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Development and Evaluation of Chitosan Coated Optimized Levetiracetam loaded Nanoliposomes

Gopal Vijaykumar Lohiya, Sanket Dharashivkar, Rajeev Malviya* and Manisha Masih Singh

School of Pharmacy, Mansarovar Global University, Kolar Road, Bhopal (M.P.) - India

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Abstract

The development of chitosan-coated nanoliposomes has emerged as a promising strategy for enhancing the intranasal delivery of therapeutic agents targeting the central nervous system. In this study, optimized Levetiracetam-loaded nanoliposomes (Opt-LEV-NLs) were coated with 0.1% and 0.3% chitosan to improve nasal uptake and mucoadhesion. The formulations were evaluated for vesicle size, entrapment efficiency, in-vitro release, surface morphology, zeta potential, and pH to select the best formulation for brain targeting. Results demonstrated that 0.1% chitosan-coated nanoliposomes (Chit-NLs) retained an optimal particle size (151.72 ± 1.37 nm), suitable for nasal delivery, with a satisfactory entrapment efficiency (64.56 ± 1.03%) and effective drug release (82.51 ± 2.15%). In contrast, 0.3% Chit-NLs exhibited larger particle sizes (> 300 nm), lower release rates, and reduced suitability for intranasal delivery.

TEM and zeta potential analyses confirmed the successful chitosan coating and improved mucoadhesive properties. Based on these findings, 0.1% Chit-NLs were selected as the optimized formulation for further studies. This research supports the potential of chitosan-coated nanoliposomes for enhancing the bioavailability of Levetiracetam via the intranasal route.

Keywords: Chitosan, nanoliposomes, Levetiracetam, intranasal delivery, drug delivery system, brain targeting, mucoadhesion, optimized formulation

Introduction

The delivery of therapeutic agents to the brain has remained a significant challenge due to the presence of the blood-brain barrier (BBB), which restricts the entry of many drugs from the systemic circulation into the central nervous system (CNS) [1,2]. To overcome this limitation, non-invasive methods such as intranasal drug delivery have gained attention as a promising alternative [3,4]. Intranasal delivery bypasses the BBB and allows direct access to the brain through the olfactory and trigeminal pathways [5]. Among the various drug delivery systems, nanoliposomes have emerged as a versatile platform due to their ability to encapsulate both hydrophilic and lipophilic drugs, protect them from degradation, and enhance their bioavailability [6,7].

Levetiracetam, an anticonvulsant used in the treatment of epilepsy, has shown potential for brain targeting via intranasal delivery [8,9]. However, optimizing its delivery remains a challenge.

***Corresponding Author**
E.mail: rajeevrcp33@gmail.com

Quinolinederivatives Recent advancements in nanotechnology have proposed the use of chitosan, a biocompatible and mucoadhesive polymer, to coat nanoliposomes for enhanced nasal uptake and extended drug release [10]. Chitosan-coated nanoliposomes adhere to the nasal mucosa, improving drug residence time and absorption [11,12].

In this study, optimized Levetiracetam-loaded nanoliposomes (Opt-LEV-NLs) were formulated and coated with varying concentrations of chitosan (0.1% and 0.3%). The objective was to evaluate their particle size, entrapment efficiency, in-vitro release, and other physicochemical properties to determine the most suitable formulation for intranasal delivery [13,14]. This approach aims to enhance the bioavailability and therapeutic efficacy of Levetiracetam, making it a potential candidate for brain-targeted delivery [15].

Material and Methods

Materials

Levetiracetam was obtained as a gift sample from the pharmaceutical industry. Other chemicals and reagents used in the study were of analytical reagent grade.

