Ind. J. Pharm. Edu. Res., 2024; 58(3s):s828-s836.
https://www.ijper.org

Original Article

QBD-Powered Design and Optimization of Nanostructured Lipid Carriers Loaded with BCS class IV Anticancer Drug

Pamujula Naga Haritha[1,*], Kunchithapatham Janakiraman[1], Katla Venu Madhav[2], Padavala Sunil Kumar Chaitanya[3]

[1]Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, INDIA.
[2]Department of Pharmaceutics, St. Pauls College of Pharmacy, Turkyamjal, Hyderabad, Telangana, INDIA.
[3]Department of Pharmaceutical Analysis, St. Pauls College of Pharmacy, Turkyamjal, Hyderabad, INDIA.

ABSTRACT

Background: The therapeutic efficacy of an active Pharmaceutical ingredient depends on its solubility in body fluids. The low bioavailability of nearly 90% of new active Pharmaceutical ingredients and 40% of the existing molecules is attributed to their poor solubility. The current study aimed to improve the oral bioavailability of lapatinib by designing and optimizing nanostructured lipid carriers for it. **Materials and Methods:** The formulation utilized the microemulsion technique as a method of preparation and the Box Behnken design was used for optimization. **Results:** The average particle size, drug entrapment, and release, in percentages, were observed to be 237.09 nm, 72.32%, and 74.66% respectively. **Conclusion:** *In vitro* studies proved that NSLC significantly releases a drug more than the marketed formulation.

Keywords: QbD, Box Behnken design, Lapatinib, Nanostructured lipid carriers, Dissolution improvement, Microemulsion technique.

Correspondence:
Mrs. P. Naga Haritha
Research Scholar, Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, INDIA.
Email: harithasunilp.hs@gmail.com

Received: 25-05-2023;
Revised: 01-11-2023;
Accepted: 15-05-2024.

INTRODUCTION

The dynamics of drug absorption from human GIT are cumbersome and influenced by a variety of physicochemical, physiological, and formulation-related factors.[1,2] As per BCS solubility and permeability are the factors that control oral drug absorption.[3] An estimated 40% of marketed drugs are poorly water soluble and therefore exhibit poor oral bioavailability.[4,5] Poor bioavailability of a drug is a major setback and en route compromised performance. This problem mandates the administration of high doses leading to toxicity.[6,7]

In 2020 carcinoma of the breast has been identified as the most commonly diagnosed form of cancer with over 2.26 million new cases and a death toll of nearly 685000 globally. As per IARC breast cancer is the fifth among the most deadly forms of cancer. Lapatinib is an antineoplastic indicated in lung and breast cancers. It was approved for metastatic breast cancer in combination with capecitabine by USFDA. Lapatinib is a Human Epidermal growth factor Receptor type 2 (HER2/ERBB2) and Epidermal Growth factor Receptor (HER1/EGRF/ERBB1) inhibitor. The clinical benefit of lapatinib was greatly hindered by its poor solubility. Since lapatinib was classified under BCS class IV a special focus on solubility and permeability is mandatory.[8]

Hence Lapatinib was selected to be formulated as Nanostructured Lipid Carriers (NSLCs) a second-generation lipid-based drug delivery systems that are beneficial over solid nanoparticles, the first-generation lipid-based drug delivery systems. Solid and liquid lipids along with emulsifiers are used for the preparation of NSLCs, the incorporation of liquid lipids minimizes the structured misorientations of solid lipids resulting in a less ordered crystalline arrangement. Hence it is selected to formulate as Nanostructured Lipid Carriers (NSLCs).[9-12]

MATERIALS AND METHODS

Lapatinib was Procured from MSN Laboratories Pvt. Ltd., Hyderabad, India, Cholesterol, Mustard oil, and Tween 80 were purchased from Quali-Chem, Hyderabad. All of the chemicals were of analytical reagent grade and utilized exactly as they were given to us.

Screening of Excipients

Selection of liquid lipids

The saturation solubility of the medication in different liquid lipids was tested by putting an excess quantity of lapatinib in 1 mL of different oils in 2 mL glass vials. In a mechanical shaker, the glass vials were firmly closed and continuously agitated for

DOI: 10.5530/ijper.58.3s.84

72 hr at 37°C to achieve equilibrium. Following that, liquid lipid and drug mixes were centrifuged at 10,000 rpm for 10 min at 37°C.[13] The supernatant was separated, diluted in ethanol, and the saturation solubility was determined using a UV technique at 309 nm.

