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Original Article

# APPROACH TO OPTIMIZE THE SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM FOR AZILSARTAN MEDOXOMIL USING BOX BEHNKEN DESIGN AND DESIRABILITY FUNCTION

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**ABSTRACT**

**Objective:** Develop and optimize a novel self-micro emulsifying drug delivery system (SMEDDS) for enhancing the water solubility of Azilsartan (AZL) by employing the Box-Behnken design and the desirability function.

**Methods:** The formulation of AZL-SMEDDS consists of clove oil (oil component), Tween 20 (surfactant), propylene glycol (co-surfactant) as the independent variables and the active drug. Using a 3-level Design, the impact of independent variables on the formulation was examined. These variables' specified ranges are 20-40 mg, 50-80 mg, and 5-30 mg for X1, X2 and X3 respectively. Particle size (Y1), PDI (Y2), and dissolution % (Y3) were the response variables investigated in this study.

**Results:** The results indicated that the optimal values for Clove oil (X1), Tween 20 (X2), and Propylene glycol (X3) were determined to be 28.69, 76.45, and 24.93 (mg), respectively. Based on these optimized conditions, the predicted data points for the response variables Particle Size (Y1), Polydispersity (Y2), and dissolution % (Y3) were determined to be 59.85 nm, 0.729 and 55.406%, respectively.

**Conclusion:** The empirical results obtained from the optimized formulation exhibited a strong correlation with the predicted values. The optimized AZL-SMEDDS formulation demonstrated a rapid rate of drug solubility and greater bioavailability than AZL powder.

**Keywords:** Box behnken design, Azilsartan, SMEDDS


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## INTRODUCTION

Due to its more affordable production procedure than sterile dosage forms, oral administration is one of the primary methods for delivering medications into the human body [1]. It is a preferred alternative because it allows for self-administration and has good patient compliance. The poor solubility of pharmaceuticals in BCS classes II and IV indicates low bioavailability following oral administration [2]. About 70% of newly developed medications exhibit this pattern, which can be explained by a change in drug discovery techniques from trial-and-error-based approaches to computer-aided drug design [3]. Rapid first-pass metabolism, P-gp efflux, and pre-systemic drug clearance are additional key factors that affect oral bioavailability [4, 5]. Different formulation strategies have been used to overcome these concerns. For example, solid dispersions [6, 7], nanosuspensions [8], solid lipid nanoparticles [9], liquisolid compacts [10], and SMEDDS/SNEDDS [11], have all been prepared by scientists to increase aqueous solubility. Pro-liposomes [12], inclusion complexation [13, 14], particle derivatization [15], and salt production [16] are other strategies that have been investigated.

George Box and Donald Behnken developed the Box-Behnken Design (BBD) as a sort of experimental design in 1960. BBD is an autonomous quadratic design as in contrast to factorial or fractional factorial designs. It is characterized by all of the variables having three levels (-1, 0,+1) [17, 18]. For analyzing the relative importance of many variables that affect a formulation's characteristics, experimental designs such as BBD are significant [19-21]. They provide an organized approach to systematically change the parameters and analyze the responses that occur [22]. This enables researchers to fig. out the interactions between the appropriate variables and the responses that they want.

The aim of the present work was to utilize BBD, to develop and optimize SMEDDS for Azilsartanmedoxomil (AZL) to improve its solubility and bioavailability. The study focused on investigating the influence of 3-independent variables, namely clove oil (X1), Tween 20 (X2), and propylene glycol (X3), on various parameters, including particle size (Y1), polydispersity (Y2), and dissolution % (Y3). The optimized AZL-SMEDDS formulation was assessed based on particle size, polydispersity, and zeta potential values. Further, a comparison was made between the simulated drug dissolution profiles of the optimized formulation and the pure AZL.

## MATERIALS AND METHODS

### Materials

Azilsartan was a gift sample from ESaiPharma Pvt Ltd, Parawada. Visakhapatnam, India. Clove oil, Tween 20, Propylene glycol were procured from Merck laboratories and all the other reagents used were of analytical grade.

### Solubility studies

The saturation solubility of AZL was evaluated in aqueous solutions containing water and phosphate buffers at pH levels of 5.4, 6.8, and 7.8. Each medium was prepared in separate flasks, with an accurately weighed amount of AZL (approximately 40 mg) added to each flask. Subsequently, the flasks were positioned onto a REMI magnetic stirrer, which was set to maintain a consistent rotational speed of 200 revolutions per minute (rpm). The flasks were maintained at a controlled temperature of 37±0.5 degrees Celsius for a period of 24 h. Subsequently, the solutions underwent centrifugation at a speed of 2000 revolutions per minute (rpm) for a duration of 15 min. The supernatants derived from the centrifuged samples were subsequently diluted using the media corresponding to each sample. The measurement of optical density at a wavelength of 286 nm was conducted using an UV spectrophotometer for each diluted solution. Subsequently, the solubility of AZL was determined based on these recorded absorbance values, as shown in table 1. In order to ensure precision, all experiments were replicated thrice [23].

