Advances in Bioresearch
Adv. Biores., Vol 16 (6) November 2025: 33-45
©2025 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.6.3345

Advances in Bioresearch

ORIGINAL ARTICLE

Formulation and Characterization of Clopidogrel Bisulfate-Loaded Nanosponges for Enhanced Solubility and Sustained Oral Delivery

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ABSTRACT
Clopidogrel bisulfate (CPB) is a widely prescribed antiplatelet agent for cardiovascular disorders but suffers from poor solubility, low oral bioavailability, and stability issues, limiting its therapeutic potential. To overcome these challenges, CPB-loaded nanosponges were developed using ethyl cellulose and polyvinyl alcohol via the emulsion solvent diffusion method. Formulations were optimized using Box-Behnken design to evaluate the influence of polymer concentration and stirring speed on particle size, drug loading, and entrapment efficiency. The optimized formulation exhibited nanosized particles (~190 nm) with high entrapment efficiency (92%). Characterization through FTIR, DSC, SEM, and TEM confirmed drug-polymer compatibility and uniform nanosponge morphology. In vitro release studies demonstrated a sustained, diffusion-controlled release pattern with 97% drug release over 6 hours, while accelerated stability studies confirmed physicochemical stability for 3 months. Overall, the CPB nanosponge system improved solubility, stability, and controlled release, presenting a promising oral delivery approach to enhance therapeutic efficacy and patient compliance in cardiovascular therapy.
Keywords: *Clopidogrel Bisulfate, Nanosponges, Drug Delivery, Controlled release, cardiovascular disease.*

Received 24.09.2025 Revised 03.10.2025 Accepted 14.11.2025

How to cite this article:
Kanchan Sanjivan K and Kiran S B. Formulation and Characterization of Embelin Nanoemulsion-Loaded Nanogel: Enhanced Solubility and Antifungal Enzyme Inhibition. Adv. Biores., Vol 16 (6) November 2025: 33-45.

INTRODUCTION

Coronary artery disease (CAD) and ischemic stroke are cardiovascular diseases (CVDs), which are responsible of the highest morbidity and mortality in the globe. Most CVDs are caused by atherosclerosis or a condition in which the linings of the arteries are covered with a plaque that prevents the circulation of blood [1]. This may result in heart attacks, strokes and other health related complications. High cholesterol, smoking and diabetes are risk factors with regards to CVDs. As the number of CVDs continues to increase globally, pharmacological management is part of the foundation of treatment to mitigate complications and extend patient outcomes. Antiplatelet therapy is one of the corner-stone therapies of treatment of CVDs particularly among patients at risk of thrombosis [2]. Suppression of the platelet aggregation through the P2Y 12 receptor by clopidogrel bisulfate (CPB) is left as a classic example of antiplatelet medications. It is liberally prescribed to treat coronary artery disease or after percutaneous coronary interventions (PCI) patients. There are issues with CPB despite its efficiency with the chief issue being linked to its low aqueous solubility, which affects aqueous solubility on bioavailability and therapeutic efficacy [3].

CPB is Class II BCS drug, insoluble, high permeability, non-uniform absorption, unpredictable bioavailability. Clopidogrel is compounded by the fact that it is metabolized in the first-pass (primarily through CYP2C19), of which there is genetic polymorphism in this enzyme, and thereby different

individuals tend to have varying drug activation. Such limitations have lead to the development of superior drug delivery systems design to amplify the bioavailability and reduce inter-patient variability and therapeutic efficacy [4].

Nanosponges (NS), a potential drug delivery system is one that has been of interest because of their properties of enhancing the solubility and bioavailability of such drugs which are poorly water soluble such as CPB. These nanopores are also capable of trapping hydrophilic and hydrophobic drugs providing both controlled release and greater stability [5]. As shown by previous literature, the dissolution rate and bioavailability of BCS Class II drugs can be increased significantly by the use of ethyl cellulose-based NS [6]. Moreover, polymeric matrices such as ethyl cellulose and polyvinyl alcohol have been demonstrated to enable improvement of drug encapsulation and sustained release studies. In spite of these developments, CPB has been formulated into NS only in a limited fashion and research is still necessary to streamline these systems to a clinical level. Existing formulations continue to be problematic with respect to stability, scalability, and patient compliance [7].

This paper seeks to address the formulation difficulties of CPB by creating a nanosponge drug delivery system to enhance its solubility, stability and release. The aim is to develop clopidogrel-loaded NS with ethyl cellulose and polyvinyl alcohol, entrap them in size "0" hard gelatin capsules, improve the oral bioavailability and reduce the side effects. The paper will also assess drug-excipient compatibility, drug loading efficiency and release kinetics. In addition, the ability to evaluate the physical and chemical stability of the formulation under accelerated conditions will be conducted in the form of stability analysis. Lastly, it is to be targeted at the delivery of a sustained-release formulation to improve treatment outcome and adherence.

MATERIAL AND METHODS

Reagents and instruments

CPB was employed as the major material and was used in this study and this was obtained in Otto Chemie Pvt Ltd, Mumbai. The ingredients of the formulated NS, that is, Ethyl Cellulose (EC), Polyvinyl alcohol (PVA) are analytical grade, and these were sourced through Research Lab Fine Chemistry Industries, Mumbai, India. Additional raw materials such as Dichloromethane (DCM), and Ethanol were purchased at Research chem Mumbai and utilized in the preparation procedure. Analytical grade chemicals were used without any further purification.

Preparation of Clopidogrel-Loaded Nanosponges

Different amounts of polyvinyl alcohol and ethyl cellulose can be used to create nanosponges. After dissolving the drug in 10 mL of ethanol and the dispersed phase, which contained ethyl cellulose, in 20 mL of dichloromethane, the two solutions were combined and gradually added to a known amount of polyvinyl alcohol in 100 mL of the aqueous continuous phase. Using a magnetic stirrer, the reaction mixture was agitated for two hours at 1000 rpm. After being filtered, the nanosponges were dried for 24 hours at 40°C in an oven. To make sure that all remaining solvents were eliminated, the dried nanosponges were kept in vacuum desiccator [5].

Experimental Design

A box-behnken design was utilized to optimize the formulation of CPB-loaded NS using Design-Expert® software (version 13, Stat-Ease Inc., USA). Three independent variables—Ethyl Cellulose (EC), Polyvinyl Alcohol (PVA), and Stirring speed—were studied at three levels: Low (-1), Medium (0), and High (+1). The dependent variables evaluated included % Drug Diffusion (DD), % Entrapment Efficiency (EE), Particle Size (PS), and % Practical Yield (PY). 15 experimental runs were performed, and the formulations were analyzed for the aforementioned variables. The data were analyzed using ANOVA to determine the significance of main effects and interactions. Polynomial models and response surface plots were generated, and optimal conditions were selected based on the desirability function to achieve minimum particle size and maximum % EE. The optimized formulation was prepared in triplicate to assess reproducibility, followed by further characterization [8].