Selection of Solid Lipids

A precisely weighed amount (1 g) of the solid lipids was collected and heated to 4-5°C above their melting point with continuous stirring using a magnetic stirrer with a hot plate at 200 rpm. Lapatinib was added in 1mg increments until entirely dissolved in the molten solid lipids, at which point the amount of solid lipids necessary to solubilize the medication was estimated. The experiment was done three times, and the findings were provided as mean value (mg/g)±SD.[13]

Selection of Surfactant

The highest entrapment capacity, particle size, and polydispersity index are the parameters considered to select the surfactants. NSLCs were prepared using different surfactants with selected solid and liquid lipids. The prepared NSLCs were evaluated for particle size and PDI.

Preparation of NSLCs

The Lapatinib Nanostructured Lipid Carriers (LTNSLCs) were formulated by using the microemulsion technique. The solid lipid was melted and combined with the liquid lipid to solubilize the drug. This is considered the lipid phase. The surfactant and lipids were heated to the same temperature to constitute the aqueous phase. To create an oil in water hot emulsion that is thermodynamically stable, both phases were combined and gently agitated. Now this is immediately dispersed into excess of cold water (0-4°C) with agitation, sonication, and filtration.[9]

DOE for optimization of NSLCs

Statistical optimization of NSLC formulation was accomplished by Box Behnken-Design (BBD). Total lipid content (A), Surfactant percentage (B), and sonication time (C) were considered as independent variables, and particle size (Response 1), percentage drug entrapment efficiency (Response 2), and percentage drug release (Response 3) as dependent factors. The BBD places three identical points at the center point and the midpoints of each edge of a multidimensional cube. Table 1, therefore, displays the independent variables' low, medium, and high values, which were established based on the findings of the exploratory trials. Each component that could affect the formulation features was subject to limits based on the observations. By utilizing design experts version 13 with 3-factor and 3-level BBD NSLCs were optimized. The design comprises 15 experimental runs with the computerized quadratic equation as follows;

$$Y = b0 + b1A + b2B + b3C + b12AB + b13AC + b23BC + b11A2 + b22B2 + b33C2$$

Where Y is the measured response for each combination of the factor levels, b0 is constant, b1, b2, and b3 are linear coefficients, b12, b13, and b23 are the interaction coefficients in the middle of the three factors, and b11, b22, and b33 are the quadratic coefficients of the observed experimental values for the independent variables.[14,15] The observed responses in the BBD design for LTNSLCs formulation optimization are shown in Table 2.

Characterization of LTNSLCs

Drug Excipient Compatibility studies

A Shimadzu FTIR Spectrophotometer (Shimadzu, Tokyo, Japan) was used for the FT-IR spectroscopic investigation, and the FT-IR spectra were acquired in the wavelength range 4000-400 cm^{1}. The process involved dissolving a 5 mg sample in KBr and compressing it into discs in a hydraulic press at a pressure of 5 tonnes for 5 min. The FT-IR spectra was obtained for Pure drug (Lapatinib) and combination of Lapatinib and physical mixture of excipients. (Cholesterol, mustard oil and Tween 80).

The drug excipient compatibility studies were also performed by using Diffrential Scanning Colorimetry method for pure drug and combination of pure drug with the physical mixture of the other excipients.

Particle-size and PDI

The optimised formulation's particle size and PDI were determined using Scanning Electron Micrography. The Zeta potential of the optimized formulation was measured in a medium filled in polystyrene cells at 25°C. PDI was determined using suitable formula.[16]

Entrapment Efficiency

The quantity of drug entrapped in the nanocarrier is a measure of drug entrapment efficiency which is assessed with respect to the total amount of drug added. Percentage drug loading capacity is a measure of the drug in a unit weight of a nanocarrier system calculated by the total amount of formulation. It is determined in relation to the formulation's overall weight. The ultracentrifuge method was used to calculate the LTNSLCs' percentage drug loading and entrapment efficiency. Suitable dilutions of a specified quantity of LTNSLC were prepared with dimethyl sulfoxide. The dispersions were filled in a 10 mL centrifugation tube and centrifuged at 55,000 RPM for 30 min at ambient temperature. The drug from the supernatant was filtered and the concentration was calculated by UV-visible spectrophotometer by measuring the absorbance at 302 nm. Further the percentage drug loading and percentage Entrapment Efficiency (%EE) were calculated by using the following formulae;[17]

Table 1: Design of Formulation by Box Behnken Design.

	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Run	A: Total Lipid	B: Surfactant	C: Sonication Time	Particle size	Entrapment	Drug release
	%	%	Min	nm	%	%
1	3	5	10	235.71	76.47	73.47
2	5	3	2	247.25	83.51	71.48
3	3	3	6	298.62	73.79	64.19
4	1	1	6	209.76	66.47	92.13
5	3	3	6	298.29	71.56	63.87
6	1	5	6	197.64	58.54	76.58
7	5	3	10	231.67	92.12	69.83
8	1	3	2	194.21	66.79	76.52
9	5	1	6	240.71	73.32	72.5
10	3	1	10	219.78	67.58	75.52
11	3	1	2	229.74	65.13	79.24
12	3	3	6	296.67	72.91	62.46
13	5	5	6	237.43	82.93	87.33
14	3	5	2	209.24	62.35	76.53
15	1	3	10	209.67	71.42	78.25

Table 2: Selection of the Surfactant on the Basis of Particle Size and PDI.