### Preparation of pseudo ternary phase diagram

Using a water titration method, pseudo-ternary phase diagrams were constructed to determine the concentration of individual components in the existing range at room temperature. Different combinations of oil, surfactant, and co-surfactant were categorized for phase studies. The surfactant and co-surfactant (referred to as Smix) were blended in different weight ratios (1:0, 1:1, 1:1, 1:2, and 2:1, w/w) within each

group. To create each phase diagram, the oil was mixed with a specific surfactant mixture ratio (Tween 20: propylene glycol) at various weight ratios (ranging from 1:9 to 9:1) and thoroughly blended. Each isotropic mixture was titrated with water at a gradual rate.

The transformation from a clear to a cloudy physical state was visually perceived and documented on a three-component phase diagram comprising three constituents without drug. Three axes, representing oil, Smix, and water, respectively, were shown in the diagram generated using CHEMIX School 7. The experiments were replicated three times, and consistent observations were obtained throughout the replications [24-26].

An analysis was conducted to ascertain the self-emulsification region based on the weight ratios of the components. This analysis ensured that they exhibited nanosize characteristics and visually acceptable attributes, such as solution clarity, non-segregation, and spontaneous micro emulsification. Subsequently, the boundaries of the self-microemulsification domain were employed to ascertain an acceptable range for the three distinct or independent variables. This step was crucial to ensure that the experimental points generated from the BBD fell within the self-microemulsification domain (table 2). The ranges of the input (independent) variables were determined based on the ternary diagram as follows:

The quantity of clove oil (X1) ranged from 20 to 40 mg.

The quantity of Tween 20 (X2) ranged from 50 to 80 mg.

The quantity of propylene glycol (X3) ranged from 5 to 30 mg.

**Table 2: Factor values in BBD**

| Input variables | Symbols | Levels | | |
|---|---|---|---|---|
| | | Low (-1) | Middle (0) | High (+1) |
| X1 = Number of milligrams of clove oil employed | A | 20 | 30 | 40 |
| X2 = Quantity of Tween 20 added (mg) | B | 50 | 65 | 80 |
| X3 = Quantity of propylene glycol added (mg) | C | 5 | 17.5 | 30 |
| Dependent variables | | | Goal | |
| Y1 = Particle size (nm) | | | Minimum | |
| Y2 = PDI | | | Minimum | |
| Y3 = Dissolution % of AZL | | | Maximum | |

**Preparation of azilsartanmedoxomil-loaded self-micro emulsifying drug delivery system**

Using pseudo ternary phase diagrams, the ideal Smix ratio (2:1) was identified and subsequently, this specific ratio was applied during the development of the SMEDDS formulation. In all experimental preparations, the quantity of AZL remained consistent. In this experiment, accurate measurements of clove oil and Smix (in a 2:1 ratio) were obtained and subsequently combined. The mixture was subjected to magnetic stirring for duration of 15 min. The drug was dispersed in a mixture comprising oil and surfactant mixture at a concentration of 40 mg. The dispersion process involved continuous mixing until the AZL compound was fully dissolved. The developed samples were stored at an ambient temperature of 25 °C until they were ready for subsequent utilization [26].

**Box–behnken design**

Table 3 presents the outcomes of 17 randomized experimental trials, which involved the specified independent variables. These variables were acquired from a $3^3$ BBD, and the responses were recorded. The study utilized a total of five replicates at the center point, marked with an asterisk, to enhance the accuracy of predicting variances across the entire design space.

Input variables were established using the self-microemulsification domain's boundaries on the ternary phase diagram of SMEDDS. Each variable was assigned three levels as detailed in table 2. Design Expert software (version 13.0.7, Stat-Ease, Inc., Minneapolis, MN, USA) was utilized to create the BBD matrix and the resulting data were subsequently analyzed by fitting into a quadratic model [27].

The mathematical model employed for approximation involves a polynomials of degree two, represented as

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_2^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

For further optimization, a desirability function was implemented, proposed by Derringer and Suich [28] in which the main objective is to identify an optimal and well-balanced point within the design space which meets the dependent factors' predetermined objectives. The optimization goals were outlined in table 2.