Table 1: Independent Variables Used in Design of Experiment Software

Factor Code	Factor Name	Units	Type	Range (Minimum – Maximum)	Coded Levels	Mean	Standard Deviation
A	EC (Ethyl Cellulose)	mg	Numeric	5.00 – 30.00	−1 = 5, +1 = 30	17.50	9.45
B	PVA (Polyvinyl Alcohol)	mg	Numeric	0.30 – 2.00	−1= 0.30, +1 = 2.00	1.15	0.6425
C	Stirring Speed	RPM	Numeric	1000 – 1200	−1 = 1000, +1 = 1200	1100	75.59

Organoleptic Properties, Solubility, Melting Point: The organoleptic properties of CPB were observed, including its color, odor, and appearance. Solubility studies were carried out in various solvents (methanol, DMSO, dichloromethane, water, etc.) to determine the solubility profile of the drug. The melting point of CPB was determined using a melting point apparatus.

FTIR: FTIR spectra of CPB, its 1:1 mixture with Polyvinyl Alcohol (PVA) and Ethyl Cellulose (EC), and pure CPB were recorded using a PerkinElmer Ultra Two FTIR spectrometer. The spectra were obtained over a wavenumber range of 4000 to 400 cm^{-1}. A small amount of each sample was placed onto a diamond crystal and pressure was applied to ensure proper contact. Background spectra of KBr pellets were recorded before analyzing the test samples. The spectra of the drug-excipient mixtures were compared to the pure drug to identify any potential interactions, indicated by shifts or the appearance of new peaks.

DSC: DSC analysis was performed on pure CPB (API) and its formulation (Clopidogrel-loaded nanosponges) using a PerkinElmer DSC 4000 (PerkinElmer, USA). The samples were heated from 30°C to 300°C at a heating rate of 10°C/min under a nitrogen flow of 20 mL/min to maintain an inert atmosphere. The thermal behaviors, including the onset of melting, phase transitions, and any potential changes in crystallinity or morphology, were recorded. The thermograms of the formulation were compared with those of the pure API to identify any differences in melting points, polymorphic transitions, or potential interactions between CPB and excipients in the formulation [9].

Field Emission Scanning Electron Microscopy (FE-SEM): FE-SEM was exploited to examine the peripheral morphology and characteristics of NS of CPB. The sample was coated with a gold-palladium layer under ambient conditions before being examined with a SEM (Nova Nano SEM NPEB303) at 5000 x magnification in an argon environment [10].

Transmission Electron Microscopy: For TEM analysis, a dilute suspension of Clopidogrel-loaded NS was prepared in distilled water and sonicated to ensure uniform dispersion. A drop of the suspension was placed onto a carbon-coated copper grid and allowed to air-dry. If required, the grid was negatively stained with 1% phosphotungstic acid for contrast enhancement. After drying, the grid was examined under a transmission electron microscope at an accelerating voltage of 80–120 kV. The resulting images were used to observe the morphology and particle size distribution of the NS [11].

Capsule Formulation: Encapsulation into Hard Gelatin Capsules (Size0): The optimized Clopidogrel-loaded NS were encapsulated into size "0" hard gelatin capsules. The capsules were filled with the NS to a total weight of 400 mg per capsule, using a capsule filling machine.

Drug Loading, Entrapment Efficiency: The drug loading and entrapment efficiency of the NS were determined by extracting the drug from the NS using an appropriate solvent and quantifying it using the UV-Vis spectrophotometric method.

In Vitro Drug Release and Kinetics: In vitro drug release studies were performed using the USP dissolution apparatus at 100 rpm in a dissolution medium (pH 7.4) at 37 ± 2°C. The release data was fitted into different release models (e.g., zero-order, first-order, Higuchi, Korsmeyer-Peppas) to determine the release mechanism.

Stability Study (ICH Guidelines): Stability studies of the final capsule formulation were conducted under accelerated conditions (e.g., 40°C ± 2°C / 75% RH ± 5% RH) as per ICH guidelines. Physical and chemical stability was assessed at regular intervals for a couple of months.

RESULTS AND DISCUSSION

Development of Clopidogrel Bisulfate Nanosponges:

CPB-loaded NS were formulated using the emulsion solvent diffusion method with ethyl cellulose (EC) as the polymer and polyvinyl alcohol (PVA) as the stabilizer. The organic phase was prepared by dissolving 100 mg of CPB and 20 mg of EC in 10 mL of dichloromethane (DCM) and 5 mL of ethanol. Separately, 1% w/v PVA solution was prepared by dissolving 1 g of PVA in 100 mL of distilled water with mild heating and stirring, then cooled to room temperature. The organic phase was added dropwise into the aqueous phase under continuous stirring at 1000-1200 rpm and emulsified for 2 hours at room temperature. Following solvent diffusion and evaporation, the NS were collected by centrifugation at 14,000 rpm for 30 minutes at 4 °C, washed with distilled water, and dried in a hot air oven at 40 °C for 24 hours. The dried NS were stored in amber glass vials inside a desiccator until further use.

Experimental Design

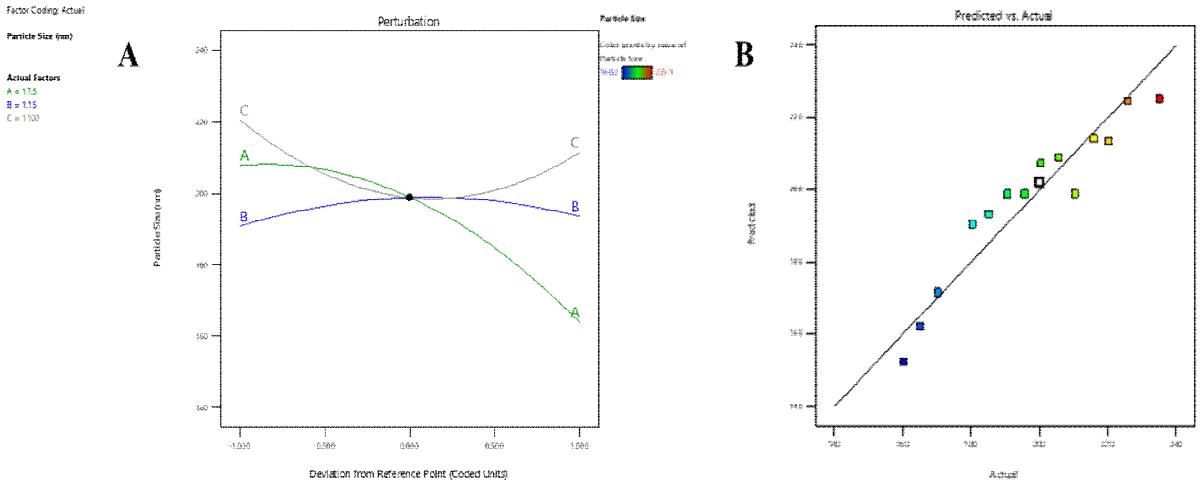
CPB-loaded NS were developed using a 3^2 factorial design, and the effects of ethyl cellulose (EC), polyvinyl alcohol (PVA), and stirring speed on particle size and entrapment efficiency (%EE) were evaluated. Particle size ranged from 160.2 to 235.1 nm, and %EE varied between 83.0% and 92.0%, as

