RESEARCH PAPER

Formulation, Development and Characterization of Nanostructure Lipid Carriers of Dabigatran Etexilate

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Received: 12th Mar, 2026 | **Revised:** 24th Mar, 2026 | **Accepted:** 14th Apr, 2026 | **Available Online:** 30th Apr, 2026

ABSTRACT

Nanostructured lipid carriers (NLCs) were developed to enhance the oral delivery of dabigatran etexilate (DGE), addressing its poor solubility and bioavailability (7.2%) limitations. Compritol 888 ATO and Capmul MCM were selected as solid and liquid lipids, respectively, based on solubility studies showing 72.23 ± 0.126 mg/g and 73.5 ± 0.526 mg/mL capacities, with poloxamer 188 as surfactant yielding 219.33 ± 4.52 nm particle size and 84.45 ± 1.12% entrapment efficiency (EE). Formulation optimization via Box-Behnken design (24 runs) identified key variables: solid:liquid lipid ratio (79.9:20.1), surfactant concentration (1.6%), HSH speed (19,992 rpm), and sonication (2.9 min), achieving 94.42% predicted EE and 136.85 nm size; optimized batch showed 91.12 ± 2.52% EE, 153.8 nm size (PDI 0.247), +15 mV zeta potential, and spherical morphology by TEM. Ex vivo chicken ileum permeation revealed superior flux compared to pure drug. Lyophilized NLCs (trehalose 1:5) retained 89.12 ± 1.47% entrapment efficiency post-60 days during ICH stability studies.

Keywords: Nanostructured lipid carriers, Dabigatran etexilate, Box-Behnken design, Entrapment efficiency, Solubility enhancement, Oral bioavailability, Lyophilization, Stability study

How to cite this article: Solanki S, Patel K. Formulation, Development and Characterization of Nanostructure Lipid Carriers of Dabigatran Etexilate. Int J Drug Deliv Technol. 2026;16(39s): 871-879. DOI: 10.25258/ijddt.16.39s.107

Source of support: Nil.

Conflict of interest: None

1. INTRODUCTION

Liposomes are traditional models of lipid-based formulation invented in 1965.There was a need to develop new approaches that overcome liposome's drawbacks. So novel formulations were introduced called Lipid nanoparticles (LNPs). 1st generation LNPs were invented in 1990 as a substituent carrier of liposome, emulsion and polymeric nanoparticles called Solid Lipid Nanoparticles (SLNs). Solid lipids can be highly purified triglycerides, complex glycerides mixture, and surfactants used in the range of about 0.5 to 3% for improvement in solubility. After formulation of SLN, polymeric lipid transition may take place and solid lipid recrystallizes and converts into high energetic lipid form i.e. α and β form. These are highly unstable forms and tend to convert into stable forms i.e., β- and β modifications, stable form acquired perfect crystalline structure [1].

The crystalline structure allows little space for the host drug molecule. As a consequence drug expulsion usually occurs in a storage period. The Complexity of lipid components contributes to limited drug loading capacity which may not able to reach therapeutic drug levels. Limited loading capacity may influence drug release pattern during storage, which contribute to physical instability of SLNs system [2].

The mentioned SLN drawbacks boosted the development of the 2nd generation lipid nanoparticle termed as Nanostructured lipid carriers (NLCs) in 1999.Nanostructured lipid carrier (NLC) comes under lipid based delivery [3]. Lipids used in the formulation of the NLC is generally used are physiologically acceptable, biodegradable and most of the excipients possess GRAS (Generally Recognise as Safe) status, approved by regulatory authorities for human use, which have generally low or no toxicity. The lipidic phase of NLC comprises of a mixture of a spatially different lipid molecules, corresponding to a blend of a solid and a liquid lipid (e.g., oil), in a fraction that generally varies between 70:30 and 90:10.The addition of a liquid lipid in NLCs leads to crystal structure with more imperfection in matrix [4, 5, 6]. The presence of

oil prevents perfect recrystallization of solid lipid and improvement of drug solubility in lipid matrix. Liquid lipids, such as fatty acids, triglycerides, and monoglycerides, are a key component of nanostructured lipid carriers (NLCs). They are used to create structural imperfections in solid lipids, which can lead to a less ordered crystalline arrangement. This arrangement can help prevent drug leakage and increase the drug load [7, 8, 9]. Solid and liquid lipids present in formulation adjust the pathway of drug transport through lymphatic system instead of portal vein, which decreases possibilities of first-pass drug metabolism, because lymph travels directly to systemic circulation and bypass liver [10].

