# DEVELOPMENT OF ERLOTINIB ENCAPSULATED SELF-ASSEMBLED MIXED MICELLES: OPTIMIZATION AND *IN VITRO* EVALUATION

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**ABSTRACT**

For the treatment of lung cancer, erlotinib is used as primary treatment. Erlotinib is an epidermal growth factor receptor inhibitor, however it is deposited in normal cells also and clinicians do not prefer it. This constraint opens the way for development of targeted therapy. Mixed micelles via self-assembly have the functionality to improve the delivery of hydrophobic drugs, and improve the pharmacokinetics of the loaded drug. Pluronic® F127 and tocopheryl polyethylene glycol succinate were used to prepare micelles. Box-Behnken design was applied to optimize formulation. With optimum ratio, micelles were characterized, and pharmacokinetic parameters were predicted. Design batches $F_1$ to $F_{15}$, showed the range of 42-133 nm size and 55-82 % of entrapment. Critical micelles concentration was found to be $3 \times 10^{-5}$ M. Drug release of optimized mixed micelles was found 84.91± 1.58 % in 72 h. In a nutshell, self-assembled mixed micelles would be a suitable delivery platform for targeting anticancer agents.

**Keywords**: Erlotinib, lung cancer, EGFR inhibitor, QbD, self-assembled mixed micelles, pharmacokinetic analysis

## INTRODUCTION

According to the American Lung Association, there were 2.1 million of cases for lung cancer in 2018, at which 1.8 million patients did not survive[1,2]. As a pharmacotherapy, erlotinib and gefitinib are promising inhibitors of epidermal growth factor inhibitors (EGFR), approved by U.S. Food and Drug Administration (USFDA)[3]. EGFR is shown to be over expressed in human carcinoma such as lung and breast cancers. By inhibiting EGFR, the downstream signaling cascade gets blocked, and results in reduction in malignant cell proliferation[4].

For treatment of non-small cell lung cancer (NSCLC), erlotinib as tarceva® oral tablet is given as first line therapy, which shows bioavailability upto 60 %[5]. Furthermore, erlotinib has pH dependent solubility that delineates the rate limiting step. Knowing its high solubility at acidic conditions with approximate value of 0.4 mg $mL^{-1}$ at pH of approximately 2 as compared to basic and neutral pH, it becomes more preferable to cap erlotinib at preferable pH range[6]. Erlotinib HCl (TarcevaVR)®, in salt form was developed and different colloidal nano carrier systems have been studied to improve its solubility-based issues along with its pharmacological action as an approach for the improvement of bioavailability and targeting efficiency to the lung.

Our study mainly focusses, on developing a novel micellar system, which can be efficacious building blocks for hydrophobic drugs. Mixed micelles require, low critical micellar concentration (CMC) as compared to single polymer[7]. Pluronic® F127 and TPGS (Tocopheryl polyethylene glycol succinate) were selected as polymeric carriers to form mixed micelles. Pluronic F® 127 is itself a block co polymer of hydrophobic polypropylene oxide and hydrophilic polyethylene oxide. It has hydrophilic-lipophilic balance (HLB) value of 22. Hydrophobic drug molecules aggregate in the hydrophobic polypropylene oxide (PPO) cores[8]. Drug molecules cannot be drawn away from the core by the harmless hydrated polyethylene oxide (PEO) coronas. As a result, the hydrophobic drugs' solubilities significantly rise in an aqueous media, increasing the drugs' bioavailability[9]. Another polymer, TPGS, is known as a potential candidate for p-glycoprotein inhibition with HLB value of 13.2. Mixed micelles are prepared using the above two polymers, which have two different HLB values and can be stable in aqueous media. Quality by Design (QbD) is used to get optimized formulations which were characterized for poly dispersivity index (PDI), particle size, entrapment efficiency, and *in vitro* drug release