shown in Table 1. ANOVA revealed that all three factors significantly influenced both responses ($p < 0.05$). Higher EC levels improved entrapment efficiency but slightly increased particle size due to viscosity effects. Increased PVA concentration led to better emulsification and smaller particles, while moderate stirring speed (1100–1200 rpm) provided optimal dispersion. The optimized formulation showed a particle size of 190.7 nm with 92.0% entrapment efficiency, indicating effective nanosponge formation and drug encapsulation (Figure 1).

Table 2: Box-Behnken Design

	Factor 1	Factor 2	Factor 3	Response 1	Response 2
Run	A:EC	B: PVA	C: Stirring speed	Particle Size	EE
	mg	mg	RPM	nm	%
1	5	1.15	1200	235.1	88.2
2	17.5	1.15	1100	210.4	89.9
3	17.5	1.15	1100	190.7	92
4	30	0.3	1100	165.3	84.8
5	5	1.15	1000	225.8	87.3
6	17.5	2	1200	200.5	90
7	30	2	1100	160.2	85.6
8	30	1.15	1000	180.4	83.5
9	5	2	1100	205.6	90.5
10	30	1.15	1200	170.3	84.2
11	17.5	2	1000	215.9	89
12	17.5	0.3	1000	220.2	88
13	17.5	1.15	1100	195.7	91.6
14	17.5	0.3	1200	200.1	90.8
15	5	0.3	1100	185.2	83

The final quadratic equation obtained in terms of coded variables was: Particle Size = 198.93 – 21.94A + 1.42B – 4.54C – 6.37AB – 4.85AC + 1.17BC – $13.07A^2$ – $6.79B^2$ +$17.03C^2$



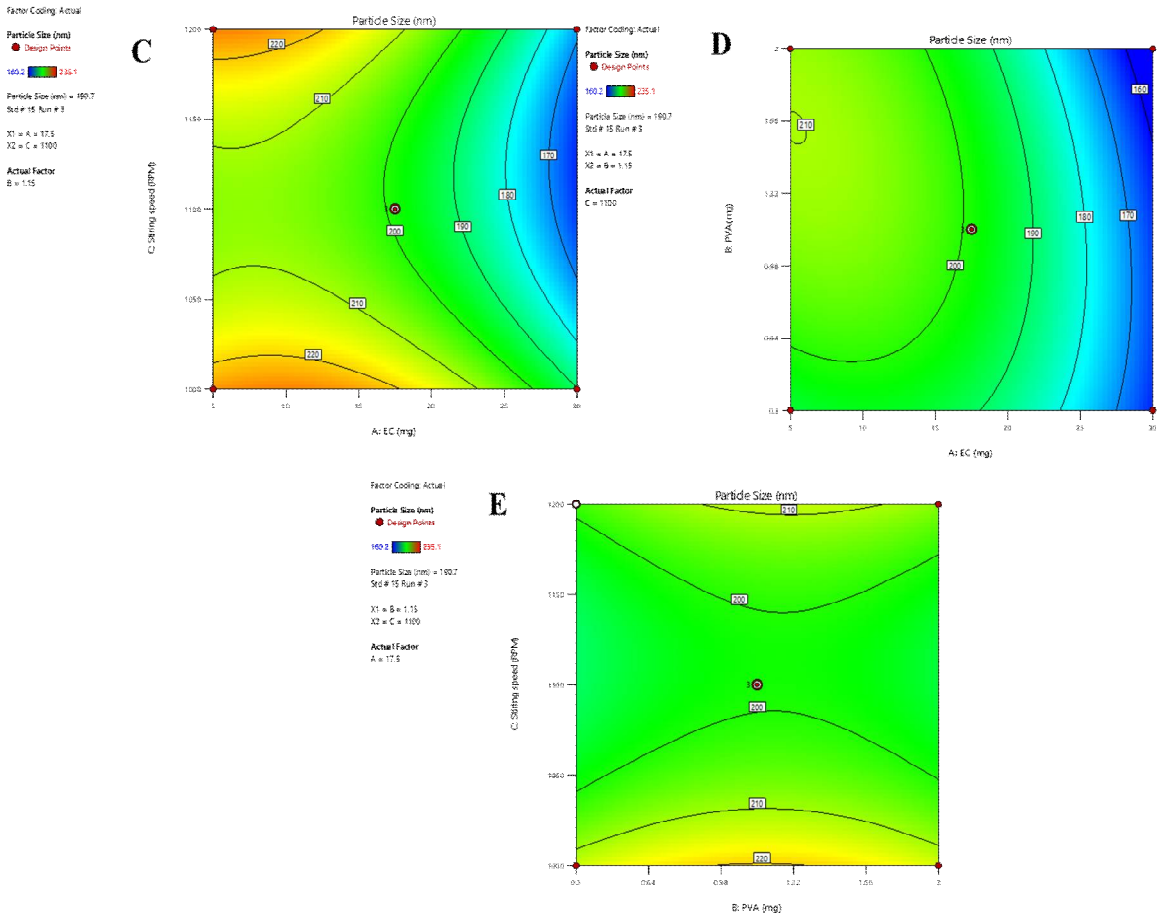
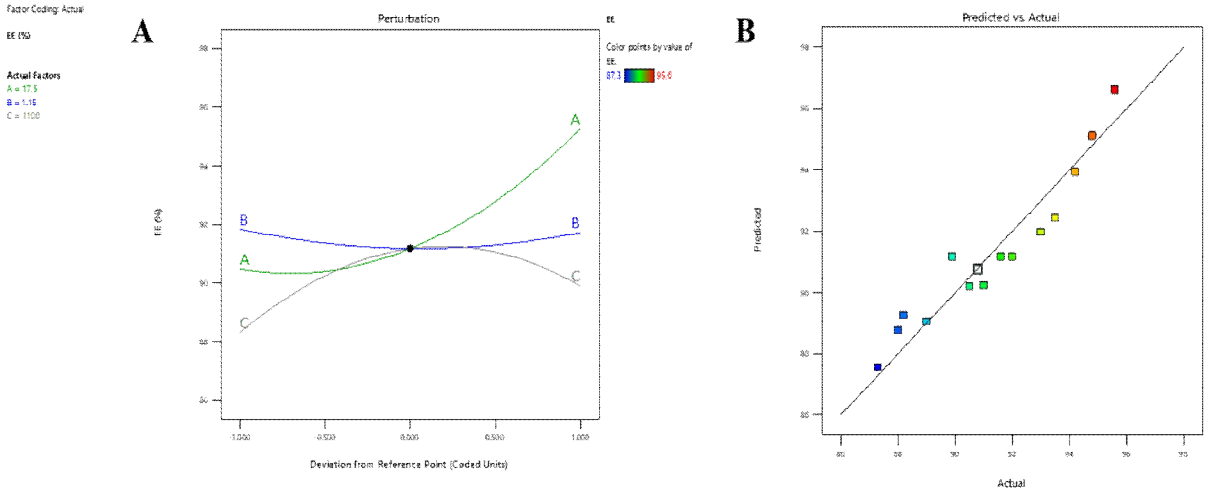


