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Formulation and Evaluation of Niosomes of Clopidogrel for the Treatment of Peripheral Artery Disease

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ABSTRACT

Peripheral Artery Disease (PAD) is a progressive vascular condition that significantly elevates the risk of thrombotic events. Clopidogrel, a widely used antiplatelet agent, is limited by systemic side effects and poor bioavailability. This study focuses on the formulation and evaluation of Clopidogrel-loaded niosomes to enhance therapeutic efficacy through improved encapsulation, stability, and controlled release. Among the developed formulations, the optimized niosomal formulation (F2) demonstrated high drug entrapment efficiency (94.60 ± 16.90% initially and 89.47 ± 2.50% after 3 months), indicating excellent drug loading capability. In vitro drug release studies revealed a sustained and controlled release profile, with F2 releasing 3.22 ± 0.38 mg (approximately 39% of the total drug load) of Clopidogrel over 24 hours, outperforming F3, which released only 2.50 ± 0.64 mg (15%). Stability studies confirmed the physical robustness of F2, with no significant change ($p > 0.05$) in vesicle size or entrapment efficiency over a 3-month period at 4 °C, unlike F1 and F3, which exhibited significant increases in particle size. The nanoscale vesicle size of F2, maintained through a balanced 1:1 cholesterol-to-surfactant ratio, contributed to its enhanced stability and drug release properties. The optimized surfactant composition improved vesicle rigidity and integrity, essential for prolonged release and targeted delivery. Importantly, the encapsulation of Clopidogrel in niosomes may reduce systemic side effects such as gastrointestinal irritation, offering a promising alternative to conventional formulations for the effective management of PAD.

Keywords: *Clopidogrel, Niosomes, Peripheral Artery Disease, Nanocarrier, Thin Film Hydration, Drug Delivery*

1. INTRODUCTION

Peripheral Artery Disease (PAD) is a common and progressive circulatory disorder characterized by the narrowing or blockage of peripheral arteries, primarily in the lower extremities, due to atherosclerosis [1]. This condition affects more than 200 million individuals worldwide and is strongly associated with increased risks of cardiovascular morbidity and mortality, including myocardial infarction and stroke. The typical clinical manifestation of PAD includes intermittent claudication, rest pain, and in severe cases, critical limb ischemia [2]. Effective management of PAD aims to reduce symptoms, improve quality of life, and prevent thrombotic complications [3-4].

Clopidogrel, a thienopyridine class antiplatelet agent, is widely prescribed for patients with PAD to prevent platelet aggregation and reduce the risk of cardiovascular events [5-6]. It exerts its pharmacological effect by irreversibly inhibiting the P2Y12 subtype of ADP receptors on platelets, thereby blocking ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, which is essential for platelet aggregation [7]. However, Clopidogrel's clinical utility is hindered by several limitations, including low and variable oral bioavailability due to extensive first-pass hepatic metabolism, gastrointestinal irritation, and the potential for bleeding and systemic toxicity. These challenges necessitate the development of alternative drug delivery systems that can improve the pharmacokinetic profile of Clopidogrel while minimizing its adverse effects [8-10].

In recent years, niosomes have emerged as promising nanocarrier systems for enhancing the delivery of therapeutic agents. Niosomes are vesicular systems formed by the self-assembly of nonionic surfactants in an aqueous environment, often stabilized by the inclusion of cholesterol [11-12]. These bilayered structures can encapsulate both hydrophilic and lipophilic drugs, offering numerous advantages such as improved drug stability, sustained release, targeted delivery, biocompatibility,

and reduced toxicity. Importantly, niosomes can modulate the pharmacokinetic behavior of encapsulated drugs, protect labile drugs from degradation, and reduce dosing frequency [13-15]. The rationale behind employing niosomal encapsulation for Clopidogrel lies in its potential to overcome first-pass metabolism and to provide controlled release, thereby achieving prolonged therapeutic levels and reducing systemic exposure. Moreover, by localizing the drug delivery and improving membrane permeability, niosomes can significantly enhance drug bioavailability. The choice of surfactant and cholesterol composition is critical, as it influences vesicle size, entrapment efficiency, membrane rigidity, and release characteristics [16]. Span 60, a nonionic surfactant with a high phase transition temperature and long alkyl chain, is particularly suitable for forming stable niosomes with sustained release properties [17-18].