Dabigatran Etexilate (DGE) is a potent, synthetic, non-peptide competitive thrombin inhibitor belonging to BCS class II. DGE has several advantages over warfarin, such as rapid onset and offset of action, comparatively few drug interactions and side effects. DGE is an inactive pro-drug which is converted to dabigatran, the active form, by esterase-catalysed hydrolysis in the plasma and liver, producing a rapidly acting, competitive and reversible direct inhibitor of thrombin. Thrombin, a serine protease, is responsible for the conversion of fibrinogen to fibrin in the coagulation cascade. Inhibition of thrombin consequently prevents thrombus development. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. However, despite its therapeutic potential, DGE faces certain challenges that can limit its efficacy. Such challenge is its poor water solubility. Solubility of DGE is strongly pH dependent with increased solubility at acidic pH. The low bioavailability of DE (7.2%) after oral administration is attributed to its low solubility and P-gp efflux [11] which hinders its dissolution and absorption in the gastrointestinal tract, leading to suboptimal bioavailability. Furthermore, DGE undergoes extensive first-pass metabolism in the liver, resulting in a significant reduction in its systemic exposure and bioavailability. This is particularly problematic as the first-pass metabolism can rapidly degrade a substantial portion of the drug before it reaches the systemic circulation, thereby diminishing its therapeutic effect. In light of these considerations, the present study aims to develop and characterize DGE loaded lipid nanoparticles. (LNPs) These LNPs are designed to encapsulate DGE within a lipid matrix, thereby improving its solubility and stability [12].

By formulating DGE as lipid nanoparticle, we anticipate that the drug will be protected from degradation, facilitating its absorption through the lymphatic route and enabling direct entry into the systemic circulation. This approach holds the potential to enhance the bioavailability of DGE and maximize its therapeutic benefits.

2. MATERIALS AND METHODS

2.1 Materials

The active pharmaceutical ingredient Dabigatran Etexilate is obtained as a gift sample from Alembic Pharmaceuticals Ltd., Vadodara, India. Other excipients like dynasan 114, Dynasan 116, and Dynasan 118, were obtained as gift sample from Sasol, Germany. Precirol ATO 5, Compritol 888 ATO, Transcutol HP were kindly supplied from Gatteffose pvt. Ltd Mumbai, India. Capmul GMS 50K, Capmul MCM, Captex 355 EP, Captex 200 P, Acrysol EL 135 were obtained as gift sample from Abitec Corporation limited. The surfactants Poloxamer 188 and Poloxamer 407 were purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Trehalose (cryoprotectant) was obtained from Sigma-Aldrich Pvt. Ltd. All other chemicals, reagents, and solvents used in the study were of analytical grade.

2.2 Selection of solid lipid

A solubility study was conducted to choose the appropriate lipid. Different lipids (1 gm each) were heated to a temperature 10°C above their respective melting points. Then, 75 mg of DGE was dissolved in each melted lipid [13,14]. The solubility of DGE in the various lipids is presented in the Table 1.

2.3 Selection of liquid lipid

The solubility determination of DGE in various liquid lipids was performed by taking 2ml of fixed liquid lipids and solubility was checked by adding DGE in increments of 1mg until it failed to dissolve further in the liquid lipids [15]. The amount of drug solubilise in liquid lipid was determined.

2.4 Selection of surfactant

Surfactant selection was based on drug entrapment efficiency by formulating nanostructure lipid carrier (NLC) at a solid-lipid ratio of 70:30. Tween 20, tween 80, poloxamer 407, poloxamer 188 at a concentration of 1% were used as surfactant of choice.75 mg DGE was added at a high shear homogenisation (HSH) speed of 10000rpm. HSH time selected was 10 min and the sonication time was 2 min.