Figure 1: (A) Perturbation plot showing the effect of formulation variables on particle size, (B)Predicted vs. actual plot for particle size model validation, (C) Interaction plot between ethyl cellulose (EC) concentration and stirring speed on particle size, (D) Interaction plot showing the combined effect of ethyl cellulose (EC) and polyvinyl alcohol (PVA) concentrations on particle size, (E) Interaction plot between polyvinyl alcohol (PVA) concentration and stirring speed on particle size.

The equation for entrapment efficiency generated was:

$$EE = 91.17 + 2.39A - 0.06B + 0.80C + 0.83AB - 0.05AC - 0.20BC + 1.70A^2 + 0.60B^2 - 2.07C^2$$



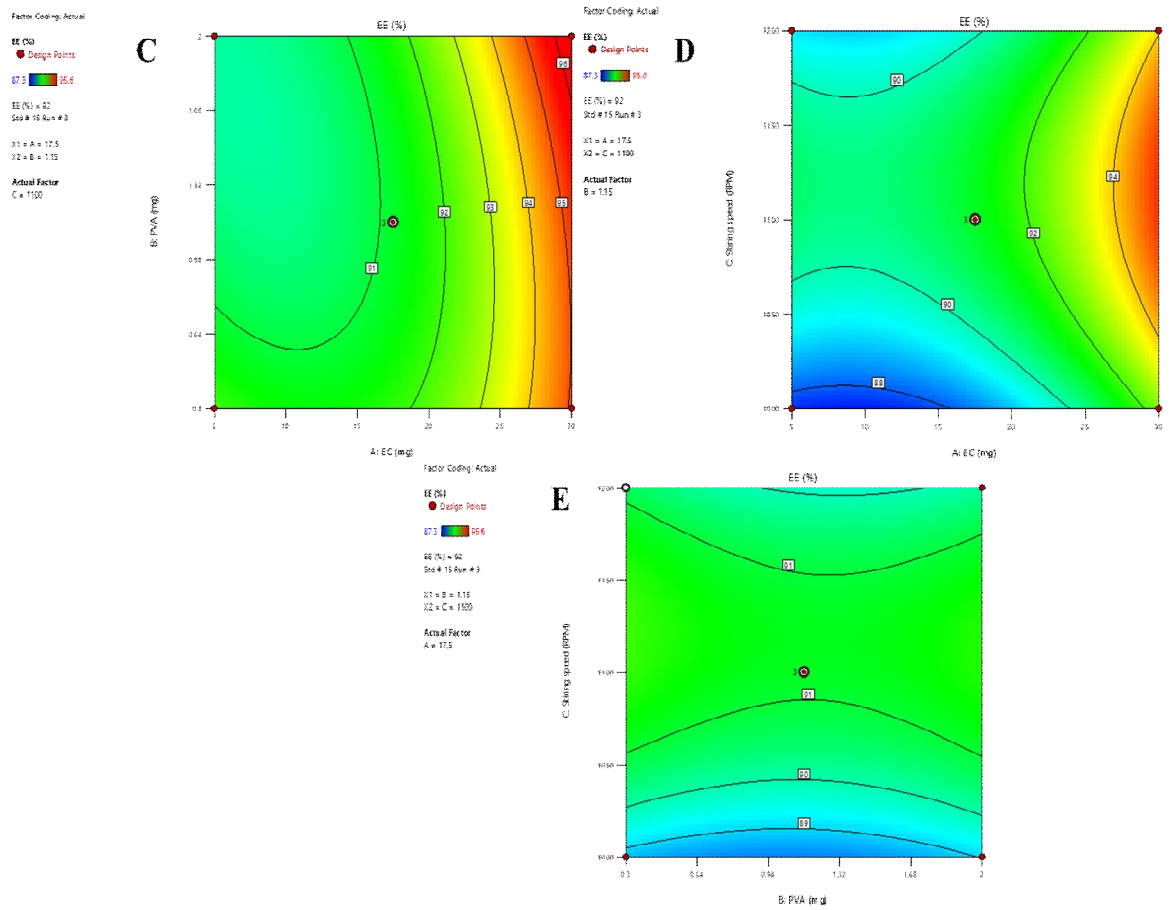


Figure 2: (A) Perturbation plot showing the effect of formulation variables on entrapment efficiency, (B) Predicted vs. actual plot for particle size model validation, (C) Interaction plot between ethyl cellulose (EC) concentration and stirring speed on entrapment efficiency (D) Interaction plot showing the combined effect of ethyl cellulose (EC) and polyvinyl alcohol (PVA) concentrations on entrapment efficiency, (E) Interaction plot between polyvinyl alcohol (PVA) concentration and stirring speed on entrapment efficiency.

Nanosponges Characterization

Particle Size, PDI, and Zeta Potential:

The particle size distribution of the optimized CPB-loaded nanosponge formulation was evaluated using dynamic light scattering (DLS). The formulation exhibited a hydrodynamic diameter of 385.7 nm with a polydispersity index (PDI) of 0.235, indicating a moderately narrow and uniform size distribution. The diffusion coefficient was measured at 1.1 $\mu m^2/s$, and transmittance was 85.3%, reflecting good optical clarity and particle dispersion. The intensity distribution curve displayed a primary peak around 380–400 nm, suggesting effective nanosponge formation within the nanometric range. These results confirm the successful production of nanoscale particles with acceptable homogeneity suitable for oral drug delivery. For the Clopidogrel formulation, the zeta potential was -20.5 mV, suggesting good colloidal stability.