Name of the surfactant	Particle Size	PDI
Soyalecithin	260.1±1.31	0.389±0.001
Tween 80	370.3±2.2	0.345±0.001
Polaxomer	398.2±1.49	0.456±0.001
Polyoxyl Castor oil	454.7±2.36	0.501±0.001

$$\%EE = \text{total amount of drug} - \text{the amount of free drug/total amount of drug} X100$$

$$\%\ \text{Drug loading} = \text{total amount of drug} - \text{the amount of free drug/total amount of NSLCs} X100$$

In vitro Drug release study

The *in vitro* drug release studies were performed by using a Franz diffusion cell with 25 mL capacity. A dialysis membrane with molecular weight 12-14 kDa was used as diffusion membrane. Phosphate Buffer Solution (PBS) of pH 7.4 was used as a medium for conducting release studies. Before conducting the experiment the diffusion membrane was cut into pieces of required size and soaked in the PBS pH 7.4 for nearly 48 hr. The PBS was filled in the bottom compartment of the cell and above that the dialysis membrane was placed followed by placing the first compartment. The sample solution was prepared by mixing the required quantity of LTNSLC (equivalent to 2 mg of API) in buffer solution and pre-incubated at 37ºC for 30 min before the experiment. Lapatinib (pure drug) was dissolved in ethanol and incubated with the buffer solution. Both the samples were introduced into the Franz diffusion cell and stirred by magnetic stirrer at 50 rpm. The s samples were withdrawn every 15 min and then replacing them with the same amount of the fresh solution to maintain the sink condition. The drug release was determined by using a UV-vis Spectrophotometer at 300 nm.[18]

Stability Studies

The drug-loaded nano structured lipid carriers were held for three months at room temperature and under accelerated settings to investigate their physical stability. Samples were taken at 0, 1, 3 and 6 month intervals and analysed for particle size and percentage entrapment efficiency. The shelf-life of optimised nanolipid carriers was also investigated.[19]

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies

The Drug excipient compatibility studies performed by FTIR and DSC are shown in the following Figures 1a and b. The spectras of pure drug and the combination of pure drug along with that of the physical mixture of excipients had revealed that there is no incompatibility among the drug and the excipient used in the formulation.

Drug Solubility in Solid and Liquid Lipids

Among all the different kinds of lipids used, 12 mg of the drug was solubilized in cholesterol and 9mg in mustard oil. Hence

Table 3: Summary results of regression analysis, SD and % CV with responses 1, 2 and 3 for the quadratic model equation.

Quadratic model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Response 1	0.9969	0.9913	0.9519	3.28	1.38
Response 2	0.9897	0.9717	0.8672	1.49	2.06
Response 3	0.9868	0.9630	0.8136	1.56	2.10

Table 4: Stability Studies of Optimised LNSLCs.

Time (months)	0	1	3	6
Condition	25±2°C/60±5% RH			
PS (nm)	197.1±2.3	197.1±2.3	199.2±1.2	200.3±1.3
EE (%)	92.12±1.79	92.12±1.79	90.36±0.79	90.32±0.62
Condition	Ambient Temperature			
PS (nm)	197.1±2.3	197.1±2.3	199.2±1.2	200.3±1.3
EE (%)	92.12±1.79	92.12±1.79	90.36±0.79	90.32±0.62
Condition	40±2°C/75±5% RH			
PS (nm)	197.1±2.3	197.1±2.3	199.2±1.2	200.3±1.3
EE (%)	92.12±1.79	92.12±1.79	91.46±0.72	91.32±0.69