The overall desirability function D is defined as the geometric average of the individual desirability functions of each response as shown in an equation where n is the number of responses [29].

$$D = \left( \prod_{i=1}^{n} di \right)^{1/n}$$

**Table 3: Design matrix and the corresponding observed responses**

| Run | X1 (mg) | X2 (mg) | X3 (mg) | Y1 (nm) | Y2 | Y3 (%) |
|---|---|---|---|---|---|---|
| 1 | 30 | 80 | 30 | 60.51±4.2 | 0.729±0.048 | 54.36±1.3 |
| 2 | 20 | 50 | 17.5 | 57.26±2.8 | 0.823±0.003 | 75.36±1.3 |
| 3[a] | 30 | 65 | 17.5 | 60.15±4.6 | 0.723±0.037 | 57.28±1.7 |
| 4[a] | 30 | 65 | 17.5 | 60.24±4.6 | 0.724±0.043 | 54.78±1.4 |
| 5 | 20 | 65 | 5 | 56.38±5.0 | 0.826±0.082 | 74.98±1.0 |
| 6 | 20 | 65 | 30 | 57.45±5.5 | 0.821±0.002 | 75.82±0.1 |
| 7 | 40 | 65 | 5 | 64.48±5.2 | 0.839±0.043 | 72.98±2.3 |
| 8 | 40 | 50 | 17.5 | 66.28±4.7 | 0.824±0.085 | 44.98±3.2 |
| 9[a] | 30 | 65 | 17.5 | 60.23±3.2 | 0.725±0.022 | 58.65±0.9 |
| 10 | 30 | 50 | 30 | 61.23±5.6 | 0.728±0.050 | 56.36±1.0 |
| 11[a] | 30 | 65 | 17.5 | 60.12±4.2 | 0.741±0.045 | 52.26±2.8 |
| 12 | 30 | 80 | 5 | 60.21±4.5 | 0.743±0.031 | 73.69±0.1 |
| 13 | 40 | 80 | 17.5 | 62.58±3.9 | 0.825±0.035 | 45.68±2.3 |
| 14 | 20 | 80 | 17.5 | 58.36±3.2 | 0.824±0.010 | 74.49±1.7 |
| 15 | 40 | 65 | 30 | 62.52±5.0 | 0.826±0.016 | 47.61±1.4 |
| 16 | 30 | 50 | 5 | 60.54±3.9 | 0.745±0.050 | 73.98±1.1 |
| 17[a] | 30 | 65 | 17.5 | 60.12±4.5 | 0.726±0.043 | 50.08±1.5 |

[a]Center points in experimental region. Response data are presented as mean±SD (n=3). Y1= Particle size; Y2,=PDI; Y3= dissolution % after 15 min.

**Table 1: Saturation solubility of AZL in various excipients**

| Excipients | Solubility of AZL (mg/ml) |
|---|---|
| Castor oil | 20±0.013 |
| Sesame oil | 24±0.025 |
| Soyabean oil | 20±0.003 |
| Clove oil | 42.5±0.003 |
| Olive oil | 1±0.018 |
| Linseed oil | 4±0.95 |
| Tween 20 | 54±0.09 |
| Span 20 | 2.5±0.012 |
| Span 30 | 7±0.01 |
| Span 60 | 10±0.045 |
| MC | 5±0.01 |
| HPC | 5±0.07 |
| HPMC | 5±0.016 |
| Triethanolamine | 20±0.006 |
| Triethanolamine lauryl sulphate | 29±0.008 |
| Glycerol | 20±0.010 |
| Ethanol | 45±0.045 |
| Propylene glycol | 68±0.016 |
| PEG 400 | 24±0.010 |
| PEG 600 | 28±0.008 |
| PEG 1500 | 35±0.13 |
| PEG 6000 | 38±0.17 |

*Results of solubility (mean±SD, n= 3)

### Dissolution analysis *in vitro*

The *in vitro* drug release was studied in 900 ml of distilled water, with pH levels of 5.4, 6.8, and 7.4, using the USP type-I apparatus. Size "1" rigid gelatin capsules were filled with the contents and placed in the revolving basket. The dissolving medium's temperature was held constant at 37±0.5 °C. Aliquots of 5 ml were taken out and subjected to filtration at regular intervals of 5, 10, 15, 20, 25, 30, 35, 40, and 45 min. The optical density of the filtered samples was then measured using an UV spectrophotometric approach at a wavelength of 286 nm. The concentration of the AZL was calculated using a standard calibration curve [30].

## RESULTS AND DISCUSSION

### Solubility studies

The screening for a suitable excipient for the AZL-SMEDDS formulation, capable of solubilizing a significant amount of AZL, was conducted through a saturation solubility study. Among the oils, surfactants and co-surfactants tested as shown in table 1, clove oil, Tween 20 (HLB=16.7) and propylene glycol were selected as they showed the highest solubility and compatibility.