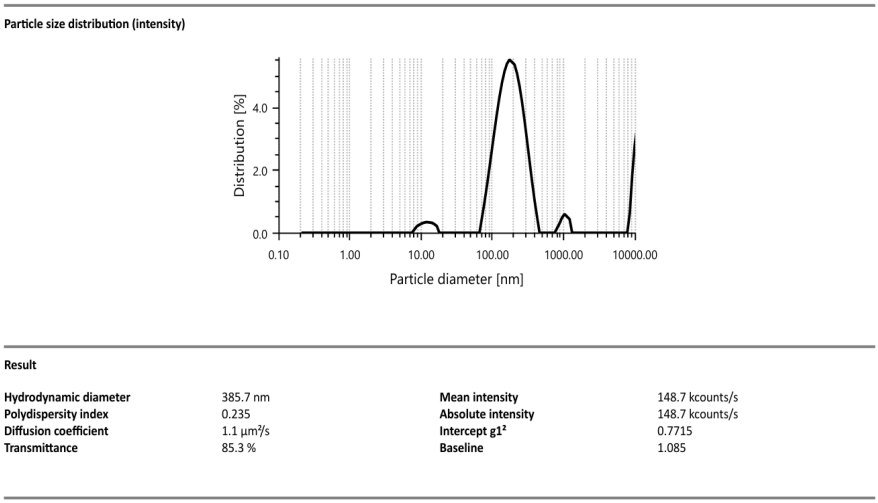


Figure 3: Particle size of the optimized Clopidogrel bisulfate-loaded nanosponge

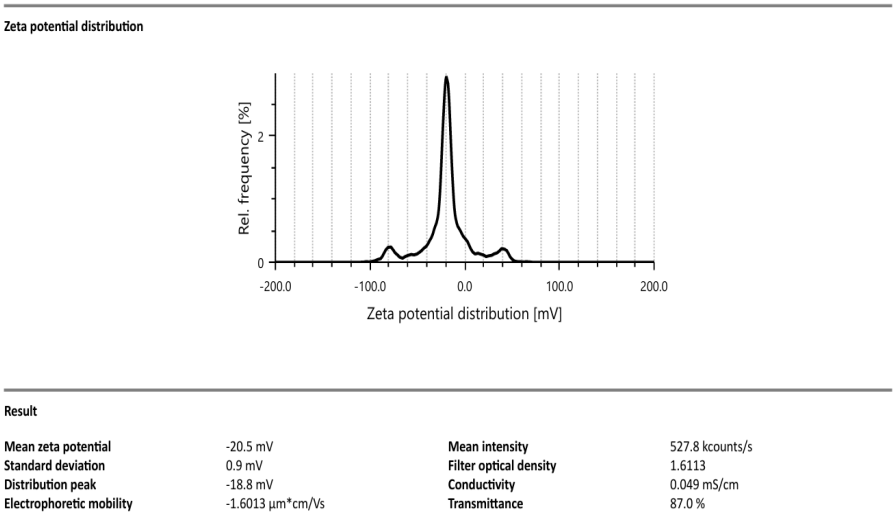


Figure 4: Zeta Potential of the optimized CPB-loaded nanosponge

FTIR Analysis

FTIR spectroscopy was utilized to assess the compatibility and possible interactions between CPB and PVA. As shown in Figure 5 (Clopidogrel Bisulfate – 5A, PVA – 5B, and their mixture – 5C), characteristic peaks of CPB were observed at 1751.01 cm^{-1} (C=O), 1438.38 cm^{-1} (aromatic C=C), and 1220.95 cm^{-1} (C–O), while PVA showed major peaks at 1751.56 cm^{-1} and 1221.87 cm^{-1}. The physical mixture spectrum retained key peaks from both components, with slight shifts and changes in intensity, indicating weak intermolecular interactions such as hydrogen bonding. These findings confirm the absence of significant chemical incompatibilities and support the successful formulation of CPB-loaded NS.

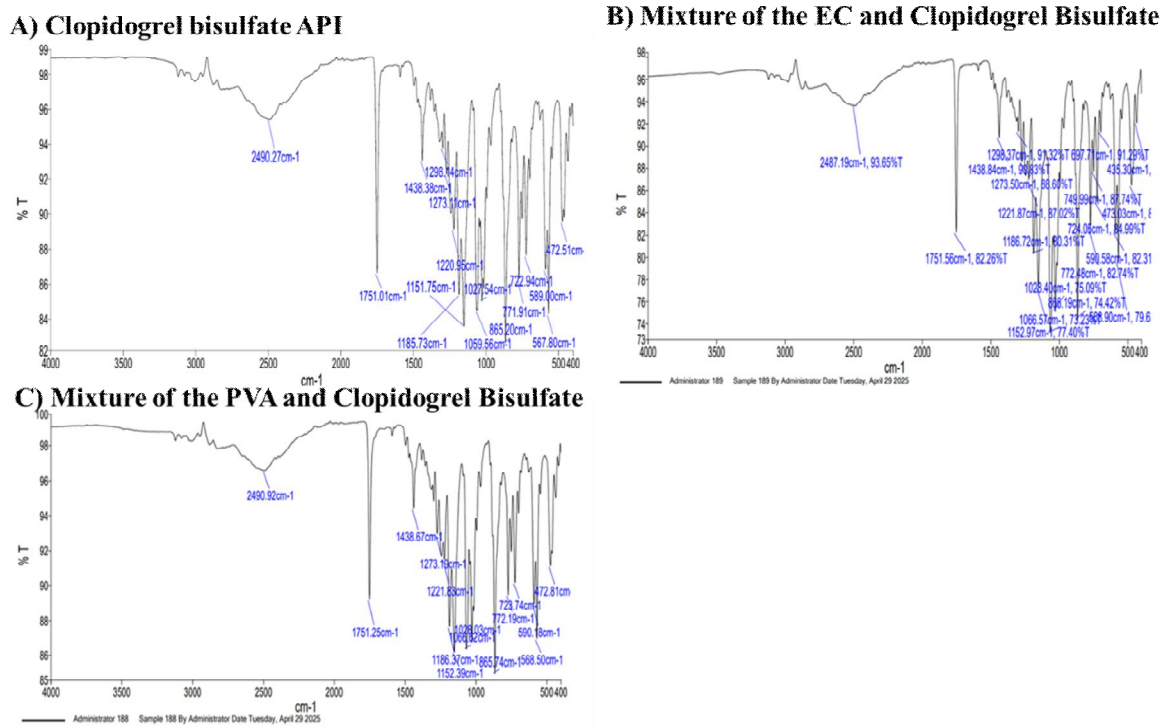


Figure 5: (A) FTIR spectra of CPB API, (B) FTIR of 1:1 Mixture of the EC and CPB, (C) FTIR of 1:1 Mixture of the PVA and CPB.

DSC

As shown in Figure 6, the DSC thermogram of the pure drug (Figure 6A) exhibited a sharp endothermic peak at 177.0 °C, with onset and endset temperatures at 172.8 °C and 181.4 °C, respectively, corresponding to the melting point of crystalline CPB, indicating its pure and crystalline nature. In contrast, the DSC thermogram of Clopidogrel-loaded NS (Figure 6B) showed the absence of a distinct melting peak, suggesting a reduction in crystallinity and possible molecular dispersion of the drug within the polymer matrix. This transformation from crystalline to amorphous form confirms the successful encapsulation of CPB into the NS.