2.5 Compatibility study

Fourier Transform Infra-Red (FTIR) spectroscopy was used to find the drug- excipient compatibility using Nicolt 6700 model, Thermo scientific [16].

2.6 Method of preparation of NLC

NLCs of dabigatran etexilate (DGE-NLCs) were prepared using the high-speed homogenization followed by ultrasonication method due to its simplicity, reduced processing time, and high efficiency. Solid lipid was melted at 10^0c above its melting point and drug was dissolved in melted lipid and liquid lipid was added. Surfactant was dissolved into double distilled water and heated to same temperature as of melted lipid. Hot aqueous Surfactant solution was added into drug lipid mixture. Mixture was homogenized using high speed homogenizer at different rpms, minutes and different sonication cycles to get dispersion. Dispersion was then centrifuged at 8000 RPM for 10 min to remove lipid and unentrapped drug as they settled down into centrifuge tube which was filtered using whatman filter (pore size 46*57).Supernatant was collected which was containing drug loaded NLC. The final dispersion of DGE-NLCs was stored for further characterization. [17]

2.7 Optimization of formulation using Box-Behnken Design

BBD is a response surface methodology (RSM) tool used under DOE that is efficient for 3-level factorial designs. It reduces the number of experiments compared to full factorial designs, thus saving time and resources. The experimental results were generated using design expert software (version 13). The four independent factors were, SS:LL ratio (mg), surfactant concentration (%), HSH speed (rpm) and sonication time (minutes) and the two dependent factors were entrapment efficiency(EE) % and particle size in nm. A total of 24 batches were prepared and evaluated for optimization. To validate the reliability and predictive accuracy of the developed optimization model, checkpoint batches were selected from the predicted optimal region of the 3D response surface plots [18].

2.8 Characterization of NLC

2.8.1 Particle size

The particle size analysis of the formulations was performed using a Malvern Zetasizer 2000MS device (Malvern Instruments, Worcestershire, UK) and laser diffraction with a beam length of 2.40mm [19].

2.8.2 Drug entrapment

The % EE of NLC dispersion was determined by quantifying the free drug in the supernatant and sediment. A 10 ml aliquot of the NLCs dispersion was centrifuged. The supernatant was collected, and the lipid content was precipitated by adding methanol, as drug is soluble in methanol while the lipids are not. The precipitate was filtered, and the resulting filtrate was designated as Solution 1.The sediment was further treated by adding methanol, followed by filtration, and the resulting filtrate was designated as Solution 2. Solutions 1 and 2 were combined and analyzed using a UV-Visible spectrophotometer at 315 nm to determine the concentration of the free drug [20].

$$\%\ \boldsymbol{Entrapment\ Efficiency} = (\boldsymbol{Total\ Drug} - \boldsymbol{Free\ Drug}) / (\boldsymbol{Total\ Drug}) \times 100$$

2.8.3 Zeta potential

The zeta potential of the dispersion was used to determine the surface charge of the prepared DGE-NLCs. 1 ml of the dispersion was diluted with 10 ml of distilled water before being analysed with a (Zetasizer Nano ZS; Malvern Instrument,Malvern, UK) for zeta potential [21].

2.8.4 TEM study

TEM analysis the morphological properties of NLCs formulated optimally. The sample was prepared by placing a drop of NLC dispersion diluted with distilled water on a copper grid slide and letting it air dry. After air drying the material, it was examined under a transmission electron microscope [22].

2.8.5 In vitro dissolution studies

The in vitro drug release behaviour of DGE loaded NLC, freeze dried NLCs and pure drug suspension was studied and compared [23].

2.8.6 Ex vivo study

Ex-Vivo drug studies were conducted to determine drug penetration into the intestinal membrane. According to the reviewed research, nanoparticles enter the lymphatic system via the small intestine, which has a dense population of payer's patches. The intestines of chickens that had already been slaughtered were used in an ex-vivo investigation. The ileum was isolated and separated from the rest of the chicken digestive system and immersed into the Ringer PSS solution while providing aeration. Tissue was carefully dissected free of the mesenteric adhesions and washed in a PSS solution. 1ml of the NLCs dispersion was inserted into the ileum after one end was tied off with thread. Leaks can be prevented by tying the other end as well. A constant temperature of 37 ±0.5 ℃ was maintained in a beaker containing 200 ml of phosphate-buffered saline (PBS) with a pH of 7.4. Then the tissue was put into the beaker. The amount of DGE released into the dissolving liquid was measured by spectrophotometry at 315 nm, and samples of 5 ml were taken at regular intervals. After each sample was taken, the volume of the dissolving medium was restored with a fresh volume of PBS [24].

