Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 941-946
DoI-10.004687/1000-9035.2025.127

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Formulation Development And Characterization Of Solid Lipid Nanoparticles Of Dabigatran Etexilate

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Article Information
Received: 17-07-2025
Revised: 12-08-2025
Accepted: 22-10-2025
Published: 05-12-2025

Keywords
Dabigatran etexilate, solid lipid nanoparticles, factorial design, bioavailability enhancement, controlled release, Compritol 888 ATO.

ABSTRACT

Background: **Dabigatran etexilate is a direct thrombin inhibitor with low oral bioavailability (6–7%) due to poor aqueous solubility, extensive first-pass metabolism, and P-glycoprotein–mediated efflux. To overcome these limitations, Solid Lipid Nanoparticles (SLNs) offer a promising lipid-based delivery system capable of enhancing solubility, permeability, and controlled drug release.**

Objective: **To formulate, optimize, and characterize dabigatran etexilate–loaded solid lipid nanoparticles (DE-SLNs) to improve stability and sustain drug release.**

Materials and Methods: **SLNs were prepared using high-speed homogenization followed by ultrasonication. Lipid and surfactant screening identified Compritol® 888 ATO and Poloxamer 188 as optimal excipients. A 3^2 full factorial design evaluated the influence of drug:lipid ratio (1:10–1:20) and surfactant concentration (1–3%) on particle size and entrapment efficiency. The optimized formulation was characterized for particle size, PDI, zeta potential, morphology (TEM), drug entrapment, and in vitro drug release using the dialysis bag technique.**

Results: **Compritol® 888 ATO showed the highest drug solubility (72.23 ± 0.126 mg/g). The optimized batch (drug:lipid ratio 1:11; 1% Poloxamer 188) exhibited a particle size of** 169.12 ± 5.45 nm**, PDI of** 0.343**, drug entrapment efficiency of** 78.12 ± 4.23%**, and zeta potential of** –35.5 mV**, indicating good stability. TEM imaging confirmed spherical, smooth-surfaced nanoparticles. In vitro release studies showed sustained release (97.84% at 24 h) compared to rapid release of the pure drug (98.95% at 6 h). The optimized formulation was successfully lyophilized into a** 650 mg sachet equivalent to 75 mg dabigatran etexilate**.**

Conclusion: **DE-SLNs were successfully developed with optimal physicochemical properties, high entrapment efficiency, and sustained drug release. This lipid-based nanocarrier system shows strong potential to enhance dabigatran stability and oral bioavailability, offering a promising alternative to conventional formulations.**

INTRODUCTION:

Dabigatran etexilate is an orally administered direct thrombin inhibitor widely used for the prevention and treatment of thromboembolic disorders, including deep vein thrombosis, pulmonary embolism, and stroke prophylaxis in atrial fibrillation. Despite its therapeutic significance, the oral bioavailability of dabigatran etexilate remains markedly low (approximately 6–7%), primarily due to its poor aqueous solubility, extensive first-pass metabolism, and substrate affinity for P-glycoprotein (P-gp) efflux transporters. These

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biopharmaceutical limitations necessitate the development of an advanced drug delivery system capable of enhancing solubility, permeability, and overall absorption.

Lipid-based nanocarriers, particularly **Solid Lipid Nanoparticles (SLNs),** have emerged as promising systems for the delivery of poorly water-soluble drugs. SLNs combine the advantages of traditional colloidal carriers such as emulsions and liposomes with improved physical stability, controlled drug release, biodegradicity, and ease of large-scale production. Their lipid matrix remains solid at both room and body temperatures, enabling efficient drug encapsulation and protecting the active molecule from degradation. Additionally, SLNs can modulate drug release, improve intestinal uptake, inhibit efflux pumps, and enhance lymphatic transport—mechanisms highly suitable for drugs like dabigatran etexilate that show low permeability and significant pre-systemic elimination.

Given these advantages, formulating dabigatran etexilate into SLNs may address its pharmacokinetic drawbacks and significantly improve oral bioavailability. However, the successful development of such a system requires careful selection of lipid components, surfactants, and manufacturing parameters to obtain nanoparticles with optimal particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, and drug release characteristics.

Therefore, the present research focuses on the **formulation, optimization, and comprehensive characterization of solid lipid nanoparticles loaded with dabigatran etexilate** using suitable lipid matrices and surfactants.