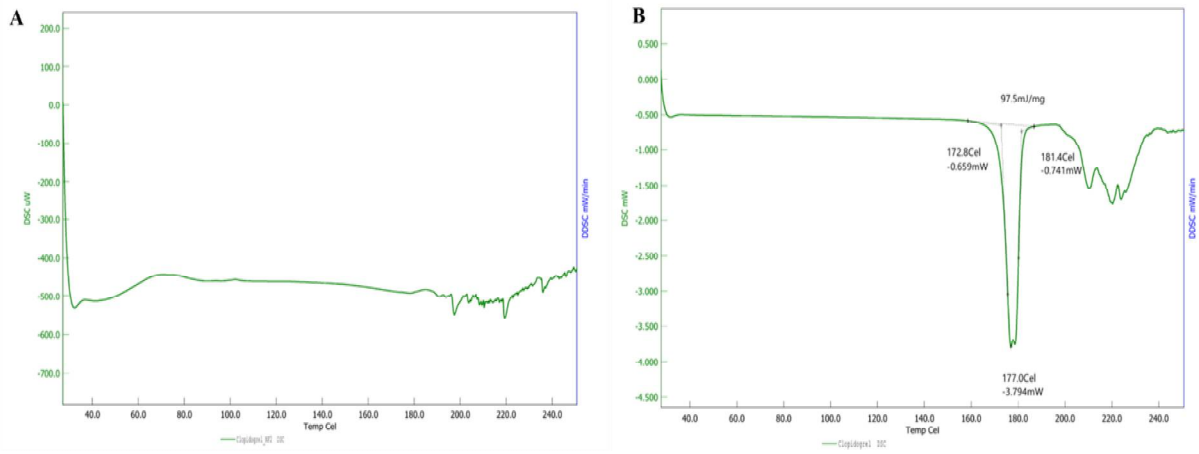


Figure 6: (A) DSC thermogram of CPB API, (B) CPB NS

SEM

Scanning Electron Microscopy (SEM) was employed to analyze the surface morphology and particle size of Clopidogrel-loaded NS. As shown in Figure 7 (A) demonstrates that the NS possess a spherical shape with a smooth and uniform surface, indicating successful formulation. Figure 7 (B), captured at a lower magnification, provides detailed particle size measurements, revealing sizes ranging from 0.10 µm to 0.48 µm. The narrow size distribution and absence of significant agglomeration suggest good formulation

stability and homogeneity. These morphological features are ideal for enhancing drug loading and release behavior, confirming the suitability of the NS for drug delivery applications.

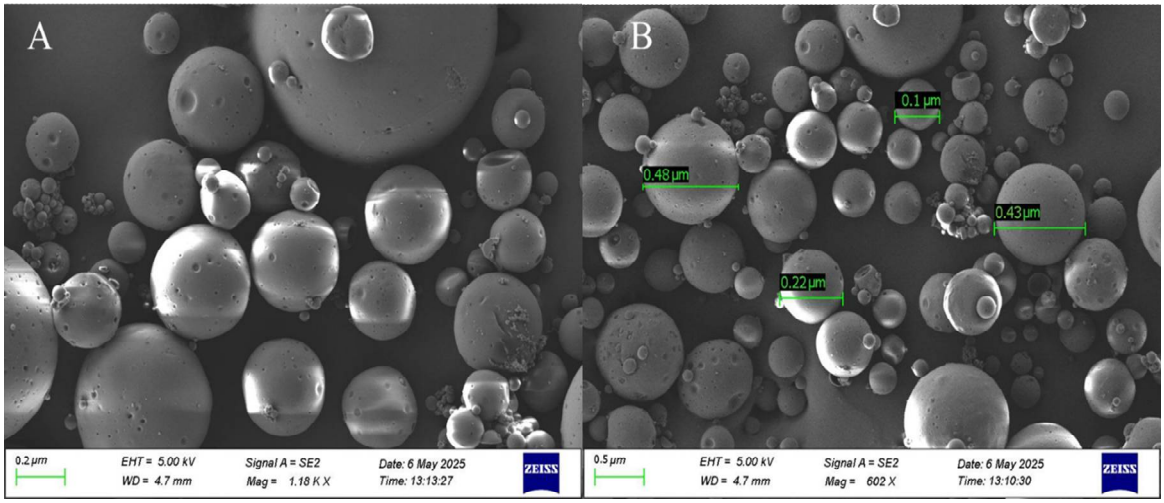


Figure 7: SEM images of Clopidogrel-loaded NS. (A) Surface morphology showing spherical and smooth particles at higher magnification (1.18 KX). (B) Particle size distribution observed at lower magnification (602X), with sizes ranging from 0.10 µm to 0.48 µm.

TEM

TEM analysis was carried out to further evaluate the internal morphology and size of the Clopidogrel-loaded NS. As depicted in **Figure 8**, the TEM image reveals well-dispersed, spherical nanoparticles with a smooth surface and uniform shape. The particles appear in the nanometer range, with sizes consistently below 200 nm, confirming their nanoscale nature. The absence of aggregation and the clear particle boundaries indicate good stability and efficient nanosponge formation, supporting their potential for enhanced drug delivery applications.

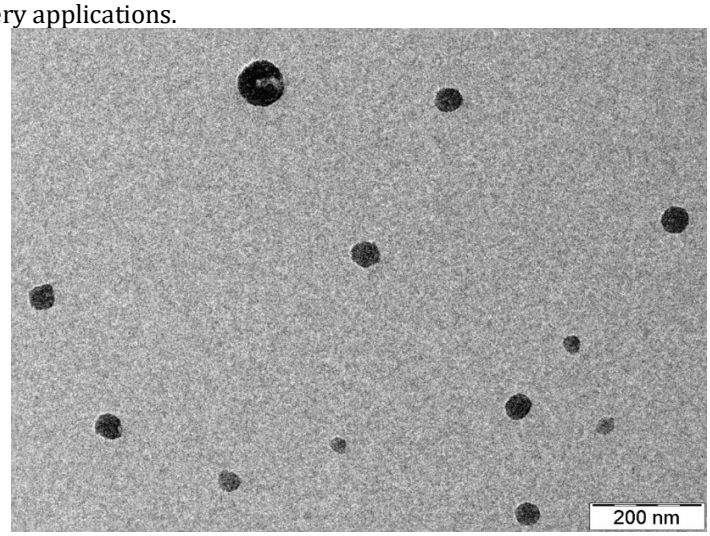


Figure 9: TEM image of Clopidogrel-loaded NS showing uniform, spherical nanoparticles with sizes below 200 nm and well-dispersed morphology.