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**Table I: Box-Behnken design matrix for erlotinib loaded self-assembled micelles with independent variable and dependent variables**

| Std. order | Run order | Pt Type | Blocks | Amt of Pluronic® F 127 (mg) ($X_1$) | Amt of TPGS (mg) ($X_2$) | Solvent volume (mL) ($X_3$) | Micellar size (nm) ($Y_1$) | % Entrapment Efficiency ($Y_2$) |
|---|---|---|---|---|---|---|---|---|
| 15 | 1 | 0 | 1 | 67.5 | 7.5 | 7.5 | 85.33±2.3 | 72.83±0.22 |
| 8 | 2 | 2 | 1 | 90 | 7.5 | 10 | 48.36±3.1 | 79.3±0.15 |
| 6 | 3 | 2 | 1 | 90 | 7.5 | 5 | 57.13±1.67 | 79.12±0.17 |
| 7 | 4 | 2 | 1 | 45 | 7.5 | 10 | 116.2±2.25 | 59.21±0.12 |
| 14 | 5 | 0 | 1 | 67.5 | 7.5 | 7.5 | 85.33±1.34 | 72.83±0.21 |
| 3 | 6 | 2 | 1 | 45 | 10 | 7.5 | 100.2±1.66 | 62.45±0.35 |
| 2 | 7 | 2 | 1 | 90 | 5 | 7.5 | 62.84±1.23 | 71.32±0.32 |
| 12 | 8 | 2 | 1 | 67.5 | 10 | 10 | 75.71±1.94 | 73.33±0.25 |
| 9 | 9 | 2 | 1 | 67.5 | 5 | 5 | 105±1.23 | 68.71±0.15 |
| 5 | 10 | 2 | 1 | 45 | 7.5 | 5 | 116.9±2.21 | 58.74±0.14 |
| 10 | 11 | 2 | 1 | 67.5 | 10 | 5 | 72.59±2.15 | 72.92±0.19 |
| 1 | 12 | 2 | 1 | 45 | 5 | 7.5 | 133.7±2.34 | 55.23±0.13 |
| 11 | 13 | 2 | 1 | 67.5 | 5 | 10 | 106.8±1.78 | 69.24±0.23 |
| 13 | 14 | 0 | 1 | 67.5 | 7.5 | 7.5 | 85.33±2.34 | 72.83±0.22 |
| 4 | 15 | 2 | 1 | 90 | 10 | 7.5 | 43.22±1.45 | 82.13±0.11 |

study. Calculation of pharmacokinetic data was done using PK Solver.

## MATERIALS AND METHODS

### Materials

Erlotinib was received as sample drug from BDR Pharmaceuticals International Pvt. Ltd., Mumbai, India. Pluronic® F127 (PEG-PPG-PEG, MW-12600) was purchased from Sigma Aldrich Chemical Pvt. Ltd., India. (Tocopheryl polyethylene glycol succinate) TPGS was purchased from Sigma Aldrich Chemical Pvt. Ltd., India. Ethanol (99.5 % purity) was procured from Sigma-Aldrich Chemical Pvt. Ltd., India.

### Preparation of self-assembled mixed micelles

Erlotinib loaded self-assembled mixed micelles were prepared by the solvent evaporation method[10,11]. With different mass ratios of Pluronic F® 127 and TPGS, erlotinib (25 mg) was mixed. The drug and polymers were sonicated and dispersed in ethanol, which is a water-miscible organic solvent. Using a micropipette, the prepared dispersion was added to pure water. It was then, stirred for 3 h to allow the ethanol to completely evaporate. The final formulation was lyophilized to get stability in formulation.

### Optimization of product variables using full factorial design

In this research work, we have optimized formulation by Box-Behnken design[12]. The selected independent variables are concentration of Pluronic® F127 ($X_1$) with low level 45 mg and high level 90 mg, the concentration of TPGS ($X_2$) with low level 5 mg and high level 10 mg, and the solvent volume ($X_3$) with low level 5 mL and high level 10 mL. Micelle size ($Y_1$) and percent entrapment efficiency ($Y_2$) were used to optimize the influence of independent variables. Design matrix is as shown in Table I, and was evaluated with the Minitab 19 program.