2.8.7 Lyophilization

The NLC formulation was mixed with cryoprotectant trehalose at a ratio of 1:5 to NLC formulation and deep

frozen (-20°C) for 24 hr. The substance was then lyophilized for roughly 72 hr at -52°C and 0.002 mbar pressure to produce lyophilized NLC powder [25].

3. Results and Discussion

3.1 Selection of solid lipid

The solubility study revealed that Compritol 888 ATO exhibited a high drug solubilization capacity (72.23 ± 0.126 mg/g), indicating its suitability as a solid lipid component in the development of nanostructured lipid carriers (NLCs). Compritol 888 ATO, being a long-chain glyceride (glyceryl behenate), provides a highly ordered crystalline structure; however, its ability to solubilize a significant amount of drug suggests favourable drug–lipid interactions, which are essential for efficient drug incorporation into the lipid matrix.

Table: 1 solubility of DGE in solid lipid

Sr. No	Drug +Lipid	Solubility(mg/g)
1	Dynasan 114	50.452 ± 0.423
2	Dynasan 116	54.13 ± 0.923
3	Dynasan 118	57.12 ± 0.698
4	Compritol 888 ATO	72.23 ± 0.126
5	Precirol 5 ATO	32.65 ± 0.023
6	Capmul GMS 50 K	41.98 ± 0.634

Data are represented as Mean ±SD, n= 3

3.2 Selection of liquid lipid

The solubility results (shown in Table: 2) indicate that Capmul MCM possesses a high drug solubilization capacity (73.5 ± 0.526 mg/mL), which is particularly advantageous for the development of NLCs**.** In NLC systems, the selection of an appropriate liquid lipid plays a critical role in enhancing drug loading and minimizing drug expulsion during storage. The superior solubilizing ability of Capmul MCM can be attributed to its medium-chain mono- and diglyceride composition, which provides a less ordered lipid matrix when combined with solid lipids, thereby creating structural imperfections within the NLC.

Table: 2 Solubility of DGE in liquid lipid

Liquid Lipid	Drug Solubility (mg/ml)
Capmul MCM	73.5 ± 0.526
Acrysol EL 135	61.5 ± 0.512
Captex 355 EP	41.0 ± 0.591
Transcutol HP	52.0 ± 0.478
Captex 200 P	51.3 ± 0.325

Data are represented as Mean ±SD, n= 3

3.3 Selection of surfactant

The surfactant screening study(Table: 3)demonstrated that poloxamer 188 produced optimized NLCs with a particle size of 219.33 ± 4.52 nm and high entrapment efficiency (84.45 ± 1.12%). The reduced particle size is attributed to efficient interfacial tension reduction and steric stabilization, preventing aggregation during homogenization and sonication. The high %EE indicates effective drug retention within the lipid matrix, supported by the 70:30 solid–liquid lipid ratio, which creates structural imperfections. These results suggest that poloxamer 188 enhances nanoparticle stability and drug loading, making it a suitable surfactant for developing stable and efficient DGE-loaded NLC formulations.

Table: 3 Selection of surfactant

Batch	Surfactant	Particle Size(nm)	%EE
DGE 1	Tween 20	285. 29±3.74	63.22±0.32
DGE 2	Tween 80	297.12±2.45	61.25±0.28
DGE 3	Poloxamer 407	268.56±5.58	65.54±0.68
DGE 4	Poloxamer 188	219.33±4.52	84.45±1.12

