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# PALBOCICLIB LOADED SOLID LIPID NANOPARTICLES BY BOX-BEHNKEN DESIGN: SOLUBILITY ENHANCEMENT

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**Keywords:**

Palbociclib, Breast cancer, Solid lipid nanoparticles, Box-Behnken design

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**ABSTRACT:** The purpose of the present study was to optimize palbociclib-loaded solid lipid nanoparticles (SLNs) by evaluating the relationship between design factors and experimental data. A three-factor, three-level Box-Behnken design (BBD) was used for the optimization procedure, choosing the amount of tricapric, cremophor RH40 and soy lecithin, as independent variables. The chosen dependent variables were particle size, entrapment efficiency, and % cumulative drug released. The generated polynomial equations and response surface plots were used to relate the dependent and independent variables. The optimal nanoparticles were formulated with 08%tricapric, 09% cremophor RH40, and 6% soy lecithin. Three formulations were prepared according to these levels and found that the observed responses were close to the predicted values of the optimized formulation. The formulation PF13 was chosen for characterization as it displayed minimum particle size (103 nm), PI of 0.47, the zeta potential of -16 mV, maximum drug release of 98% in 12h. Fourier transform infrared spectroscopy (FT-IR) study indicated that the drug was entrapped in nanoparticles with no significant interaction between drug and excipients used. The optimized formulation showed a sustained zero-order release which followed the Peppas model. The formulation was stable when stored according to ICH guidelines for 6 months.

**INTRODUCTION:** Palbociclib is a medication developed by Pfizer for the treatment of HR-positive and HER2-negative breast cancer. It is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6. Palbociclib was the first CDK4/6 inhibitor to be approved as a cancer therapy. It exhibits poor oral bioavailability of 46 % owing to its poor aqueous solubility and first-pass metabolism.

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Hence solid lipid nanoparticles can be considered as a suitable drug delivery system to improve the poor oral bioavailability of palbociclib [1]. Solid lipid nanoparticles (SLNs) can entrap both lipophilic and hydrophilic drugs [2].

SLNs combines the advantage of colloidal carriers, vesicular carriers, and polymeric carriers as physiologically acceptable systems, non-toxic, biocompatible, scalability and in imparting the controlled release of drug from lipid matrix [3]. Furthermore, SLNs augment the lymphatic transport of the lipophilic drugs, irrespective of the route of administration, and therefore increase the systemic availability of drug molecules. Nano drug formulations can impart many physical and biological advantages, such as improved solubility

and pharmacokinetics (PK), enhanced efficacy, reduced toxicity and increased tissue selectivity, compared with conventional medicines [4]. The response surface methodology (RSM) is useful in simultaneously analyzing process variables when variable interactions are very complicated. Many studies have demonstrated the value of RSM for establishing the optimal formulation in various drug delivery systems. This study used the Box-Behnken design (BBD), an RSM design because it requires fewer runs in a 3-factor experimental design than all other RSM designs and is particularly useful when extreme treatment combinations need to be avoided5.In the present research, palbociclib SLN was formulated and optimized using Box-Behnken design (BBD).

## MATERIAL AND METHODS:

**Materials used:** The drug palbociclib was obtained from Hetero drugs Ltd, Hyderabad.. The excipients tricapric, cremophor RH 40, soy lecithin and solvents chloroform, methanol were purchased from Merck Specialties Pvt Ltd, Mumbai, India.

**Preparation of palbociclib SLN:** Palbociclib SLNs were prepared by a hot emulsification/ultrasonication method. According to the partitioning results, tricapric was selected as a solid lipid to formulate palbociclib - SLNs. Palbociclib (125 mg), tricapric (%) were dissolved in a mixture of chloroform and methanol (1:1) (20 mL). The solvent was then completely removed using a rotary evaporator. The drug-embedded lipid layer was melted by heating at 75 °C. An aqueous phase was then formulated by dissolving the surfactant and co-surfactant(%) cremophor RH40 and soy lecithin in double-distilled water and adding it to the molten lipid phase. This was followed by homogenization for 3 min. Coarsehotoilina water emulsion was obtained, which was then ultrasonicated using a probe sonicator. Finally, the obtained hot nanoemulsion was allowed to cool to room temperature to prepare palbociclib –SLNs [6-8].

**Experimental Design:** A 33 BBD employed for optimizing the main, interaction, and quadratic effects of formulation components on characteristics of SNEDDS. Seventeen experiments run randomly for chosen independent variables that include 5 repetitions at the center (asterisk-marked) obtained from 3 factor, 3-level BBD, and their subsequent responses noted 11-14. The variables that were chosen as dependent and independent are specified in **Tables 1** and **2**.

The BBD matrix obtained using Design Expert® software (Version7.0, Stat-Ease Inc., Silicon Valley, CA, USA), the second-order quadratic equations are as:

$$Y = \beta_1 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

Y - Level of the measured response

$\beta_0$ – intercept

$\beta_1$ to $\beta_9$ - regression coefficient

$X_1$, $X_2$, and $X_3$ - main effects

$X_1X_2$, $X_2X_3$, and $X_1X_3$ - interaction between the main effects

$X_1^2$, $X_2^2$ and $X_3^2$ - quadratic terms of independent variables.