### Characterization of self-assembled mixed micelles Size determination[13,14]

In all batches, dynamic light scattering DLS measurements were performed using a photon correlation spectrometer from Malvern Instruments Ltd., UK's Zetasizer NanoZS. The data represent the average of three different samples, and were obtained from the

**Table II: Calculated drug levels at different times from self-assembled micelles**

| Time after absorption | Blood amount after absorption | | | | | | | | | | | | | Total amount of blood after absorption | Conc. (ng $mL^{-1}$) at times |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.00 | 0.00 | | | | | | | | | | | | | 0 | 0.00 |
| 0.25 | 0.00 | | | | | | | | | | | | | 0.00 | 0.00 |
| 0.50 | 0.00 | 1.33 | | | | | | | | | | | | 1.33 | 0.10 |
| 0.75 | 0.00 | 1.32 | | | | | | | | | | | | 1.32 | 0.10 |
| 1.00 | 0.00 | 1.32 | 0.48 | | | | | | | | | | | 1.80 | 0.13 |
| 1.50 | 0.00 | 1.30 | 0.47 | | | | | | | | | | | 1.78 | 0.13 |
| 2.00 | 0.00 | 1.29 | 0.47 | 1.25 | | | | | | | | | | 3.01 | 0.22 |
| 2.50 | 0.00 | 1.28 | 0.46 | 1.24 | | | | | | | | | | 2.98 | 0.21 |
| 3.00 | 0.00 | 1.27 | 0.46 | 1.22 | 0.74 | | | | | | | | | 3.69 | 0.26 |
| 3.50 | 0.00 | 1.26 | 0.46 | 1.21 | 0.73 | | | | | | | | | 3.65 | 0.26 |
| 4.00 | 0.00 | 1.24 | 0.45 | 1.20 | 0.72 | 0.52 | | | | | | | | 4.14 | 0.30 |
| 4.50 | 0.00 | 1.23 | 0.45 | 1.19 | 0.71 | 0.51 | | | | | | | | 4.10 | 0.29 |
| 5.00 | 0.00 | 1.22 | 0.44 | 1.18 | 0.71 | 0.51 | 0.86 | | | | | | | 4.92 | 0.35 |
| 5.50 | 0.00 | 1.21 | 0.44 | 1.17 | 0.70 | 0.50 | 0.85 | | | | | | | 4.87 | 0.35 |
| 6.00 | 0.00 | 1.20 | 0.43 | 1.16 | 0.69 | 0.50 | 0.84 | 0.92 | | | | | | 5.74 | 0.41 |
| 9.00 | 0.00 | 1.13 | 0.41 | 1.09 | 0.66 | 0.47 | 0.80 | 0.87 | | | | | | 5.42 | 0.39 |
| 12.00 | 0.00 | 1.07 | 0.39 | 1.03 | 0.62 | 0.44 | 0.75 | 0.82 | 3.98 | | | | | 9.10 | 0.65 |
| 18.00 | 0.00 | 0.95 | 0.35 | 0.92 | 0.55 | 0.40 | 0.67 | 0.73 | 3.55 | | | | | 8.11 | 0.58 |
| 24.00 | 0.00 | 0.85 | 0.31 | 0.82 | 0.49 | 0.35 | 0.60 | 0.65 | 3.16 | 2.29 | | | | 9.52 | 0.68 |
| 36.00 | 0.00 | 0.67 | 0.24 | 0.65 | 0.39 | 0.28 | 0.48 | 0.52 | 2.51 | 1.82 | | | | 7.57 | 0.54 |
| 48.00 | 0.00 | 0.54 | 0.19 | 0.52 | 0.31 | 0.22 | 0.38 | 0.41 | 2.00 | 1.45 | 4.70 | | | 10.72 | 0.77 |
| 60.00 | 0.00 | 0.43 | 0.15 | 0.41 | 0.25 | 0.18 | 0.30 | 0.33 | 1.59 | 1.15 | 3.74 | | | 8.52 | 0.61 |
| 72.00 | 0.00 | 0.34 | 0.12 | 0.33 | 0.20 | 0.14 | 0.24 | 0.26 | 1.26 | 0.91 | 2.97 | 4.17 | | 10.94 | 0.79 |
| 84.00 | 0.00 | 0.27 | 0.10 | 0.26 | 0.16 | 0.11 | 0.19 | 0.21 | 1.00 | 0.73 | 2.36 | 3.31 | | 8.69 | 0.62 |
| 96.00 | 0.00 | 0.21 | 0.08 | 0.21 | 0.12 | 0.09 | 0.15 | 0.16 | 0.80 | 0.58 | 1.88 | 2.63 | 0.00 | 6.91 | 0.50 |
| 97.00 | 0.00 | 0.21 | 0.08 | 0.20 | 0.12 | 0.09 | 0.15 | 0.16 | 0.78 | 0.57 | 1.84 | 2.58 | 0.00 | 6.78 | 0.49 |
| 98.00 | 0.00 | 0.21 | 0.07 | 0.20 | 0.12 | 0.09 | 0.14 | 0.16 | 0.77 | 0.56 | 1.81 | 2.53 | 0.00 | 6.65 | 0.48 |
| 99.00 | 0.00 | 0.20 | 0.07 | 0.19 | 0.12 | 0.08 | 0.14 | 0.15 | 0.75 | 0.55 | 1.77 | 2.49 | 0.00 | 6.52 | 0.47 |
| 100.00 | 0.00 | 0.20 | 0.07 | 0.19 | 0.11 | 0.08 | 0.14 | 0.15 | 0.74 | 0.54 | 1.74 | 2.44 | 0.00 | 6.40 | 0.46 |