2. MATERIALS AND METHODS

2.1 Materials

Clopidogrel Bisulfate (CLO), the active pharmaceutical ingredient used in this study, was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. Non-ionic surfactants including various grades of Spans and Tweens were procured from S.D. Fine Chemicals, Mumbai, and used as received. Cholesterol, which serves as a membrane stabilizer in niosomal formulations, was also purchased from S.D. Fine Chemicals. Ethanol of analytical grade was supplied by LOBA Ltd., and was used for the preparation of solvent systems. Additional chemicals used for buffer preparation and analytical procedures included potassium dihydrogen phosphate, sodium hydroxide, and chloroform, all of which were of analytical grade and procured from Qualigen, Mumbai.

2.2 Preformulation Studies

2.2.1 Melting Point Determination

The melting point of the drug sample (CLO) was determined using a standard melting point apparatus. A small quantity of the drug was introduced into a thin-walled capillary tube, approximately 8 cm in length and 1 mm in internal diameter, sealed at one end. The loaded capillary tube was then inserted into the apparatus and subjected to controlled heating. The temperature at which the drug sample transitioned from solid to liquid was recorded as its melting point [19].

2.2.2 FTIR Spectroscopy and Compatibility Studies of Clopidogrel Bisulfate

FTIR analysis of the drug (CLO) was conducted using the potassium bromide (KBr) pellet method on a Shimadzu spectrometer. Samples were prepared by homogenously dispersing 20 mg of the test material in 200 mg of KBr, followed by pellet formation under a hydrostatic pressure of 5.2 N/cm². Spectral data were collected over a wavenumber range of 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1} to facilitate detailed identification and compatibility assessment [20-21]. The physicochemical compatibility between Clopidogrel and other excipients was evaluated using FTIR spectroscopy.

2.2.3 Determination of λ max and construction of calibration curve

A stock solution of Clopidogrel bisulfate was prepared by dissolving 50 mg of the drug in 5 mL of methanol, followed by dilution to 50 mL with PBS (pH 7.4) in a volumetric flask. Subsequently, this stock solution was further diluted to obtain a working standard solution of 100 µg/mL. Serial dilutions were then performed to achieve concentrations of 10, 20, 30, 40, and 50 µg/mL. The UV spectrum of the CLO standard solutions (20 µg/mL) was recorded within the wavelength range of 200–400 nm using PBS (pH 7.4) as the blank.

2.2.4 Solubility Study of Clopidogrel bisulfate

The solubility of Clopidogrel bisulphate was determined by using the shake flask method. In this method, the drug was added to 10 mL of different solvents and shaken at a predetermined time. An excess amount of Clopidogrel was added to a saturation level. The flask was kept on an orbital shaker for 24 h. After a specified time, the solution was filtered, and the filtrate was collected for analysis. The sample was analyzed after suitable dilution using a UV-Visible spectrophotometer at the maximum wavelength of 240 nm.

2.2.5 Partition Coefficient Determination

The partition coefficient (Log P) of CLO was determined using the shake-flask method. A total of 100mg of the drug was dissolved in a biphasic system comprising 10 mL of chloroform and 10 mL of water. The concentration of Clopidogrel bisulfate in each phase was then quantified using a UV-Visible spectrophotometer at the wavelength of maximum absorbance (240 nm). The Log P value was calculated based on the ratio of drug concentrations in the organic and aqueous phases.