**TABLE 1: COMPOSITION OF PALBOCICLIB SLNS FORMULATION BYBBD**

| F. no. | Palbociclib (mg) | Tricapric (%) | Cremophor RH40 (%) | Soy Lecithin (%) | Tween 80 (ml) | Chloroform:Methanol (1:1) | Distilled Water (mL) |
|---|---|---|---|---|---|---|---|
| PF1 | 125 | 4 | 3 | 4 | 0.5 | 20 | Q.S |
| PF2 | 125 | 8 | 3 | 4 | 0.5 | 20 | Q.S |
| PF3 | 125 | 4 | 9 | 4 | 0.5 | 20 | Q.S |
| PF4 | 125 | 6 | 6 | 4 | 0.5 | 20 | Q.S |
| PF5 | 125 | 4 | 6 | 2 | 0.5 | 20 | Q.S |
| PF6 | 125 | 8 | 6 | 2 | 0.5 | 20 | Q.S |
| PF7 | 125 | 4 | 6 | 6 | 0.5 | 20 | Q.S |
| PF8 | 125 | 8 | 6 | 6 | 0.5 | 20 | Q. S |
| PF9 | 125 | 6 | 3 | 2 | 0.5 | 20 | Q.S |
| PF10 | 125 | 6 | 9 | 2 | 0.5 | 20 | Q.S |
| PF11 | 125 | 6 | 3 | 6 | 0.5 | 20 | Q.S |
| PF12 | 125 | 6 | 9 | 6 | 0.5 | 20 | Q.S |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PF13 | 125 | 8 | 9 | 6 | 0.5 | 20 | Q.S |
| PF14 | 125 | 6 | 9 | 4 | 0.5 | 20 | Q.S |
| PF15 | 125 | 6 | 6 | 4 | 0.5 | 20 | Q.S |
| PF16 | 125 | 4 | 3 | 6 | 0.5 | 20 | Q.S |
| PF17 | 125 | 4 | 9 | 4 | 0.5 | 20 | Q.S |

**TABLE 2: LIST OF DEPENDENT AND INDEPENDENT VARIABLES IN IN BOX-BEHNKEN DESIGN**

| ***Independent variables*** | | | ***Levels*** | | |
|---|---|---|---|---|---|
| **Variable** | **Name** | **Units** | **Low (-1)** | **Middle (0)** | **High (+1)** |
| A | Amount of Tricapric | % | 4 | 6 | 8 |
| B | Amount of Cremophor RH40 | % | 3 | 6 | 9 |
| C | Amount of Soy Lecithin | % | 2 | 4 | 6 |
| ***Dependent variable*** | | | ***Goal*** | | |
| Y1 | Particle size | Nm | Minimize | | |
| Y2 | Entrapment Efficiency | % | Minimize | | |
| Y3 | Drug release after 12 Hrs | % | Maximize | | |

**Characterization of Palbociclib loaded SLN:** Measurement of particle size, zeta potential, drug content, and entrapment efficiency (EE%) [15, 16, 17] were calculated as per reported procedures.

***In-vitro* Release Study:** *In-vitro* release studies were performed in 0.1N HCl (pH 1.2) using modified franz diffusion cell and dialysis membrane having pore size 2.4 nm, molecular weight cut-off between 12,000-14,000 was used. The membrane was soaked in double-distilled water for 12 h. SLN dispersion (2 mL) was placed in the donor compartment, and the receptor compartment was filled with 50 mL of release media. During the experiments, the solution in the receptor side was maintained at 37 °C ± 0.5 °C and stirred at 50 rpm with magnetic stirring bars for 2 h. Then, the pH was increased to pH 6.8 for the remaining 10 h. An aliquot of the sample (5 mL) was taken from the dissolution medium at different times 0.5, 1, 2, 3, 4, 6, 8, and 12 h time points; samples were withdrawn and analyzed by UV-visible spectrophotometer at 263 nm. Data obtained from in-vitro release studies were fitted to various kinetic equations to find out the mechanism of palbociclib release from SLN [18].

**Kinetic Model Fitting:** To elucidate the mode and mechanism of drug release, the data from the in-vitro release study were fitted into various kinetic models such as zero-order, first-order, Higuchi's, and Korsmeyer–Peppas model [19, 20].

**Characterization of Optimized SLN Formulation:** Characterization of optimized formulation by Fourier transform infrared spectroscopy (FT-IR), particle size, zeta potential, SEM studies, and Stability studies were performed as per the procedures mentioned in the reference.

## RESULTS AND DISCUSSIONS:

**Physico-chemical Evaluation of palbociclib SLNs:** Developed palbociclib SLNs (PF1-PF17) were physicochemical evaluated in terms of particle size, entrapment efficiency, drug content, and zeta potential. The drug content of all formulations ranged between 96-99%, with formulation PF13 displaying maximum drug content. The EE of all formulations ranged between 78-93%with a maximum value of 93.32% displayed by formulation PF13.

