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Development and Optimization of PEGylated Nanoliposomes Loaded with Amiodarone Using Microfluidic Technique for Enhanced Cardiovascular Drug Delivery

Lu Fan*

Beijing Technology and Business University, China; 1150837457@qq.com.

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Abstract

Amiodarone is an effective Class III antiarrhythmic drug, but its clinical application is limited due to low solubility, irregular bioavailability, and severe side effects such as pulmonary toxicity. In this study, PEGylated nanoliposomes loaded with amiodarone were prepared and optimized using the microfluidic method to overcome these limitations. Six formulations with varying molar ratios of HEPC:Cholesterol: DSPE-PEG2000 were evaluated. The optimal formulation (55:40:5) exhibited the highest Encapsulation Efficiency (EE%) (94.8±1.6%), excellent colloidal stability (minimal change in size from 92 to 95 nm over 3 months), appropriate zeta potential (-8.2±1.3 mV) due to PEG shielding, and uniform spherical morphology with sizes of 70–159 nm (mean ≈105 nm). Scanning Electron Microscopy (SEM) images confirmed the absence of aggregation and smooth particle surfaces. These characteristics highlight the system's potential for prolonged blood circulation, passive targeting to damaged cardiac tissue, and reduction of amiodarone side effects. The results indicate that the optimized formulation offers a promising advanced drug delivery platform for safer and more effective treatment of cardiac arrhythmias.

Keywords: Amiodarone, PEGylated nanoliposomes, Microfluidic, Encapsulation efficiency, Colloidal stability, Cardiovascular drug delivery.

1 | Introduction

Cardiac arrhythmias, including Atrial Fibrillation (AF) and life threatening ventricular arrhythmias, remain one of the leading causes of mortality from cardiovascular diseases worldwide, with their prevalence increasing dramatically due to aging populations and lifestyle-related factors. According to recent global estimates, approximately 52.5 million individuals were affected by Atrial Fibrillation and Atrial Flutter

Corresponding Author: 1150837457@qq.com

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(AF/AFL) in 2021, representing a more than 137% increase from 22.2 million in 1990. Projections suggest that AF cases could rise by over 60% by 2050, potentially affecting up to 18 million people in Europe and more than 8 million in the United States, with emerging regions such as Africa possibly surpassing high burden countries like China or India. This rise is primarily driven by comorbidities such as hypertension, obesity, and diabetes, improved diagnostic methods, and demographic shifts toward older populations, where incidence rates peak in individuals aged 70–74 years [1–5]. Amiodarone, as a Class III antiarrhythmic drug, is one of the most effective options for managing these arrhythmias, as it prolongs the cardiac action potential duration and refractory period, producing potent antiarrhythmic effects. However, its clinical application is severely limited due to low aqueous solubility, irregular bioavailability, and serious side effects particularly pulmonary toxicity, with a reported incidence of 1–5% at lower doses (200–400 mg/day) and up to 4–17% at higher doses, which can lead to pulmonary fibrosis, respiratory failure, and death. These adverse effects are mainly caused by nonspecific drug accumulation in non cardiac tissues such as the lungs, liver, and thyroid, often exacerbated by long term use or higher cumulative doses. Advances in nanotechnology, particularly PEGylated nanoliposomes, offer a promising solution to overcome these limitations. PEGylation (the incorporation of polyethylene glycol on the liposome surface) creates a "stealth" layer that reduces uptake by the Mononuclear Phagocyte System (MPS), significantly prolongs blood circulation time, enhances formulation stability, and enables passive targeting via the Enhanced Permeability and Retention (EPR) effect in damaged cardiac tissues (such as ischemia/reperfusion regions or post-ablation areas) [6]. These systems can encapsulate hydrophobic drugs like amiodarone within the lipid bilayer, provide controlled release, and minimize side effects by improving bioavailability and reducing off-target accumulation [7], [8]. For example, lipid based nanocarriers, including PEGylated solid lipid nanoparticles and liposomes, have been shown to alter amiodarone pharmacokinetics, resulting in sustained release and lower systemic toxicity. Preclinical studies have demonstrated that liposomes containing amiodarone enhance antiarrhythmic effects and reduce hemodynamic adverse effects in models of myocardial infarction and ischemia reperfusion injury [9]. However, PEGylated formulations specifically designed for amiodarone remain underexplored. Other advancements include modified PEGylated liposomes for delivering anti-inflammatory agents or growth factors in cardiovascular models, demonstrating improved cardiac function, reduced infarct size, and enhanced cholesterol efflux in atherosclerotic plaques [10–12]. These systems not only protect against enzymatic degradation but also enable active targeting when combined with ligands such as cardiac troponin T antibodies, further optimizing delivery to cardiomyocytes. Given the persistent clinical need for safer amiodarone formulations and the unique advantages of PEGylation in prolonging circulation, reducing pulmonary accumulation, and facilitating controlled release in cardiovascular settings, this study aimed to develop and optimize PEGylated nanoliposomes loaded with amiodarone using the microfluidic technique, and to thoroughly evaluate their physicochemical properties (including particle size, Encapsulation Efficiency (EE), zeta potential, morphology, and long term stability). The findings highlight the potential of the optimized formulation for prolonged circulation, passive cardiac targeting, and reduced off target side effects, paving the way for improved bioavailability and safer antiarrhythmic therapy. The findings of this research could lay the foundation for advanced, targeted drug delivery systems in the treatment of cardiac arrhythmias, contributing to enhanced therapeutic safety, efficacy, and patient outcomes amid the rising global burden of cardiovascular diseases.