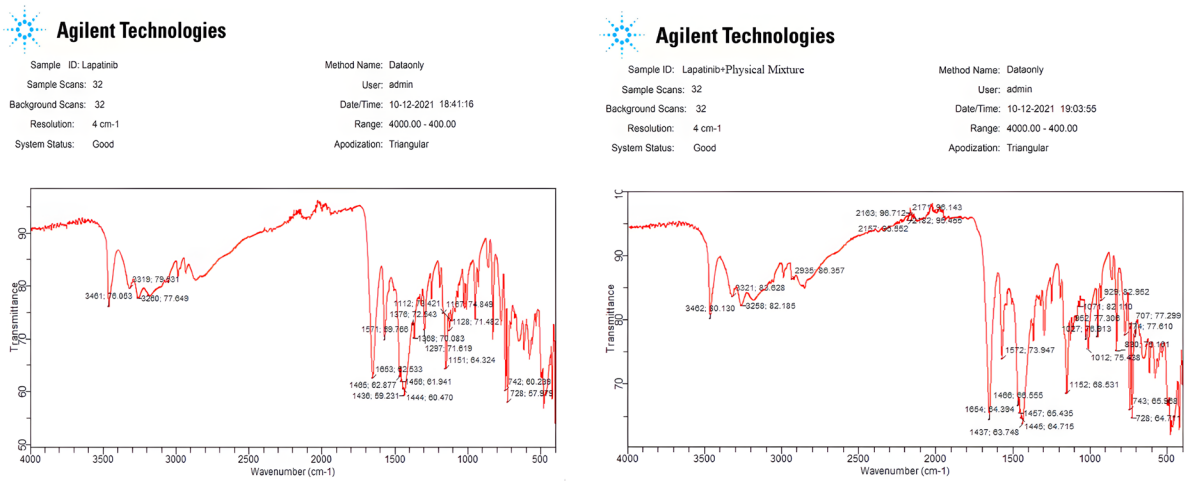

Figure 1a: FTIR Spectra of Lapatinib Pure drug and Lapatinib and Physical Mixture of excipients.

cholesterol and mustard oil were selected as solid and liquid lipids respectively. The results are shown as Figure 2a and 2b.

Selection of Surfactant

The solubility of the drug in the lipids can be stabilized by using surfactants. Depending on the particle size and PDI attained, Tween 80 was selected as a surfactant. The results are shown in Table 2.

Optimization of LTNSLCs by BBD

With three center points 15 experimental runs have been generated for formulations by BBD. The three independent variables were taken and the range was as follows. R1: Particle size (nm) 194.21-298.62 nm, R2: entrapment efficiency (%) 58.54%-92.12%, and R3: Percentage drug release (%) 62.45%-92.16%. The quadratic model was suitably fitted to the formulations. The values of %CV, SD, and R^2 of all three responses were given in Table 3; the effect of independent variables, total lipid, surfactant concentration, and sonication time on dependent variables is graphically represented.

Response 1(R1): Particle size and independent factors.

The average particle size overall experimental runs, which is between the minimum and highest values of 194.21 nm and 298.62 nm particle size, was determined to be 237.09 nm.

$$\text{Particle size}=297.86+18.22A-2.50B+2.05C+2.21AB-7.76AC+9.11BC-39.70A^2-36.78B^2-37.46C^2$$

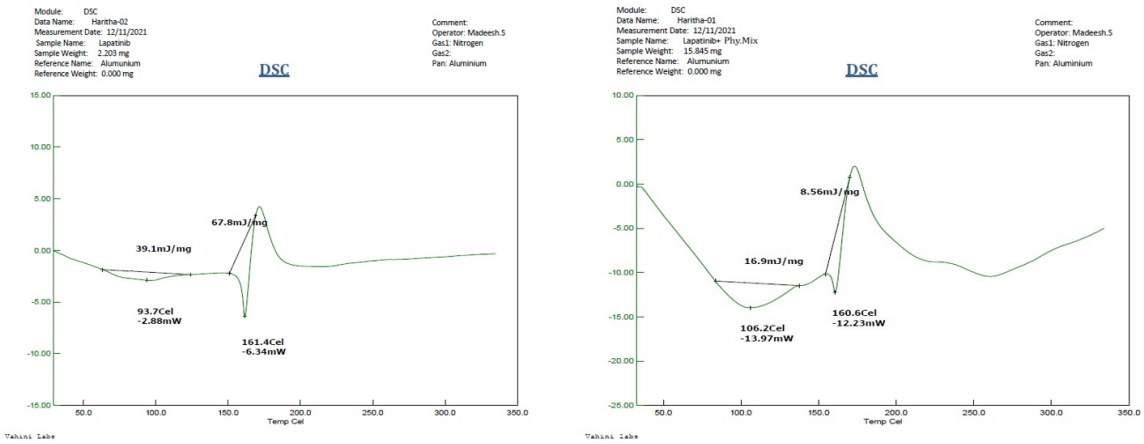

Figure 1b: DSC thermogram of Lapatinib Pure drug and Lapatinib and Physical Mixture of excipients.

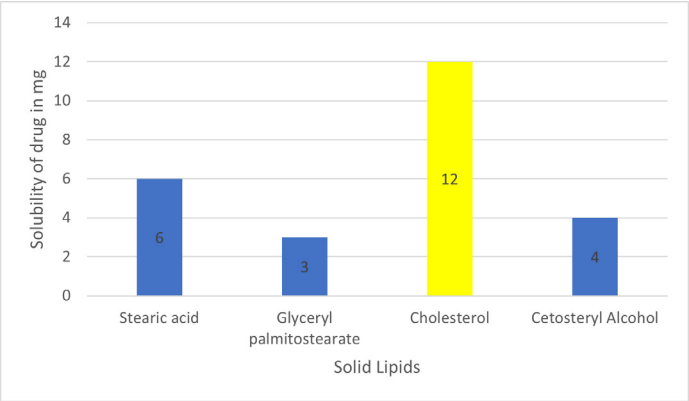

Figure 2a: Selection of solid lipids based on the solubility of the drug.