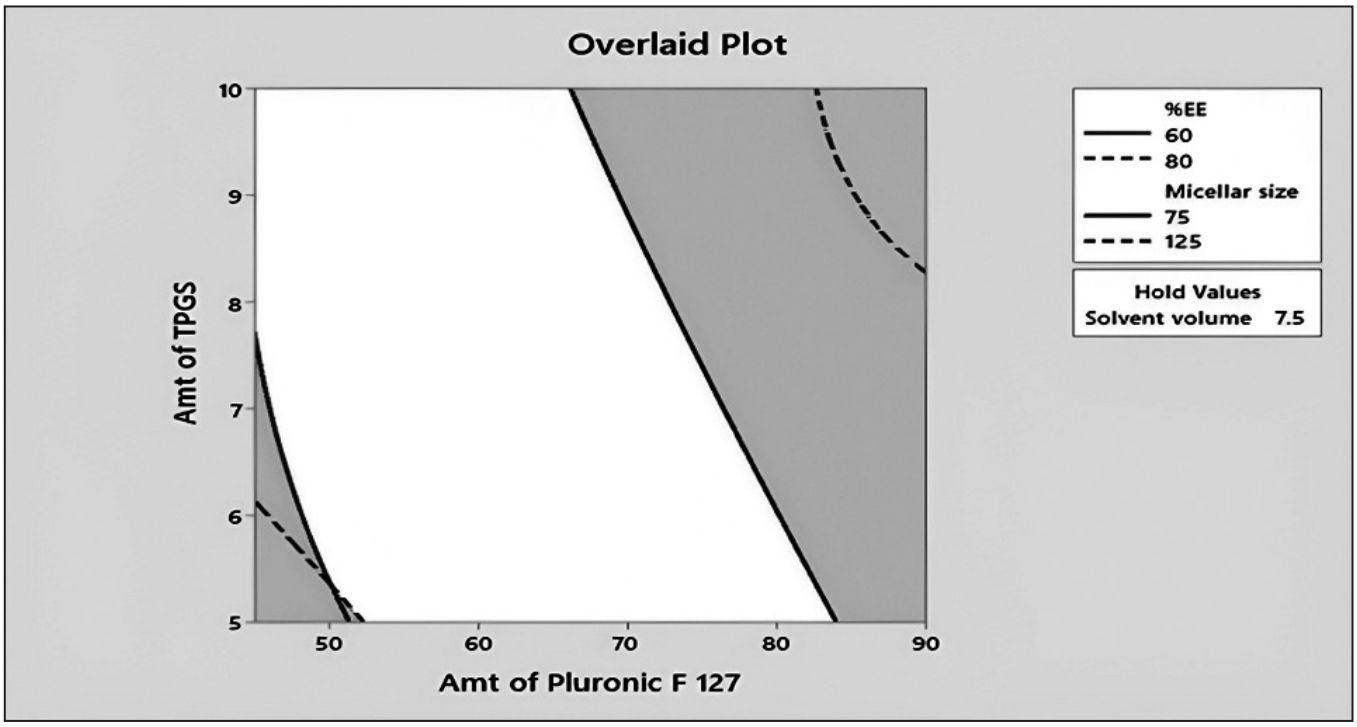


**Fig. 1: Overlaid plot of erlotinib loaded self-assembled mixed micelles**

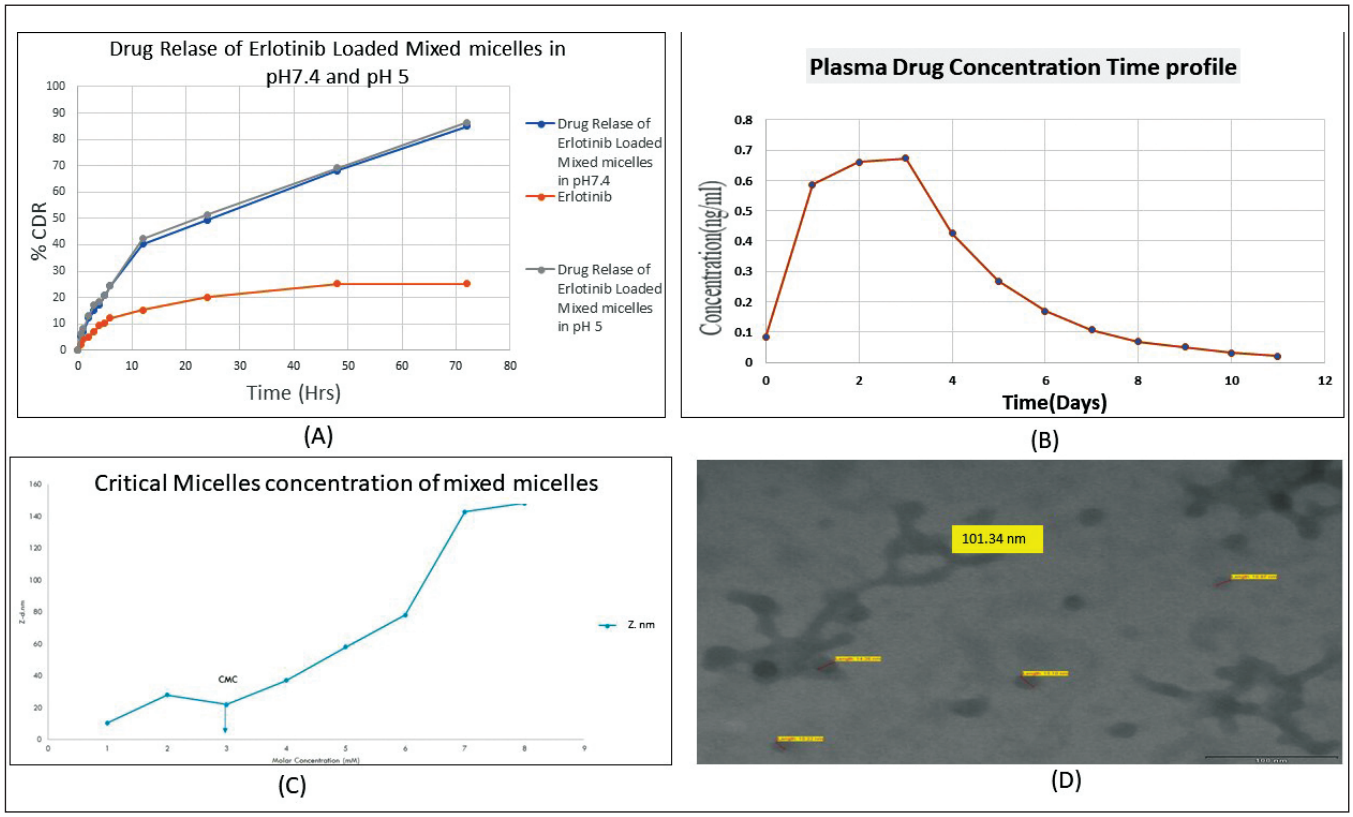


**Fig. 2: (A) *In vitro* drug release of self assembled mixed micelles at pH 7.4 and 5. (B) Plasma drug concentration time profile of self assembled mixed micelles (C) CMC value of self assembled mixed micelles (D) TEM image of self assembled mixed micelles**

