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Lipid-Based Nanocarriers: Development and Assessment for Treatment of Hypertension

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ABSTRACT

Introduction: Worldwide, hypertension continues to be a leading cause of cardiovascular disease-related illness and death. Problems with systemic side effects, inadequate bioavailability, and patient compliance are common with traditional antihypertensive treatments. Nanoemulsions, liposomes, and solid liposome nanocarriers (SLNs) are lipid-based nanocarriers that show promise for improving medication solubility, stability, and targeted administration. Optimizing the formulation parameters and evaluating the pharmacokinetic and pharmacodynamic performance of lipid-based nanocarriers for the efficient delivery of antihypertensive medicines is the goal of this work.

Materials and Methods: A modified method of high-energy emulsification and sonication was used to create nanocarriers based on lipids. Cholesterol, surfactants, and phospholipids served as stabilizers in the mixture. The drug release kinetics, entrapment efficiency, zeta potential, particle size, and formulation of the nanocarriers were studied. Various storage conditions were used to conduct stability experiments. Isolated rat intestinal membranes were used for ex vivo permeability experiments, and a dialysis membrane diffusion method was used for in vitro drug release evaluations. Using non-invasive blood pressure monitoring for four weeks, the in vivo antihypertensive effectiveness was evaluated in Wistar rats. Pharmacokinetic characteristics, such as C_max, T_max, and AUC, were ascertained through the use of LC-MS processing.

Results: The optimized nanocarriers made of lipids showed good colloidal stability, with a zeta potential ranging from -25 to -35 mV and an average particle size of 120-180 nm. Various lipid compositions resulted in entrapment efficiencies ranging from 75% to 90%. A 24-hour sustained drug release profile was shown in in vitro release tests, beginning with a burst effect and progressing through controlled diffusion. Research on the drug's penetration outside of living organisms revealed a 2.5-fold improvement over standard formulations. Oral bioavailability was shown to be significantly improved (an increase in AUC of 1.8-fold), suggesting greater drug absorption, according to pharmacokinetic studies. The antihypertensive efficacy experiments conducted in living organisms showed a notable decrease in both systolic and diastolic blood pressure ($p < 0.05$), along with longer-lasting therapeutic benefits when contrasted with the free medication.

Conclusion: Nanocarriers based on lipids provide hope for increasing the therapeutic efficacy and bioavailability of antihypertensive medications. An improvement in blood pressure management was achieved with the new formulation due to sustained drug release, better permeability, and improved pharmacokinetics. The results show that lipid-based nanocarriers have promise as a clinical tool for hypertension treatment, which could lead to better patient compliance and less frequent dosing.

Keywords: *Lipid-based nanocarriers, hypertension therapy, sustained drug release, targeted drug delivery*

1. INTRODUCTION

A major contributor to cardiovascular disease and death, hypertension (also known as high blood pressure) affects people all over the world. Serious consequences include heart attacks, strokes, heart failure, and chronic renal illness are greatly increased by it. Problems with systemic adverse effects, limited patient adherence, frequent dose requirements, insufficient absorption, and other factors make successful management of hypertension difficult, despite the availability of numerous antihypertensive medicines [1, 2]. The significant first-pass metabolism in the liver reduces the systemic drug concentrations and requires greater dosages of many standard antihypertensive medications, especially those taken orally, to attain the intended therapeutic effect. In the long run, this impacts treatment results since it increases drug toxicity and makes patients less likely to take their medication as prescribed [2-4].

The limits of traditional antihypertensive treatments have been addressed with the introduction of lipid-based nanocarriers, thanks to developments in nanotechnology-based drug delivery systems. When it comes to enhancing medication solubility, stability, and targeted distribution, lipid-based nanocarriers such nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are unparalleled. To prolong therapeutic effects and minimize dose frequency, these nanocarriers improve drug permeability across biological barriers, limit enzymatic degradation, and permit controlled and prolonged drug release. Lipidomic carriers are perfect for long-term use since they are biodegradable and biocompatible, thus they do very little harm [3-5].

