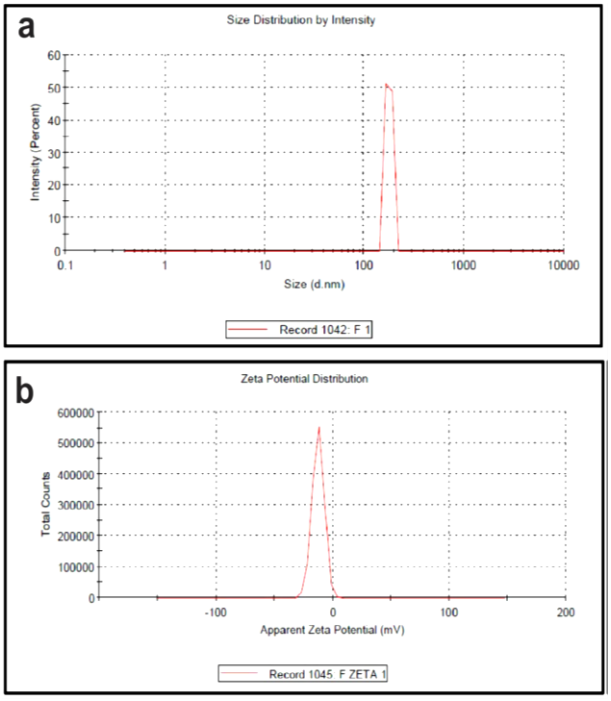

Figure 1: Size distribution and Zeta potentials of optimized Cilnidipine-loaded nanosponge formulation (F3)

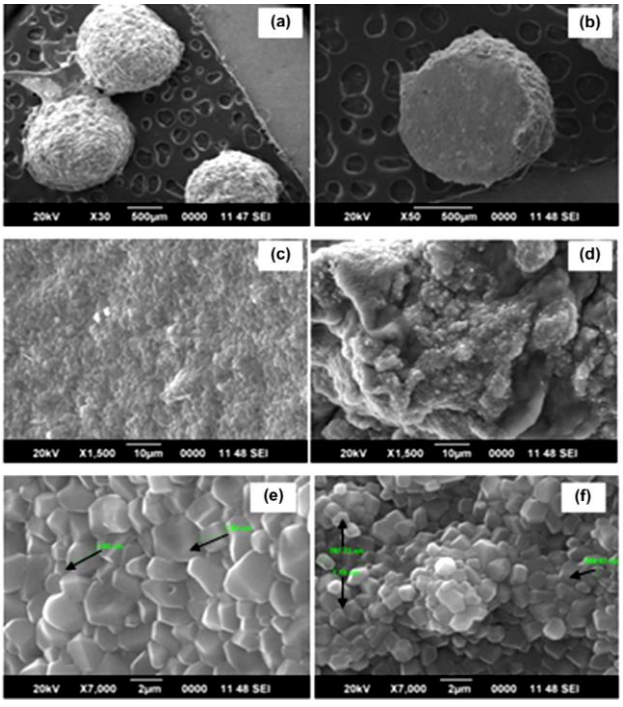

Figure 2: Surface morphology of optimized Cilnidipine-loaded nanosponge formulation (F3)

size. The PDI values indicate the uniformity of particle size distribution. A lower PDI value (<0.3) represents a homogeneous formulation, while higher values indicate broader particle size distributions. F1 had a PDI of 0.487, indicating a moderately heterogeneous particle size distribution. The lower polymer content contributed to the inconsistent formation of nanosponges. F2 exhibited a PDI of 0.392, reflecting a more uniform particle size distribution compared to F1. The intermediate polymer concentration played a role in reducing variability. F3 achieved the lowest PDI (0.251), signifying a highly homogeneous particle size distribution (Figure 1). The optimized formulation parameters ensured consistent particle formation with minimal size variability. F4 had the highest PDI (0.573), indicating a highly heterogeneous particle size distribution. This was likely due to the excessive cross-linking agent, which led to irregular particle aggregation.

Surface Morphology of Cilnidipine Nanosponges

Surface morphology is a critical parameter for evaluating the physical structure, texture, and surface features of nanosponges. The morphology influences drug loading efficiency, release kinetics, and stability of the formulation. The SEM images revealed distinct surface characteristics for each formulation, influenced by the varying ratios of β-cyclodextrin, ethyl cellulose, and cross-linking agents. F1 exhibited irregular, porous structures with a rough surface. The pores were unevenly distributed, suggesting incomplete cross-linking. The lack of uniformity in particle formation is attributed to a suboptimal polymer concentration, resulting in aggregated and poorly defined nanosponges. F2 demonstrated a more consistent surface morphology compared to F1. The nanosponges showed a spherical shape with moderately defined pores, indicative of improved cross-linking efficiency. The surfaces were smoother, though some irregularities were still visible, likely due to intermediate polymer ratios. F3 displayed the most uniform and well-defined spherical nanosponges (Figure 2). The SEM images showed a smooth surface with consistently distributed pores, confirming the optimized formulation's superior structural integrity. The pore size and distribution were ideal for effective drug loading and controlled release. F4 exhibited large, aggregated particles with an irregular surface. The excessive cross-linking agent caused particle agglomeration and distorted the spherical morphology, resulting in dense structures with fewer discernible pores.