measurements that were performed three times at 25 °C after 5 minutes of equilibration. The polydispersity index was studied to determine the distribution of the molecular mass in the polymer. Surface morphology of polymeric micelles of pure drug and colloidal dispersion was captured using a transmission electron microscope (Philips, Philips XL 30 ESEM)[22].

### Encapsulation efficiency and drug loading[15,16]

Erlotinib loaded mixed micelles were filtered from 0.22µ size syringe to remove excess unreacted material. The sample was dissolved in the organic solvent methanol with 15 minutes sonication, so that the mixed micelles broke down and the erlotinib leached out. 1 mL sample solution of drug was taken and diluted further to 10 mL with methanol. The ultraviolet (UV) absorbance was measured at 246nm. The following equations (1 and 2) were used, respectively, to determine entrapment efficiency (EE percent) and drug loading (DL percent).

$$\text{Entrapment efficiency \%} = \frac{(\text{Weight of Encapsulated drug}}{\text{Weight of feeding drug)}} \text{ X } 100 \quad \text{---(1)}$$

$$\text{Drug loading \%} = \frac{\text{Weight of Encapsulated drug}}{\text{Weight of polymer}} \text{X} 100 \quad \text{---(2)}$$

### Critical micelles concentration

The CMC (critical micelles concentration) value of TPGS and Pluronic® F127 was measured by dynamic light scatter technique. The samples with concentrations 0.01 mM and 0.05 mM were prepared in deionized water and ethanol, respectively, in ratio of 4:1 and variations in light intensity were recorded for each sample. The graph of light intensity and the sample's molar concentration were plotted[17].

### *In vitro* release

The best-performing batch of drug-loaded mixed micelles was tested for drug release utilizing the Franz Diffusion cell through dialysis bag technique[18], in physiological conditions of phosphate buffer (pH 7.4 as well as pH 5) at 37.0±0.5 °C with 100 rotation per minutes (RPM). The amount of lyophilized mixed micelles which is equivalent to 25 mg were weighed and dispersed in 10 mL of phosphate buffer (pH 7.4 and 5). The above dispersion was filled in donor compartment and receiver compartment was filled with 40 mL of phosphate buffer. 1 mL of the sample was taken. The experiment was carried out in triplicate to check reproducibility.

### Pharmacokinetic study

Pharmacokinetic data were best fitted by compartmental model using PK solver software. The mean plasma concentration profile after the intravenous administration of the mixed micelles, to avoid preclinical studies at initial stage of experiment were calculated via convolution technique, that is a known technique with potential to predict the timely profiles of *in vivo* pharmacokinetic behavior as well as *in vitro-in vivo correlation (IVIVC)*[19].

Amount of drug release =
(Percentage of drug release * dose of drug)/100 ----------(3)

After absorption phase, elimination phase starts which will follow the first order, kinetics. By combining all the determined drug quantities for each time as per equation 3, along with computation of total quantity of drug present in blood at each periodic interval. The final step was to calculate the drug's blood concentration by following equation 4.

$$\text{Predicted Conc. (mcg mL}^{-1}) = \frac{\text{(Predicted total blood amount (mg) after absorption X Bioavailability X Body Weight)}}{\text{Vd}} \text{ X } 100 \quad \text{----------(4)}$$

## RESULTS AND DISCUSSION

### Optimization of erlotinib loaded self-assembled micelles using Box-Behnken design

Box-Behnken design for erlotinib loaded self-assembled micelles was analyzed using Minitab and ANOVA statistical analysis. $F_1$ to $F_{15}$ batches showing the range of 42-133 nm size and entrapment efficiency% ranges from 55 % - 82 %, as shown in Table I.

