RESEARCH ARTICLE

Formulation, Optimization and Characterization of Ticagrelor Loaded NLCs Formulation

Ahire Sujeetkumar Ishwarlal[1*], Gupta Revathi A[2]

[1]*Ph.D Cell, Dr. A. P. J. Abdul Kalam University, Indore, India*
[2]*Institute of Pharmacy (IOP), Dr. A. P. J. Abdul Kalam University, Indore, India*

Received: 21st Mar, 2025; Revised: 11th May, 2025; Accepted: 22nd May, 2025; Available Online: 25th Jun, 2025

ABSTRACT
Ticagrelor is a P2Y12 inhibitor for cardiovascular issues and it works by preventing platelet aggregation, thus reducing the risk of thrombotic events. ticagrelor has shown potential benefits in rheumatoid arthritis when combined with methotrexate. Ticagrelor's role in reducing cardiovascular events may be beneficial for patients with rheumatoid arthritis who are at increased risk for cardiovascular issues. The present study was aimed to formulate, optimize and evaluated ticagrelol loaded NLCs using Box-Behnken design was used. The design was implemented to statistically optimise the factors that were independent: drug: lipid ratio (X1), the surfactant concentration (X2), and soy lecithin concentration (X3), as well as to investigate the main effect, interaction effects, and quadratic effects of these formulation-ingredients on the dependent (response) factor: Entrapment Efficiency (Y1) and *in-vitro*% drug release (Y2). The independent variables and by combining the above components in variable concentrations (levels), 14 batches were created and evaluated based on the response.
Keywords: Ticagrelor, Cardiovascular, Optimization, Drug release
How to cite this article: Ahire Sujeetkumar Ishwarlal, Gupta Revathi A. Formulation, Optimization and Characterization of Ticagrelor Loaded NLCs Formulation. International Journal of Drug Delivery Technology. 2025;15(2):558-61. doi:10.25258/ijddt.15.2.24
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Controlled and Novel Drug Delivery which was only a dream or at best a possibility is now a reality. During the last decade and half pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. Nanoparticles (including nanospheres and nanocapsules of size 10-200nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organ/or tissue, as carriers of DNA in gene therapy, and in their abilities to deliver proteins peptides and genes through peroral route.[1,2]

Ticagrelor [$C_{23}H_{28}F_2N_6O_4S$] having Chemical name (1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5 propyl sulfanyl triazolo[4,5-d] pyrimidin-3-yl]-5-(2hdroxyethoxy) cyclopentane1,2-diol is antithrombotic agent. It has a plasma half-life of approximately 8 hours, while the active metabolite has a plasma half-life of approximately 12 hours. The complete structure of all ticagrelor metabolites is not well defined. Position 5 of the cyclopentane ring is where ticagrelor can be dealkylated to get the active AR-C124910XX.AR-C124910XX's cyclopentane ring can be further glucuronidases or the alkyl chain attached to the sulphur can be hydroxylated. Ticagrelor can also be glucuronidases or hydroxylated. Additionally, ticagrelor can be N-dealkylated to create AR-C133913XX, which is then hydroxylated or further glucuronidated.[3]

MATERIALS AND METHODS

Procurement of Drug

The drug Formulation of Ticagrelor was obtained as a gift sample

Formulation of Ticagrelor Loaded NLCs

Glyceryl monostearate and lecithin were weighed and placed in a clean beaker. The mixture was heated above the melting point of glycerol monostearate (around 70-80°C) untilfully melted. Once the lipid was completely melted, methanol was added to the mixture to dissolve the lipid phase components, forming a clear solution. Equal amounts of Tween 80 and Poloxamer 188 were dissolved in distilled water in a separate beaker. This aqueous phase was then heated to the same temperature as the lipid phase to ensure both phases were at similar temperatures. The aqueous phase was slowly added to the lipid phase while stirring continuously using a magnetic stirrer. The mixture was stirred until a homogenous emulsion was formed. The emulsion was then transferred to a homogenizer. It was homogenized at 4000 rpm for 15 minutes to reduce droplet size. The emulsion was then subjected to sonication using