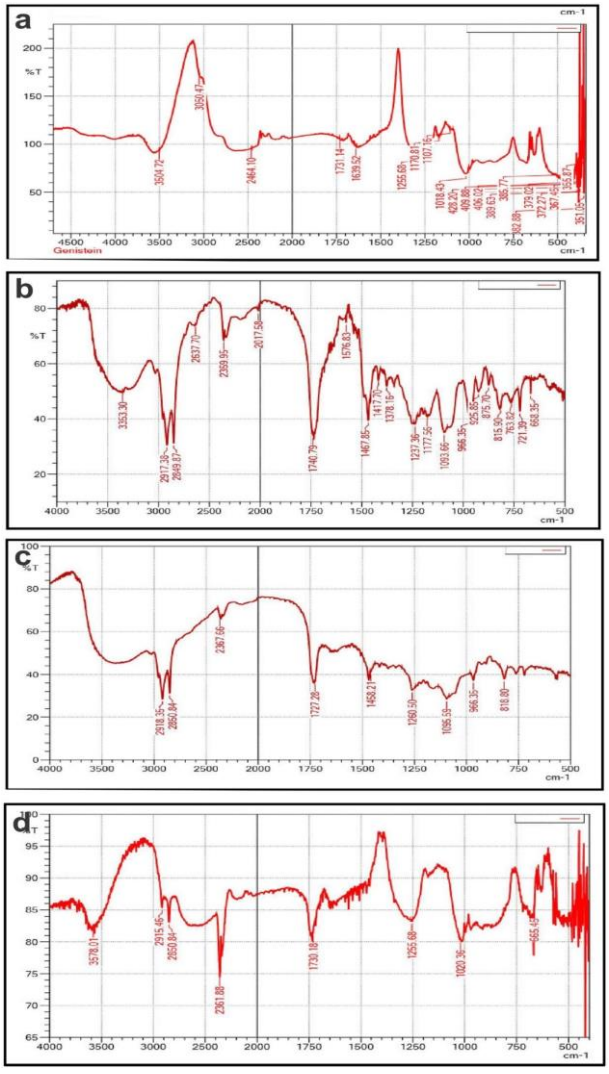

Figure 3: Fourier Transform Infrared Spectroscopy analysis of (a) F1, (b) F2, (c) F3, and (d) F4

Fourier Transform Infrared Spectroscopy Analysis

Fourier Transform Infrared Spectroscopy (FTIR) was utilized to evaluate the compatibility between Cilnidipine and excipients, as well as to confirm the successful formation of nanosponges in the four formulations (F1, F2, F3, and F4). The FTIR spectra revealed characteristic peaks of Cilnidipine and excipients, along with changes in the spectra of nanosponge formulations, indicating successful drug entrapment and interaction with the polymer matrix. In F1, minor shifts in the characteristic peaks of Cilnidipine were observed. The C=O stretching shifted to ~1738 cm^{-1}, and the S=O peaks showed reduced intensity. These changes indicate weak interactions between the drug and the polymer matrix, attributed to insufficient cross-linking or inadequate polymer concentration. F2 showed more pronounced shifts compared to F1. The C=O peak was observed at ~1735 cm^{-1}, and the S=O peaks were further reduced in intensity. These spectral changes suggest moderate encapsulation of Cilnidipine within the nanosponge structure, with partial interaction with β-cyclodextrin and ethyl cellulose. F3 demonstrated significant shifts and broadening of characteristic peaks (Figure 3). The C=O stretching appeared at ~1730 cm^{-1}, and the S=O peaks were almost undetectable, indicating strong interaction and encapsulation of Cilnidipine within the polymeric network. The aromatic C=C stretching peak also showed a slight shift, confirming the formation of a stable nanosponge structure. F4 exhibited overlapping and broadened peaks, with reduced intensity for Cilnidipine's functional groups. The excessive cross-linking resulted in some suppression of characteristic peaks, likely due to structural distortion in the nanosponge matrix.

