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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].

In this study, Clopidogrel-loaded niosomes were formulated using the thin-film hydration technique and evaluated for key parameters including particle size, entrapment efficiency, in vitro drug release, and physical stability. Special attention was given to optimizing the surfactant-to-cholesterol ratio to achieve a formulation that offers high drug loading, sustained release, and long-term stability. Additionally, the potential for reducing systemic side effects through controlled release was explored, highlighting the clinical relevance of this delivery system for PAD management. By addressing the pharmacokinetic limitations of conventional Clopidogrel therapy and improving its delivery profile through niosomal encapsulation, this study aims to contribute a novel and potentially more effective approach to the treatment of PAD.

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. All chemicals and reagents were used without further purification, and double-distilled water was used throughout the study for solution preparation and hydration steps.

2.2 Preparation of Niosomes

Niosomes were prepared using the thin-film hydration technique, a widely accepted method for forming stable vesicular systems. In this process, Span 60 and cholesterol were accurately weighed and dissolved in a chloroform:methanol mixture (2:1 v/v) in various molar ratios (1:1, 2:1, and 3:1) 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. This led to the formation of a thin, uniform lipid film along the inner wall of the flask. The dried film was then hydrated with phosphate-buffered saline (PBS, pH 7.4) containing a known amount of Clopidogrel, followed by vortexing to facilitate the formation of multilamellar vesicles [20]. To reduce the particle size and obtain uniform nanosized vesicles, the resulting suspension was sonicated using a probe sonicator for a defined duration. The prepared niosomal dispersions were stored at 4 °C for further characterization [21-22].

Table 1: Composition of CLO-Loaded Niosomes

Formula	CLO (mg)	Span 60 (mg)	Cholesterol (mg)
F1	100	100	100
F2	100	200	100
F3	100	300	100

2.3 Characterization of Niosomes

2.3.1 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). These parameters are critical indicators of the stability and performance of the vesicular system. Vesicle size influences the drug release rate, cellular uptake, and biodistribution, while zeta potential provides insight into the surface charge and colloidal stability of the formulation [23-24].

Prior to analysis, the niosomal dispersion was diluted appropriately with double-distilled water to avoid multiple scattering effects and ensure accurate measurement. The average hydrodynamic diameter (mean vesicle size) and polydispersity index (PDI) were recorded to assess the size distribution and homogeneity of the vesicles. 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]. A high absolute zeta potential value (either positive or negative, typically > ±25 mV) suggests sufficient repulsion between particles, reducing the risk of aggregation during storage. The results were reported as the mean of three measurements for each formulation, and all analyses were performed at 25 ± 1 °C under standard operating conditions [26].

2.3.2 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]. This process effectively separated the unentrapped (free) drug present in the supernatant from the drug-loaded vesicles, which formed a pellet at the bottom of the centrifuge tube. 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]. A blank sample containing PBS was used for baseline correction. The total amount of drug initially added during niosome preparation was known, and the amount of free drug detected in the supernatant was subtracted from this to obtain the quantity of drug entrapped within the vesicles [29]. Entrapment efficiency was then calculated using the following equation:

$$EE\% = \left(\frac{\text{Total Drug} - \text{Free Drug}}{\text{Total Drug}}\right) \times 100$$

All measurements were performed in triplicate to ensure accuracy and reproducibility. A higher entrapment efficiency indicates a more efficient formulation, which is desirable for achieving prolonged therapeutic effects and reducing dosing frequency.

2.3.3 Morphological Analysis

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 Transmission Electron Microscope (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. The niosomes were expected to appear as well-defined, spherical or near-spherical vesicles with uniform morphology, confirming successful vesicle formation and nanoscale structure [31-32].

2.3.4 In Vitro Drug Release

The in vitro release profile of Clopidogrel from the niosomal formulations was evaluated using the dialysis bag diffusion technique, which simulates the controlled release behavior of the drug under physiological conditions. The study was conducted in phosphate-buffered saline (PBS, pH 7.4), selected to mimic the pH of systemic circulation, at a constant temperature of 37 ± 0.5°C, corresponding to normal human body temperature [33-34].