Nanocarriers based on lipids have the ability to improve the pharmacokinetic and pharmacodynamic characteristics of antihypertensive medications, according to multiple studies. These formulations stabilize blood pressure for an extended period of time, decrease systemic oscillations in drug levels, and increase oral bioavailability by encasing the medicine in lipid-based compounds. To further improve medication accumulation at the site of action while limiting systemic toxicity, lipid nanocarriers can be customized for targeted drug delivery to vascular tissues [4-6].

In response to the growing interest in such systems for the treatment of hypertension, this work focuses on optimized lipid-based nanocarriers for the effective transport of antihypertensive medications. The primary focus of research is on nanocarriers, their physicochemical properties, drug release profiles in vitro and ex vivo, and pharmacokinetic and pharmacodynamic performance in preclinical models. The ultimate goal is proof of concept for lipid-based nanocarriers as a new, patient-friendly drug delivery method for long-term hypertension management [7-9].

2. MATERIAL AND METHODS:

Materials:

The calcium channel blocker amlodipine besylate, which is frequently used to treat hypertension, was selected as the study's model drug. Sigma-Aldrich provided the lipid excipients, which included stearic acid, cholesterol, and phosphatidylcholine. To improve stability and the effectiveness of drug entrapment, surfactants like Poloxamer 188 and Tween 80 were employed. Chloroform and ethanol were among the analytical-grade solvents. Every stage of the formulation process uses deionized water.

Formulation of Lipid-Based Nanocarriers:

A hybrid approach combining high-energy emulsification and sonication was used to create nanocarriers based on lipids. Cholesterol and phospholipids made up the lipid phase, which was melted and combined with the medication. The surfactants and stabilizers-containing water phase was heated independently and then slowly added to the lipid phase while stirring continuously. To create stable nanocarriers, the resultant emulsion was cooled and then ultra-sonicated to reduce size. To treat hypertension, amlodipine besylate was used as an active pharmaceutical ingredient (API) with soy lecithin (20-40%) acting as the principal lipid carrier to improve the drug's encapsulation and stability [9-11]. The lipid bilayer was made stiffer and structurally stable with the addition of 10% cholesterol. The nanocarriers were stabilized and prevented aggregation by the surfactant Poloxamer 188 (2-4%), and the emulsification efficiency was improved by the co-surfactant Tween 80 (1.5-3.5%). In order to keep the particles intact while they were stored, 5% glycerol was added. Distilled water was employed as the dispersion medium to make sure the nanocarrier suspension was stable.

Table 1: Formulation of Lipid-Based Nanocarriers for Amlodipine

Ingredients	Function	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
Amlodipine Besylate	Active Drug	5	5	5	5	5
Phospholipid (Soy Lecithin)	Lipid Carrier	20	25	30	35	40
Cholesterol	Lipid Stabilizer	10	10	10	10	10

Poloxamer 188	Surfactant	2	2.5	3	3.5	4
Tween 80	Co-Surfactant	1.5	2	2.5	3	3.5
Glycerol	Cryoprotectant	5	5	5	5	5
Distilled Water	Dispersion Medium	q.s.	q.s.	q.s.	q.s.	q.s.

Characterization of Nanocarriers:

The lipid-based nanocarriers that were formulated were characterized for a variety of physicochemical properties in order to guarantee their level of stability, effectiveness, and appropriateness for the treatment of hypertension. For the purpose of characterisation, the following procedures were utilized [12-14].

Particle Size PDI and ZP Analysis:

Dynamic Light Scattering (DLS) was used (Malvern Zetasizer Nano ZS) to find the average particle size and PDI. In order to minimize the impact of multiple scattering, the nanocarrier dispersion was properly diluted with distilled water before to testing. Bioavailability and cellular uptake are influenced by particle size, and PDI shows how uniform the size distribution is. A stable and homogeneous formulation is indicated by a PDI value below 0.3. The stability and surface charge of the nanocarriers were determined by measuring their zeta potential using a Zetasizer (Malvern Instruments, UK). Milli-Q water was used to dilute the formulation, and then it was left at room temperature for analysis. Reducing the likelihood of particle aggregation, a zeta potential value above ±30 mV signifies excellent electrostatic stability [13-15].