### Preparation of pseudo ternary phase diagram

The microemulsion phase was determined by observing the clarity and transparency of the formulation upon dilution, as assessed through visual examination of the samples. Pseudo ternary phase diagrams demonstrated that the zone of microemulsion was biggest in the case of a formulation containing a 2:1 mixture of Tween 20 and propylene glycol (Smix) (fig. 1). Better stability will be provided by maintaining a 2:1 ratio of Tween 20 to propylene glycol. Clove oil as the oil, Tween 20 as the surfactant, and propylene glycol as a co-surfactant were chosen according to the results obtained based on solubility and emulsification property.

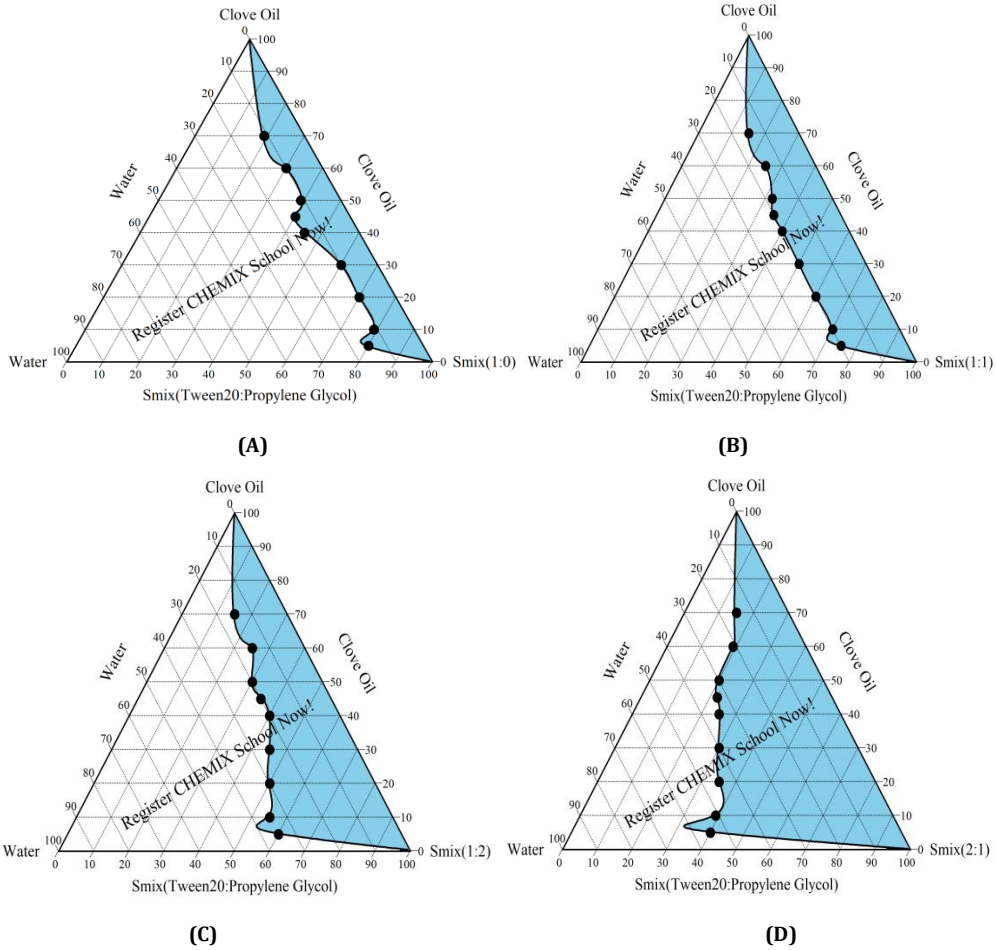


**Fig. 1: Ternary phase diagram of clove oil–Smix–water system. A (1:0), B (1:1), C (1:2), D (2:1)**

**Preparation of azilsartanmedoxomil-loaded SMEDDS**

The ternary phase diagram's (fig. 1) shaded zone, which marks the boundary of the self-microemulsification domain, was utilized to determine the range of independent variables oil, surfactant and co-surfactant.

**Box–behnken design**

Each answer that was polynomials of degree two obtained Analysis of Variance, lack-of-fit, and multiple correlation coefficient ($R^2$) tests. With a model *P*-value under 0.05, the quadratic model fits the data the best [31, 32]. $R^2$ greater than 0.6 is preferable, and more than 0.9 is desirable as shown in table 4.