### Interpretation for micellar size

Micellar size was analyzed by ANOVA and regression statistics. Linear fit model for micelles size gives polynomial equation 5 which was found to be as follows:

**Micellar size =** 259.1 - 0.851 Amt of Pluronic® F 127 - 16.44 Amt of TPGS -3.43 Solvent volume - 0.00565 Amt of Pluronic® F 127* Amt of Pluronic® F 127 + 0.403 Amt of TPGS* Amt of TPGS + 0.348 Solvent volume*Solvent volume + 0.0 617 Amt of Pluronic F® 127* Amt of TPGS - 0.0359 Amt of Pluronic® F 127* Solvent volume + 0.053 Amt of TPGS*Solvent volume. -----(5)

From ANOVA statistics, the F-value of 200.45 delineates that the model is significant with 0.01% noise chance. A P-value less than 0.0500 indicates significant model with $X_1$ and $X_2$ model terms. The predicted $R^2$ of 0.9618 is near to adjusted $R^2$ of 0.9771.

From coefficient values, we can interpret that all three independent variables negatively impact micellar size. Coefficient value suggests that amount of TPGS is high impact independent variable compared to other variables. At high TPGS concentrations, many analyses reveal a decrease in core radii. This was followed by decreased aggregation number, and increased micelle number, density (N). These findings point to a micellization process involving fewer surfactant units, during which residues were combined to form new micelles[20]. The inclusion of additional TPGS polymers may also have contributed to the decrease, as they may have improved the interaction between the hydrophobic chains and the constituents of both polymeric combinations, leading to a more compact structure[21].

### Interpretation for % Entrapment efficiency (EE)

% Entrapment efficiency was analyzed by ANOVA. For entrapment efficiency, a quadratic fit model was used. The polynomial equation for entrapment efficiency was found to be as follows;

**% Entrapment efficiency =** -6.6 + 1.248 Amt of Pluronic® F 127+ 3.98 Amt of TPGS + 0.77 Solvent volume - 0.00692 Amt of Pluronic F® 127* Amt of Pluronic F® 127 0.247 Amt of TPGS* Amt of TPGS - 0.038 Solvent volume* Solvent volume + 0.0160 Amt of Pluronic F® 127* Amt of TPGS - 0.0013 Amt of Pluronic F® 127* Solvent volume - 0.005 Amt of TPGS* Solvent volume. ------(6)

From ANOVA statistics, the observed F-value of 33.02 delineates that the model evaluation is significant with noise of 0.06% chance. A P-value less than 0.0500 indicates significant model with $X_1$, $X_2$, $X_1^2$ model terms. The predicted $R^2$ of 0.9537 is near to adjusted $R^2$ of 0.9825.

From coefficient values, we can predict that all three independent variables positively impact entrapment efficiency, which suggests that as the amount of polymer increases, entrapment efficiency increases. Coefficient value also suggests that amount of TPGS is high impact independent variable compared to other variables. As concentration of the polymer increases, drug loading also increases. As concentration of polymer increases more carrier is available for entrapment drug. Hydrophobic-hydrophobic interaction of drug with polymer is also one of the mechanism which increases entrapment[20].

An overlaid plot for self-assembled mixed micelles is shown in Fig. 1. From the overlaid plot two check point batches were prepared and evaluated for % EE and micellar size. The micellar size for check point batch 1 was 113.6 ± 2.76 nm and % EE was 78.25 ± 0.11. Moreover, checkpoint batch 2 has micellar size 103.5 ± 1.45 nm and % EE 66.34 ± 0.19, respectively.

## Characterization of erlotinib loaded mixed micelles

### Size determination

The design batches ranged micellar size from 43.22 to 133.7 nm, as shown in Table I. The increase in Pluronic® F127 concentration was related to the increase in particle size. The greater chain length of PEO (polyethylene oxide) provides higher hydrophilicity, which increases micellar size, which is linked to the ratio of PEO to PPO (polypropylene oxide) block[22]. TPGS, on the other hand, has the opposite effect on micellar size as compared to Pluronic®F127. One of the reasons, is that TPGS has a hydrophobicity that interacts with the PEO block, resulting in a more compact structure. Micelles of a smaller size aggregate more efficiently in tumors, and enable more consistent medication release[23]. Optimized check point batch 1 was evaluated for surface morphology. Erlotinib loaded self-assembled micelles were found to be spherical in shape. Morphology is shown in Fig. 2(D).