MATERIAL AND METHODS:

Dabigatran etexilate was obtained as a gift sample from Alembic Pharmaceuticals Ltd., Vadodara, India. The lipids Dynasan 114, Dynasan 116, and Dynasan 118 were procured from Sasol Germany GmbH. Compritol® 888 ATO and Precirol® ATO 5 were kindly supplied by Gattefossé India Pvt. Ltd., Mumbai, India. 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.

PREPARATION OF DABIGATRAN ETEXILATE–LOADED SOLID LIPID NANOPARTICLES (DE-SLNS):

Solid lipid nanoparticles of dabigatran etexilate (DE-SLNs) were prepared using the **high-speed homogenization followed by ultrasonication method** due to its simplicity, reduced processing time, and high efficiency. Compritol® 888 ATO was heated to **10 °C above its melting point** to obtain a clear molten lipid phase. Dabigatran etexilate (DE) was dispersed in the molten lipid under constant stirring to obtain a uniform drug–lipid mixture. Separately, Poloxamer 188 (surfactant) was dissolved in purified water and heated to the **same temperature as the molten lipid** to prevent premature solidification. The hot aqueous surfactant solution was then added to the molten drug–lipid phase. The resulting coarse emulsion was subjected to **high-speed homogenization at 15,000 rpm for 10 minutes,** followed by **ultrasonication for 2 minutes** to reduce particle size and form a nanoemulsion. Upon cooling to room temperature, the nanoemulsion solidified to form solid lipid nanoparticles. The obtained SLN dispersion was centrifuged at **8000 rpm for 10 minutes** to remove excess lipid and unencapsulated drug. The supernatant containing the DE-SLNs was carefully collected and filtered using a **46 × 57 µm membrane filter** to remove any remaining particulate matter. The final dispersion of DE-SLNs was stored for further characterization.

SELECTION OF LIPID:

A solubility study was conducted to select the most suitable lipid for the formulation of solid lipid nanoparticles (SLNs). Different solid lipids (1 g each) were accurately weighed and heated to **10 °C above their respective melting points** to obtain a uniform molten mass. The solubility of Dabigatran Etexilate (DE) in different solid lipids was evaluated to identify an optimal lipid matrix for SLN formulation. Among all the lipids tested, Compritol 888 ATO exhibited the highest solubility for DE (72.23 ± 0.126 mg/g), indicating superior drug–lipid compatibility. The significantly higher solubility in Compritol 888 ATO suggests enhanced drug incorporation capacity, reduced risk of drug expulsion during storage, and improved formulation stability. Therefore, Compritol 888 ATO was selected as the lipid of choice for developing DE-loaded solid lipid nanoparticles. (Table: 1)

Table: 1 Selection of Lipid

Sr. No	Drug +Lipid	Solubility (n=3)
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

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SELECTION OF SURFACTANT

A surfactant selection study was conducted to identify the most suitable stabilizer for the formulation of DE-loaded solid lipid nanoparticles (DE-SLNs). Poloxamer 188 at a concentration of 2% w/v produced the most desirable nanoparticle characteristics. The formulation containing 1:15 drug-to-lipid ratio with 2% Poloxamer 188 resulted in a mean particle size of 199.25 ± 0.32 nm, indicating efficient reduction of interfacial tension and formation of uniformly dispersed nanosized particles. Furthermore, the same formulation exhibited a high drug entrapment efficiency of 82.65 ± 3.12%, demonstrating that Poloxamer 188 effectively stabilized the lipid matrix and enhanced drug incorporation. These findings confirm that 2% Poloxamer 188 is the optimal surfactant concentration for producing stable, high-entrapment DE-SLNs with nanoscale particle size.

OPTMIZATION OF DE LOADED SOLID LIPID NANOPARTICLES

A 3^2 full factorial design was employed to systematically optimize the formulation variables influencing the development of Dabigatran Etexilate–loaded solid lipid nanoparticles (DE-SLNs). In this design, two independent factors were studied—Drug:Lipid Ratio (Factor A) and Surfactant Concentration (Factor B)—each at three levels. This generated a total of nine experimental runs, allowing comprehensive evaluation of both the main effects and interaction effects of these formulation parameters. Factor A (Drug:Lipid ratio) was assessed at levels: 1:10, 1:15, and 1:20, while Factor B (Poloxamer 188 concentration) was evaluated at 1%, 2%, and 3%. The responses analyzed included mean particle size and percentage drug entrapment efficiency, which are critical attributes governing the performance of SLNs. The 3^2 factorial design enabled identification of the optimal combination of formulation variables that produced nanoparticles with desirable physicochemical properties, demonstrating its effectiveness in formulation development as per Table:2.