Accurately measured volumes of niosomal suspension, equivalent to a fixed dose of Clopidogrel, were 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 (e.g., 0.5, 1, 2, 4, 6, 8, 12, and 24 hours), 5 mL aliquots of the external medium were withdrawn and immediately replaced with an equal volume of fresh PBS to maintain sink conditions. The collected samples were filtered, if necessary, and analyzed for Clopidogrel content using a UV-Visible spectrophotometer at a wavelength of 240 nm, previously determined as the drug's λmax in PBS. A calibration curve was prepared using standard solutions of Clopidogrel to ensure accurate quantification [37-38]. All measurements were carried out in triplicate, and the cumulative amount of drug released at each time point was calculated and expressed as a percentage of the total drug content [39-40].

3. RESULTS AND DISCUSSION

3.1 Vesicle Size and Zeta Potential

The optimized niosomal formulation, prepared using a Span 60 to cholesterol molar ratio of 2:1, exhibited a mean vesicle size of 162.4 ± 5.2 nm, as determined by dynamic light scattering (DLS). This nanoscale size is ideal for enhancing

bioavailability, promoting cellular uptake, and enabling passive targeting through the enhanced permeability and retention (EPR) effect, especially in pathological conditions like Peripheral Artery Disease where endothelial permeability may be altered. The narrow size distribution also indicates the formulation's uniformity and suitability for systemic administration.

In addition to the favorable size profile, the formulation displayed a zeta potential of –28.5 ± 1.3 mV, which reflects a moderately high negative surface charge. This negative charge is primarily attributed to the orientation of the non-ionic surfactant molecules (Span 60) in the vesicle membrane and their interaction with the aqueous environment. A zeta potential in this range generally indicates strong electrostatic repulsion between vesicles, which minimizes particle aggregation and contributes to the physical stability of the dispersion over time. Stable zeta potential values are essential for long-term storage and for maintaining consistent drug delivery characteristics. The combination of a nanometric vesicle size and a sufficiently negative zeta potential suggests that the optimized formulation (F2) has the structural integrity and colloidal stability necessary for effective in vivo performance, with reduced risk of vesicle fusion or precipitation during storage or after administration.

3.2 Entrapment Efficiency

The highest entrapment efficiency was achieved with the Span 60 to cholesterol molar ratio of 2:1, resulting in an entrapment efficiency (EE%) of 78.3 ± 3.7%. This superior drug loading can be attributed to the optimal bilayer rigidity and hydrophobicity provided by this specific lipid composition. At this ratio, cholesterol sufficiently stabilizes the niosomal bilayer by filling the gaps between the surfactant molecules, which enhances membrane packing and reduces permeability. This structural reinforcement minimizes drug leakage, thereby improving the retention of Clopidogrel within the vesicles.

Conversely, lower cholesterol content (e.g., 1:1 ratio) may lead to a less ordered bilayer with increased membrane fluidity, which can cause premature drug leakage. On the other hand, excessive cholesterol (e.g., 3:1 ratio) may disrupt the regular arrangement of surfactant molecules, creating imperfections in the bilayer that also reduce drug entrapment. Therefore, the 2:1 ratio represents a balanced composition that maximizes vesicle integrity and drug encapsulation by achieving an ideal combination of membrane rigidity and hydrophobic interaction between the lipid components and Clopidogrel.

This finding underscores the critical role of cholesterol in modulating vesicle architecture and drug encapsulation, and highlights the importance of optimizing surfactant-to-cholesterol ratios for achieving efficient niosomal formulations.

3.3 Morphological Analysis

Transmission Electron Microscopy analysis of the optimized niosomal formulation revealed spherical vesicles characterized by smooth and intact surfaces, indicative of well-formed bilayer structures. The vesicles appeared discrete and uniformly distributed without signs of aggregation or fusion, confirming the homogeneity and colloidal stability of the formulation. The observed morphology aligns with the nanoscale size measurements obtained via DLS, further validating the successful formation of stable, nanosized vesicles. The smooth surface texture and spherical shape are critical for enhancing vesicle stability and facilitating efficient drug encapsulation and controlled release. These morphological characteristics suggest that the formulation possesses the necessary structural integrity for effective in vivo delivery of Clopidogrel.