### Encapsulation efficiency and drug loading

The effectiveness of entrapment for all the design matrix batches are given in Table I. As the quantity of polymer increases, so does drug loading and entrapment, which is related to the production of additional micelles over the critical micelles concentration (CMC) value. $F_{15}$ has the highest entrapment rate at 82.13 %. Pluronic® F127 and TPGS levels are highest in the $F_{15}$ batch. A higher concentrations of Pluronic® F127 not able to improve drug loading. Pluronic® F127 is not able to provide much hydrophobicity. Addition of TPGS to the mixed micelles enhanced percent drug loading and percent entrapment efficiency because of the hydrophobic van der Waals contacts between the aromatic ring and hydrocarbon chain of TPGS, the PPO segment of Pluronic® F127 and the erlotinib[24].

### Critical micelles concentration (CMC)

For 4:1 ratio of mixed micelles, the CMC value was found to be $3.3 \times 10^{-5}$ M, as shown in Fig. 2 (C). The CMC value dropped as the TPGS proportion increased. As a result, when diluted, the combined micelles may have better physical stability. This was most likely owing to

increased hydrophobic interactions in the inner core of micelles between the polypropylene oxide segment and the vitamin E component of TPGS[25].

### *In vitro* drug release

We have performed dissolution study of erlotinib solution and mixed micelles check point batch 1 (shown in Fig. 2 (A)). Because of the hydrophobicity of erlotinib, the solution releases only 25.32 % which indicates very poor drug release. At pH 7.4, erlotinib-loaded polymeric micelles release 84 % of the drug. There was an initial burst discharge. Polymeric micelles first release 49.32 % in 24 h. The fast breakdown of the micellar system caused by cohesion, a higher concentration gradient, and sink conditions or the surface deposited drug molecule in the system might explain the burst release of erlotinib from mixed micelles. Because prolonged release of erlotinib from micelles at physiological pH might minimize deleterious effects associated with nonspecific absorption of erlotinib, the reduced drug release at pH 7.4 could be advantageous. The greater partition coefficient of erlotinib in the acidic medium compared to micellar core might explain the enhanced drug release at pH 5 (86.47 %).

### Pharmacokinetic study

Table II shows, the pharmacokinetic parameters with time of the developed model formulation[25]. This profile was created by calculating medication levels at various intervals after absorption[19]. We have chosen the CA compartment model in the PK solver program based on the highest $R^2$ value.

The plasma concentration–time profiles are depicted in Fig. 2(B). Related to the early burst release of erlotinib, which is likely due to the hydrophilic portion of Pluronic® F127, the peak concentration (Cmax) was anticipated to be achieved within 72 h of injection for check point batch 1, but then the forecasted drug concentrations steadily dropped[26,27]. The anticipated Cmax (0.67 ng $mL^{-1}$) dropped as the TPGS was employed in self-assembled micelles. The MRT of erlotinib-loaded mixed micelles was increased to 168 h. As a result, if we compare the frequency of administration of marketed preparations, the self-assembled micelles might be anticipated to significantly decrease, resulting in improved patient compliance.

## CONCLUSION

The development of self-assembled mixed micelles was carried out using solvent diffusion followed by lyophilization process. The detailed optimization of lyophilized nanomicelles was performed using response surface methodology. The graphical representation shows the influence of polymer concentration on micelle size and entrapment efficiency. The CMC value was found to be $3.3 \times 10^{-5}$ M concentration for mixed polymer to load the required amount of drug. The desired nanometer size was obtained, imparting target efficiency at tumor site. The zeta potential value shows negative charge to accumulate at tumor tissue cell membrane. The optimum drug release profile was observed at blood pH 7.4 and pH 5 at tumor site. Moreover, to predict the *in vivo* absorption profile of developed formulation, one compartmental analysis using PK solve software was performed, which showed higher mean residence time of erlotinib from the micellar system, which proved more bioavailability of the dosage form.

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