**Author for Correspondence: ahiresujeet290@gmail.com*

Table 1: Selected factors and their levels

S. No.	Independent variables	Levels	
		Low	High
1.	X1: Drug to lipid ratio	2	6.5
2.	X2: Concentration of surfactant (%)	1	3
3.	X3: Concentration of soy lecithin (%)	0.15	0.3

Table 2: Response variable with units

S. No.	Response variables	Units
1.	Y1: Entrapment Efficiency	%
2.	Y2: *In-vitro* % drug release	%

ultra sonication. The sonication was performed for 15 minutes to further reduce the droplet size and improve the stability of the emulsion. Care was taken to avoid overheating during this process.[4]

Optimization of Ticagrelor Loaded NLCs

To optimise the SLN, the Box-Behnken design was used. The design was implemented to statistically optimise the factors that were independent: drug: lipid ratio (X1), The surfactant concentration (X2), and soy lecithin concentration (X3), as well as to investigate the main effect, interaction effects, and quadratic effects of these formulation-ingredients on the dependent (response) factor: Entrapment Efficiency (Y1) and *in-vitro*% drug release (Y2). The selected factors and their levels are shown in Table 1. The independent variables are shown in table 1, and by combining the above components in variable concentrations (levels), 14 batches were created and evaluated based on the response, which is shown in table 3 and responses are shown in table 2.[5]

Characterization of the Ticagrelor Loaded NLCs

Particle Size and Polydispersity Index (PDI) Analysis

It was determined by using dynamic light scattering (DLS).[6,7]

Zeta Potential

It was determined using Malvern Zetasizer.[6,7]

Percent Drug Entrapment

To determine EE, the 1.5 ml SLNs were subjected to centrifugation, allowing th e0.1ml of free, non-entrapped drug to be separated from the nanoparticles. The amount of free drug in the supernatant was taken in the 10 ml of volumetric and volume was made with the help of methanol using analytical methods of UV spectrophotometry.[6,7]

In-vitro % Drug Release Study

The 10 ml of SLN solution was typically placed in a phosphate-buffered saline (PBS) using dialysis bag, and incubated at 37°C to mimic body temperature. Here phosphate-buffered saline (PBS) used was of pH 1.2 for first 2 hrs and in pH 6.8 for rest of 22 hrs. At predetermined time intervals, samples of 1 ml from the release medium arew ithdrawn and diluted upto 10 ml and analysed using U.V. spectrophotometry at 255 nm, while fresh medium of same amount was replenished to maintain sink conditions. The cumulative amount of drug released over time is plotted to generate a release profile, which helps in understanding how the SLNs behave in the body.[6,7]

Shape and Surface Morphology

This was done using transmission electron microscopy (TEM).[6,7]

RESULTS AND DISCUSSION

The observed responses of Ticagrelor loaded NLCs using BBD were presented in table 4. The reaction rate, Entrapment Efficiency (Y1), and *in-vitro* % drug release (Y2) ranged from 78.87 to 94.68% and 64.71 to 92.73% respectively. The 3D surface plots in Figures 1 and 2 provide a comprehensive visualization of the interaction between the drug-to-lipid ratio and surfactant concentration on both *in-vitro* drug release and entrapment efficiency.

The optimized formula was obtained from design expert software by applying different factors of X1, X2, and X3 as given in table 4.

Particle size (Figure 3) of optimized batch was found to be **160.40 nm** and polydispersity index was found to be **0.278.** Zeta potential (figure 4) of optimized batch was found to be **-24.9 mv**

The percentage drug entrapment was found in the range of 78.87 to 94.68% and of the optimized formulation was found to be 85.64 % and shown in table 5. Cumulative *in-vitro* % drug release study of optimized Ticagrelor loaded NLCs was found to be 93.68±0.18 % upto 30 hours and data