Preparation of Levetiracetam-Loaded Nanoliposomes

Levetiracetam-loaded nanoliposomes were prepared using the modified thin film dehydration-rehydration method as previously described by Elsayed et al., 2011 and Luca et al., 2015. The required amounts of Phospholipon 90 G, cholesterol, and levetiracetam were dissolved in a chloroform and methanol mixture (2:1, v/v) in a round-bottom flask.The solvent was evaporated using a rotary evaporator (Hahnshin Scientific Co., Korea) under vacuum to form a thin lipid layer on the inner wall of the flask.The lipid film was kept under vacuum overnight to ensure complete removal of residual organic solvent.Tween 80 was then added, followed by hydration with NSB (pH 6.5) and agitated for 1 hour at the transition temperature (Tm) of the lipid.The resulting multilamellar vesicles were extruded through polycarbonate membrane filters (0.4 µm, 0.2 µm, and 0.1 µm) using a stainless steel filter holder (Axiva Sichem Pvt. Ltd.) to obtain unilamellarvesicles.The vesicles were sonicated on ice with a HD100 ultrasonic probe (Hielscher, Germany) and subsequently centrifuged at 25,000 × g at 4°C for 1 hour to remove free drug.The prepared nanoliposomes were stored at 2–8°C for further characterization.

Optimization of Levetiracetam-Loaded Nanoliposomes

Optimization was achieved using Design of Experiments (DOE) to study variables affecting particle size, drug entrapment efficiency, and drug release profile. The process involved two main stages: Plackett-Burman Design (PBD) for variable screening, followed by Response Surface Methodology (RSM) for detailed optimization.

Plackett-Burman Design for Variable Screening

The PBD was used to screen significant formulation variables influencing particle size, entrapment efficiency, and drug release. The design involved 11 factors and 12 experimental runs. The factors considered are shown in Table 1.

Table 1: Plackett-Burman Design Factors

S.No	Factor	Level-Low (-1)	Level-High (+1)
1	Phospholipids (µmol)	40	100
2	Cholesterol (µmol)	30	60
3	Tween 80 (% V/V)	1	3
4	Drug (% W/W)	5	10
5	Organic solvent (ml)	5	10
6	Rotary evaporator speed (rpm)	30	60
7	Temperature (°C)	35	50
8	Aqueous volume (ml)	5	10
9	Agitation time (minutes)	30	60
10	Sonication time (sec)	120	600
11	Annelation time (hours)	1	2

Response Surface Methodology (RSM) for Optimization

After screening, RSM was employed to optimize significant factors using a three-level Box-Behnken Design (BBD) for analyzing the main, interaction, and quadratic effects of the variables.

The independent variables and their ranges are shown in Table 2.

Table 2: RSM Independent Variables and Responses

Independent Variables (X)	Level (Coded)
Phospholipid (µmol) (X1)	Low (-1): 40
	Medium (0): 70
	High (+1): 100
Cholesterol (µmol) (X2)	Low (-1): 30
	Medium (0): 45
	High (+1): 60
Sonication time (sec) (X3)	Low (-1): 120
	Medium (0): 360
	High (+1): 600

Evaluation of Levetiracetam Loaded Nanoliposomes

Vesicle Size Determination of Nanoliposomes

The average particle size of the developed nanoliposomes was determined using photon correlation spectroscopy with a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). Samples were diluted in PBS (1:20 dilution) and filtered through a 0.45 nm membrane filter before analysis. The scattering angle was maintained at 173º, and the temperature at 25ºC. Measurements were performed in triplicate to obtain average values.

Entrapment Efficiency (% EE) of Nanoliposomes

The entrapment efficiency (% EE) of the drug-loaded nanoliposomes was evaluated using ultracentrifugation-filtration. The liposomal suspension was filtered and ultracentrifuged at 25,000×g for 45 minutes at 4ºC using a Beckman Coulter LE 80. The concentration of free drug in the supernatant was diluted with methanol and analyzed by UV-Spectrophotometry at 306.5 nm (Shimadzu, UV-160).

In-vitro Release

The release of levetiracetam from nanoliposomes was measured using an in-vitro dialysis method with a cellophane dialysis bag (MW cutoff 12,000 kDa, Himedia, India). Two milliliters of the levetiracetam-loaded nanoliposome formulation were placed in a dialysis tube and submerged in 100 ml nasal saline buffer (NSB; pH 6.5), maintained at 37± 0.5°C under constant stirring at 120 rpm. Aliquots of 2 ml were collected at 0.5, 1, 2, 4, 6, 8, and 12 hours, with replacement by fresh NSB. The concentration of released drug was analyzed by UV-spectrophotometry, and cumulative release was calculated.