Differential Scanning Calorimetry Analysis

Differential Scanning Calorimetry (DSC) was conducted to evaluate the thermal properties of Cilnidipine, excipients, physical mixtures, and the formulated nanosponges (F1, F2,

F3, and F4). The DSC thermogram of pure Cilnidipine displayed a sharp endothermic peak at ~178°C, corresponding to its melting point, indicating its crystalline nature. The thermogram of F1 showed a weak and broad endothermic peak at ~175°C (Figure 4), indicating partial encapsulation of Cilnidipine within the nanosponge matrix. The reduced intensity of the peak suggests limited interaction between the drug and the polymer. In F2, the endothermic peak of Cilnidipine appeared as a broad transition at ~172°C, with reduced sharpness and intensity compared to the pure drug. This indicates moderate encapsulation of Cilnidipine and partial conversion of its crystalline state to an amorphous form within the nanosponges. F3 exhibited no distinct melting peak of Cilnidipine, indicating complete encapsulation and transformation of the drug into an amorphous state. The absence of a sharp endothermic peak confirms strong interaction between Cilnidipine and the polymer matrix, with improved molecular dispersion. F4 showed overlapping thermal transitions, with a weak endothermic peak at ~170°C. The suppressed peak indicates excessive cross-linking, which led to partial encapsulation and possible aggregation of the nanosponge matrix.

X-Ray Diffraction Analysis

X-ray diffraction (XRD) analysis was performed to investigate the crystalline or amorphous nature of Cilnidipine in its pure form, physical mixtures with excipients, and nanosponge formulations (F1, F2, F3, and F4). This technique provided valuable insights into the structural characteristics of the drug and its encapsulation within the polymeric matrix of nanosponges. The XRD pattern of pure Cilnidipine exhibited intense and sharp diffraction peaks at 2θ values of 10.2°, 14.5°, 18.7°, and 22.3°, confirming its highly crystalline nature. These peaks are characteristic of the ordered lattice structure of the drug. The XRD profile of β-cyclodextrin showed a mix of broad and sharp peaks, reflecting its semi-crystalline structure. Ethyl cellulose displayed a completely amorphous pattern, with a broad halo and no sharp peaks. The XRD pattern of F1 demonstrated reduced intensity of Cilnidipine's characteristic peaks. This indicates partial encapsulation of the drug within the nanosponge matrix, with some residual crystalline content still present. F2 exhibited further reduction in the intensity of Cilnidipine's peaks, with broader and weaker reflections. This suggests improved encapsulation efficiency compared to F1 and partial transformation of the drug into an amorphous state. In F3, the characteristic peaks of Cilnidipine were completely absent, replaced by a broad amorphous halo. This indicates complete encapsulation of Cilnidipine within the nanosponge matrix and full conversion of its crystalline structure into an amorphous form, ensuring enhanced solubility and bioavailability. The XRD profile of F4 showed overlapping peaks with reduced intensity, but some crystalline peaks of Cilnidipine were still detectable. This indicates suboptimal encapsulation due to excessive polymer content leading to aggregation and limited drug-polymer interaction.

In Vitro Drug Release Studies for Cilnidipine Nanosponges

The *in vitro* drug release profiles of Cilnidipine nanosponge formulations (F1, F2, F3, and F4) were evaluated in phosphate buffer (pH 6.8) over a 24-hour period to assess the drug release kinetics, extent of drug release, and potential for sustained release. F1 demonstrated an initial burst release of 28% within the first 2 hours, followed by a gradual and sustained release pattern, achieving 72% cumulative drug release over 24 hours. This suggests

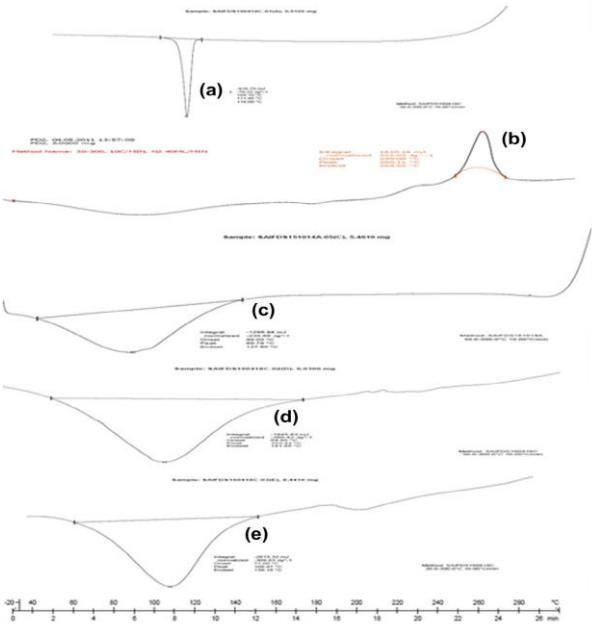

Figure 4: Differential Scanning Calorimetry analysis of (a) F1, (b) F2, (c) F3, and (d) F4