2.3 Preparation of Niosomes

Niosomes were prepared using the thin-film hydration technique. Span 60 and cholesterol were accurately weighed and dissolved in a chloroform:methanol mixture (2:1 v/v) in various molar ratios to study the effect of lipid composition on vesicle characteristics (Table 1) [19]. The resulting solution was transferred to a round-bottom flask and subjected to solvent evaporation using a rotary evaporator at 60 °C under reduced pressure. The dried film was then hydrated with PBS, pH 7.4 containing a known amount of Clopidogrel, followed by vortexing to facilitate the formation of multilamellar vesicles [20]. The prepared niosomal dispersions were stored at 4 °C for further characterization [21-22].

Table 1: Composition of CLO-Loaded Niosomes

Ingredients	Formulations				
	F1	F2	F3	F4	F5
CLO (mg)	100	100	100	100	100
Span 60 (mg)	100	50	150	100	200
Cholesterol (mg)	100	150	50	200	100
Diethyl ether (ml)	16	16	16	16	16
Methanol (ml)	4	4	4	4	4
PBS pH 7.4 (ml)	20	20	20	20	20

2.4 Characterization of Niosomes

2.4.1 Vesicle Size and Zeta Potential

The vesicle size and zeta potential of the prepared niosomal formulations were determined using Dynamic Light Scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments, UK) [23-24]. A lower PDI value (<0.3) was indicative of a uniform and monodisperse system. Zeta potential measurements were conducted to evaluate the electrostatic stability of the niosomes [25-26].

2.4.2 Entrapment Efficiency (EE%)

To determine EE%, an aliquot of the freshly prepared niosomal suspension was subjected to ultracentrifugation at 15,000 rpm for 60 minutes at 4 °C using a refrigerated centrifuge [27]. The supernatant was carefully collected and analyzed for free Clopidogrel content using a UV-Visible spectrophotometer at a wavelength of 240 nm, the λmax of Clopidogrel in phosphate buffer (pH 7.4) [28-29].

2.4.3 Transmission Electron Microscopy (TEM)

A small aliquot of the niosomal dispersion was first diluted appropriately with distilled water to achieve optimal particle distribution. A drop of the diluted sample was then carefully placed onto a carbon-coated copper grid and allowed to stand for 1–2 minutes to enable adsorption of vesicles onto the grid surface. Excess fluid was gently removed using filter paper to avoid disturbing the vesicles. To enhance contrast and visualize structural details, the sample was negatively stained with 1% (w/v) phosphotungstic acid (PTA) or uranyl acetate, depending on the specific TEM protocol. After staining, the grid was allowed to dry completely at room temperature under a dust-free environment [30]. The prepared grid was then mounted onto the specimen holder and observed under a TEM (e.g., JEOL or equivalent model) operating at an accelerating voltage typically between 80–120 kV. Images were captured at various magnifications to assess vesicle shape, surface smoothness, and approximate size distribution [31-32].

2.4.4 Scanning Electron Microscopy (SEM)

The surface morphology of the niosomes was analyzed using a scanning electron microscope. A small amount of the niosomal formulation was placed on an aluminum stub and allowed to dry under vacuum. The dried sample was then coated with a thin layer of gold using a sputter coater to enhance conductivity. SEM imaging was performed at an appropriate accelerating voltage, and surface characteristics such as shape, texture, and aggregation were examined [32].

2.4.5 *In Vitro* Drug Release

The *in vitro* release profile of Clopidogrel from the niosomal formulations was evaluated using the dialysis bag diffusion technique. The study was conducted in PBS, pH 7.4, at a constant temperature of 37 ± 0.5°C [33-34]. Accurately measured volumes of niosomal suspension was placed in a pre-soaked dialysis membrane (molecular weight cut-off: 12,000–14,000 Da). The dialysis bag was securely tied at both ends to prevent leakage and then immersed in a beaker containing 100 mL of PBS (pH 7.4). The beaker was placed on a magnetic stirrer set to 100 rpm to maintain uniform mixing and to ensure consistent diffusion of the drug across the membrane [35-36]. At predetermined time intervals 5 mL aliquots of the external medium were withdrawn and analyzed for Clopidogrel content using a UV-Visible spectrophotometer at a wavelength of 240 nm [37-40].