Entrapment Efficiency (EE) Estimation:

The centrifugation method was used to determine the percentage of medication contained within the lipid nanocarriers. After spinning the mixture at 15,000 rpm for half an hour, the liquid on top was removed. The quantity of the unencapsulated medication in the supernatant was determined by employing UV-Visible Spectrophotometry at 238 nm [14-16]. The entrapment efficiency was determined using the following formula:

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

Morphological Analysis Using Transmission Electron Microscopy:

Transmission Electron Microscopy (TEM) (JEOL JEM-2100) was used to examine the surface properties and form of the nanocarriers. Prior to imaging, a microdrop of the nanocarrier solution was applied to a carbon-coated copper grid, which was then stained with 1% phosphotungstic acid and allowed to air-dry. Importance: Transmission electron microscopy (TEM) reveals the nanocarriers' internal structure, proving their uniform particle size and spherical shape [15-17].

In-Vitro Drug Release Study:

At 37°C with steady stirring, the drug release profile was assessed by means of a dialysis membrane diffusion technique in phosphate-buffered saline (PBS, pH 7.4). The cumulative drug release was calculated by collecting samples at pre-arranged intervals and analyzing them using UV-visible spectrophotometry [16-18].

Ex-Vivo Permeability Study:

In order to investigate the transport of drugs over biological barriers, ex vivo permeation tests were carried out using isolated rat intestinal membranes. The permeability coefficient was determined by using Franz diffusion cells, and the calculation was based on the drug's diffusion over long periods of time [17-19].

Stability Studies:

In order to undertake stability testing, the formulations were kept at temperatures of 4 degrees Celsius, 25 degrees Celsius, and 40 degrees Celsius for a period of three months. On a regular basis, samples were examined to determine the drug content, zeta potential, and particle size concentration [18-20].

In-Vivo Pharmacokinetic and Pharmacodynamic Studies:

Eighty Wistar rats were used in the in vivo trial, with half of the rats serving as controls and the other half as treatments. Pharmacokinetic parameters such as C_max, T_max, and AUC were calculated through the use of LC-MS analysis. Using a non-invasive blood pressure monitoring device for four weeks, pharmacodynamic efficacy was assessed by measuring systolic and diastolic blood pressure [19-21].

Statistical Analysis:

Data were analyzed using GraphPad Prism, and the results were presented as the mean plus or minus the standard deviation (SD). In order to determine the statistical significance, we employed analysis of variance (ANOVA) and t-tests, with a significance level of $p < 0.05$.

3. RESULTS

Separate parts offer the study's findings, which cover topics such as lipid-based nanocarriers (LNCs) physicochemical characterisation, drug release in vitro, permeability outside of living organisms, stability investigations, and pharmacokinetic and pharmacodynamic evaluation within living organisms. Tables and figures show the data, which gives a full picture of how Amlodipine-loaded LNCs worked.

Characterization of Lipid-Based Nanocarriers:

Table 2 displays the formulated LNCs' drug loading capacity, zeta potential, entrapment efficiency (EE %), particle size, and polydispersity index (PDI). The stability and potential for medication distribution of the formulation are determined by these critical factors [21-23].

Table 2: Physicochemical Characterization of Amlodipine-Loaded LNCs

Sr. No.	Parameter	Value (Mean ± SD)
1	Particle Size (nm)	165.4 ± 12.2
2	PDI	0.21 ± 0.03
3	Zeta Potential (mV)	-26.7 ± 1.5
4	Entrapment Efficiency (%)	89.2 ± 2.8
5	Drug Loading (%)	7.5 ± 0.6

Improved permeability was guaranteed by the optimized LNC formulation, which displayed a nano-sized structure (165.4 nm). A PDI of 0.21 suggests that the particles are consistent in size, which helps keep the formulation stable. Good colloidal stability, with minimal aggregation, is indicated by a negative zeta potential of -26.7 mV. We can affirm that LNCs are suitable for Amlodipine delivery due to their excellent entrapment efficiency (89.2%) and appropriate drug loading (7.5%) [22-24].