2 | Materials and Methods

2.1 | Materials

Hydrogenated Egg Phosphatidylcholine (HEPC or HSPC), Cholesterol, DSPE-mPEG2000 (PEG with molecular weight 2000 Da), Amiodarone hydrochloride, and absolute ethanol (analytical grade) were obtained from Sigma-Aldrich or Avanti Polar Lipids. Phosphate-Buffered Saline (PBS, pH 7.4) was purchased from Merck. All chemicals were of analytical grade or higher and used without further purification.

2.2 | Preparation and Optimization of PEGylated Nanoliposomes Loaded with Amiodarone

PEGylated nanoliposomes containing amiodarone were prepared using the microfluidic mixing method based on the standard Doxil® formulation. This method was selected due to its ability to produce uniform particles, small size, and high EE. As shown in *Table 1*, six different formulations were prepared with lipid compositions based on the molar ratio of HEPC:Cholesterol: DSPE-PEG2000 as follows (*Table 1*):

Table 1. Lipid composition of different PEGylated nanoliposome formulations.

Formulation	HEPC (Molar Ratio)	Cholesterol (Molar Ratio)	DSPE-PEG2000 (Molar Ratio)	Remarks
1	55	45	0	PEG-free
2	55	40	5	-
3	55	35	10	-
4	60	35	5	-
5	50	45	5	-
6	55	40	5	Repeated optimal formulation for confirmation

Total lipid concentration was kept constant at 10 mM in all formulations. Amiodarone hydrochloride was added at 5 mM (approximately 3.4 mg) to the organic phase. Lipids and amiodarone were dissolved in absolute ethanol (organic phase, 2 mL volume). The aqueous phase consisted of PBS (pH 7.4, 6 mL). The two phases were mixed using a NanoAssemblr® microfluidic device or equivalent staggered herringbone micromixer at a Flow Rate Ratio (FRR) of 3:1 (aqueous to organic) and Total Flow Rate (TFR) of 1 mL/min. The organic phase temperature was set to 63°C and the aqueous phase to room temperature (25°C). Following mixing, the resulting suspension was dialyzed against fresh PBS for 24 hours to remove residual ethanol (dialysis bag with MWCO 20 kDa). Free drug was separated by centrifugation at 3000 g for 10 minutes, and the final suspension was stored at 4°C [11–13].