2.4.6 Stability Studies

The stability assessment focused on three key parameters: particle size (PS), polydispersity index (PDI), and entrapment efficiency (EE%). Particle size and PDI were measured using dynamic light scattering (DLS) to monitor any changes in size distribution or potential aggregation, which are critical indicators of colloidal stability. Measurements were performed at the end of the 3-month period and compared to the initial values to assess any statistically significant deviations [40].

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Melting point

The melting point of the Clopidogrel bisulfate sample was determined to be 183 ± 1.5 °C, which closely aligns with the reported literature value of 184 °C.

3.1.2 FTIR Spectroscopy and Compatibility Studies

The FTIR spectrum exhibited characteristic sharp peak at approximately 1750 cm^{-1} corresponding to the C=O stretching of the ester group. A peak around 1600 cm^{-1} indicative of aromatic C=C stretching vibrations. A prominent band near 1250–1300 cm^{-1}, associated with C–O stretching of the ester and ether linkages. Broad absorption in the range of 3200–3500 cm^{-1}, attributed to N–H stretching vibrations (Table 2 and Figure 1).

Table 2: Characteristic FTIR Absorption Peaks of Clopidogrel Bisulfate

Wavenumber (cm^{-1})	Type of Vibration
3484.86	N–H stretching
2954.20, 3077.37	CH stretch
1752.42	C=O stretching
1673.74	C=C stretching
1277.70	C–O stretching
1068.03	C–N and S=O stretching

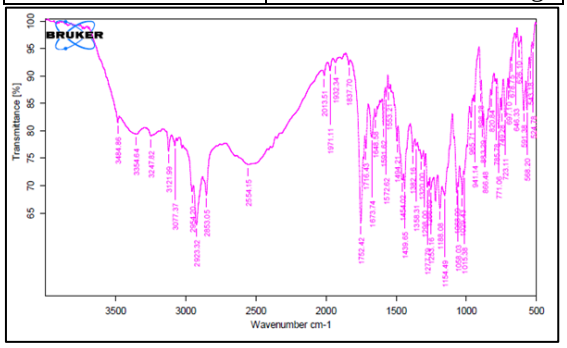

Figure 1: FTIR spectra of Clopidogrel bisulfate

3.1.3 Determination of λ max and construction of calibration curve

The quantitative estimation of Clopidogrel bisulfate was performed using a double-beam UV-Visible spectrophotometer in PBS pH7.4 as the solvent. The drug exhibited a distinct absorption maximum (λmax) at 240 nm, which was used as the analytical wavelength for all measurements (Figure 2A). A calibration curve was constructed by plotting absorbance against concentration, and it demonstrated excellent linearity within the tested range. The correlation coefficient (R^2) was found to be 0.9978 (Table 3 and Figure 2B).

Table 3: Calibration Curve Data for Clopidogrel Bisulfate in PBS pH7.4

S. No.	Concentration (µg/mL)	Absorbance
1	0	0
2	10	0.0824
3	20	0.1595
4	30	0.2359
5	40	0.3246
6	50	0.4015

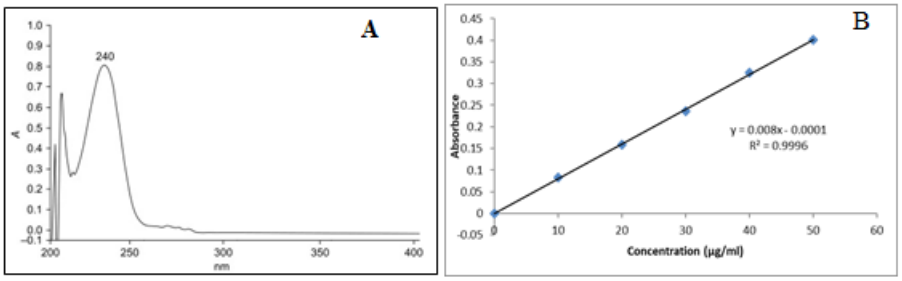

Figure 2: (A) UV spectra of CLO (λ max 240nm) (B) Calibration Curve for Clopidogrel Bisulfate