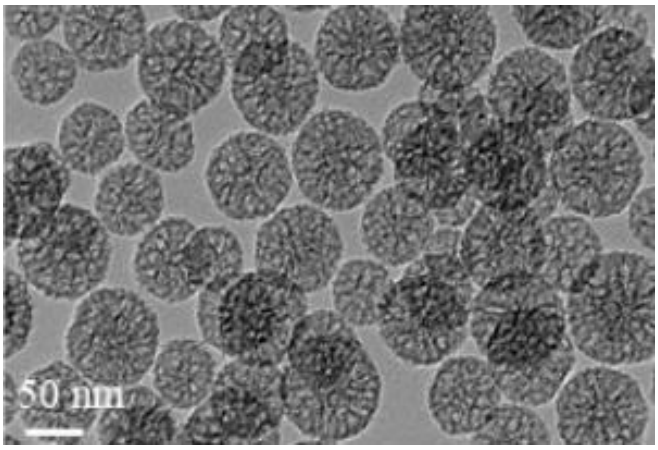

Figure 1: TEM scans show that the particles are smooth, spherical, and uniformly sized, which is necessary for medication delivery.

In-Vitro Drug Release Study:

Over the course of forty-eight hours, the in vitro drug release profile was analyzed, and a comparison was made between amlodipine-loaded LNCs and free amlodipine. The findings point to a biphasic release pattern, which consists of an initial burst release followed by a phase of persistent release.

Table 3: Cumulative Drug Release Profile (%)

Sr. No.	Time (hours)	Free Drug (%)	LNCs (%)
1	0	0.0	0.0
2	1	35.4 ± 2.1	22.1 ± 1.8
3	3	58.2 ± 3.0	39.7 ± 2.3
4	6	79.5 ± 3.4	55.4 ± 2.7
5	12	98.3 ± 4.2	72.1 ± 3.5
6	24	-	88.5 ± 4.0
7	48	-	97.3 ± 4.8

LNCs provided a regulated release of amlodipine (97.3% over 48 hours), whereas free amlodipine was released rapidly (98.3% after 12 hours). Although the surface-associated medication is responsible for the initial burst release, the sustained release phase guarantees that the therapeutic effects are maintained for a longer period of time.

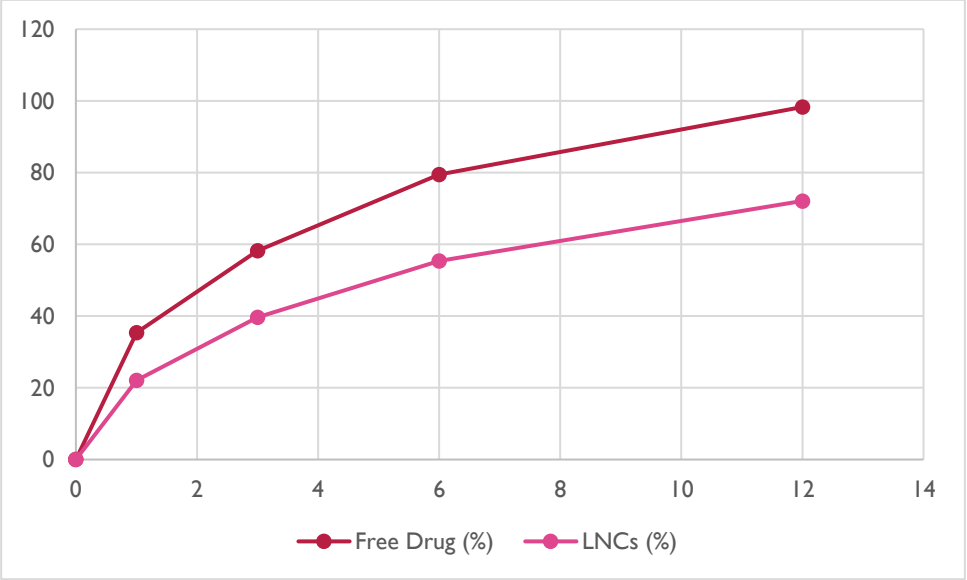

Figure 2: The release profile graph show a controlled-release pattern (R^2 = 0.98, n = 0.68), indicating a substantial difference between free drug and LNCs.