The model *P*-values for the responses in the Analysis of Variance relate to the particle size, polydispersity index and dissolution %, respectively. Dependent variables fit the quadratic model as *P*-values are all less than 0.05. The lack-of-fit test was carried out to assess the adequacy of the quadratic model in fitting the responses Y1, Y2, and Y3. The obtained *P*-values for these responses were 0.3047, 0.8088, and 0.1361, respectively. Consequently, it can be concluded that all the responses exhibited a lack-of-fit that was not statistically significant, as indicated by the *P*-values exceeding 0.1. The $R^2$ values for Y1 is 0.9924, Y2 is 0.9928 and Y3 0.9230. These values indicate that the regression equations have a high level of confidence, exceeding 92%, in their ability to predict the observed values for responses better than the mean. In table 4, the coefficients (intercepts of variables) with multiple terms ($X_1*X_2$, $X_1*X_3$, and $X_2*X_3$) as well as the coefficients (intercepts of factors) with higher order terms ($X_1^2$, $X_2^2$, and $X_3^2$) represent interaction and quadratic effects respectively.

**Table 4: Interpretation of observed results**

| Response | Factors | Coefficient | *P*–value | ANOVA |
|---|---|---|---|---|
| Particle size | Intercept | 60.172 | | F = 102.20, $R^2$= 0.9924 |
| | $X_1$ | 3.301 | <0.0001 | Model *P*-value<0.0001 |
| | $X_2$ | -0.456 | 0.0057 | *P*-value of lack of fit = 0.3047 |
| | $X_3$ | 0.0125 | 0.9174 | |
| | $X_1X_2$ | -1.2 | 0.0002 | |
| | $X_1X_3$ | -0.7575 | 0.0025 | |
| | $X_2X_3$ | -0.0975 | 0.5718 | |
| | $X1^2$ | 0.2665 | 0.1402 | |
| | $X2^2$ | 0.6815 | 0.0038 | |
| | $X3^2$ | -0.231 | 0.1926 | |
| PDI | Intercept | 0.7278 | | F = 107.63, $R^2$ = 0.9928 |
| | $X_1$ | 0.0025 | 0.2981 | Model *P*-value<0.0001 |
| | $X_2$ | 0.0001 | 0.9568 | *P*-value of lack of fit = 0.8088 |
| | $X_3$ | -0.0061 | 0.0284 | |
| | $X_1X_2$ | 0.00001 | 1.0000 | |
| | $X_1X_3$ | -0.002 | 0.5451 | |
| | $X_2X_3$ | 0.0008 | 0.8184 | |
| | $X1^2$ | 0.0940 | <0.0001 | |
| | $X2^2$ | 0.0022 | 0.4916 | |
| | $X3^2$ | 0.0062 | 0.0819 | |
| Dissolution percentage | Intercept | 54.61 | | F = 9.32, $R^2$ = 0.9230 |
| | $X_1$ | -11.175 | 0.0004 | Model *P*-value=0.0038 |
| | $X_2$ | -0.3075 | 0.8666 | *P*-value of lack of fit = 0.1361 |
| | $X_3$ | -7.685 | 0.0033 | |
| | $X_1X_2$ | 0.3925 | 0.8795 | |
| | $X_1X_3$ | -6.5525 | 0.0341 | |
| | $X_2X_3$ | -0.4275 | 0.8688 | |
| | $X1^2$ | 4.38375 | 0.1145 | |
| | $X2^2$ | 1.13375 | 0.6553 | |
| | $X3^2$ | 8.85375 | 0.0083 | |

ANOVA, analysis of variance; PDI, polydispersity index; AZL, azilsartan

**Influence of formulation composition factors on responses**

The size of the droplets plays a pivotal role in SMEDDS as it has a great impact on drug release rate and absorption. Table 4 demonstrates that all independent variables exerted a significant influence on particle size, as indicated by the term *P*-value being less than 0.05. Nevertheless, the impact of X1 and X2 on particle size was found to be more substantial compared to the influence of X3. However, it was observed that the co-surfactant exhibited a substantial interaction with the oil phase, as indicated by the significant *P*-value ($P$<0.05) for the interaction term X1X3, which had an impact on the particle size of the microemulsion. A decrease in the quantity of X1 led to a corresponding rise in particle size. In contrast, the quantities of X2 and X3 exhibited distinct effects on particle size. The observed consequences can be attributed to the inherent characteristic of self-emulsification [40]. 3D response plot for Y1 is depicted in fig. 2, with X3 being held constant at a moderate level.

The particle size distribution index (PDI) provides information on the size distribution of the microemulsion that is formed by SMEDDS. X1, X2 and X1X3 and quadratic interaction between oil ($X_1^2$) and co-surfactant ($X_3^2$) were all found to significantly affect the PDI (*P*-value 0.05). The variation in the quantity of co-surfactant (X3) did not yield considerable effects on the polydispersity index (PDI). However, it did exhibit an interesting quadratic effect and interact with the oil component in a significant manner. Fig. 3 depicts the response surface plot illustrating the relationship between the (PDI) and the varying levels.

