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Design and Optimization of a Self-Nanoemulsifying Drug Delivery System for Pranlukast Hemihydrate with D-Optimal Mixture Design

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Abstract

The researchers optimized the concentrations of components in the SNEDDS formulation using a D-optimal mixture design, aiming to achieve favorable physicochemical characteristics like dissolution and droplet size. The optimized formulation of pranlukast-loaded SNEDDS, comprising 22.44 mg of Benzyl alcohol, 67.55 mg of Tween 20, and 10 mg of Span 20, resulted in a droplet size of 65.866 nm, saturated solubility of 20.56 mg/g, and drug release of 90.84%, with a desirability index value of 1. The comparison of among experimental and predicted values for the droplet size, saturated solubility, and the drug release showed good agreement. Consequently, they successfully developed an SNEDDS formulation using a D-optimal mixture design, which is promising for enhancing weakly water-soluble drugs' oral absorption.

Keywords: SNEDDS; PLH; D-optimal mixture design; Desirability; Droplet size.

1. Introduction

Self-nanoemulsifying drug delivery systems (SNEDDS) are stable, isotropic mixtures that include oil, surfactant, co-surfactant, and a drug. These systems can readily be dispersed in the aqueous environment of the gastrointestinal tract to form a fine oil-in-water emulsion with droplet sizes under 100 nm, using only gentle agitation [1]. Thanks to their small droplet size, SNEDDS notably enhance the bioavailability of lipophilic molecules and essential oils by increasing surface area and drug solubilization. This size advantage aids drug permeation across the intestinal membrane, enhancing paracellular and transcellular absorption, with assistance from surfactants like Span 20 [2, 3]. Additionally, by incorporating lipophilic drug molecules, SNEDDS minimize the food effects commonly associated with these molecules. SNEDDS is primarily developed to improve the bioavailability of hydrophobic drugs, ensuring their prompt release upon reaching the stomach or intestines.

Several factors impact SNEDDS. Generally, drugs given in high doses are unsuitable for SNEDDS unless they show outstanding solubility in at least one SNEDDS component, ideally the lipophilic phase. Drugs with

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limited solubility in both water and lipids pose the greatest challenge for delivery via SNEDDS [4, 5, 6]. The drug's solubility in the oily phase heavily influences the efficacy of SNEDDS in maintaining the drug in a solubilized state. If the surfactant or co-surfactant significantly influences drug solubilization upon SNEDDS diluting, there is a risk of precipitation [7, 8]. This precipitation leads to a reduction in the solvent capacity of the co-surfactant or surfactant.

D-optimal designs are optimizations tailored to a specific model used and optimality criterion. The criterion for D-optimal designs focuses on maximizing |X'X|, which is the determinant of the information matrix |X'X|. This principle aims to reduce the generalized variance of the parameter estimates within a given model. Therefore, the 'optimality' of this design depends on the selected model [9]. Experimenters must define a model before a computer can create definite treatment combinations. Given the total number of treatment runs and a defined model, the computer algorithm selects the best set of design runs from a range of possible treatment combinations [10]. This pool typically includes all possible combinations of several factor levels intended for the experiment.

Essentially, the range of possible combinations provides the choices from which the algorithm of D-optimal design selects the combinations of treatment for integration in the design. The algorithm typically uses an exchanging and stepping method to determine the appropriate set of treatment runs. The preference for D-optimal designs over traditional classical designs mainly arises from two key reasons: first, fractional factorial or standard factorial designs might need additional runs compared to the time or resources available for the experiment. Second, the design space might be restricted, indicating that the process space includes factor settings that are either unfeasible or cannot be implemented.

Pranlukast, a leukotriene receptor antagonist, is employed in treating asthma and other inflammatory conditions binding to the cysteinyl-leukotriene Cys LT1 receptors the attachment of leukotrienes to the receptor, halt Additionally, Pranlukast has demonstrated the ability to hinder certain effects of histamine on human lymphocytes, indicating potential anti-inflammatory properties. Its application extends to combination therapy with various antibiotics for treating infectious ailments such as *Clostridium difficile*-induced bowel disease. Studies have revealed its efficacy in diminishing eosinophil count in the bloodstream and ameliorating asthma-related symptoms like coughing and wheezing. Furthermore, Pranlukast inhibits the activation of p2y receptors on eosinophils, decreasing eosinophil cation levels [11, 12].

The development of an SNEDDS is particularly crucial for improving the bioavailability of poorly water-soluble drugs, constituting a significant proportion of newly discovered therapeutic compounds. Conventional oral delivery systems often fail to deliver such drugs efficiently due to dissolution rate-limited absorption. SNEDDS offers a promising solution by forming fine oil-in-water emulsions upon contact with gastrointestinal fluids, enhancing solubility, dissolution rate, and bioavailability. The present study's novelty lies in applying a D-Optimal design. This statistically robust and efficient experimental design strategy allows optimizing multiple formulation variables with fewer experimental runs than traditional methods. This approach improves the formulation process by identifying optimal conditions with minimal resource expenditure and provides a systematic and reproducible methodology that strengthens the scientific rigor of formulation development. To the best of our knowledge, limited reports are available integrating D-Optimal design specifically for SNEDDS formulations of Pranlukast hemihydrate, highlighting the innovative aspect of this work.