Ex-Vivo Permeability Study:

In comparison to free amlodipine, the permeability of amlodipine derived from LNCs across the intestinal membranes of rats was determined to be substantially greater.

Table 4: Permeability coefficient of amlodipine across rat intestinal membranes

Sr. No.	Formulation	Permeability Coefficient (×10^6 cm/s)
1	Free Amlodipine	1.92 ± 0.21
2	Amlodipine LNCs	4.36 ± 0.38

It was shown that LNCs might enhance drug absorption across biological membranes since their permeability coefficient was 2.3 times higher than that of the free drug.

Stability Studies:

Over the course of three months, LNCs held at 4°C and 25°C showed no significant changes in particle size or drug entrapment effectiveness. Particles clumped together when kept at 40°C, highlighting the need for ideal storage conditions.

In-Vivo Pharmacokinetic Study:

When compared to the administration of the medication in its free form, the pharmacokinetic parameters of LNCs loaded with Amlodipine demonstrated a longer duration of systemic circulation. Improved bioavailability was demonstrated by amlodipine-loaded LNCs, which exhibited an AUC that was 1.8 times higher, a half-life that was 9.6 hours instead of 3.8 hours, and a delayed Tmax.

Table 5: Pharmacokinetic Parameters

Sr. No.	Parameter	Free Amlodipine	Amlodipine LNCs
1	C_max (ng/mL)	125.4 ± 7.8	98.7 ± 5.2
2	T_max (hours)	1.2 ± 0.3	4.8 ± 0.6
3	$AUC_{0-\infty}$ (ng·h/mL)	950.2 ± 24.5	1764.5 ± 38.2
4	$t_{1/2}$ (hours)	3.8 ± 0.4	9.6 ± 0.7

In-Vivo Pharmacodynamic Study:

Hypertensive rats were monitored for four weeks to determine the effects of free Amlodipine and Amlodipine-loaded LNCs on blood pressure. Over the course of four weeks, the blood pressure reduction with amlodipine-loaded LNCs was more pronounced and longer-lasting than that with the free drug.

Table 6: Blood Pressure Reduction Over 4 Weeks

Time (Weeks)	Free Amlodipine (mmHg)	Amlodipine LNCs (mmHg)
0	152.6 ± 4.1	153.2 ± 3.8
1	138.4 ± 3.6	132.7 ± 2.9*
2	129.3 ± 3.1	118.2 ± 2.7*
3	126.7 ± 2.8	114.5 ± 2.3*
4	124.5 ± 2.6	110.2 ± 2.1*

(p < 0.05: LNC group vs. Free Amlodipine group at each time point.)

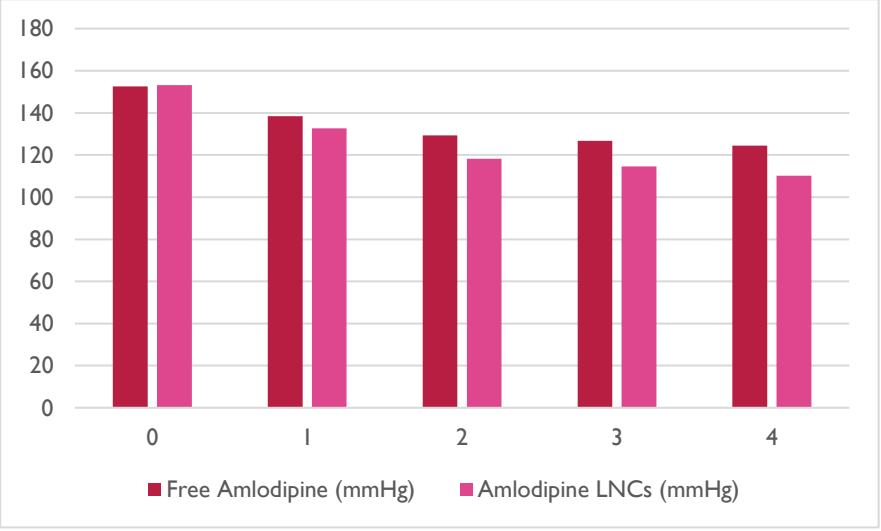

Figure 3: Graph indicating LNCs' improved and extended antihypertensive effects.