In vitro drug release and Kinetics

The in vitro drug release study of Clopidogrel-loaded NS showed a sustained release pattern, with approximately 97% of the drug released within 6 hours, as depicted in the cumulative release graph. To understand the release kinetics, the data were fitted into various models. Among these, the Higuchi model exhibited the best fit with an R^2 value of 0.9699, indicating diffusion-controlled release. This was closely followed by the Zero-order model (R^2 = 0.9847), suggesting a constant release rate. The Hixson-Crowell model (R^2 = 0.9664) also supported the erosion-based release mechanism, while the First-order (R^2 = 0.9287) and Korsmeyer-Peppas (R^2 = 0.9121) models were slightly less predictive. These findings suggest that the drug release from NS is primarily diffusion-controlled with elements of matrix erosion.

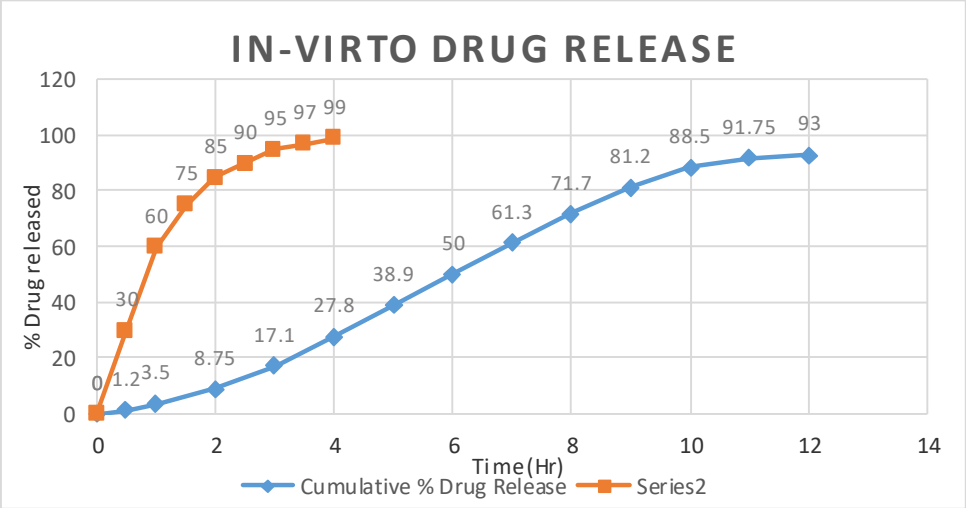


Figure 10: In-vitro Drug Release Profile of Clopidogrel Bisulfate Nanosponges and Pure Clopidogrel Bisulfate

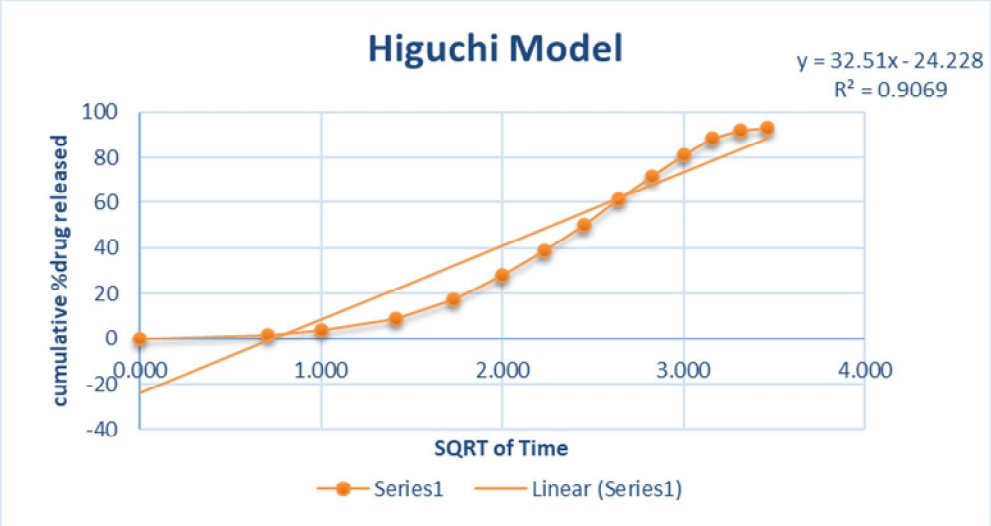


Figure 11: Higuchi Model Plot of Cumulative % Drug Released

Stability Study

Stability studies of Clopidogrel-loaded NS were conducted at 40 ± 2°C and 75% ± 5% RH over a period of three months. Throughout the study, the formulation showed no significant changes in physical appearance, with the color remaining white to off-white and only slightly off-white at the third month. Drug content decreased slightly from 92.5 ± 0.4% initially to 91.6 ± 0.5% at three months, while moisture content increased marginally from 2.0 ± 0.1% to 2.3 ± 0.1%. These results indicate that the formulation remains stable under accelerated storage conditions.

Time (Months)	Storage Condition	Physical Appearance	Color	Drug content (%)	Moisture content (%w/w)
0 (initial)	40°C ± 2°C / 75%RH ± 5% RH	No change	White to off white	92.5 ± 0.4	2.0 ± 0.1
1		No change	White to off white	92.2 ± 0.3	2.1 ± 0.1
2		No change	White to off white	91.8 ± 0.4	2.2 ± 0.1
3		No change	Slightly off white	91.6 ± 0.5	2.3 ± 0.1

Table 3: Stability Study Report

DISCUSSION

Using ethyl cellulose and polyvinyl alcohol, the current study effectively created and described a nanosponge-based CPB delivery system using the emulsion solvent diffusion approach. With a particle size of roughly 190.7 nm, high entrapment effectiveness (92.0%), and sustained in vitro drug release (~97% over 6 hours), the improved NS showed promising physicochemical characteristics that suggested effective encapsulation and controlled release potential. These results highlight the viability of employing NS to overcome the solubility and bioavailability issues related to CPB, a BCS Class II medication.