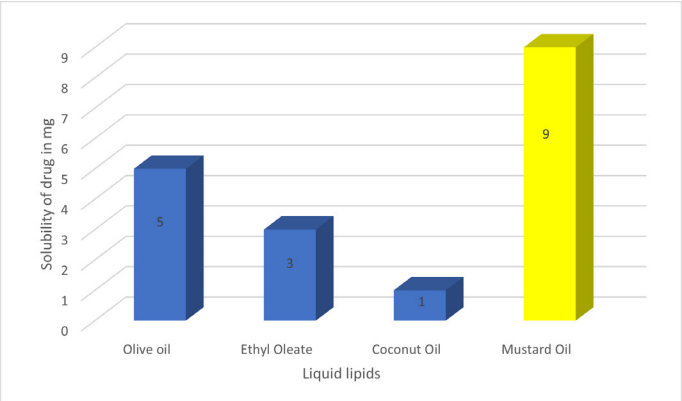

Figure 2b: Selection of liquid lipids based on the solubility of the drug.

The aforementioned equation leads to the conclusion that as the total lipid content rises, so does the particle size, which may indicate a reduction in the emulsifying process' effectiveness and an increase in particle agglomeration.[20] The length of the sonication has very little bearing on the size of the LTNSLCs (Figure 3).

Response 2 (R2): The impact of independent factors on the effectiveness of entrapping.

Between 58.54 to 92.12%, the average entrapment effectiveness was determined to be 72.32%.

$$\text{Entrapment Efficiency} = 72.75 + 8.58A + 0.97B + 3.73C + 4.39AB + 0.99AC + 2.92BC + 4.07A^2 - 6.51B^2 + 1.64C^2$$

According to the aforementioned equation, the amount of lipids affects entrapment efficiency and an increase in lipids results in a rise in entrapment efficiency since the medication is trapped within an oil-enriched lipid core.[21] The surfactant may initially boost entrapment efficiency before decreasing as a result of the surfactant's own entrapment in NSLCs. The impact of sonication duration is, however, minimal (Figure 4).

R3: Percentage Drug Release and the Impact of Independent Variables.

The average percentage drug release of all the experimental runs was found to be 74.66% which lies between 62.45% and 92.16%.

$$\text{Percentage drug release} = 63.51 - 2.79A + 0.68B - 0.83C + 7.60AB - 0.84AC + 0.16BC + 8.23A^2 + 10.40B^2 + 2.28C2$$

It was shown that the drug release pattern from LTNSLCs is significantly influenced by the total lipid and surfactant content. The proportion of medication is directly proportional to lipid content. Based on the point prediction approach of BBD, the LTNSLCs formulation was optimised. The optimised batch containing the medication had an average particle size of 117.2±3.2 nm. Entrapment effectiveness was determined to be 93.53-1.4% and drug release percentage to be 87.01-1.5%, respectively. These values were discovered to be nearer the predictions. Additional characterisation was done on the optimised formulation and shown as Figure 5.

Scanning Electron Micrography

SEM was used to visualise the surface morphology and mean diameter of an optimised Lapatinib-loaded NSLC formulation. SEM pictures revealed a nearly spherical surface of the optimised Lapatinib-loaded NLC formulation with uniform size distribution (200 nm), correlating with zeta sizer particle size