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded to evaluate the thermal properties of levetiracetam, lyophilized optimized nanoliposomes (Opt-LMT-NLs), and placebo nanoliposomes, with 3% mannitol as a cryoprotectant (Verma et al., 2017; Cabral et al., 2004). The samples were sealed in aluminum pans and scanned from 20°C to 300°C at a heating rate of 10°C/min using a Perkin Elmer Pyris 6 DSC. An empty aluminum pan served as a reference standard, and nitrogen gas was used as a purge gas at a flow rate of 20 ml/min.

X-Ray Diffraction (XRD)

X-ray diffraction measurements of the drug and lyophilized Opt-LMT-NLs were performed using a diffractometer with Cu-K radiation (Ultima IV, I.R. Technology Services PVT. LTD.; US). The diffraction pattern was recorded over a 2θ angle range of 10° to 80°, with 40 kV voltage and 30 mA current settings.

Chitosan Coating of Optimized Levetiracetam-Loaded Nanoliposomes

To enhance nasal residence time and reduce naso clearance, the optimized nanoliposomes (Opt-LTG-NLs) were coated with chitosan to improve mucoadhesion on the nasal mucosa. Chitosan (0.1% and 0.3% w/v) was dissolved in a 0.1% v/v aqueous solution of acetic acid, stirred overnight at room temperature, and filtered through a 2 µm membrane filter. The lamotrigine-loaded nanoliposomes were then added dropwise to the chitosan solution under stirring at 25°C for 1 hour. The coated vesicles were ultracentrifuged at 15,000 rpm for 30 minutes at 4°C, washed with nasal saline buffer, and stored.

Evaluation of Chitosan-Coated Optimized Levetiracetam-Loaded Nanoliposomes

i) Vesicle Size Determination

The particle size of the chitosan-coated nanoliposomes was determined using photon correlation spectroscopy, as described for uncoated nanoliposomes.

ii) Entrapment Efficiency (% EE)

Entrapment efficiency for the chitosan-coated nanoliposomes was evaluated using the ultracentrifugation-filtration method, as previously described.

iii) In-vitro Release

The drug release profile of chitosan-coated nanoliposomes was evaluated using the in-vitro dialysis method detailed earlier.

iv) pH Determination

The pH of the optimized and chitosan-coated nanoliposomes was measured using a glass electrode pH meter (Mettler Instruments, Giessen, Germany).

v) Zeta Potential Study

The zeta potential of both optimized and chitosan-coated nanoliposomes was measured using a Zetasizer after dilution with distilled water.

vi) Surface Morphology Study

Transmission electron microscopy (TEM) was performed to study the surface morphology of the chitosan-coated and uncoated nanoliposomes. The samples were prepared by diluting with distilled water and placing a drop on carbon-coated copper grids. The excess liquid was blotted with tissue paper, and the samples were stained with 1% phosphotungstic acid. The grids were air-dried and analyzed using a Philips Tecnai G20 TEM.

Results and Discussion

Optimization of Levetiracetam Loaded Nanoliposomes Using Design of Experiment (DOE)

Screening of Variables by Plackett-Burman Design (PBD)

In the development of nanoliposomes for intranasal drug delivery systems, particle size and the release pattern of nanoliposomes through the nasal mucosa are critical parameters. The Plackett-Burman design (PBD) is useful for the initial screening of factors in the preparation of nanoliposomes, identifying their significant effects on responses, such as particle size, entrapment efficiency (%EE), and in-vitro drug release. These results are represented in a Pareto chart, where the factors are arranged according to their significance.

After conducting the 12 experimental runs (Table 1), 11 factors were analyzed, and three were found to have the most significant influence:

- Phospholipid amount (X1)
- Sonication time (X10)
- Cholesterol content (X2)

In Vitro Release

The Pareto chart showed that sonication time had the greatest negative effect on vesicle size, while phospholipids and cholesterol had a positive effect.

Particle size: Increased sonication time reduced vesicle size, while increasing phospholipid and cholesterol amounts led to larger vesicles.

Entrapment efficiency: The %EE was influenced positively by phospholipids and cholesterol but negatively by sonication time. Higher concentrations of phospholipids and cholesterol improved drug entrapment, while prolonged sonication reduced it.