The particle size of the drug-loaded nanoparticles was found to be in the range of 103 to 239 nm. The nanoformulations exhibited a negative surface charge with the inclusion of palbociclib, which clearly suggested the orientation of palbociclib in the lipid matrix with long-term stability.

The zeta potential of all 17 formulations ranged between 15-29 mV.

***In-vitro* Dissolution Testing of Palbociclib SLNs:** The dissolution profiles of plain palbociclib and palbociclib SLNs formulation in simulated intestinal [23]. The drug release from the formulation PF13was shown to be 98.91%, whereas the marketed product was shown to be 86.28% after 12 h **Fig. 1-3**. This result suggested that the SLNs formulation significantly enhanced the dissolution of palbociclib. The enhanced dissolution may be due to the decrease in crystallinity and the increase in solubility of the drug. The increase in cumulative drug released is mainly attributed to rapid self-

emulsification of the formulations due to instantaneous dispersion in the medium after the dissolution of the capsule shell. As the amount of free energy required in forming an emulsion is very low, this results in the spontaneous formation of an oil-water interface. This increases the water penetration of lipid droplets, resulting in disruption of the interface and thereby decreasing the particle size and eventually increasing the release rate

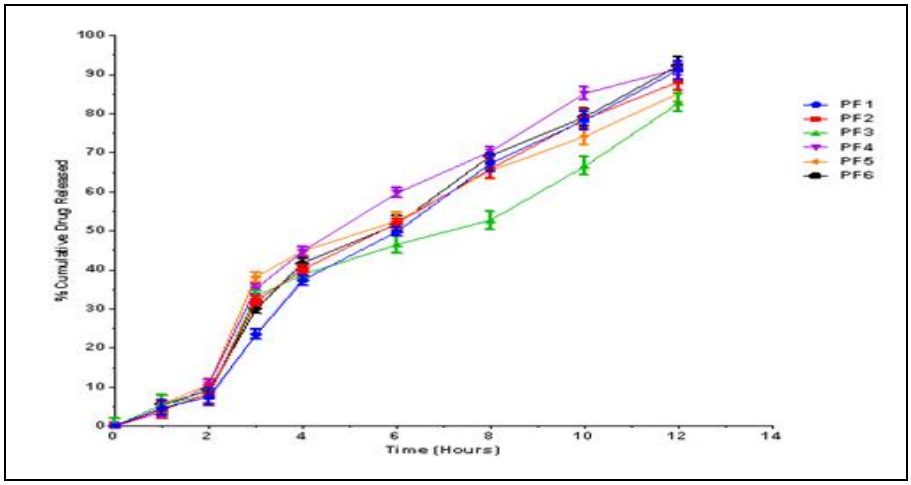


**FIG. 1: *IN-VITRO* DRUG RELEASED PROFILE OF PREPARED PALBOCICLIB LOADED SOLID LIPID NANOPARTICLES PF1-PF6**

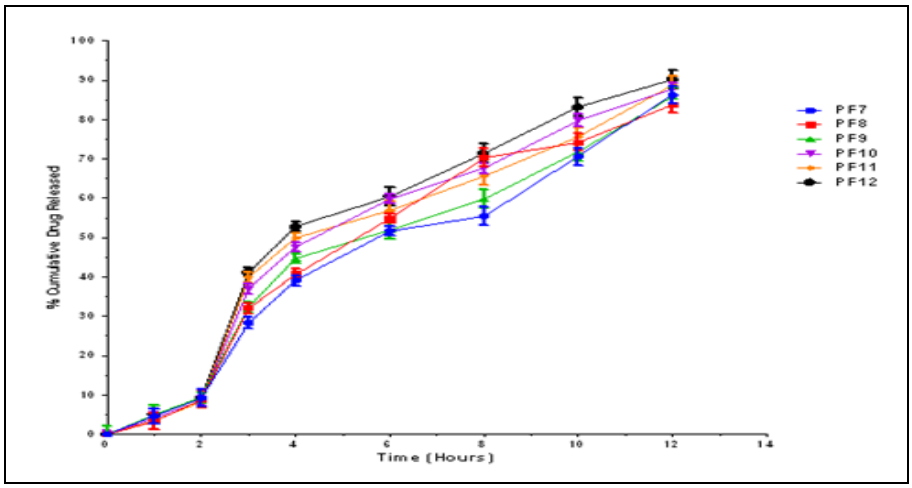


**FIG. 2: *IN-VITRO* DRUG RELEASED PROFILE OF PREPARED PALBOCICLIB LOADED SOLID LIPID NANOPARTICLES PF7-PF12**

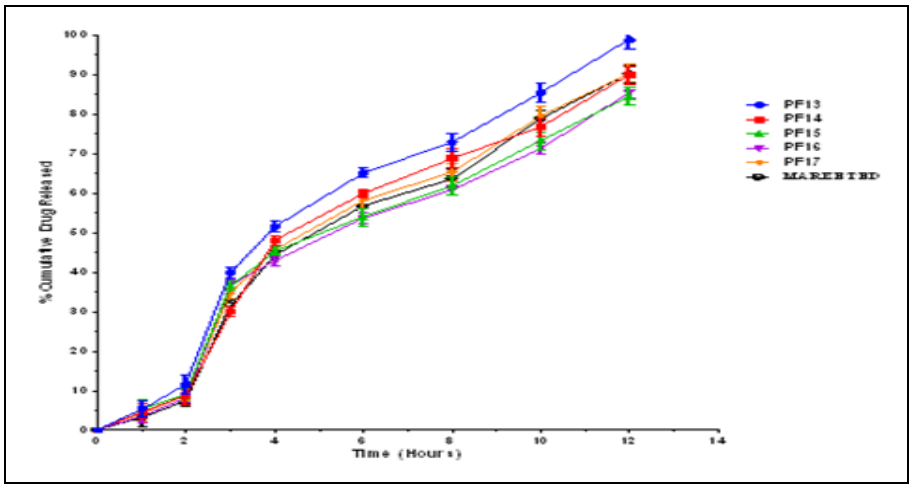


**FIG. 3: *IN-VITRO* DRUG RELEASED PROFILE OF PREPARED PALBOCICLIB LOADED SOLID LIPID NANOPARTICLES PF13-PF17**

**TABLE 3: RELEASE KINETICS OF MARKETED FORMULATION OF PALBOCICLIB SLNS**

| Formulation | Correlation Coefficient ($r^2$) | | | | Diffusional Exponent (n) | Inference |
|---|---|---|---|---|---|---|
| **Marketed** | **Zero Order** | **First Order** | **Higuchi Equation** | **Korsmeyer -Peppas** | **Korsmeyer -Peppas** | **Zero-order & Super case II transport** |
| | 0.949 | 0.866 | 0.872 | 0.921 | 1.095 | |
| **PF13** | 0.961 | 0.895 | 0.881 | 0.944 | 1.115 | Zero-order & Super case II transport |