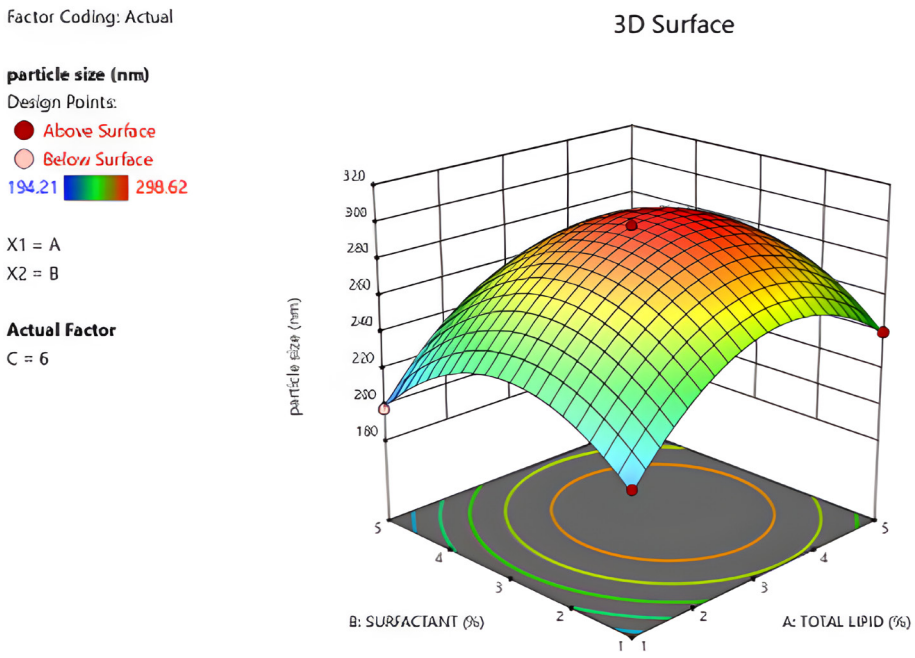

Figure 3: Effect of independent variables on Particle size.

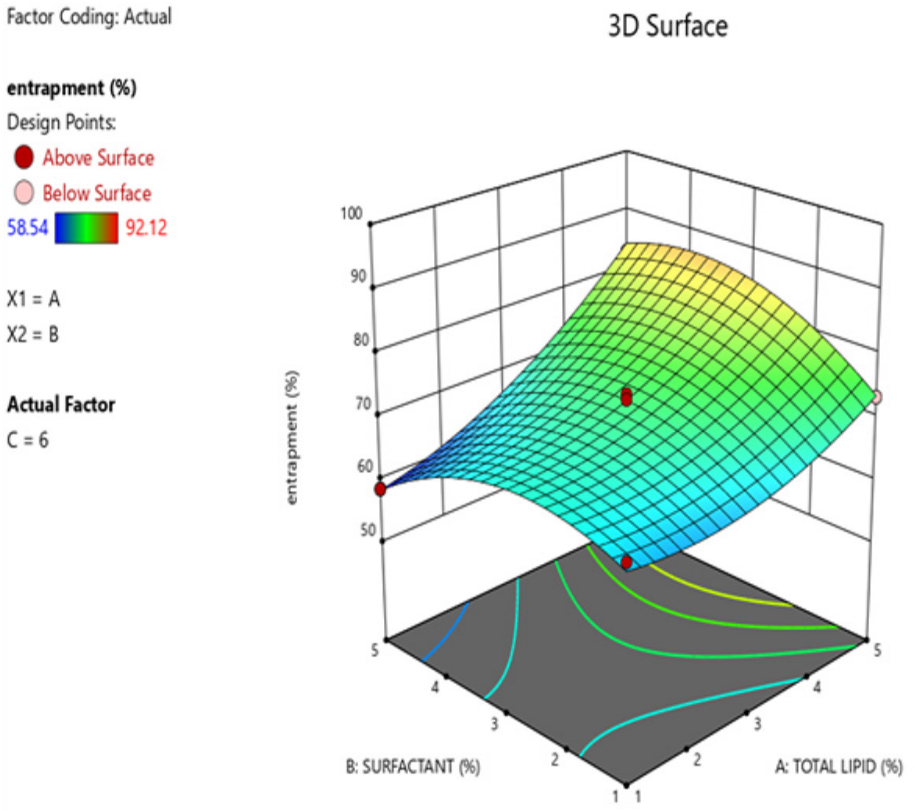

Figure 4: Effect of independent variables on entrapment efficiency.

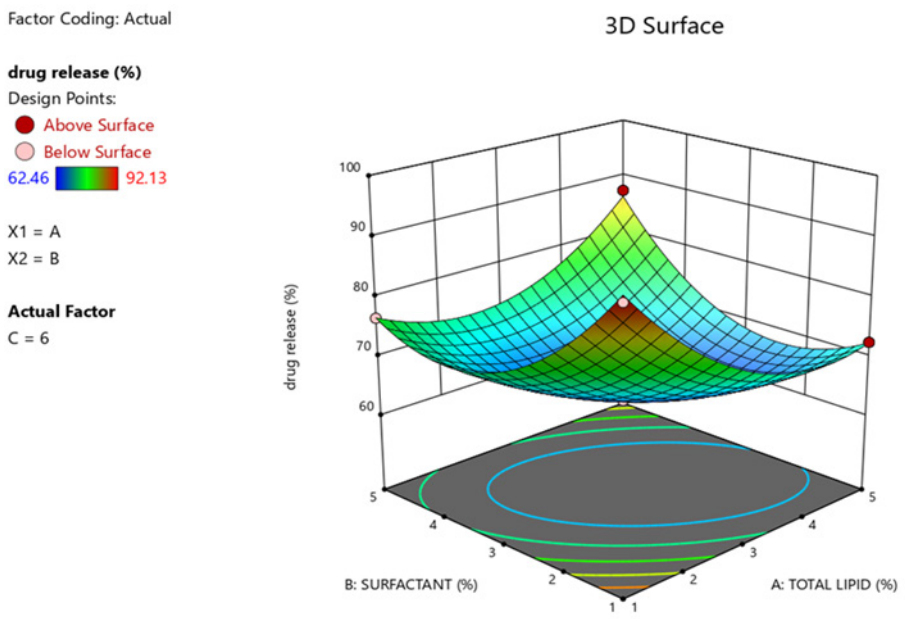

Figure 5: Effect of independent variables on Percentage drug release.