In-vitro release: Both sonication time and phospholipids increased the release of vesicles, while cholesterol reduced it. Addition of Tween 80 also increased the release rate but had minimal effect on particle size and entrapment.

Based on these findings, sonication time (X10), phospholipid amount (X1), and cholesterol content (X2) were chosen as the most significant independent variables for further optimization under Response Surface Methodology (RSM).

Analysis of Significant Variables by Response Surface Methodology (RSM)

Following the PBD, a 3-factor, 3-level Box-Behnken design-response surface methodology (BBD-RSM) was employed for further optimization. The independent variables included sonication time, phospholipid amount, and cholesterol content, while the responses were vesicle size (Y1), entrapment efficiency (Y2), and in-vitro release (Y3). The 17 runs generated by the Design Expert software are shown in Table 2.

Quadratic models were found to be the best fit for these responses. The predicted and actual responses were highly accurate, as confirmed by statistical design (Table 2).

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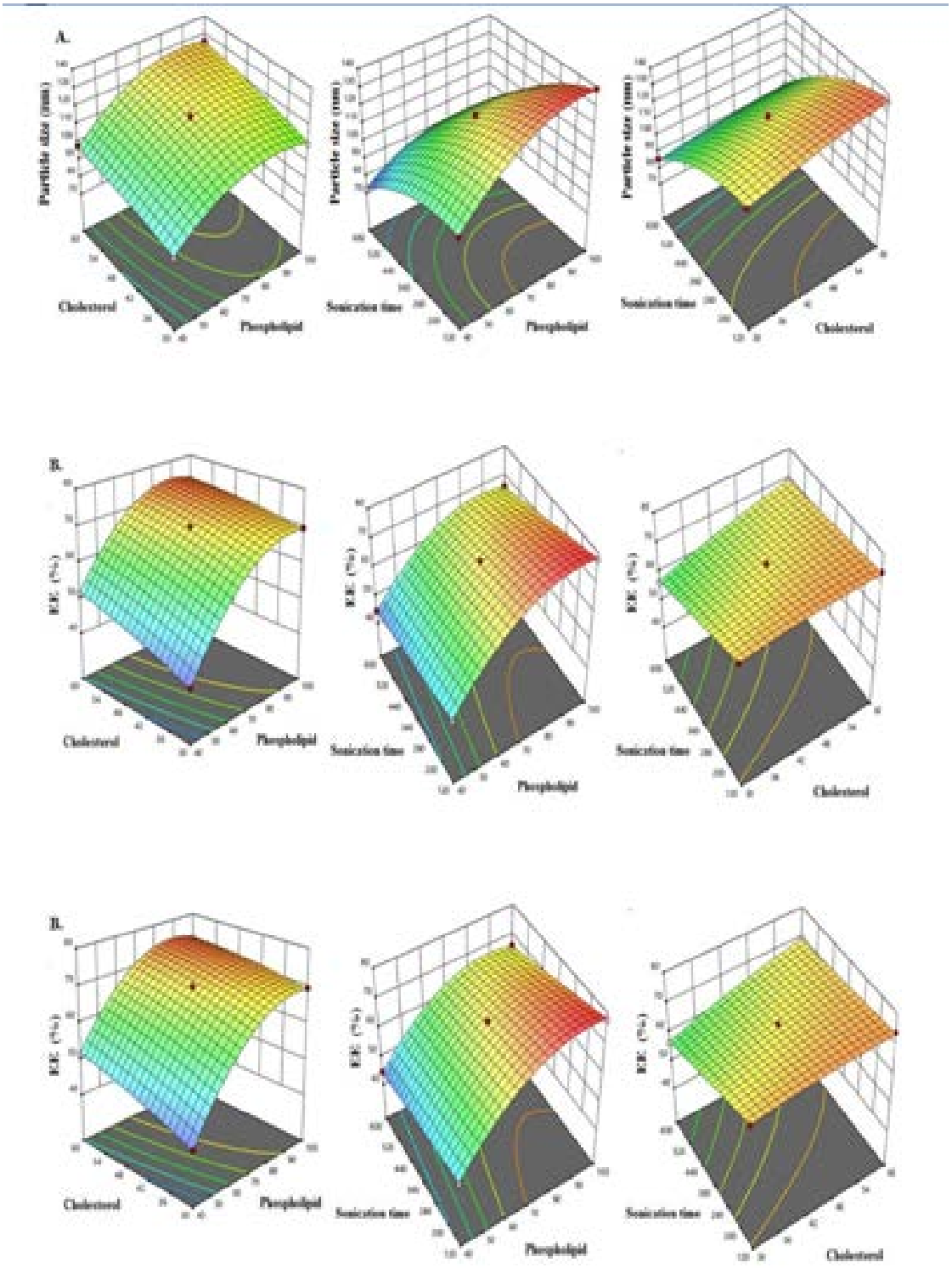