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The drug release percentage after 15 min was notably affected by the amounts of oil and co-surfactant. On the other hand, the quantity of surfactant did not have a significant impact on drug release. However, it is worth noting that the surfactant exhibited a significant interaction with the co-surfactant ($X_2X_3$), surpassing the main effects of oil (X1) and co-surfactant (X3). Furthermore, the highest coefficient (1.13375) for the quadratic effect of X2 on Y3 demonstrated a statistically significant negative influence. This observation can be inferred as well from the data presented in fig. 4, which illustrates that at a lower concentration of added oil, the value of Y3 exhibited a slight increase followed by a subsequent decrease as the amount of co-surfactant added decreased from 30 to 5 mg. However, when the X3 variable decreased from 30 to 5 mg, there was a significant decrease in the Y3 variable at high levels of X1. Remarkably, despite the absence of any kind of known impact on Y1, X3 exhibited significant effects on Y3. Hence the size of the droplet has an impact on the rate of drug release and absorption. The rapid emulsification of the formulation during the initial dissolution rate may give rise to its manufacturing.

**Table 5: The predicted and observed values of optimized AZL-SMEDDS**

| Responses | Predicted value | Observed value | % Bias |
|---|---|---|---|
| Y1 | 59.85 | 55.25 | 7.68 |
| Y2 | 0.729 | 0.694 | 4.80 |
| Y3 | 55.406 | 59.87 | -8.05 |

AZL-SMEDDS, azilsartan self micro emulsifying drug delivery system, % Bias = (predicted value–observed value)/predicted value X 100