Table 3: SLN of Ticagrelor as per Box-behnken Design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Ticagrelor (mg)	40	40	40	40	40	40	40	40	40	40	40	40	40	40
GMS (mg)	170	80	80	80	260	260	17	260	80	170	260	170	170	170
Poloxamer (mg)	1.7	0.8	0.4	1.2	2.6	2.6	0.85	1.3	0.8	2.55	3.9	2.55	0.85	1.7
Tween (mg)	1.7	0.8	0.4	1.2	2.6	2.6	0.85	1.3	0.8	2.55	3.9	2.55	0.85	1.7
Soy lecithin (mg)	0.15	0.15	0.3	0.225	0.3	0.15	0.225	0.225	0.225	0.15	0.3	0.225	0.3	0.225
Methanol (ml)	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 4: Optimized formula

S. No	Drug: lipid ratio	Amount of surfactant (%)	Amount of Co - surfactant (mg)	Entrapment Efficiency (%)	*In Vitro* drug release (%)
1	4.36	3.00	0.225	85.643	93.68

and drug release plot is shown in table 6 and figure 5. TEM image of Ticagrelor loaded NLCs is shown in figure 6.

CONCLUSION

Results of the study revealed the slow and sustained release of Ticagrelor from the NLCs. It indicated the smooth surface and spherical shape of the particle with size range of upto 140-150 nm.