Figure 1: 3D-Contour plot for (A) particle size; (B) Entrapment efficiency (% EE); (C) In-vitro release.

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Table 1: Experimental Runs for Plackett-Burman Design (PBD)

Run	Factor X1 (µmol)	Factor X2 (µmol)	Factor X3 (% V/V)	Factor X4 (% w/w)	Factor X5 (ml)	Factor X6 (rpm)	Factor X7 (ºC)	Factor X8 (ml)	Factor X9 (min.)	Factor X10 (Sec.)	Factor X11 (hr)	Response R1 Particlesize (nm)±SD	Response R2 EE(%)±SD	Response R3 *In-vitro* release(%) ±SD
1.	100	60	1	6	5	80	30	10	60	120	2	152.20±3.25	80.20±3.10	60.23±2.35
2.	40	30	1	12	5	80	50	5	60	600	2	65.20±2.01	60.23±0.75	75.65±2.23
3.	100	30	3	12	10	40	30	5	60	120	2	152.61±2.90	58.23±0.01	68.14±1.62
4.	100	60	3	6	5	40	50	5	60	600	1	100..23±2.52	89.87±3.71	89.51±4.49
5.	100	60	1	12	10	80	30	5	30	600	1	123.45±2.82	75.26±2.32	89.62±3.56
6.	40	30	1	6	5	40	30	5	30	120	1	156.45±2.53	69.45±4.15	71.24±1.45
7.	40	60	1	12	10	40	50	10	60	120	1	135.37±3.77	75.51±3.59	56.14±1.48
8.	40	60	3	12	5	40	30	10	30	600	2	78.31±1.73	61.38±2.42	75.24±3.41
9.	100	30	3	12	5	80	50	10	30	120	1	145.45±3.45	86.23±2.16	75.42±2.62
10.	100	30	1	6	10	40	50	10	30	600	2	75.58±3.46	81.12±3.17	78.38±2.76
11.	40	30	3	6	10	80	30	10	60	600	1	56.47±2.79	59.47±0.25	52.65±2.87
12.	40	60	3	6	10	80	50	5	30	120	2	104.45±0.06	65.81±1.92	55.76±2.09

Table 2: Observed and Predicted Values for Box-Behnken Design (BBD)