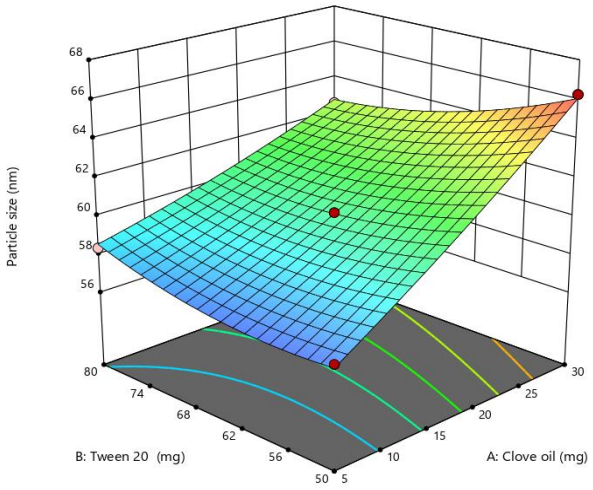



**Fig. 2: 3D response plot on Y1 at the median-level of X3**

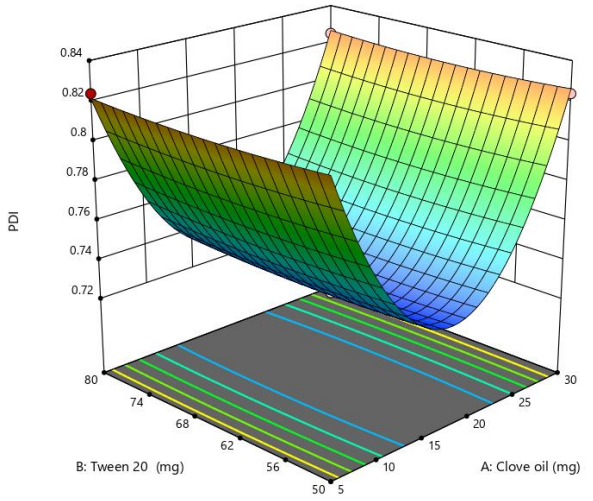



**Fig. 3: 3D plot on Y2 at the median-levels of X3**

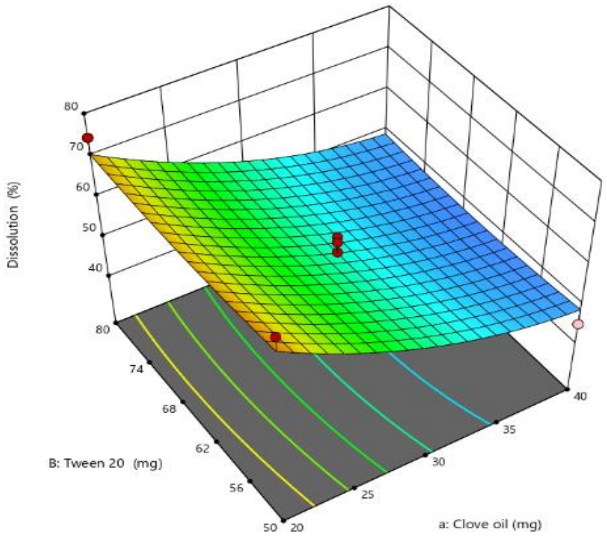



**Fig. 4: 3D plot on the Y3 at median levels of X3**

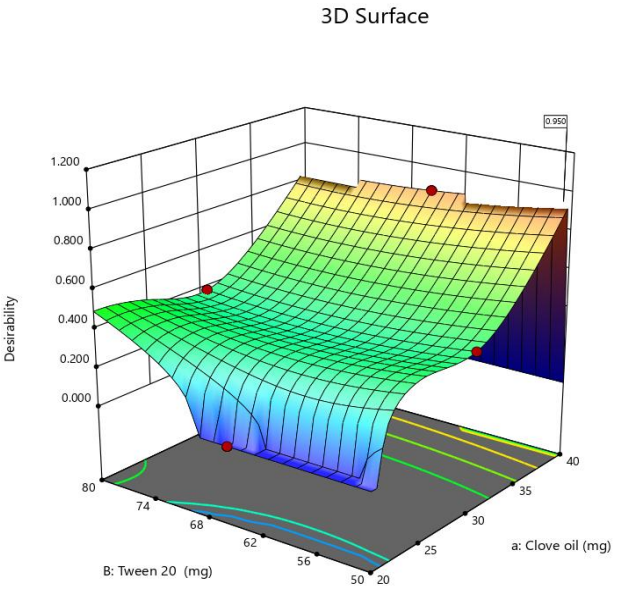


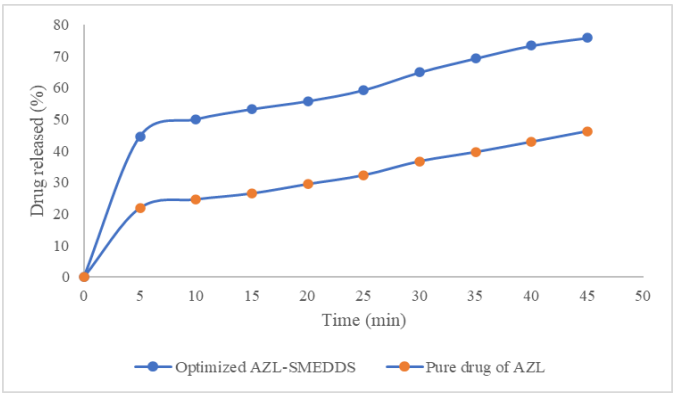

**Fig. 5: 3D response plot showing the overall desirability (*D*) as a function of X1 and X2**

**Desirability function**

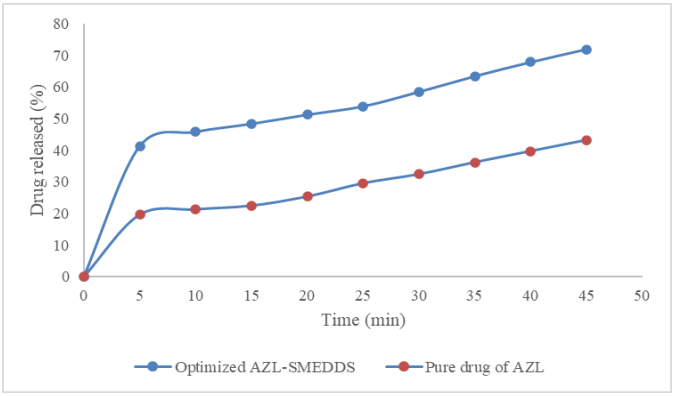
To optimize the AZL-SMEDDS formulation, a desirability function was employed, enabling the simultaneous achievement of multiple objectives such as particle size and PDI and drug release after 15 min. The application of optimization (desirability) function in multi-dimensional optimization involves merging several responses into a single metric through mathematical calculations [36]. To model the data, polynomials of degree two, equation was utilized, and the response surface of the desirability function was visualized in fig. 5, taking into account the ranges of variables X1 and X2. The optimized levels for variables X1, X2, and X3 were determined as 28.69, 76.45, and 24.93, respectively. Correspondingly, the predicted values for response variables Y1, Y2, and Y3 were estimated to be 59.85, 0.729, and 55.406%, respectively. These results were presented in table 5, showing a correlation between predicted and observed values, confirming the effectiveness and reliability of the BBD and desirability function in the optimization process. In order to assess the stability of the o/w microemulsion, the surface charge of microemulsion droplets from the optimized AZL-SMEDDS formulation was measured. The zeta potential of the optimized AZL-SMEDDS formulation was found to be-2.94±0.3 mV (mean±standard deviation, n=3). Interestingly, the SMEDDS formulation without the drug also exhibited a negative charge [37].