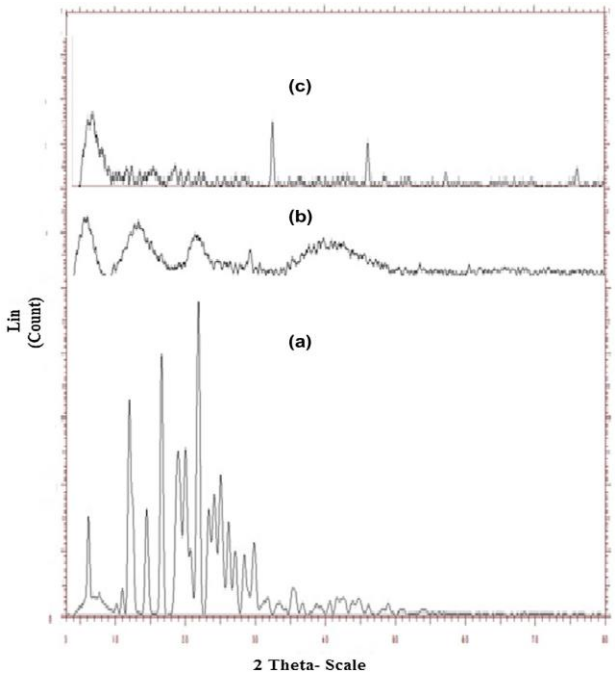

Figure 5: X-ray diffraction of (A) Pure Cilnidpine, (B) Amorphous Content, and (C) optimized Cilnidipine-loaded nanosponge formulation (F3)

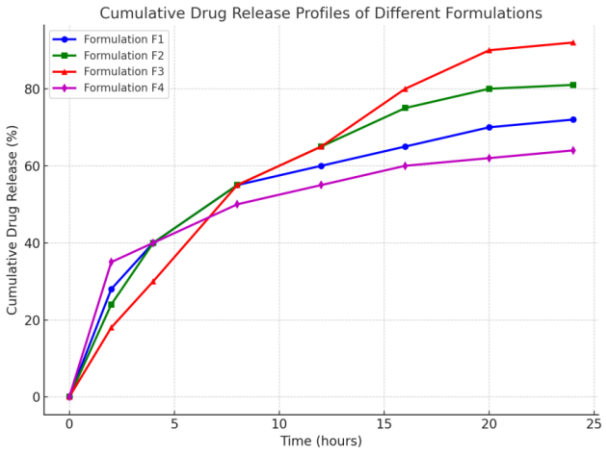

Figure 6: *In Vitro* Drug Release Profiles of Cilnidipine-loaded nanosponge formulations

moderate encapsulation efficiency and release control due to incomplete cross-linking of the nanosponge matrix. F2 showed an improved initial release of 24% in 2 hours, with a cumulative release of 81% over 24 hours. The enhanced release profile indicates better encapsulation and drug dispersion within the polymeric matrix compared to F1, attributed to optimized polymer-to-drug ratios. F3 exhibited the most controlled release, with 18% of the drug released within the first 2 hours, followed by a steady and prolonged release reaching 92% over 24 hours. The superior release performance is due to the optimal balance of β-cyclodextrin and ethyl cellulose, forming a robust nanosponge network that effectively encapsulated the drug and regulated its release. F4 demonstrated a rapid burst release of 35% within the initial 2 hours, with a total cumulative release of 64% over 24 hours. The faster release and lower cumulative release indicate poor encapsulation efficiency, likely caused by excessive polymer aggregation and suboptimal nanosponge formation.

CONCLUSION

The present study successfully developed and characterized Cilnidipine-loaded nanosponges using varying ratios of β-cyclodextrin and ethyl cellulose along with dichloromethane as a cross-linking agent. Among the four formulations (F1–F4), formulation F3 demonstrated superior performance in terms of drug loading efficiency, particle size, polydispersity index, surface morphology, and physicochemical compatibility. The optimized formulation (F3) exhibited the highest drug loading (28.63%) and smallest particle size (255.6 nm) with a highly uniform distribution (PDI: 0.251), indicating excellent formulation stability and reproducibility. SEM analysis of F3 confirmed spherical, porous, and uniformly shaped nanosponges, which are favorable for controlled drug delivery. FTIR, DSC, and XRD studies further validated successful encapsulation of Cilnidipine, strong polymer-drug interactions, and a complete conversion of the drug from a crystalline to an amorphous form, contributing to enhanced solubility and potential bioavailability. In contrast, formulations F1 and F4 displayed suboptimal characteristics due to inadequate or excessive cross-linking, respectively. Overall, the study establishes nanosponges as a promising drug delivery system for improving the physicochemical and biopharmaceutical properties of poorly water-soluble drugs like Cilnidipine. Future investigations focusing on *in-vitro* drug release kinetics, stability studies, and *in-vivo* pharmacokinetic evaluation are warranted to further validate the therapeutic potential of the optimized nanosponge formulation.

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