3.4 Compatibility study

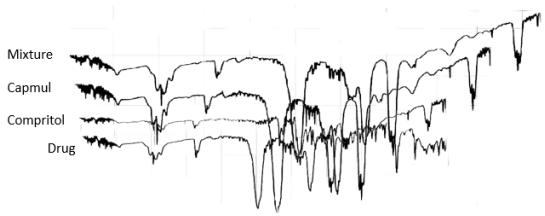

Figure 1: FTIR spectrum of DGE, Compritol, Capmul MCM and the mixture

The FTIR spectrum (Figure: 1) confirmed compatibility between the drug and excipients, as all characteristic peaks of the drug were retained in the formulation without significant shifts, disappearance, or formation of new peaks. The observed peaks (N-H- 3348 cm^{-1}, C-H- 1739 cm^{-1})were within standard ranges(N-H- 3300-3500 cm^{-1}, C-H- 1405-1850 cm^{-1}), indicating preservation of the drug's chemical structure. Minor changes in peak intensity or broadening may be due to physical interactions such as hydrogen bonding or molecular dispersion within the lipid matrix. These findings suggest the absence of chemical incompatibility and confirm that the drug remains stable during formulation. Thus, the selected excipients are suitable for developing a stable and effective nanostructured lipid carrier system.

3.5 Optimization of formulation using Box-Behnken Design

The optimization of nanostructured lipid carriers (NLCs) demonstrated that formulation and process

variables significantly influenced both drug entrapment efficiency (DE%) and particle size (PS). Increasing the solid lipid ratio from 70 to 80% generally enhanced entrapment efficiency due to improved matrix integrity, though excessively high solid lipid levels occasionally increased particle size. Surfactant concentration showed a critical role; higher levels (2%) reduced particle size and improved DE% by stabilizing the emulsion and preventing aggregation.

High shear homogenization (HSH) speed and sonication time markedly affected particle size reduction. Increasing HSH speed from 10,000 to 20,000 rpm and sonication time up to 2–3 minutes resulted in finer droplets and lower particle size due to efficient shear forces and cavitation effects. However, excessive processing sometimes led to marginal decreases in entrapment efficiency, possibly due to drug leakage.

The optimized formulation (Run 18 and 20) exhibited maximum DE% (~94%) with minimum particle size (~180–190 nm), indicating that a balanced combination of lipid ratio (80:20), higher surfactant concentration, elevated homogenization speed, and moderate sonication time is essential for achieving stable and efficient NLC systems.

Table: 4 Optimization of formulation by Box Behnken Design using DOE

S.No	A: Solid lipid : Liquid lipid	B: Surfactant Concentration (%)	C: HSH Speed (RPM)	D: Sonication Time (min)	Response 1 DE (%)	Response 2 PS (nm)
1	80	1.5	10000	2	83.5±1.96	345.12±3.12
2	75	2	10000	2	84.12±2.41	340.96±4.63
3	70	1	15000	2	78.45±3.32	390.1±3.12
4	70	1.5	15000	2	80.12±1.12	370.36±5.36
5	75	1.5	20000	1	85.87±1.32	290.78±7.41
6	80	1.5	15000	1	86.78±1.23	300.12±6.36
7	70	1.5	10000	2	78.41±3.98	410.1±5.85
8	75	2	15000	3	89.85±1.63	260.78±4.17
9	80	1.5	15000	3	89.45±1.36	250.32±3.25
10	75	1	20000	2	80.78±1.36	330.12±4.63
11	70	1.5	15000	3	78.1±2.74	360.85±3.74
12	75	1.5	20000	1	78.36±3.23	365.36±4.25
13	75	1	15000	3	91.87±1.10	210.14±3.96
14	80	1	15000	2	84.36±2.23	320.36±3.57
15	70	1.5	20000	2	81.36±1.96	310.74±5.26
16	75	2	15000	1	86.74±1.41	300.1±3.89
17	80	2	15000	2	92.41±2.63	240.56±5.74
18	80	1.5	20000	2	94.41±1.89	180.36±4.56
19	75	1.5	10000	3	80.78±1.41	370.41±4.41
20	75	2	20000	2	93.1±2.23	190.69±5.23
21	75	1.5	10000	1	76.32±2.36	400.32±5.74
22	70	2	15000	2	83.25±2.74	320.41±4.12
23	75	1	15000	3	80.36±1.52	330.1±6.63
24	75	1	10000	2	77.41±1.12	420.85±4.52