3.1.4 Solubility Study of Clopidogrel bisulfate

CLO exhibited significantly higher solubility in acidic media, with the maximum solubility observed in 0.1N HCl (2792.8 mg/L), PBS pH 7.4 (1295.8 mg/L). The solubility was low in water (201.8 mg/L) and 0.1N NaOH (213.08 mg/L).

3.1.5 Partition Coefficient Determination

The experimentally obtained Log P value was found to be 2.44, indicating that Clopidogrel bisulfate possesses lipophilic characteristics sufficient lipophilicity to cross biological membranes

3.2 Vesicle Size, PDI and Zeta Potential

The PS and PDI of niosomes are shown in Table 4. The size of the niosomes was found to vary between 296 and 390 nm with no significant difference (P value = 0.0627) between them. The results revealed that the niosomes prepared at a ratio of 2:1 (Span 60: cholesterol) (F5) had larger vesicle sizes. The size of drug-loaded niosomes with high ratio of Span 60: Cholesterol was found to be significantly higher ($p < 0.05$) (Figure 3A). All niosomal formulations were characterized by narrow size distributions (PDI <0.95). Formulation F5, which had the highest concentration of Span 60 (200 mg) and moderate cholesterol (100 mg), exhibited the highest negative zeta potential (–35.5 mV), suggesting improved colloidal

stability. In contrast, F2, containing the lowest amount of Span 60 (50 mg), showed the lowest absolute zeta potential value (–24.6 mV), indicating relatively lower stability.

Table 4: PS, ZP and PDI of CLO Loaded Niosomes

Formulation	PS (nm)	PDI	ZP (mV)
F1	280.56 ± 7.45	0.21 ± 0.00	-28.96 ± 0.28
F2	246.23 ± 6.84	0.16 ± 0.00	-24.62 ± 0.12
F3	325.00 ± 14.42	0.30 ± 0.00	-32.16 ± 0.19
F4	296.01 ± 11.98	0.33 ± 0.00	-26.71 ± 0.15
F5	390.00 ± 65.28	0.36 ± 0.00	-35.51 ± 0.36

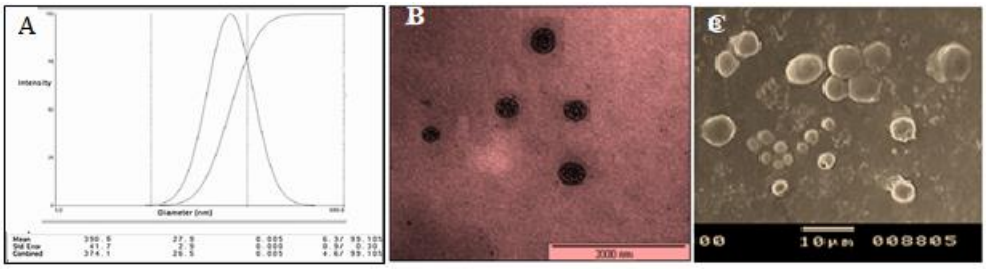

Figure 3: (A) PDI (B) TEM (C) SEM for the formulated niosomes (F5).