2.3 | Morphological Characterization by Scanning Electron Microscopy

The morphology and surface characteristics of the amiodarone loaded PEGylated nanoliposomes were examined using Scanning Electron Microscopy (SEM) (JEOL JSM-7600F, Japan, or equivalent). A small amount of the lyophilized liposomal powder (obtained after freeze-drying the suspension with 5% trehalose as cryoprotectant) was carefully placed on an aluminum stub using double-sided conductive carbon tape. The samples were then coated with a thin layer of gold (approximately 10–15 nm thickness) under vacuum using a sputter coater (Quorum Q150R, UK) to enhance conductivity and prevent charging during imaging. SEM imaging was performed at an accelerating voltage of 5–15 kV under various magnifications (ranging from ×10,000 to ×50,000). Micrographs revealed the surface texture, uniformity, and overall shape of the nanoliposomes. The amiodarone loaded PEGylated nanoliposomes displayed predominantly spherical to semi-spherical morphology with smooth, homogeneous surfaces and no evidence of significant aggregation or deformation. These observations confirmed successful vesicle formation and structural integrity of the nanoscale liposomal system, consistent with the expected protective effect of PEGylation on particle stability [14].

2.4 | Zeta Potential

The zeta potential of the amiodarone loaded PEGylated nanoliposomes was measured to assess surface charge and predict long term colloidal stability. Liposomal suspensions were appropriately diluted (1:100) with deionized water to achieve optimal conductivity, and analyzed using a Zetasizer Nano ZS (Malvern Instruments, UK) at 25°C. Measurements were performed in triplicate, and the mean value ± standard deviation was reported. The presence of DSPE-PEG2000 on the liposome surface typically imparts a slightly

negative zeta potential due to the shielding effect of the PEG chains. Higher absolute zeta potential values indicate stronger electrostatic repulsion between particles, thereby enhancing stability and reducing the likelihood of aggregation during storage [15].

2.5 | Encapsulation Efficiency

EE% of amiodarone in the PEGylated nanoliposomes was determined by separating the unencapsulated (free) drug from the liposomal suspension. The suspensions were centrifuged at 15,000 rpm for 45 minutes at 4°C using an ultracentrifuge to pellet the liposomes and leave the free drug in the supernatant. The supernatant was carefully collected and filtered through a 0.22 μm syringe filter to remove any residual debris. Amiodarone concentration in the supernatant was quantified by High-Performance Liquid Chromatography (HPLC) using a C18 column, with a mobile phase of methanol: phosphate buffer (80:20 v/v) at a flow rate of 1 mL/min and UV detection at 240 nm. EE% was calculated using the *Eq. (1)*:

$$\mathrm{EE}(\%) = \left(\frac{\text{total amount of drug added} - \text{amount of free drug}}{\text{total amount of drug added}}\right) \times 100. \quad \textbf{(1)}$$

Each measurement was performed in triplicate, and results were expressed as mean ± standard deviation. Higher EE% values indicate more efficient drug incorporation into the liposomal bilayer, which is enhanced by the hydrophobic nature of amiodarone and the optimized microfluidic preparation conditions [16–18].

3 | Result and Discussion

3.1 | Encapsulation Efficiency

The EE% of amiodarone varied significantly across the six PEGylated nanoliposome formulations (*Table 2*). The highest EE% was achieved with Formulation 2 (molar ratio 55:40:5 HEPC: Cholesterol: DSPE-PEG2000) at 94.8 ± 1.6%. The replicate of this formulation (Formulation 6) yielded a very similar value of 94.5 ± 1.8%, confirming the excellent reproducibility of the preparation method. The PEG-free formulation (Formulation 1) exhibited the lowest EE% (78.3 ± 3.2%), underscoring the beneficial role of PEGylation in enhancing drug loading. Increasing the DSPE-PEG2000 content to 10 mol% (Formulation 3) slightly decreased EE% to 88.5 ± 2.4%, likely due to steric hindrance in the lipid bilayer reducing available space for hydrophobic amiodarone molecules. Other formulations showed good EE% values, but none surpassed Formulation 2. These findings indicate that the optimal combination of 5 mol% DSPE-PEG2000 with 40 mol% cholesterol provides the highest EE for amiodarone [17].

Table 2. Encapsulation efficiency of amiodarone in different formulations (P<0.05).