3.4 In Vitro Drug Release

The optimized niosomal formulation (Span 60:Cholesterol = 2:1) demonstrated a characteristic biphasic drug release pattern during the 24-hour in vitro release study in phosphate-buffered saline (PBS, pH 7.4) at 37°C. Initially, the formulation exhibited a burst release phase within the first 2 hours, during which approximately 25–30% of Clopidogrel was rapidly released. This initial release can be attributed to the drug molecules adsorbed or loosely bound near the surface of the vesicles.

Following this, the release rate slowed considerably, entering a sustained and controlled release phase over the remaining 22 hours. This prolonged phase resulted in a cumulative drug release of approximately 92% at 24 hours (Table 2 and Figure 1), indicating that the majority of the encapsulated drug was gradually diffused through the vesicular bilayer. Such a biphasic release profile is highly desirable in therapeutic contexts as it ensures a rapid onset of action followed by prolonged maintenance of therapeutic drug levels, potentially reducing dosing frequency and enhancing patient compliance.

This controlled release behavior is primarily due to the optimized lipid composition, where the cholesterol content imparts membrane rigidity, limiting drug diffusion and stabilizing the vesicles. The nanoscale vesicle size and bilayer structure further facilitate sustained release by creating a diffusion barrier for the drug.

Table 2: Cumulative In Vitro Release of Clopidogrel from Optimized Niosomal Formulation

Time (hours)	Cumulative Drug Released (%)	Amount Released (mg)
0.5	15.2 ± 1.8	1.24 ± 0.15
1	22.7 ± 2.1	1.85 ± 0.17

Time (hours)	Cumulative Drug Released (%)	Amount Released (mg)
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

Values are expressed as mean ± SD (n=3).

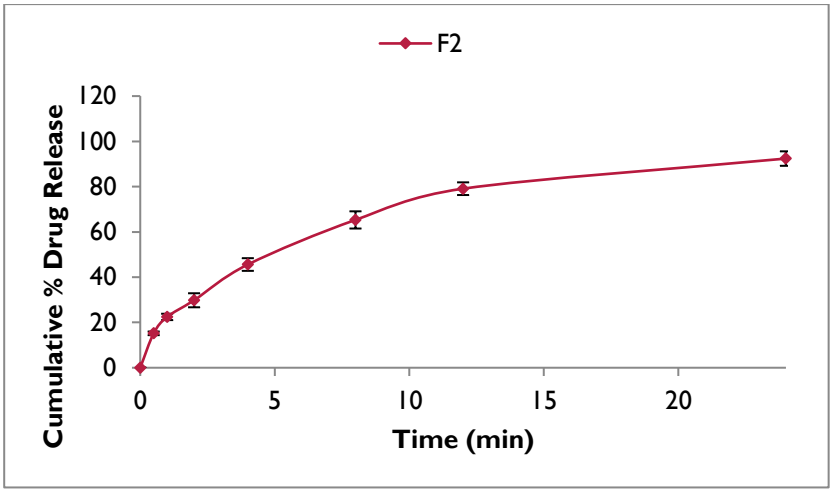

Figure 1: In Vitro Cumulative Release Profile of Clopidogrel from Optimized Niosomal Formulation (Span 60:Cholesterol = 2:1)

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 (~162 nm) and a sufficiently negative zeta potential (−28.5 mV), indicating excellent physical stability and uniformity. The entrapment efficiency of 78.3% highlights the formulation's ability to effectively encapsulate Clopidogrel, attributed to optimal bilayer rigidity and hydrophobic interactions. Morphological analysis confirmed the presence of spherical, smooth-surfaced vesicles with uniform distribution. Importantly, the in vitro drug release profile exhibited a desirable biphasic pattern with an initial burst release followed by sustained drug release, achieving approximately 92% cumulative release over 24 hours. 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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