3.3 Entrapment Efficiency

The EE % was 68.4±5.04, 61.23 ± 2.62, and 73.25±4.12%, 65.7 ± 1.9% and 78.9 ± 1.6% for F1, F2, F3, F4 and F5 respectively. Formulation F5 showed the highest entrapment efficiency (78.9%), which can be attributed to the higher concentration of Span 60 (200 mg) and optimal cholesterol level (100 mg). This composition likely enhanced vesicle formation and drug encapsulation.

3.4 TEM and SEM

TEM analysis of the optimized niosomal formulation revealed spherical vesicles characterized by smooth and intact surfaces, indicative of well-formed bilayer structures. The SEM micrograph revealed that the niosomes were predominantly spherical in shape with smooth surfaces and no visible signs of aggregation. The average particle size observed from the SEM image was approximately 390 nm, which is in good agreement with the data obtained from dynamic light scattering (DLS) (Figure 3B & C).

3.5 *In Vitro* Drug Release

The optimized niosomal formulation F5 demonstrated a characteristic biphasic drug release pattern during the 24-hour. Initially, the formulation exhibited a burst release phase of 25–30% of Clopidogrel following this, the release rate slowed considerably, entering a sustained and controlled release phase over the remaining 24 hours (Table 5 and Figure 4).

Table 5: *In vitro* Release of Clopidogrel from Optimized Niosomal Formulation mean ± SD (n=3).

Time (hours)	Cumulative Released (%)	Amount (mg)
0.5	15.2 ± 1.8	1.24 ± 0.15
1	22.7 ± 2.1	1.85 ± 0.17
2	29.8 ± 2.4	2.43 ± 0.20
4	45.6 ± 3.0	3.72 ± 0.25
8	65.3 ± 2.8	5.32 ± 0.23
12	79.1 ± 3.2	6.44 ± 0.26
24	92.4 ± 2.9	7.52 ± 0.24

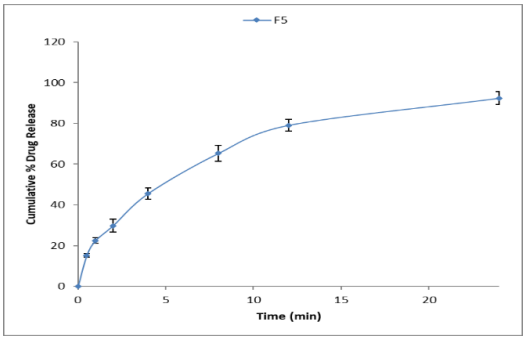

Figure 4: *In vitro* Cumulative % CLO release from Niosomal Formulation F5

3.6 Stability Study

Formulation F5 exhibited no significant change in particle size, indicating excellent physical stability ($p > 0.05$). Assessment of %EE over the same period further supported the physical stability of F5 (Table 7).

Table 7. Storage Stabilities of CLO-Loaded Niosomes (PS, PDI, and EE %) Mean ± SD (*n* = 3)

Code	PS (nm)		PDI		EE %	
	0 month	3 months	0 month	3 months	0 month	3 months
F5	394.33 ± 72.25	395.80 ± 70.25	0.33 ± 0.00	0.32 ± 0.00	78.90 ± 1.6	78.47 ± 2.50

4 CONCLUSION

The study successfully formulated and optimized Clopidogrel-loaded niosomes using the thin-film hydration method, with the Span 60: Cholesterol ratio of 2:1 emerging as the most effective composition. This optimized formulation demonstrated favorable nanoscale vesicle size and a sufficiently negative zeta potential, indicating excellent physical stability and uniformity. The entrapment efficiency of highlights the formulation's ability to effectively encapsulate. The *in vitro* drug release profile exhibited a desirable biphasic pattern. This controlled release behavior supports the potential of the niosomal formulation to maintain therapeutic drug levels, reduce dosing frequency, and minimize systemic side effects associated with conventional Clopidogrel therapy. Overall, the formulated niosomes show promise as an effective and stable delivery system for Clopidogrel, potentially improving its therapeutic efficacy in the treatment of Peripheral Artery Disease.

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