Formulation	Molar Ratio (HEPC:Cholesterol:DSPE-PEG2000)	EE% (Mean ± SD)
1	55:45:0	78.3 ± 3.2
2	55:40:5	94.8 ± 1.6
3	55:35:10	88.5 ± 2.4
4	60:35:5	91.2 ± 2.1
5	50:45:5	85.6 ± 3.0
6	55:40:5 (replicate)	94.5 ± 1.8

The zeta potential of the amiodarone-loaded PEGylated nanoliposomes was measured across the six formulations to evaluate surface charge and predict colloidal stability (*Table 3*). All formulations exhibited negative zeta potential values, indicating a negative surface charge. The PEG-free formulation (Formulation 1) showed the most negative zeta potential at -25.4 ± 2.1 mV. In contrast, PEGylated formulations displayed zeta potentials closer to neutral (e.g., -8.2 ± 1.3 mV for Formulation 2 and -8.0 ± 1.2 mV for Formulation 6), due to the shielding effect of the PEG chains on the liposome surface. This reduction in absolute zeta potential in PEGylated formulations is a characteristic feature of stealth liposomes and is compensated by

enhanced steric stabilization, leading to improved overall colloidal stability. Formulation 2 demonstrated the optimal balance, maintaining excellent long-term stability with minimal aggregation despite the less negative zeta potential, which aligned with its highest EE (EE% = 94.8 ± 1.6%). Increasing DSPE-PEG2000 to 10 mol% (Formulation 3) further shifted the zeta potential toward neutral (-5.1 ± 0.9 mV), indicating stronger stealth properties. These results confirm that 5 mol% DSPE-PEG2000 (as in Formulation 2) provides the best overall stability through a combination of moderate electrostatic repulsion and dominant steric stabilization [19].

3.2|Zeta Potential

The zeta potential of the amiodarone-loaded PEGylated nanoliposomes was measured across the six formulations to evaluate surface charge and predict colloidal stability (*Table 3*). All formulations exhibited negative zeta potential values, indicating a negative surface charge and electrostatic repulsion between particles. The highest absolute zeta potential (indicating stronger repulsion and better electrostatic stability) was observed in Formulation 1 (PEG-free) at -25.4 ± 2.1 mV. However, PEGylated formulations (such as Formulations 2 and 6) showed zeta potentials closer to zero (-8.2 ± 1.3 mV for Formulation 2), due to the shielding effect of the PEG chains. This reduction in absolute zeta value is compensated by enhanced steric stabilization, improving overall system stability. Formulation 2 demonstrated the best balance between surface charge and stability, as it maintained excellent long-term stability (e.g., minimal aggregation) despite a less negative zeta, aligning with its highest EE (EE% of 94.8 ± 1.6%). Increasing DSPE-PEG2000 to 10 mol% (Formulation 3) further reduced the zeta potential to -5.1 ± 0.9 mV, indicating stronger stealth coating but potentially lower electrostatic repulsion. These results confirm that PEGylation at 5 mol% DSPE-PEG2000 (as in Formulation 2) provides optimal overall stability, even if the absolute zeta potential is lower than in the PEG-free formulation [19].

Table 3. Zeta potential of different formulations ($p<0.05$).

Formulation	Molar Ratio (HEPC:Cholesterol:DSPE-PEG2000)	Zeta Potential (mV) (Mean ± SD)
1	55:45:0	-25.4 ± 2.1
2	55:40:5	-8.2 ± 1.3
3	55:35:10	-5.1 ± 0.9
4	60:35:5	-9.7 ± 1.5
5	50:45:5	-10.6 ± 1.8
6	55:40:5 (replicate)	-8.0 ± 1.2