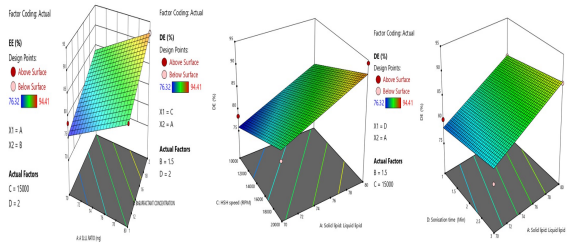

Figure 1: 3D surface plot for drug entrapment (%)

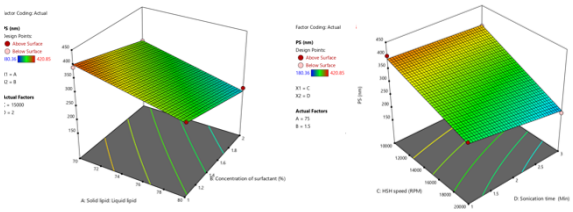

Figure 2: 3D surface plot for particle size (%)

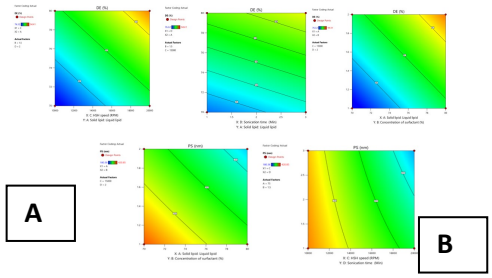

Figure 3: Contour plot [A] Drug entrapment, [B] Particle size

To validate the reliability and predictive accuracy of the developed optimization model, checkpoint batches were selected from the predicted optimal region of the 3D response surface plots.

Table: 5 Results of checkpoint batches

A: Solid lipid : Liquid lipid	B: Surfactant Concentration (%)	C: HSH Speed (RPM)	D: Sonication Time (min)	Predicted DE (%)	Actual DE (%)	Predicted PS (nm)	Ac PS
74	1.4	12000	1.3	79.11	76.12±1.56	375.52	382.1
79	1.2	17000	2.5	87.35	83.23±2.35	261.30	268.4

The minor deviations between predicted and actual values may be attributed to experimental variability and processing limitations. However, the low percentage error indicates a strong correlation between predicted and experimental responses, confirming the adequacy and reliability of the optimization model. Thus, the selected design successfully predicts formulation performance within an acceptable range, demonstrating robustness and suitability for NLC optimization.

To determine the optimal formulation, a desirability function approach was employed. This method is particularly effective for multi-response optimization, as it enables the simultaneous consideration of multiple

formulation objectives by transforming each response into a dimensionless desirability value (d), ranging from 0 (least desirable) to 1 (most desirable). The overall aim is to identify a formulation that best meets all predefined response criteria.

Table: 6 Results of optimized batch

	A: Solid lipid : Liquid lipid	B: Surfactant Concentration (%)	C: HSH Speed (RPM)	D: Sonication Time (min)	Observed DE (%)	Obse PS (r
FINAL BATCH	79.92	1.6	19992	2.98	91.12±2.52	148.55

3.6 Characterization of NLC

The particle size analysis (Figure 4) of the optimized NLC formulation revealed a Z-average diameter of 153.8 nm with a polydispersity index (PDI) of 0.247, indicating a relatively narrow and uniform size distribution. The intensity-based distribution showed a prominent peak at 216.3 nm contributing to 95.4% intensity, suggesting that the majority of particles are within the nanometric range. The presence of a minor peak at 4428 nm (4.6% intensity) indicates a small fraction of aggregates, which is commonly observed due to occasional particle coalescence. The low PDI value (<0.3) confirms good homogeneity and stability of the formulation.