**Kinetic Analysis of Palbociclib Release Data of PF13:** It is apparent from the results are as shown in **Table 3** that the regression coefficient value closer to unity in case of zero-order plot *i.e.,* 0.961 indicates that the drug release follows a zero-order mechanism.

Further, the n value obtained from the Korsmeyer-Peppas plots, *i.e.,* 0.944 indicating non-Fickian (anomalous) transports; thus, it projected that it delivered its active ingredient by coupled diffusion and erosion for both optimized and marketed formulation.

**TABLE 4: STATISTICAL ANALYSIS RESULTS OF PARTICLE SIZE, EE, AND % CUMULATIVE DRUG RELEASE**

| Source | Particle size | | Entrapment efficiency | | % Cumulative drug release | |
|---|---|---|---|---|---|---|
| | **Sum of squares** | **p>F** | **Sum of squares** | **p>F** | **Sum of squares** | **p>F** |
| **Residual** | 4833.53 | - | 4232.45 | | 2431.66 | |
| **Lack of fit** | 2838.17 | < 0.05 | 3250.17 | < 0.05 | 3485.19 | < 0.05 |
| | **R-squared analysis** | | **R-squared analysis** | | **R-squared analysis** | |
| **$R^2$** | 0.9995 | | 0.9991 | | 0.9998 | |

**Design of Experiments:**

**Statistical Analysis of the Designed Experiment:** The range of particle size (Y1) for all batches was 103 – 239 nm. Similarly, the range for % entrapment efficiency (Y2) was 78.63% – 93.32%, and the range for the cumulative percentage of drug released in 12 h (Y3) was 83.88 –98.91 %. All responses were fitted to a second quadratic model, and the adequacy of this model was verified by ANOVA; tests provided by Design-Expert software. For all the responses, the second-order quadratic model generated the highest F value, so it was identified as the fitting model, as shown in **Table 4**.

**Effect on Particle Size (Y1):** The particle size of the nanoparticles was found to be in the range of 103-239 nm, as shown in **Table 3**. The quadratic model generated revealed that the amount of tricapric, amount of cremophor RH40, and amount of soy lecithin significantly influence the Y1. The theoretical (predicted) values and the observed values were in reasonably good agreement. The equation results indicate that B's effect is more significant than A and C **Table 4**. The perturbation plot **Fig. 4A** shows that B has the main and the major effect on Y1, followed by A & C, which have a moderate effect on Y1. The respective contour plots **Fig. 4B**.