***In vitro* drug dissolution studies**

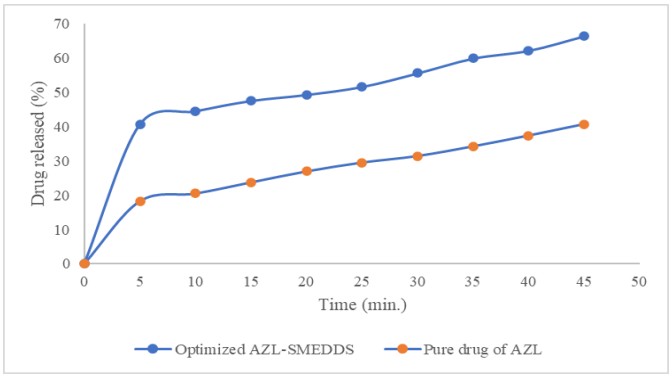
Fig. 6 illustrates results of simulated dissolution experiments comparing two formulations: optimized AZL-SMEDDS and AZL powder, both contained within hard gelatin capsules. As anticipated, the optimized AZL-SMEDDS exhibited an exceptionally rapid dissolution rate within just 5 min at various pH conditions (5.4, 6.8 and 7.4) as well as in distilled water. This rapid dissolution suggests a significant increase in the solubility of AZL in the SMEDDS formulation. On the other hand, the AZL powder demonstrated a much slower release profile, with only 30% of the drug being released within 45 min. Consequently, it is evident that the optimized AZL-SMEDDS formulation outperforms the AZL powder, showing a substantially higher dissolution rate and achieving a greater overall percentage of drug release. This improvement can be attributed to the presence of micro-sized particles in the SMEDDS formulation, which provides a larger surface area, thereby enhancing the dissolution of the drug from the formulation.



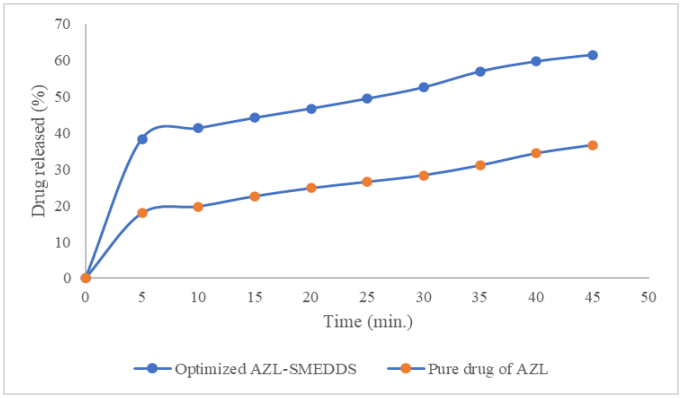

**a) pH 7.4**




**b) pH 6.8**




**c) pH 5.4**




**d) Distilled water**

**Fig. 6: *In vitro* drug dissolution of azilsartan from optimized Azilsartan-self microemulsifying drug delivery system formulation compared with pure drug of Azilsartan in (a) pH 7.4 phosphate buffer, (b) pH 6.8 phosphate buffer, (c) pH 5.4 phosphate buffer, (d) Distilled water. Data are given as mean value**

The above research work investigated the effects of three distinct variables (X1: quantity of clove oil, X2: quantity of Tween 20, X3: quantity of propylene glycol) on AZL-loaded SMEDDS. The research based primarily on particle size, polydispersity index, and the % of drug release after 15 min. The study employed a Design with $3^3$ to evaluate the effect of these variables. The analysis carried out using the BBD revealed statistically significant interaction effects and quadratic effects of the independent variables on the dependent variables. Additionally, these effects were observed when compared to the optimization approach, which involved the use of a desirability function. The optimized formulation demonstrated good observed responses that closely correlated to the predicted values. Moreover, by conducting simulated drug release studies, it was observed that the AZL-SMEDDS formulation demonstrated a more rapid dissolution of the drug in comparison to the AZL powder in its pure form. This study emphasizes the effectiveness of BBD in conducting a thorough analysis of the fundamental relationship between formulation variables and desired consequences. Furthermore, the optimization of SMEDDS holds great potential as a technique to improve the oral bioavailability of drug compounds with low water solubility, such as Azilsartanmedoxomil.

## CONCLUSION

In this study, the effects of three independent variables of AZL-SMEDDS-amount of Clove oil (X1), Tween 20 (X2), and Propylene glycol (X3) on Particle Size (Y1), Polydispersity (Y2), and dissolution % (Y3) were evaluated by three-factor, three-level BBD. The significant influence of interaction effects and quadratic effects of independent variables on dependent variables was revealed by BBD. The BBD was then followed by optimization using a desirability function. The optimized formulation displayed desirable observed responses close to the predicted values.

## ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All authors have equally contributed to the manuscript

## CONFLICT OF INTERESTS

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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