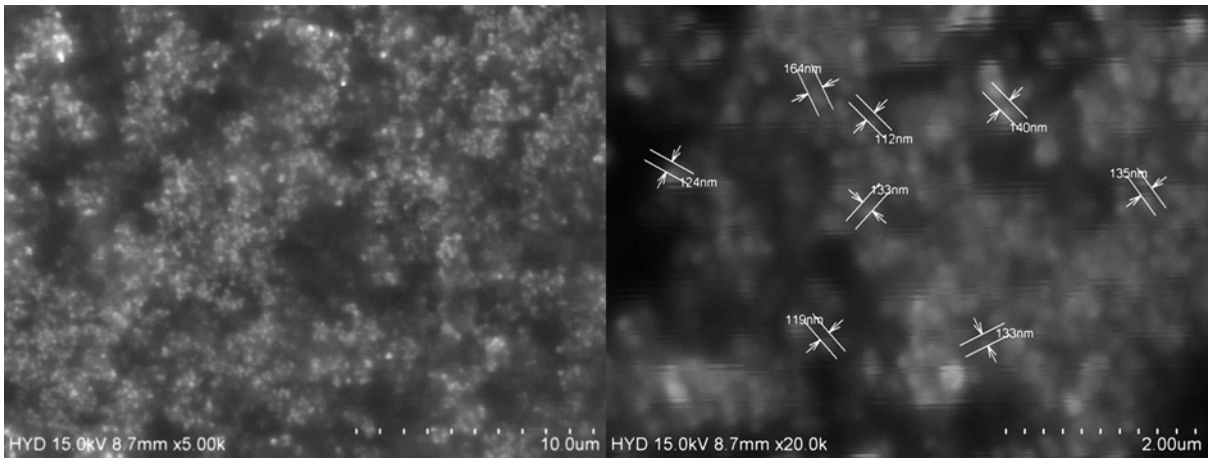

Figure 6: SEM Pictures of optimised Lapatinib Nanostructured Lipid Carriers.

measurements. The results show that the particles were spread equally and isolated from one another. The Sem pictures are shown in Figure 6.

Particle Size, Polydispersity Index and Zeta Potential

The optimized formulation's mean particle size was discovered to be 117.2±3.2 nm, and its mean PDI-which measures the drug's homogeneous distribution-was shown to be 0.60±0.06 nm. Smaller particle size suggests good miscibility and more systemic circular time. The low PDI value states the uniformity of nanoparticle distribution. Zeta potential indicates the stability of the nanoformulation. Zeta potential positive value suggests longer residence time and less uptake by the reticuloendothelial system in the blood circulation system. The results were given in Figures 7a and 7b.

Percentage Drug Release

Up to 12 hr were spent tracking the medication release % from the optimised NSLC. The proportion of drug release increased gradually over the course of the first hour, rising from 3.2% to 63.87% by the end of the period. Comparing the proportion of medication release from NSLCs to that from commercially available formulations. When compared to NSLCs, the drug release percentage from the commercialised formulation Tylidys tablet was lower. The trapping of the drug in the lipids and improvement in the solubility of the drug may be the causes of the delayed and regular release of drug from NSLCs as shown in the Figure 8.

Stability Studies

Table 4 shows the 6-month stability experiments of LNSLC at room temperature, ambient temperature, and accelerated

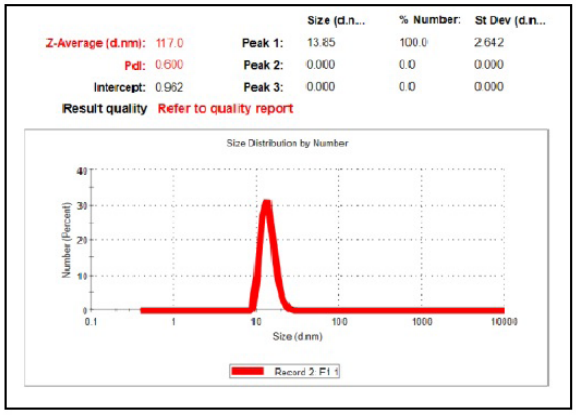

Figure 7a: Particle Size and PDI of LNSLCs.