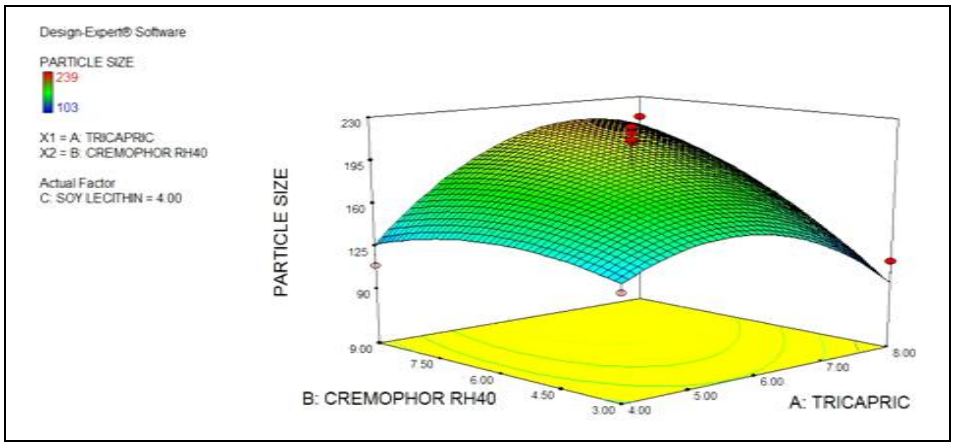


**FIG. 4A: RESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON PARTICLE SIZE FIXED LEVEL OF C**

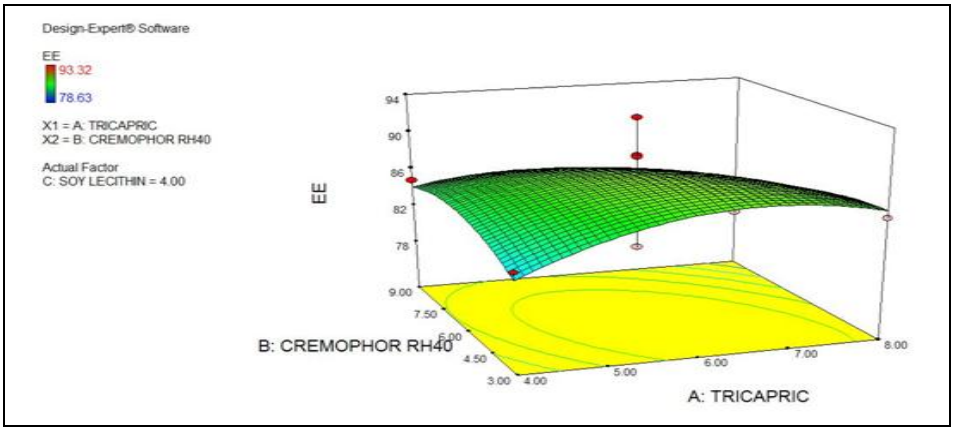


**FIG. 4B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON PARTICLE SIZE FIXED LEVEL OF C**

**Entrapment Efficiency (%):** The entrapment efficiency (%) of the SLNs was found to be in the range of 78.63% to 93.32 % as shown in **Table 3**. The quadratic model generated revealed that the amount of tricapric and amount of cremophor RH40 have a significant influence on the entrapment efficiency (%). The theoretical (predicted) values and the observed values were in reasonably good agreement as seen. Results of the equation indicate that the effect of B is more significant than A and C. The factorial equation for Entrapment Efficiency (%) showed a good correlation coefficient (0.9991) in **Table 4**. **Fig. 5** A clearly shows that B has the main and the major effect on Y2 followed by C, which has a moderate effect on Y2. The respective contour plots are as shown in **Fig. 5B**.