Table: 2 Optimization of DE loaded SLN

Batch No.	A Drug: Lipid Ratio	B Surfactant Concentration	Y_1 (nm)* Particle Size	Y_2 (%)* Drug Entrapment
D1	-1(1: 10)	-1 (1%)	154.60±5.23	79.82±2.12
D2	-1(1: 10)	0 (2%)	151.71±6.56	73.21±3.12
D3	-1(1: 10)	+1 (3%)	150.26±1.13	70.72±2.56
D4	0 (1:15)	-1 (1%)	180.7±5.12	86.18±4.23
D5	0 (1:15)	0 (2%)	169.81±8.23	82.34±5.12
D6	0 (1:15)	+1 (3%)	162.80±10.12	79.12±5.12
D7	+1 (1:20)	-1 (1%)	203.86±7.23	87.34±3.12
D8	+1 (1:20)	0 (2%)	190.92±3.81	85.24±6.16
D9	+1 (1:20)	+1 (3%)	197.94 ±1.34	81.12±4.82

Table: 3 3^2 full factorial design of Dabigatran Etexilate loaded solid lipid nanoparticles

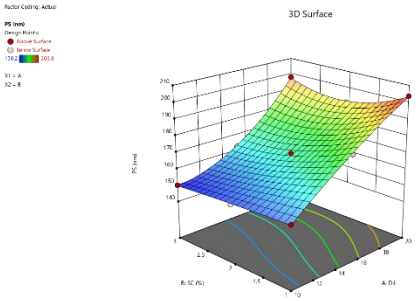
Independent Parameter	Drug: Lipid Ratio (A)			Surfactant Concentration (%) (B)		
Level	-1	0	+1	-1	0	+1
Actual Value	1:10	1:15	1:20	1%	2%	3%
Dependent Parameter	Particle Size (nm)(Y1)			Drug Entrapment (%)(Y2)		

EFFECT ON PARTICLE SIZE AND DRUG ENTRAPMENT OF DRUG TO LIPID RATIO AND DRUG ENTRAPMENT

The quadratic model generated for particle size (PS) demonstrated the combined influence of the drug:lipid ratio (A) and surfactant concentration (B) on nanoparticle dimensions. The obtained equation was:

$$PS = 167.41 + 25.02A - 8.70B - 6.38AB + 8.08A^2 + 5.53B^2$$

The positive coefficient for A indicates that increasing the drug: lipid ratio leads to larger particle sizes, likely due to increased viscosity of the lipid phase. In contrast, the negative coefficient for B reveals that higher surfactant concentrations reduce particle size by improving emulsification and droplet breakup. Although the interaction term (AB) showed a minor negative effect, both quadratic terms (A^2 and B^2) suggest nonlinear behavior, reflecting that particle size does not vary proportionally across the tested levels. Overall, the drug:lipid ratio had the most pronounced effect on particle size, while surfactant concentration contributed to particle size reduction.



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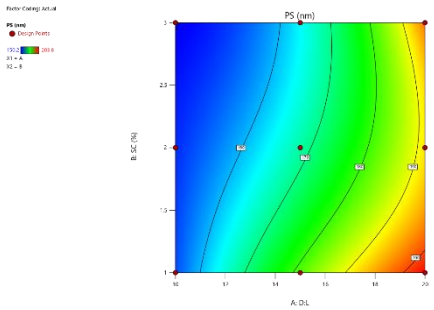

Figure: 1 Three-dimensional response surface plots & Contour Plot for particle size

The influence of formulation variables on drug entrapment efficiency (DE%) was described by the quadratic model:

$DE = 82.38 + 5.20A – 3.70B + 0.680AB – 3.18A^2 + 0.2433B^2$

where **A represents the drug:lipid ratio** and **B represents the surfactant concentration.** The positive coefficient of A indicates that increasing the lipid content enhances entrapment efficiency by providing a larger hydrophobic matrix for accommodating Dabigatran Etexilate. Conversely, the negative coefficient of B reflects a reduction in DE% at higher surfactant levels, possibly due to increased drug partitioning into the aqueous phase. The interaction term (AB) exerted only a minimal effect, whereas the significant negative quadratic term (A^2) suggests a nonlinear relationship, indicating that excessively high lipid ratios may lead to decreased entrapment. Overall, the drug:lipid ratio emerged as the most influential factor governing DE%.