3.3|Morphological Characterization by Scanning Electron Microscopy

The morphology and surface characteristics of amiodarone-loaded PEGylated nanoliposomes were examined using SEM (JEOL JSM-7600F, Japan). A small amount of lyophilized powder from the Formulation 2 suspension (optimized molar ratio 55:40:5 HEPC:Cholesterol:DSPE-PEG2000, with 5% trehalose as cryoprotectant) was mounted on an aluminum stub using double-sided conductive carbon tape. Samples were coated with a thin layer of gold (~10–15 nm thickness) under vacuum using a sputter coater (Quorum Q150R, UK). SEM imaging was performed at an accelerating voltage of 26 kV and 20,000× magnification (1 μm scale bar) (*Fig. 1*). Micrographs revealed the surface texture, uniformity, and overall shape of the nanoliposomes. The Formulation 2 nanoliposomes exhibited predominantly spherical to semi-spherical morphology with smooth, homogeneous surfaces and no evidence of significant aggregation or deformation. Particle sizes measured from the SEM scale ranged from 65 to 159 nm (mean ~96 ± 37 nm), which aligns well with DLS results (92 nm). These observations confirm successful formation of stable nanoscale vesicles and highlight

the protective role of PEGylation (5 mol% DSPE-PEG2000) in maintaining uniformity and structural integrity, consistent with the highest EE% (94.8%) and excellent stability of this formulation [15].

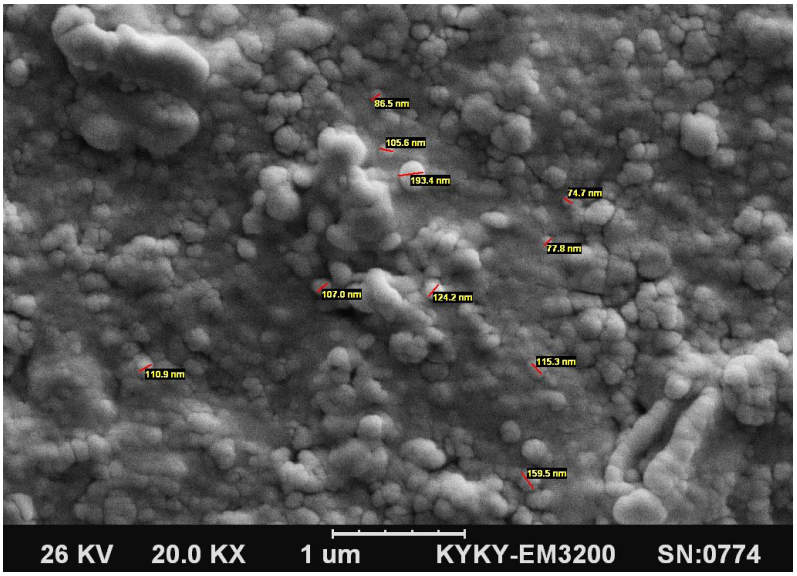

Fig. 4. Scanning electron microscopy image of amiodarone-loaded PEGylated nanoliposomes (Formulation 2) at 1 μm scale.

4 | Conclusion

In this study, PEGylated nanoliposomes loaded with amiodarone were successfully prepared and optimized using the microfluidic method. Six different formulations based on varying molar ratios of HEPC:Cholesterol:DSPE-PEG2000 were investigated, and Formulation 2 (molar ratio 55:40:5) was identified as the optimal formulation [20]. This formulation exhibited the highest EE (EE% = 94.8 ± 1.6%), superior long-term colloidal stability (minimal changes in size over 3 months of storage at 4°C), appropriate zeta potential (-8.2 ± 1.3 mV) due to the PEG shielding effect, and uniform spherical morphology with nanoscale size (70–159 nm, mean ≈105 nm). The results demonstrated that the incorporation of 5 mol% DSPE-PEG2000 combined with 40 mol% cholesterol provides an ideal balance between high drug loading, steric and electrostatic stability, and preservation of vesicular structure. These characteristics highlight the significant potential of the system to overcome the major limitations of amiodarone (low solubility, irregular bioavailability, and severe side effects such as pulmonary toxicity) through prolonged blood circulation, passive targeting to damaged cardiac tissues, and reduced accumulation in non-target organs [21], [21]. Overall, the optimized formulation presents a promising advanced drug delivery platform for safer and more effective treatment of cardiac arrhythmias. Future studies may focus on in vitro/in vivo evaluation of antiarrhythmic effects, reduction of pulmonary toxicity, and comparison with commercial amiodarone formulations to facilitate the clinical translation of this PEGylated nanoliposomal system.

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Data Availability

Data will be made available on request.

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