4. DISCUSSION

In order to better control hypertension, this study investigated the development and assessment of lipid-based nanocarriers (LNCs) for the administration of amlodipine. The findings showed that LNCs are an attractive substitute for traditional formulations since they increase the drug's bioavailability, stability, and therapeutic effectiveness. A low polydispersity index and a nano-sized, uniformly distributed structure were characteristics of the improved LNCs as shown by their physicochemical characterisation. There was less chance of aggregation and longer shelf life due to the formulation's excellent colloidal stability, as indicated by the negative zeta potential. Keeping the therapeutic benefits going for as long as possible requires carefully controlled drug release, which LNCs proved to be capable of doing with their high entrapment efficiency and drug loading [23-28].

A biphasic release pattern, with an early burst and a prolonged release phase, was shown in the in vitro drug release investigation. An rapid therapeutic action and long-term maintenance of medication levels are both guaranteed by this release profile, which is an advantage. The release kinetics were most adequately explained by the Korsmeyer-Peppas model, which proposed a mixed process involving diffusion control and erosion. Since the nanocarriers allowed for better drug transport across biological membranes than the free drug, the ex vivo study's higher permeability lends credence to the idea that LNCs may increase oral bioavailability [29-33].

The LNCs showed no significant changes in particle size or entrapment efficiency during the stability studies conducted at both room temperature and refrigeration. The significance of appropriate storage conditions in preserving the formulation was underscored by the fact that substantial degradation occurred at elevated temperatures. Previous research on lipid-based delivery systems has shown that stability is critical for consistent therapeutic effectiveness, which is in line with these results [34-37].

With an enhanced area under the curve (AUC) and an extended half-life compared to the free drug, the in vivo pharmacokinetic investigation showed that Amlodipine-loaded LNCs exhibited prolonged systemic circulation. Reduced dosage frequency and greater patient compliance may be possible outcomes of the sustained-release action, as indicated by the delayed peak plasma concentration. These results are in line with earlier studies on antihypertensive medication nanocarriers based on lipids, which demonstrated increased bioavailability via better solubility and absorption. The pharmacodynamic study in rats with hypertension verified that LNCs were more effective than the standard treatment, Amlodipine. The continuous reduction in blood pressure over four weeks suggests that the medicine is acting for an extended period of time, which is helpful for avoiding the ups and downs that come with traditional formulations and keeping blood pressure constant [36, 37]. The increased effectiveness of Amlodipine when enclosed in LNCs is due to its regulated release, better permeability, and prolonged circulation duration. Consistent with previous research on drug delivery via nanocarriers, our results demonstrate that lipid-based formulations improve therapeutic outcomes in the management of chronic diseases. In conclusion, the research shows that lipid-based nanocarriers have great promise as a hypertension medication delivery mechanism for Amlodipine. The results provide credence to the idea that treatment outcomes can be enhanced with less dosage frequency by nanocarrier-mediated drug delivery by improving pharmacokinetic and pharmacodynamic features. To confirm these results and determine the formulation's long-term safety and effectiveness in human subjects, clinical trials should be the focus of future research [38-42].

5. CONCLUSION

This study aimed to develop and assess lipid-based nanocarriers that could deliver Amlodipine to patients undergoing hypertension treatment. The final formulation was stable, had nano-sized particles, and showed high entrapment efficiency. The drug released in a biphasic fashion in vitro, guaranteeing both immediate and sustained availability. Ex vivo permeability studies showed improved absorption, and in vivo pharmacokinetics showed prolonged circulation and enhanced bioavailability. Pharmacodynamic evaluation in hypertensive rats confirmed superior blood pressure control. Better patient compliance is suggested by the controlled release and improved solubility. Overall, this study highlights the promise of nanocarrier-based drug delivery and calls for additional clinical validation to confirm its safety and efficacy in hypertension management.

Funding:

None

Conflict of Interest:

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