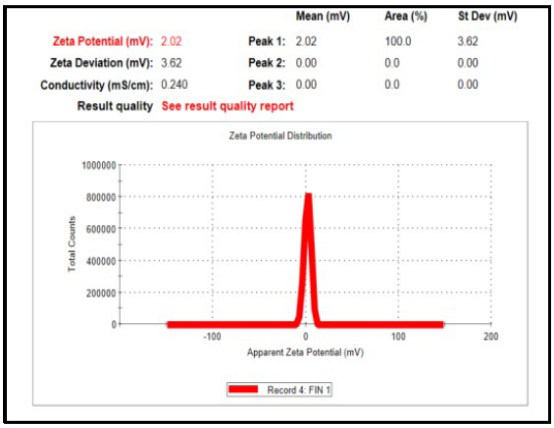

Figure 7b: Zeta Potential of LNSLCs.

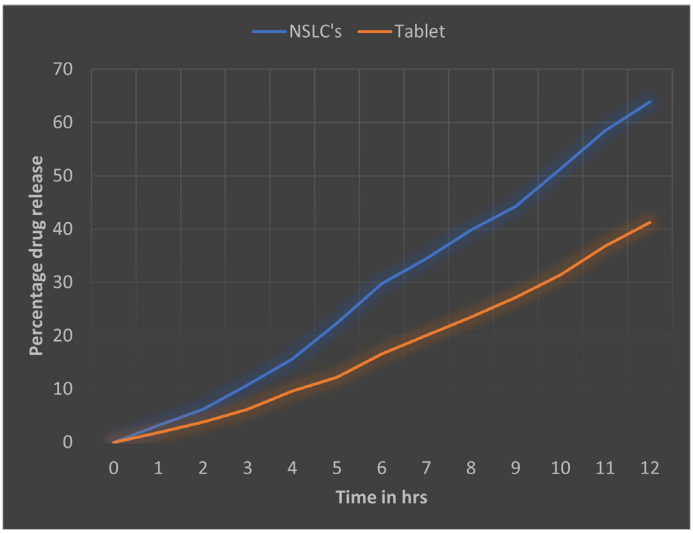

Figure 8: Comparision of drug release from NSLCs and marketed formulation.

settings. Particle size and drug entrapment efficiency were assessed in LNSLCs. The LNSLCs tested exhibited no changes in particle size or entrapment efficiency. No significant changes were observed in particle size or entrapment efficiency after 6 months period.

CONCLUSION

The design and optimisation of lapatinib (a BCS class IV medication) loaded nanostructured lipid carriers were demonstrated in the current work. The microemulsion approach was effective in creating the NSLCs, and BBD was used for optimisation. When compared to the drug release from the marketed tablets, the entrapment efficiency of the NSLCs was enhanced by the use of both solid and liquid lipids. By manufacturing lapatinib as NSLCs, the medication's bioavailability can be increased. These NSLCs demonstrated improved drug release when compared to the drug's commercial formulation.

ACKNOWLEDGEMENT

We extend our heartfelt gratitude to the Department of Pharmacy, Annamalai University, for providing the essential facilities and support necessary for the successful completion of this project. We also sincerely thank St. Pauls College of Pharmacy for their invaluable assistance and resources throughout our research. Their contributions have been instrumental in enabling us to carry out this work effectively. We appreciate the encouragement and guidance from both institutions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BCS: Biopharmaceutical Classification System; **NSLCs:** Nanostructured Lipid Carriers; **BBD:** Box-Behnken Design.

SUMMARY

This study aimed to design and optimize Nanostructured Lipid Carriers (NSLCs) for the delivery of lapatinib, a drug classified under BCS class IV due to its low solubility and permeability. The researchers employed a microemulsion technique to develop the NSLCs, which was then optimized using Box-Behnken Design (BBD) to achieve the best formulation characteristics. The NSLCs were composed of both solid and liquid lipids, which played a crucial role in enhancing the entrapment efficiency of lapatinib within the carriers.

The optimized NSLC formulation demonstrated significantly improved drug release profiles compared to the marketed lapatinib tablets. The enhanced release was attributed to the improved solubility and stability provided by the lipid-based nanostructure. This increased drug release suggests that lapatinib, when delivered through NSLCs, has the potential to achieve higher bioavailability, thus potentially improving its therapeutic effectiveness.

Overall, the study highlights the efficacy of NSLCs as a drug delivery system for lapatinib, offering a promising approach to

overcome the solubility and bioavailability challenges associated with BCS class IV drugs.

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Cite this article: Janakiraman K, Haritha PN, Venumadhav K. QBD-powered design and optimization of Nanostructured Lipid carriers loaded with BCS class IV anticancer drug. Indian J of Pharmaceutical Education and Research. 2024;58(3s):s828-s836.