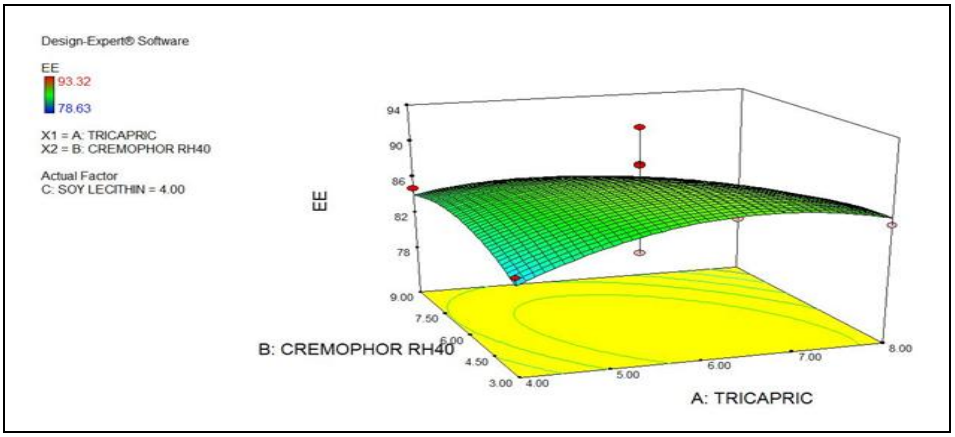


**FIG. 5A: RESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON ENTRAPMENT EFFICIENCY (%) FIXED LEVEL OF C**

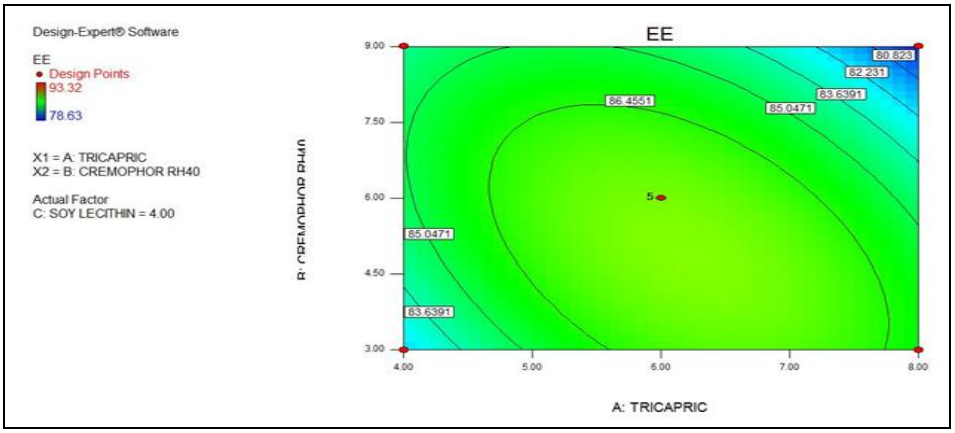


**FIG. 5B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT OF TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON ENTRAPMENT EFFICIENCY (%) FIXED LEVEL OF C**

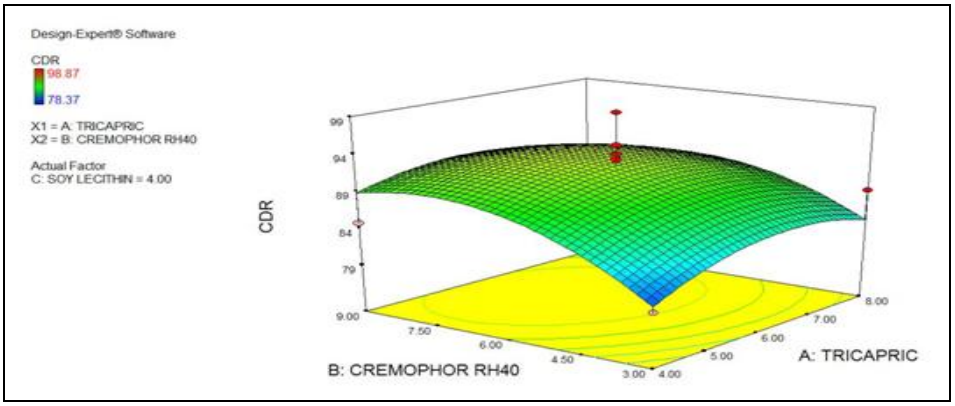


**FIG. 6A: RESPONSE 3D SURFACE PLOT SHOWING THE INFLUENCE OF AMOUNT OF TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON CUMULATIVE % DRUG RELEASED FIXED LEVEL OF C**

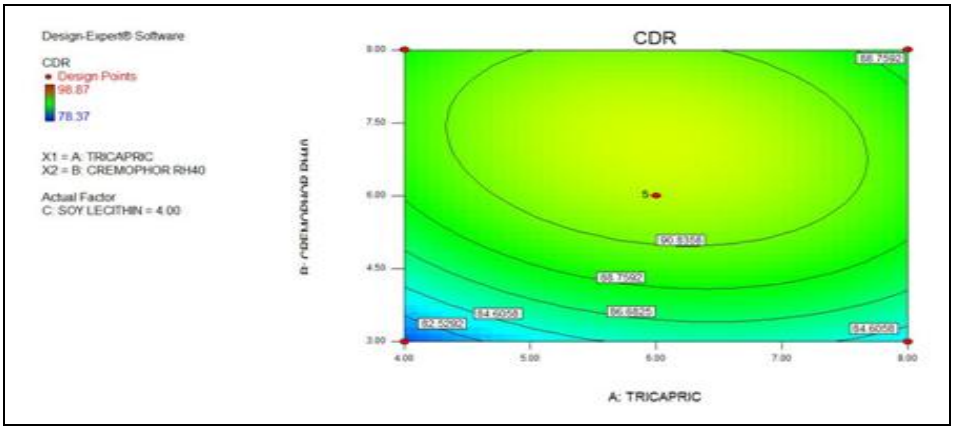


**FIG. 6B: CONTOUR PLOT SHOWING THE INFLUENCE OF AMOUNT OF TRICAPRIC AND AMOUNT OF CREMOPHOR RH40 ON CUMULATIVE % DRUG RELEASED FIXED LEVEL OF C**

**Cumulative Percent Drug Released:** The cumulative percent drug release in 12 h from the SLNs was found to be in the range of 78.37 – 98.87% **Table 3**. The quadratic model generated revealed that the amount of tricapric, amount of cremophor RH40 and amount of Soy lecithin have a significant influence on the particle size. Results of the equation indicate that the effect of B is more significant than A and C **Table 4** and **Fig. 6A** and **Fig. 6B**.

**Optimization by Desirability Function:** An optimization process was undertaken with desirability function to optimize the three responses simultaneously. The results are shown in **Table 5**.