	Independentvariables			Dependentresponses					
				Observedvalues			Predictedvalues		
F.C.	X_1	X_2	X_3	Y_1(±SD)	Y_2(±SD)	Y_3(±SD)	Y_1	Y_2	Y_3
B1	70	45	360	119.21±2.13	69.87±0.15	74.17±1.31	118.43	68.79	74.10
B2	70	45	360	118.45±1.04	68.43±2.53	73.32±1.71	118.87	68.79	74.10
B3	70	30	120	121.51±0.53	71.29±1.65	68.28±0.84	121.13	71.27	68.11
B4	100	45	600	84.51±3.01	66.43±2.31	81.63±2.91	84.06	66.16	81.43
B5	70	60	120	136.47±0.08	74.13±1.11	62.97±0.39	137.88	73.55	63.02
B6	70	45	360	117.61±2.74	67.92±1.87	75.01±3.59	118.87	68.79	74.10
B7	100	30	360	110.36±0.34	69.42±0.03	72.94±2.76	110.94	69.11	73.19
B8	40	30	360	88.41±1.05	41.54±0.06	64.24±1.15	88.44	41.29	64.21
B9	70	30	600	86.37±1.12	56.47±0.28	80.26±1.53	85.12	57.05	80.21
B10	70	60	600	92.54±0.60	69.54±2.33	79.24±0.21	92.38	69.56	79.41
B11	100	45	120	139.82±1.12	77.71±0.26	65.32±0.74	138.56	78.04	65.24
B12	40	45	120	99.47±1.53	50.26±0.81	58.45±0.52	98.31	50.53	58.65
B13	100	60	360	126.21±0.49	73.16±0.11	69.78±0.27	125.56	73.41	69.81
B14	40	45	600	72.18±0.18	44.52±1.32	70.84±2.74	72.44	44.19	70.92
B15	70	45	360	118.37±1.13	69.85±1.05	74.43±1.52	118.87	68.79	74.10
B16	40	60	360	98.17±2.41	51.45±1.22	61.94±0.76	97.81	51.76	61.69
B17	70	45	360	120.69±0.69	67.87±0.94	73.56±0.37	118.87	68.79	74.10

F.C: Formulation code; X_1 = Phospholipids (µmol); X_2= cholesterol (µmol); X_3= sonication time (minute.); Y_1= particle size (nm); Y_2= Entrapment Efficiency (%); Y_3= in-vitro release (%).

Characterization of Levetiracetam Loaded Nanoliposomes

Impact of Independent Variables on Vesicle Size (Response Y1)

Vesicle size is crucial for nanoliposomes as smaller sizes facilitate better penetration through the nasal mucosa. The quadratic polynomial equation for vesicle size (Eq. 1) indicates that phospholipids and cholesterol positively affect size, while sonication time has a negative effect. The correlation coefficient (R^2 = 0.9987) confirms a good model fit.

Polynomial Equation for Vesicle Size (Y1):

$$Y1 = +118.87 + 12.75\,X1 + 5.81\,X2 - 20.19\,X3 + 1.50\,X1X2 - 7.00\,X1X3 - 2.12\,X2X3 - 11.87\,X1^2 - 1.49\,X2^2 - 8.49\,X3^2$$

Impact of Independent Variables on Entrapment Efficiency (Response Y2)

Entrapment efficiency (%EE) measures the total drug amount incorporated into the lipid bilayer.

The quadratic polynomial equation for %EE (Eq. 2) indicates that phospholipid and cholesterol increase %EE, while sonication time decreases it.

Polynomial Equation for Entrapment Efficiency (Y2):

$$Y2 = +68.79 + 12.37\,X1 + 3.70\,X2 - 4.55\,X3 - 1.54\,X1X2 - 1.38\,X1X3 + 2.56\,X2X3 - 9.01\,X1^2 - 0.88\,X2^2 - 2.04\,X3^2$$

Impact of Independent Variables on In-Vitro Release (Response Y3)

The in-vitro release was optimized using the dialysis bag method. The quadratic equation (Eq. 3) confirmed that phospholipids and sonication time positively affect drug release, while cholesterol has a negative effect.

Polynomial Equation for In-Vitro Release (Y3):

$$Y3 = +74.10 + 10.12\,X1 + 4.95\,X2 - 5.83\,X3 - 1.73\,X1X2 + 3.65\,X1X3 - 1.19\,X2X3 - 6.47\,X1^2 - 0.76\,X2^2 - 3.28\,X3^2$$

Chitosan Coating of Optimized Levetiracetam Loaded Nanoliposomes

The optimized nanoliposomes (Opt-LEV-NLs) were coated with 0.1% and 0.3% chitosan to evaluate and select the best-coated formulation for further studies.

Evaluation of Chitosan-Coated Optimized Levetiracetam Loaded Nanoliposomes

The optimized Levetiracetam-loaded nanoliposomes, after coating with 0.1% and 0.3% chitosan, were subjected to various evaluation parameters to confirm the effectiveness of the coating process over the nanoliposome surface.