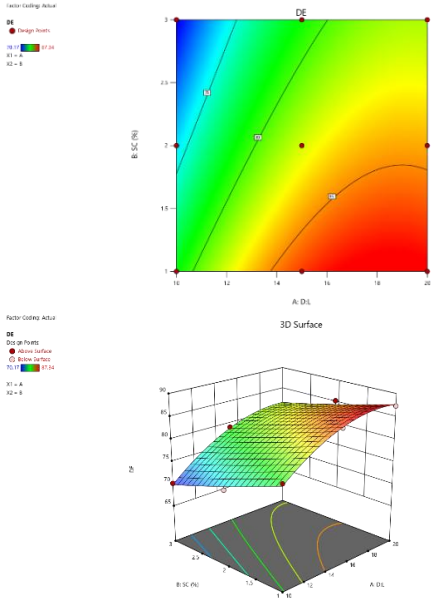

Figure: 2 Three-dimensional response surface plots & Contour Plot for Drug Entrapment

DESIRABILITY FUNCATION

The optimization of Dabigatran Etexilate–loaded solid lipid nanoparticles (DE-SLNs) was performed using a desirability function to obtain the best compromise between particle size reduction and maximum drug entrapment. Among the evaluated formulations, the batch containing a **drug:lipid ratio of 1:11** and **1% surfactant concentration (Poloxamer 188)** showed the highest overall desirability value of **0.781,** with a predicted **particle size of 160.31 nm** and **drug entrapment efficiency of 80.75%.**Experimental validation of this optimized composition yielded a **particle size of 169.12 ± 5.45 *nm and* entrapment efficiency of 78.12 ± 4.23%,** which closely matched the predicted values, confirming the reliability of the optimization model. Therefore, the formulation with a **1:11 drug:lipid ratio and 1% surfactant** was selected as the optimized DE-SLN formulation.

CHARACTERIZATION OF DE-LOADED SOLID LIPID NANOPARTICLES PARTICLE SIZE

The particle size distribution of the optimized Dabigatran Etexilate–loaded SLNs was determined using dynamic light scattering (DLS). The formulation exhibited a **Z-average particle size of 171.12 nm,** indicating successful formation of nanoparticles within the desirable nanometric range. The **polydispersity index (PDI) value of 0.343** reflect**s** a moderately narrow and uniform size distribution, suitable for maintaining colloidal stability. The intensity-weighted distribution showed a single major peak at approximately **309.2 nm (80% intensity),** confirming the monomodal nature of the dispersion. The **intercept value of 0.988** further suggests good measurement quality and reliable signal strength. Overall, the particle size analysis confirms that the optimized DE-SLN formulation possesses favorable nanoscale characteristics essential for enhanced drug delivery performance.

DRUG ENTRPMENT:

The drug entrapment efficiency of the optimized Dabigatran Etexilate–loaded SLNs was determined using an **indirect method.** The formulation was centrifuged at high speed to separate the nanoparticles from the unentrapped drug present in the supernatant. The amount of free (unentrapped) drug in the supernatant was quantified spectrophotometrically, and the entrapped drug was calculated by subtracting this value from the total drug added during formulation. The optimized batch showed a **drug entrapment efficiency of 78.12 ± 4.23%,** indicating efficient incorporation of Dabigatran Etexilate into the lipid matrix. This high entrapment efficiency confirms the suitability of the selected lipid and surfactant system for forming stable DE-loaded SLNs.

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ZETA POTENTIAL:

Zeta potential is a key indicator of the electrostatic stability of colloidal dispersions. It is determined by measuring the electrophoretic mobility of particles under an applied electric field. Aqueous colloidal systems typically exhibit negative surface charges, with zeta potential values generally ranging from –14 to –30 mV. The optimized SLN formulation showed a zeta potential of –35.5 mV, indicating strong electrostatic repulsion between particles. Such a highly negative value confirms enhanced physical stability, as increased negativity reduces the likelihood of particle aggregation.