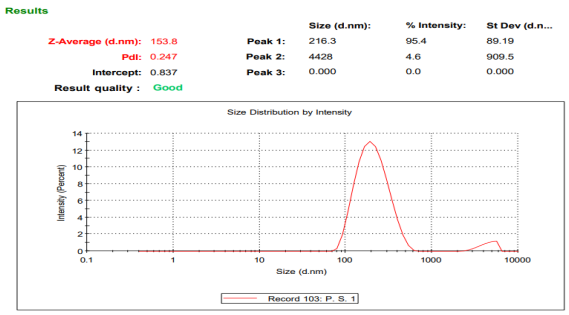

Figure 4: Mean particle size of optimized batch

The optimized NLC formulation exhibited a high drug entrapment efficiency of 91.12±2.52%, indicating effective incorporation of the drug within the lipid matrix. This high entrapment can be attributed to the optimal ratio of solid and liquid lipids, which creates an imperfect crystalline structure, thereby providing more space for drug accommodation. Additionally, adequate surfactant concentration enhances stabilization of the system and prevents drug leakage during formulation [26].

Although zeta potential values (Figure 5) above ±30 mV are typically considered indicative of strong electrostatic stabilization, the observed value (~+15 mV) suggests that the formulation stability is likely governed by a combination of electrostatic and steric stabilization, particularly due to the presence of surfactants.

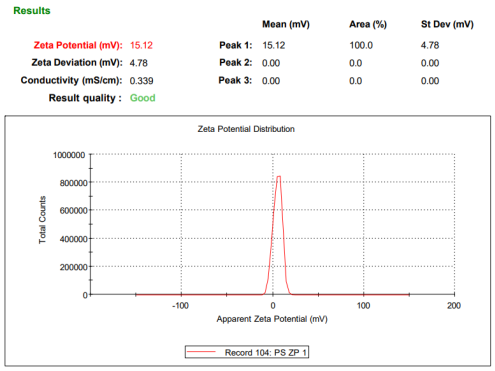

Figure 5: Zeta potential of optimized batch

The TEM image (Figure 6) shows that the NLCs are mostly round, smooth, and evenly spread out. The Image Shows Spherical particles with a solid core and an imperfect crystal lattice structure designed to accommodate more drug molecules. The particles look separate from each other, which means there is no clumping. Their shape and size confirm that the NLCs were formed properly and are in the nano-size range.

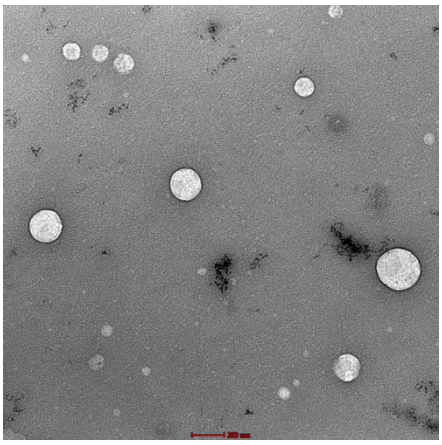

Figure 6: TEM image of optimized batch

The comparative in vitro release profile (Figure 7) demonstrates a clear distinction between the release behaviour of DGE-loaded nanostructured lipid carriers (DGE-NLC), freeze-dried DGE-NLC, and the pure drug suspension. The pure drug exhibits a rapid and almost complete release within a short duration, reaching nearly 100% cumulative drug release within approximately 6 hours. This burst release can be attributed to the poor solubility and lack of any release-retarding matrix, resulting in immediate drug diffusion into the dissolution medium.

In contrast, both DGE-NLC and freeze-dried DGE-NLC formulations show a controlled and sustained release pattern extending up to 24 hours. The initial phase (up to ~4–6 hours) indicates a moderate release, likely due to desorption of drug molecules from the nanoparticle surface, followed by a slower, diffusion-controlled release from the lipid matrix. The DGE-

NLC formulation shows slightly higher release compared to the freeze-dried formulation at most time points, suggesting that lyophilization may induce minor structural changes such as increased particle aggregation or reduced surface area, thereby marginally retarding drug release

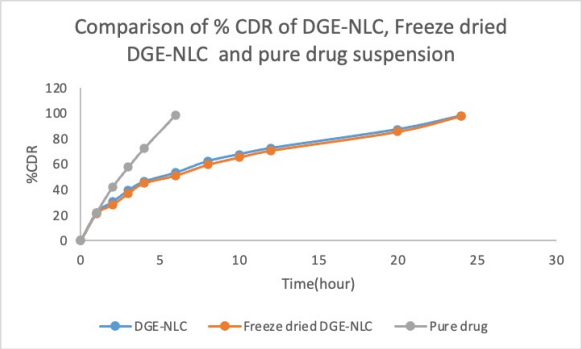

Figure 7: Comparative in-vitro drug release study of DGE-NLC, freeze dried DGE-NLC and pure drug suspension