Vesicle Size

The vesicle size of Opt-LEV-NLs was 95.95 ± 2.56 nm. After coating with 0.1% and 0.3% chitosan, the vesicle sizes increased to 151.72 ± 1.37 nm and 415.12 ± 2.72 nm, respectively. This size increase confirms the successful coating of chitosan. The 0.1% chitosan-coated nanoliposomes (Chit-NLs) remained within the desirable size range for efficient nasal uptake, while the 0.3% Chit-NLs, with a size above 300 nm, were not suitable for intranasal delivery. Studies indicate that vesicle sizes below 200 nm are optimal for brain targeting via the intranasal route. Hence, the 0.1% Chit-NLs were deemed suitable for intranasal delivery.

Entrapment Efficiency (% EE)

The entrapment efficiency (% EE) of Opt-LEV-NLs was 88.72 ± 4.11%. After coating with 0.1% and 0.3% chitosan, the drug entrapment decreased to 64.56 ± 1.03% and 71.72 ± 1.72%, respectively. The reduction in % EE is attributed to drug leakage during the coating process and the incorporation of chitosan chains into the phospholipid bilayer. The 0.3% Chit-NLs exhibited a greater reduction in % EE compared to the 0.1% Chit-NLs.

In-Vitro Release

The release behavior of Opt-LEV-NLs and Chit-NLs in NSB (pH 6.5) at 37 ± 5°C, using the cellophane dialysis bag method, showed that 0.3% Chit-NLs released 73.43 ± 1.13% of the drug, while Opt-LEV-NLs released 82.51 ± 2.15%. However, the 0.1% Chit-NLs exhibited a satisfactory release of 78.26 ± 3.15%. The increase in vesicle size after chitosan coating reduced the release rate.

Table 3: Characterization of Optimized Nanoliposomes Before and After Chitosan Coating

Formulation	Chitosan %	Particle Size (nm ± SD)	Entrapment Efficiency (% ± SD)	In-Vitro Release (% ± SD)
Opt-LEV-NLs	0 (Uncoated)	95.95 ± 2.56	88.72 ± 4.11	78.26 ± 3.15
Chit-NLs-1	0.1% (Coated)	151.72 ± 1.37	64.56 ± 1.03	82.51 ± 2.15
Chit-NLs-2	0.3% (Coated)	415.12 ± 2.72	71.72 ± 1.72	73.43 ± 1.13

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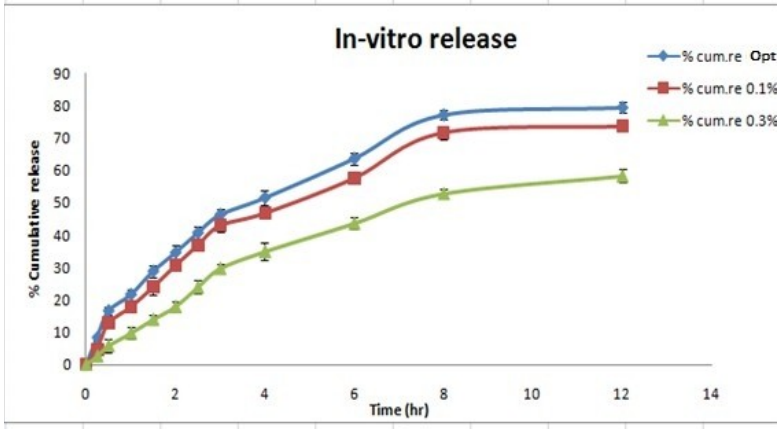


Figure 2: In- vitro drug release profile of Opt-LEV-NLs, 0.1% Chit-NLs and 0.3% Chit-NLs.

pH Determination

The pH values of all formulations were within the desirable range for intranasal delivery and did not cause irritation to the nasal mucosa (Table 4).