TRANSMISSION ELECTRON MICROSCOPY STUDY:

Transmission Electron Microscopy (TEM) was employed to investigate the morphology and structural characteristics of the optimized SLN formulation. The TEM micrograph confirmed that the nanoparticles were spherical with a smooth and uniform surface, indicating successful formation of well-defined SLNs. No rough spores or structural irregularities were observed, demonstrating good particle integrity and dispersion. The observed architecture supports the presence of a surfactant-stabilized outer layer surrounding the drug–lipid matrix core, which is favorable for achieving sustained drug release.

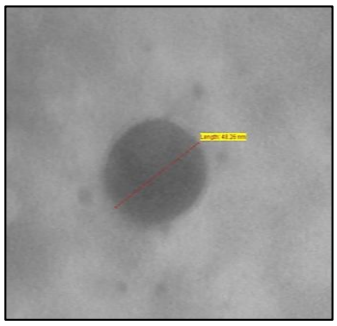

Figure: 3 Transmission Electron Microscopy Image of DE loaded SLN

IN VITRO DISSOLUTION STUDY:

The in vitro drug release profile of DE-loaded solid lipid nanoparticles (SLN) was evaluated using the dialysis bag technique. The in vitro drug release profile of DGE-loaded SLN was evaluated using the dialysis bag method, and the results were compared with the release of pure drug. The optimized SLN formulation exhibited a sustained and controlled drug-release pattern over 24 hours, whereas the pure drug showed a rapid release. During the initial phase, SLN showed 18.95% ± 1.14 release at 1 hour, which gradually increased to 52.67% ± 0.23 at 6 hours. In contrast, the pure drug released 98.95% ± 0.21 within 6 hours, indicating its fast dissolution behaviour. The SLN formulation continued to release drug in a sustained manner, reaching 82.5% ± 0.12 at 20 hours and 97.84% ± 0.8 at 24 hours. The extended release from SLN can be attributed to the encapsulation of drug within the lipid matrix and the diffusion-controlled release mechanism, which effectively prolonged drug availability compared to the pure drug.

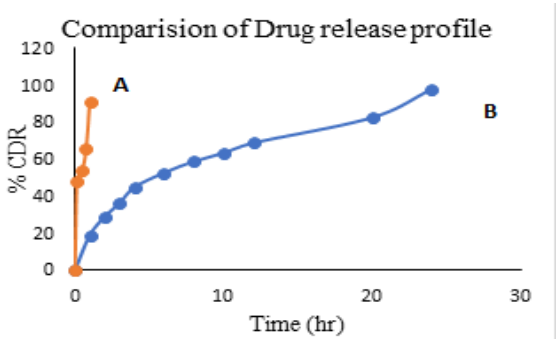

Figure: 4 Invitro Drug Release Study of A. Pure Drug B. DE loaded SLN

CONLUSION:

The present study was designed with the rationale of improving the stability, bioavailability, and controlled release of dabigatran by formulating it into solid lipid nanoparticles (SLN). Dabigatran exhibits poor aqueous stability and limited oral bioavailability; therefore, SLN were selected as a delivery system to provide lipid-based protection, enhance drug entrapment, and enable sustained release. Process and formulation parameters were systematically optimized to achieve an efficient SLN system. The optimized conditions—sonication time of 2 minutes, HSH speed of 10,000 rpm, and HSH time of 15 minutes—along with a drug-to-lipid ratio of 1:11 and 1% surfactant concentration, yielded nanoparticles of **169.12 ± 5.45 nm**, with high drug entrapment **(78.12 ± 4.23%)** and a stable zeta potential **(–35.5 mV).** These characteristics confirm the successful development of a stable and efficient SLN formulation. The formulation was further lyophilized into a **650 mg sachet equivalent to 75 mg dabigatran etexilate**, offering a practical and patient-friendly final dosage form. Overall, the SLN-based system demonstrates strong potential to overcome the limitations of conventional dabigatran delivery by enhancing stability and providing sustained release, supporting its suitability for improved therapeutic performance.

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