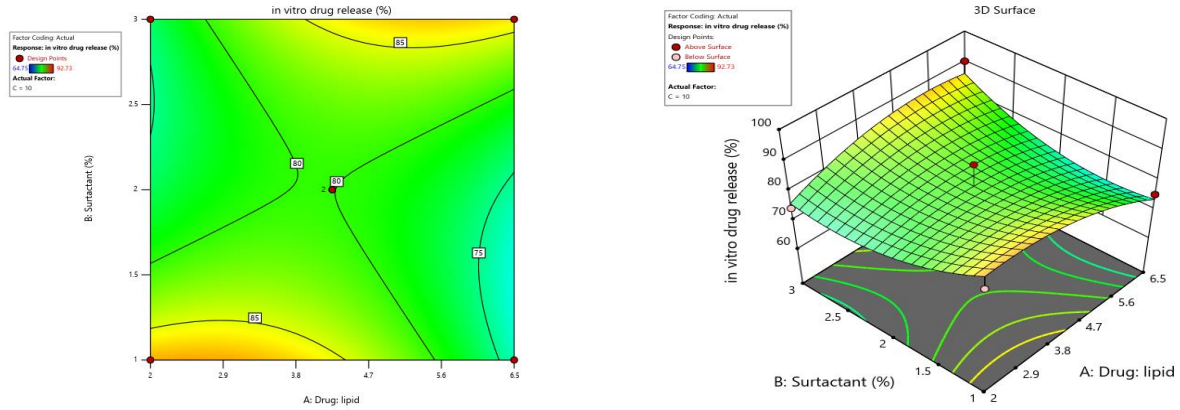

Figure 1: 3D surface plot of SLN for *in-vitro* % drug release

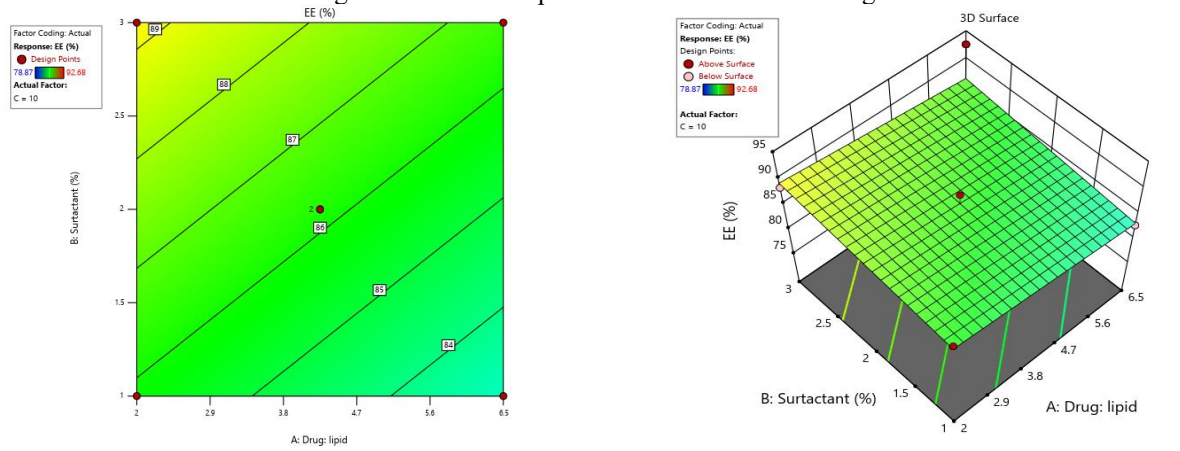

Figure 2: 3D surface plot of SLN for entrapment efficiency

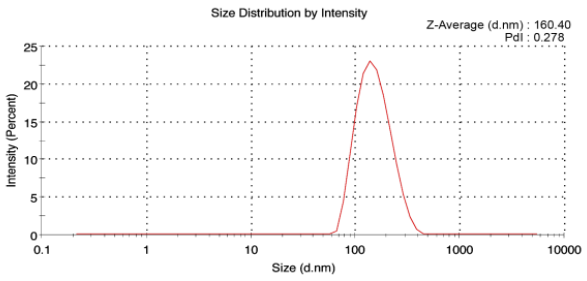

Figure 3: Particle size and PDI of optimized Ticagrelor loaded NLCs

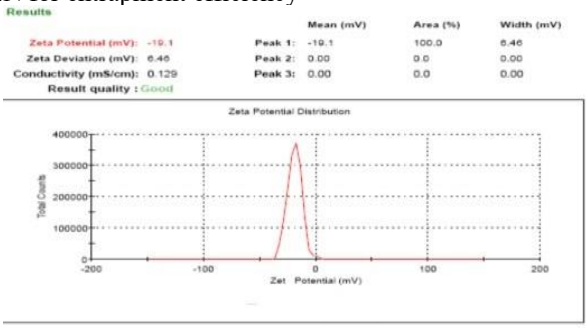

Figure 4: Zeta potential of optimized Ticagrelor loaded NLCs

Table 5: Observed response in Box-Behnken design for SLN

Formulation code	Factor 1 Drug: lipid ratio	Factor 2 Amount of surfactant (%)	Factor 3 Amount of Co surfactant (%)	Response 1 Entrapment Efficiency (%)	Response 2 *In Vitro* drug release (%)
1	4.25	2	0.15	87.39± 0.1	87.19± 1.4
2	2	2	0.15	80.64± 0.7	76.49± 1.2
3	2	1	0.3	89.46± 0.5	83.96± 1.4
4	2	3	0.225	88.37± 0.6	74.35± 1.6
5	6.5	2	0.3	80.99± 0.4	64.75± 1.4
6	6.5	2	0.15	80.10 ± 0.5	78.09± 1.8
7	4.25	1	0.225	86.76± 0.7	88.93± 1.7

Table 5: Observed response in Box-Behnken design for SLN

Formulation code	Factor 1 Drug: lipid ratio	Factor 2 Amount of surfactant (%)	Factor 3 Amount of Co surfactant (%)	Response 1 Entrapment Efficiency (%)	Response 2 *In Vitro* drug release (%)
8	6.5	1	0.225	84.78± 0.6	75.34±1.3
9	2	2	0.225	91.66± 0.4	81.93±1.9
10	4.25	3	0.15	88.37± 0.6	76.63± 1.7
11	6.5	3	0.3	94.68± 0.5	90.37± 1.9
12	4.25	3	0.225	79.09± 0.4	92.73± 1.7
13	4.25	1	0.3	78.87± 0.7	84.55±1.5
14	4.25	2	0.225	87.86± 0.8	72.85± 1.4