The ex vivo permeability study (figure 8) using chicken duodenum demonstrated the effectiveness of the DGE-NLC formulation in enhancing intestinal drug transport compared to the pure drug. The NLC formulation exhibited significantly higher cumulative drug permeation across the intestinal membrane, indicating improved absorption characteristics. This enhancement can be attributed to the nanosized particles, which provide a larger surface area and facilitate closer interaction with the mucosal membrane [27].

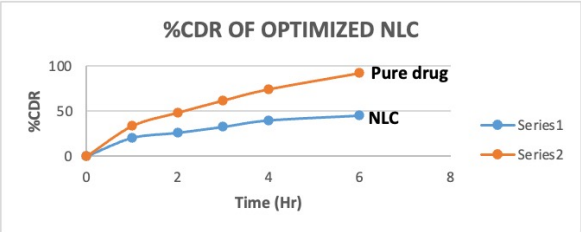

Figure 8: % CDR of optimized NLC

Lyophilization of NLCs played a critical role in enhancing long-term stability by converting the colloidal dispersion into a dry, porous powder. The inclusion of cryoprotectant, trehalose, is essential to prevent particle aggregation and preserve the structural integrity of lipid nanoparticles during freezing and sublimation. Post-lyophilization characterization (table: 7) typically showed a slight increase in particle size which may be attributed to partial aggregation during the drying process. However, efficient redispersibility upon reconstitution suggests that the formulation maintains its colloidal stability. Drug entrapment efficiency is usually retained after lyophilization, confirming that the process does not significantly affect drug distribution within the lipid matrix. Overall, the lyophilized NLC formulation demonstrates improved physical stability, ease of handling, and suitability for long-term storage without compromising its functional performance [28, 29].

Table 7: Results of lyophilized DGE loaded NLC

For Trehalose concentration 1:5			
Before		After	
Particle Size	%Drug Entrapment	Particle size	%Drug Entrapment
148.55±8.74	91.12±2.52	155.12±5.41	89.12±1.47

The stability study of lyophilized powder was performed for 60 days as per ICH guidelines. It was observed that no significant alterations were seen in the particle size nor drug entrapment efficiency. The particle size was 155.12±6.12 nm and % drug entrapment was 89.12±1.47 % at the initial stage. After a study of 60 days, it was found to be 158.42 ± 4.15 nm and 88.23 ± 2.52 % respectively.

Conclusion

The formulation of dabigatran etexilate-loaded NLCs represents a significant advancement in lipid-based drug delivery systems for poorly water-soluble anticoagulants [30]. By systematically selecting compritol 888 ATO as the solid lipid (72.23 mg/g solubility), capmul MCM as the liquid lipid (73.5 mg/mL solubility), and poloxamer 188 as surfactant, the study overcame traditional SLN limitations like drug expulsion and low payload capacity through a disrupted crystalline matrix. Box-Behnken design optimization across 24 batches pinpointed an ideal composition—79.9:20.1 solid:liquid ratio, 1.6% surfactant, 19,992 rpm homogenization, and 2.9 min sonication—yielding 91.12% entrapment efficiency, 153.8 nm size (PDI 0.247), and +15 mV zeta potential for steric-electrostatic stability. TEM confirmed uniform spherical nanoparticles with imperfect lattices enhancing drug accommodation. Ex vivo chicken ileum permeation highlighted NLC superiority over free drug, promoting lymphatic transport to evade hepatic first-pass effects. Lyophilization with trehalose (1:5) preserved integrity, with post-reconstitution values of 155.12 nm size and 89.12% EE, alongside robust 60-day ICH stability (particle size 158.42 nm, EE 88.23%).Future studies should explore in vivo pharmacokinetics, scale-up manufacturing, and clinical translation of this biocompatible, GRAS-affirmed platform to optimize DGE therapy.

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