Building on this foundation, Cyclodextrin-based NS are highly porous, cross-linked polymeric networks capable of encapsulating hydrophobic drugs within their internal cavities and interstitial pores. These structures combine hydrophilic outer surfaces with lipophilic interior nanochannels, enabling the formation of both inclusion complexes (via the cyclodextrin cavities) and non-inclusion complexes (within the 3D polymer matrix). Such architecture greatly enhances apparent aqueous solubility and stabilizes labile drugs [12]. In practice, cyclodextrin NS (often made with β-CD or its derivatives) can encapsulate a variety of drug molecules by adjusting the cyclodextrin: crosslinker ratio, tailoring pore size, and loading efficiency. The large surface area and nano-sized pores facilitate rapid drug loading and release, while the insoluble crosslinked matrix protects the entrapped drug. Indeed, NS formulations have been widely shown to improve drug solubility and reduce degradation, thereby increasing bioavailability [13]. These materials are generally biocompatible and have been administered via multiple routes, making them attractive carriers for poorly soluble drugs. For CPB, a BCS Class II antiplatelet agent with very low intrinsic solubility (~0.05 mg/mL) and modest oral bioavailability (<50%), nanosponge encapsulation dramatically improves dissolution. In one study of polymeric ethyl cellulose NS containing CPB, the optimized nanoparticles (≈87 nm) achieved near-total drug release (~97% in vitro) within the dissolution mediumouci.dntb.gov.ua. These NS particles were converted into immediate-release tablets that disintegrated in ~3 min, yielding rapid liberation of CPB (cumulative release ≈99%) following apparent zero-order kinetics [14]. Such high entrapment efficiency (~82%) and complete release far exceed the poor dissolution rate of raw clopidogrel. In comparison, a hydroxypropyl-β-cyclodextrin inclusion complex (stabilized by Tween 80) also improved CPB solubility, as evidenced by enhanced binding affinity and higher phase-solubility constants versus native β-CD [15]. The clinical impact of this solubilization is seen in pharmacodynamic assays: for example, rabbits given the CD-complexed drug showed 1.2–1.5-fold longer clotting and bleeding times than those given a marketed clopidogrel tablet, indicating greater systemic exposure [16]. Thus, NS formulations can achieve at least comparable (and in some cases better) enhancement of clopidogrel dissolution and apparent absorption relative to other solubility-enhancing systems. The release kinetics and stability profile of clopidogrel-NS formulations further underscore their advantages. The ethyl cellulose NS tablets mentioned above not only released clopidogrel steadily (zero-order kinetics) but also demonstrated excellent stability: no significant changes in drug content or dissolution were observed after 6 months under accelerated and long-term storage [17]. This contrasts with clopidogrel bisulfate's known sensitivity to heat and moisture. In fact, unformulated clopidogrel salts rapidly degrade under humid conditions, necessitating stabilizers in conventional products. The cross-linked sponge matrix likely shields CPB from hydrolysis, as evidenced by the unchanged content in stability testsouci.dntb.gov.ua. In terms of release profile, NS can be tuned for both immediate and extended release. While the tablet formulation above was immediate-release, other carriers like human serum albumin nanoparticles have demonstrated sustained clopidogrel release (up to 168 hours in vitro) [18]. Such prolonged delivery (in an intravenous stroke model) translated to dose-dependent neuroprotection, suggesting that extended-release carriers can maintain therapeutic drug levels longer. By contrast, NS could be engineered (by crosslink density or matrix composition) to slow diffusion and mimic this prolonged release if desired. Importantly, the ease of formulating NS into solid dosage forms (tablets, capsules) enhances patient compliance and manufacturing stability relative to liquid nanocarriers. When compared to other delivery platforms, clopidogrel-loaded NS offer unique benefits. Lipid-based systems have achieved large increases in clopidogrel bioavailability, but they rely heavily on surfactants and may have complex manufacturing requirements. Cyclodextrin inclusion (as above) improves solubility but typically requires encapsulation in soft gelatin capsules. NS formulations, in contrast, allow direct tableting: the optimized CPB-NS tablets achieved 99% release with favorable mechanical properties [19]. Moreover, NS formulations can achieve higher drug loading than traditional CD complexes. By forming inclusion complexes within each cyclodextrin unit and non-inclusion entrapment in the polymer network, NS can carry more drug per dose. Compared to albumin nanoparticle formulations, NS are designed for oral delivery and hence bypass the need for sterile aqueous systems; albumin nanoparticles did show excellent sustained release and efficacy in animal models of stroke [20], but NS provide a more practical oral platform for everyday antiplatelet therapy. In summary, clopidogrel

NS combine the solubility advantages of cyclodextrins with the dosing convenience of solid oral forms, potentially yielding more consistent absorption and easier handling than other nanoformulations. Enhanced solubility and controlled release from clopidogrel NS are expected to translate into better bioavailability and clinical effect. The improved dissolution mitigates the precipitation of CPB in the gastrointestinal tract, which otherwise limits its uptake. In vivo, this should increase the amount of prodrug available for metabolic activation, potentially lowering the required dose. The increased pharmacodynamic effects seen with solubilized formulations suggest that NS could similarly amplify clopidogrel's antiplatelet activity [21]. Furthermore, the demonstrated stability of CPB-NS indicates longer shelf-life and reliability of dosing. These features imply that nanosponge formulations could reduce inter-patient variability and overcome some resistance issues by delivering more consistent drug levels. Future studies should evaluate the pharmacokinetics and platelet inhibition of clopidogrel-NS in vivo, but the current evidence from dissolution, kinetics, and modeling studies provides a strong rationale that NS carriers have significant clinical potential as oral delivery vehicles for clopidogrel bisulfate.

CONCLUSION

Using ethyl cellulose and polyvinyl alcohol, the current study successfully formulates and evaluates nanosponges loaded with clopidogrel bisulfate. Desired physicochemical properties of the improved formulation included diffusion-controlled kinetics, a sustained in vitro drug release profile (~97% within 6 hours), high entrapment efficiency (92.0%), and nanoscale particle size (~190.7 nm). FTIR, DSC, SEM, and TEM characterization verified the drug's compatibility and effective encapsulation in the nanosponge matrix. Additionally, the formulation demonstrated outstanding stability under accelerated settings, suggesting that it is suitable for practical usage and long-term storage.

A promising method for getting around the solubility, bioavailability, and stability issues with the BCS Class II medication clopidogrel bisulfate is the nanosponge-based delivery system. Nanosponges are superior to conventional formulations and other cutting-edge carriers in terms of drug loading, controlled release, scalability, and simplicity of filling capsules for oral administration.

Despite the formulation's promising in vitro performance, additional in vivo pharmacokinetic and pharmacodynamic research is required to validate the improvement in bioavailability and therapeutic efficacy. Its translational potential will also be established by testing the formulation in clinical models of cardiovascular disease or thrombosis. In order to improve site-specific medication action and lessen inter-individual variability brought on by metabolic polymorphisms (such as CYP2C19), future research may also investigate surface-modified nanosponges or targeted delivery systems. Finally, to move this technique closer to commercialization, industrial-scale formulation and regulatory pathway evaluation should be taken into account.

ACKNOWLEDGMENT

The authors are thankful to the Management and Principal of KCT's R. G. Sapkal College of Pharmacy, Nashik, for providing the necessary research facilities to carry out this work.

AUTHOR CONTRIBUTIONS

All authors contributed to experimental work, data collection, drafting or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

COMPETING INTEREST STATEMENT

All authors declare that there is no conflict of interests regarding publication of this paper.

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