Table 4: pH Value of Optimized Prepared Formulations

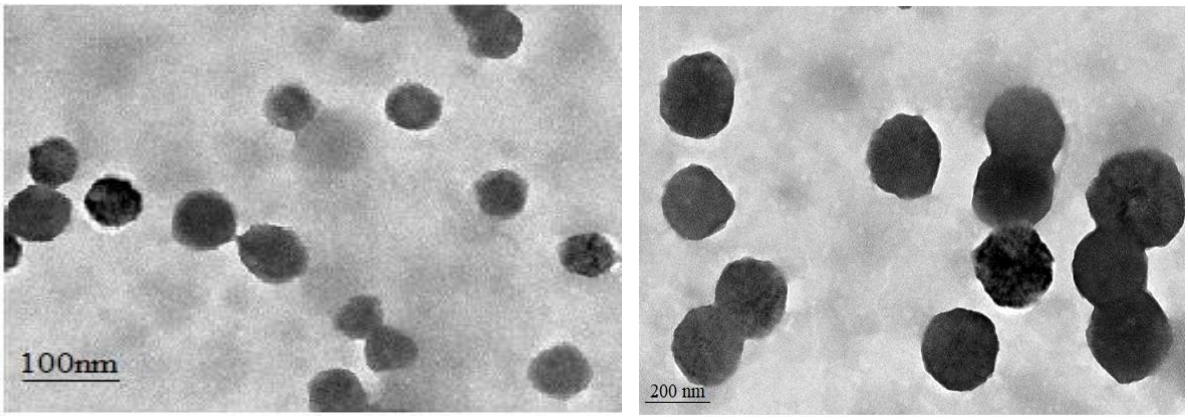
Formulation Code	pH ± SD
Opt-LEV-NLs	6.5 ± 0.17
0.1% Chit-NLs	6.4 ± 0.32
0.3% Chit-NLs	6.2 ± 0.24

Zeta Potential Study

The zeta potential of Opt-LEV-NLs was found to be -15.15 ± 0.25 mV. After coating with 0.1% and 0.3% chitosan, the zeta potential changed to +30.14 ± 0.43 mV and +35.15 ± 0.22 mV, respectively. The shift from negative to positive potential confirms the successful coating of the nanoliposomes with chitosan. The positive charge enhances the mucoadhesion of the vesicles by forming electrostatic interactions with negatively charged mucosal proteins, which is beneficial for intranasal delivery.

Surface Morphology Study

Transmission Electron Microscopy (TEM) was used to analyze the surface morphology, visual appearance, and size uniformity of Opt-LEV-NLs and Chit-Opt-NLs. TEM images showed that the vesicles were uniform in size, close to 90 nm, and exhibited homogenous size distribution (Fig. 3). The uniformity of the vesicles confirms the effectiveness of extrusion and sonication in forming unilamellar vesicles, and the increase in size confirms the chitosan coating process.



(A) **(B)**

Figure 3: TEM Image of (A) Opt-LEV-NLs (B) 0.1% Chit-NLs

After the characterization of chitosan-coated nanoliposomes in terms of particle size, entrapment efficiency, and in-vitro release, the 0.1% Chit-NLs were found to be more efficient than the 0.3% Chit-NLs. The 0.3% Chit-NLs had a larger particle size and a lower release rate, making them unsuitable for intranasal delivery. Therefore, 0.1% Chit-NLs were selected as the optimized formulation (Chit-Opt-NLs) for further studies.

Conclusion

The optimization of levetiracetam-loaded nanoliposomes identified sonication time, phospholipid amount, and cholesterol content as key variables influencing vesicle size, entrapment efficiency, and in-vitro release. The optimal formulation was determined with a phospholipid concentration of 70 µmol, cholesterol at 45 µmol, and sonication time of 360 seconds, achieving desirable characteristics for intranasal delivery.The results of this study demonstrate that 0.1% chitosan-coated Levetiracetam-loaded nanoliposomes (Chit-NLs) are a promising formulation for intranasal drug delivery. The 0.1% Chit-NLs exhibited optimal particle size, satisfactory entrapment efficiency, and effective drug release, making them suitable for brain targeting via the intranasal route. The chitosan coating not only increased the mucoadhesive properties but also improved drug retention and release. In contrast, the 0.3% chitosan-coated nanoliposomes had a significantly larger particle size and were less effective for intranasal delivery. Overall, this study highlights the potential of chitosan-coated nanoliposomes as a viable drug delivery system for improving the bioavailability and therapeutic efficacy of Levetiracetam, offering a novel approach for the treatment of epilepsy and other CNS disorders. Further studies involving in-vivo evaluation are recommended to validate the clinical applicability of this formulation.

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