The model was proven to be validated since a fine agreement existed between the predicted and observed results.

It can be seen that the experimental values were in very close agreement with the predicted values, indicating the success of the Box–Behnken design combined with a desirability function for the evaluation and optimization of SLNs formulations.

**TABLE 5: OPTIMIZED VALUES OBTAINED BY THE CONSTRAINTS APPLIES ON Y1, Y2 AND Y3**

| Independent variable | Nominal values % | Predicted values | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Particle size (Y1) (nm) | Entrapment Efficiency (%) (Y2) | %CDR (Y3) | Batch | Particle size (Y1) (nm) | Entrapment Efficiency (%) (Y2) | Percent drug release in 12 h (Y3) |
| Amount of Tricapric(A) | 8 | 103 | 93.32 | 98.91 | 1 | 103 | 93.25 | 98.75 |
| Amount of Cremophor RH40(B) | 9 | | | | 2 | 106 | 93.21 | 98.84 |
| Amount of Soy Lecithin (C) | 6 | | | | 3 | 105 | 93.18 | 98.82 |

**Characterization of Optimized SLN:**

**FTIR Study:** The FTIR of pure drug displays the carbonyl vibration in the 1900–1650 $cm^{-1}$ region of the IR spectra. The N–H stretching exhibited a bathochromic shift from 3421.24 $cm^{-1}$ to 3413.79 $cm^{-1}$, whereas the N–H bending vibration appear at 1549.67 $cm^{-1}$. No variation is observed in principal peaks of the drug in optimized formulation, indicating the compatibility between drug and excipients **Fig. 7** and **8**.

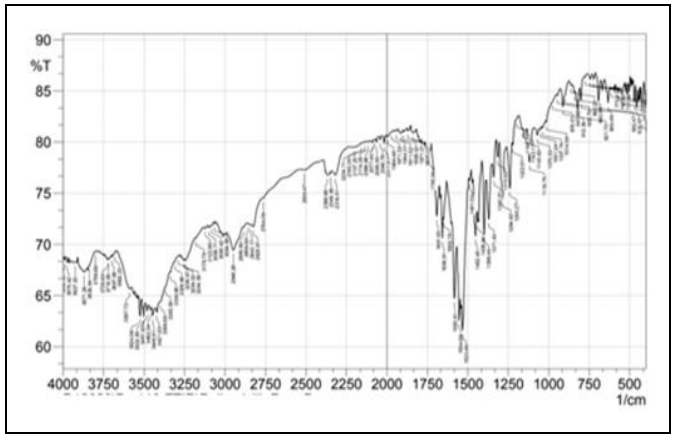


**FIG. 7: FTIR OF PALBOCICLIB PURE DRUG**

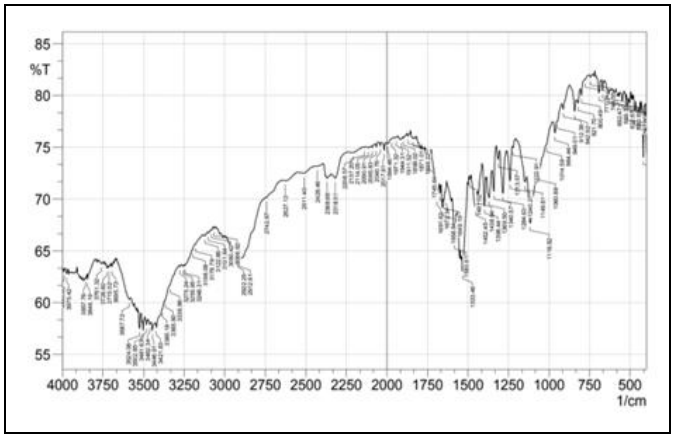


**FIG. 8: FTIR OF OPTIMIZED FORMULATION PF13**

**Droplet Size and Zeta Potential:** Droplet size distribution following nanoemulsification is critical in evaluating a nanoemulsion system. The mean globule size of the selected SLN formulation PF 13 was 103 nm with low polydispersity index, which indicates the present technology's ability to produce nanoemulsion that offers larger interfacial surface area required for drug absorption. A narrow polydispersity index of 0.47 means that the colloidal particles are homogenous in nature. The optimized SLN showed a high absolute zeta potential value of -16.0 mv. The emulsion stability is directly related to the magnitude of the surface charge **Fig. 9** and **10**.