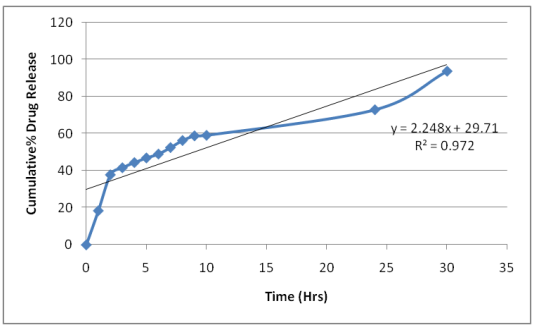

Figure 5: Cumulative *in-vitro* % drug release data of optimized Ticagrelor loaded NLCs

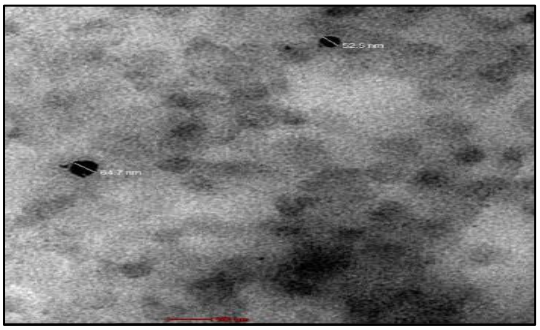

Figure 6: TEM image of optimized Ticagrelor loaded NLCs

Table 6: Drug entrapment and Drug release of Ticagrelorloaded NLCs (n=3)

S. No.	Batch No.	Percentage drug entrapment (%±SEM)
1	F1	87.39± 0.11
2	F2	80.64± 0.75
3	F3	89.46± 0.51
4	F4	88.37± 0.62
5	F5	80.99± 0.46
6	F6	80.10 ± 0.52
7	F7	86.76± 0.72
8	F8	84.78± 0.66
9	F9	91.66± 0.43
10	F10	88.37± 0.69
11	F11	94.68± 0.51
12	F12	79.09± 0.49
13	F13	78.87± 0.73
14	F14	87.86± 0.86
15	Optimized	85.643± 0.29

Acknowledgment

The authors would like to take this opportunity to express sincere gratitude to the management, Dean, faculty of Pharmacy, principal, and staff of the Dr. A.P.J. Abdul Kalam University, Indore.

REFERENCES

1. Dana T, Pathan AK, Ahmad S. Enhancing Anticancer Potential: Optimization of Allicin Extraction from Regular Garlic and Characterization of Allicin-Loaded Copper Oxide Nanoparticles. International Journal of Drug Delivery Technology. 2024;14(2):1019-1031.
2. Dwivedi S, Lalwani D, Sharma PK and Darwhekar GN. Advancing Oral Drug Delivery: The Impact of Solid Lipid Nanoparticles on Antiplatelet Therapy. European Journal of Parenteral and Pharmaceutical Sciences. 2025: 30(1):1-12.
3. Herron GC, Bates ER. Review of the ticagrelor trials evidence base. Journal of the American Heart Association. 2024;13(11):e031606.
4. Mikled P, Chavasiri W, Khongkow M. Development of dihydrooxyresveratrol-loaded nanostructured lipid carriers for safe and effective treatment of hyperpigmentation. Scientific Reports. 2024;14(1):29211.
5. Ali, M.H., Alam, O., Ali, A., Ali, M.U., Parvez, S., Aldosari, E., Baboota, S. and Ali, J., 2024. Donepezil and Embelin loaded nanostructured lipid carriers for direct brain delivery as an intervention for alzheimer's disease: Formulation design, optimization and evaluation. *Journal of Cluster Science*, *35*(4):1021-1044.
6. Abdulazeem L, Abd FG. Biosynthesis and Characterization of Gold Nanoparticles by Using Local Serratia spp. Isolate. International Journal of Pharmaceutical Quality Assurance. 2019;10(3):8-11.
7. Mahajan PM, Jadhav SA, Hussain A, Chaturvedi P, Dwivedi S.Formulation Development and Evaluation of Silver Nanoparticles Containing Plant Extract. Nanotechnology Perceptions. 2024; 20(7): 3837-3842.