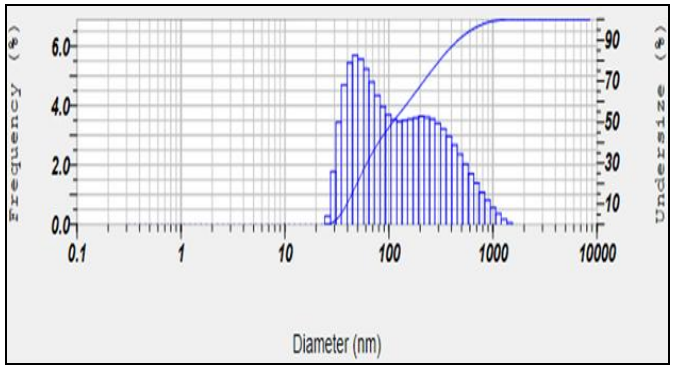


**FIG. 9: PARTICLE SIZE OF OPTIMIZED FORMULATION PF13**

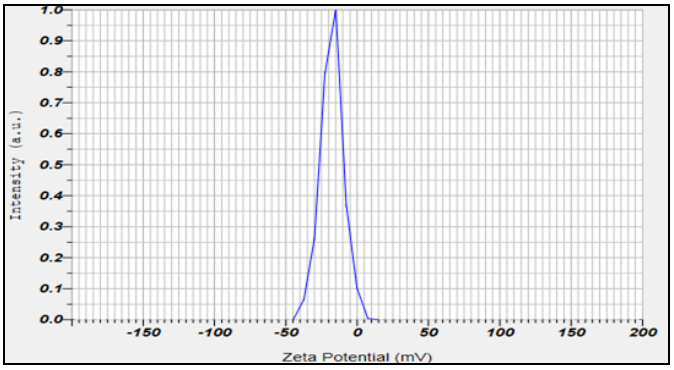


**FIG. 10: ZETA POTENTIAL OF OPTIMIZED SLN PF13**

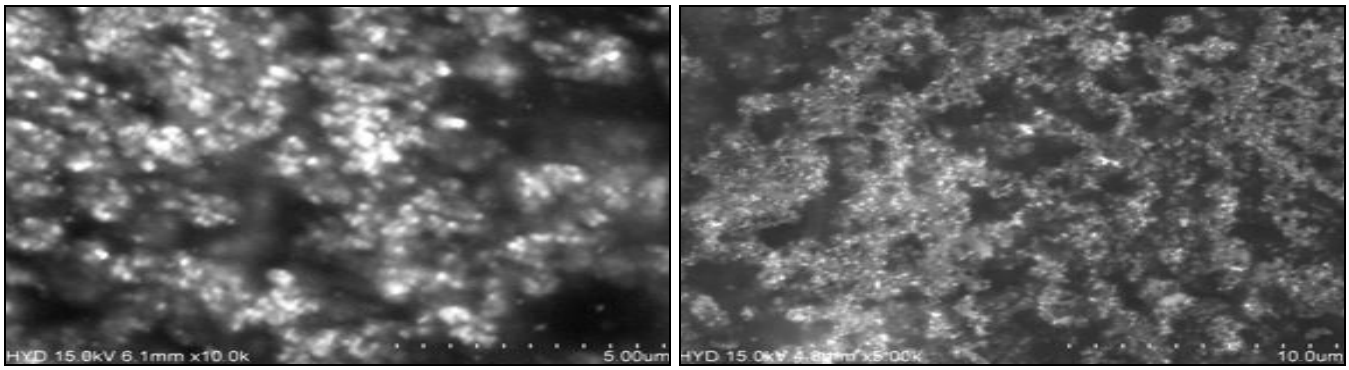


**FIG. 11: SEM OF OPTIMIZED FORMULATION**

**SEM Analysis:** The SEM data indicates spherical and uniform particles of Palbociclib optimized formulation PF 13, that are slightly porous with rougher surfaces. The roughness of surface is due to quick moisture loss from wet mass possessing higher liquid content due to porous surface **Fig. 11**.

**Stability Studies:** The formulation PF13 is found stable for 6 months with no significant variations in the values of particle size, entrapment efficiency, drug release profile and drug content value **Table 6**.

**TABLE 6: STABILITY STUDIES OF OPTIMIZED FORMULATION**

| Retest Time for Optimized formulation (PF13) | Particle Size (nm) | Entrapment Efficiency (%) | *In-vitro* drug release profile (%) | Drug content (%) |
|---|---|---|---|---|
| 0 days | 103 | 93.32±1.18 | 98.91±1.06 | 99.83±1.65 |
| 30 days | 103 | 93.25±1.09 | 98.84±1.23 | 99.83±2.12 |
| 60 days | 103 | 93.24±1.15 | 98.72±1.15 | 99.79±2.37 |
| 120 days | 103 | 93.24±1.11 | 98.68±1.20 | 99.75±2.55 |
| 180 days | 103 | 93.23±1.05 | 98.65±1.13 | 99.73±2.29 |

Values are expressed in mean± SD :( n=3)

**CONCLUSION:** In the present study, BBD was used for the optimization of SLN formulation. Controlled release profiles for more than 12 h were obtained by incorporating palbociclib into the solid matrix of tricapric based lipid nanoparticles. The use of surfactants cremophor RH40 and soy lecithin resulted in the formation SLNs with decreased particle size. For optimization, the desirable goal was fixed for various responses particle size, entrapment efficiency, and % cumulative drug release. The optimized single dose of SLN obtained using BBD the formulated SLNs were considered a promising approach to improve drug solubility and long-term stability.

**ACKNOWLEDGEMENT:** Nil

**CONFLICTS OF INTEREST:** Nil

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