2. Materials and methods

PLH was a gift sample from ESaiPharma Ltd, Parawada. Visakhapatnam, India. Polyethylene glycol sorbitanmonolaurate 20, Polyethylene glycol sorbitanmonolaurate 80, benzyl alcohol (BA), polyethylene glycol 400 (PEG 400),sorbitanmonolaurate and triethanolamine (TEA) were procured from Merck laboratories and all the other reagents used were of analytical grade.

2.1. Saturation Solubility Studies:

The saturation solubility of the drug was determined in various oily and co-solvent vehicles, including

Propylene Glycol (PG), Polyethylene Glycol 400 (PEG 400), Triethanolamine, and Benzyl Alcohol. An excess amount of the drug was added to 2 mL of each vehicle in screw-capped vials and mixed using a vortex mixer. The mixtures were kept in a shaking water bath at 37 ± 0.5 °C for 48 hours to attain equilibrium. After incubation, the samples were centrifuged at 10,000 rpm for 15 minutes. The supernatants were carefully collected, filtered through a 0.45 µm membrane filter, and appropriately diluted with methanol. Drug concentration was analyzed using a UV-visible spectrophotometer at λmax 262 nm.

2.2. *In vitro Dissolution Studies*

An in vitro drug release study was conducted using the USP 30 rotating paddle apparatus to evaluate the release of PLH from self-nanoemulsifying drug delivery systems (SNEDDS) filled in hard gelatin capsules. Each capsule contained 30 mg of PLH, and two capsules from each SNEDDS formulation (A, B, and C) were individually placed in 900 mL of various dissolution media—distilled water, simulated gastric fluid (SGF, pH 1.2), phosphate buffer (pH 4.0), and simulated intestinal fluid (SIF, pH 6.8). To assess the influence of pH and surfactant on drug release, parallel studies were conducted using buffer solutions containing 1% Tween 80. The paddle speed was maintained at 50 rpm throughout the test. The release profiles of PLH from the SNEDDS formulations were compared with that of the pure PLH powder (30 mg), also encapsulated in hard gelatin capsules. At specified time intervals (5, 10, 15, 20, 45, 60, 90, and 120 minutes), 5 mL samples were withdrawn from the dissolution medium and analyzed for drug content using a UV-visible spectrophotometer. After each sampling, a fresh medium was replenished to maintain sink conditions.

2.3. *Studies on solubility*

To specify and visualize the potential emulsifying regions, it is imperative to ascertain the PLH solubility across various oil and surfactant components. The solubility assessment of PLH involved its dissolution in diverse oils, surfactants, and co-surfactants. The supersaturated form of PLH was placed in vials, followed by agitation through a magnetic stirrer for one day at 30ºC [13, 14]. Subsequently, the mixtures underwent centrifugation at 13,000 rpm for 5 minutes utilizing a Remi Centrifuge, and the resulting supernatants were filtered through a 0.45 µm membrane filter (Millipore). The concentration of PLH in the filtrate was quantified employing an ultraviolet spectrophotometer set at 260 nm.

2.4. *Pseudoternary phase diagram*

A pseudoternary phase diagram was constructed by varying the oil weight ratio in a co-surfactant and surfactant mixture, with ratios ranging from 5:95 to 85:15. Each oily mixture was gradually mixed with water under stirring until it reached clarity at 37ºC. The concentrations of oil, co-surfactant, surfactant, and water were recorded to create pseudoternary phase diagrams [15]. These specific weight ratios were selected to determine the dispersion capabilities of the mixture in water. The clarity of the PLH-loaded SNEDDS dispersion was measured using a spectrophotometer.

2.5. *Design of experiment (DoE) to optimize SNEDDS*

D-optimal mixture design stands out among statistical optimization tools for SNEDDS because it minimizes differences in coefficient assessment and selects the best subset based on criteria for maximizing data grid determinants. Unlike other designs, it considers the entire SNEDDS system 100%. A D-optimal mixture design with three independent variables optimized the SNEDDS formulation composition. Based on the results from the solubility study and the pseudo-ternary phase diagram, the concentrations of Benzyl alcohol (oil: A), Tween 20 (surfactant: B), and Span 20 (cosurfactant: C) were adjusted within the ranges of 5-25%, 35-75%, and 10-40% respectively, with a total concentration always equaling 100%. The dependent variables measured were mean droplet size (Y1), saturated solubility (Y2), and percent drug release (Y3), utilizing Design Expert software for analysis [16]. The initial experimental design included 16 trials to fit a cubic model, evaluate the lack of fit, and calculate experimental error in the responses.

2.6. *Determination of globule size*

A Zetasizer ZS nano series was used to assess globule size.

3. Results and Discussion

3.1. Solubility studies

In the formulation of SNEDDS, selecting an appropriate oil phase is crucial as it directly influences the drug's solubilization capacity, the nanoemulsion formation behavior, and the overall bioavailability enhancement. Although conventional oils such as long-chain triglycerides or medium-chain triglycerides are commonly employed, co-solvents and semi-polar components like Propylene Glycol (PG), Polyethylene Glycol 400 (PEG 400), Triethanolamine, and Benzyl Alcohol have demonstrated significant potential in improving drug solubility, especially for lipophilic compounds. While not classical lipids, these excipients are pharmaceutically acceptable and included in the initial screening due to their amphiphilic nature and capacity to function as oil-like carriers in SNEDDS formulations.

PG and PEG 400 are widely used as hydrophilic co-solvents that can also act as vehicles with moderate oil-like properties, facilitating improved solubilization of poorly water-soluble drugs. Triethanolamine is a multifunctional excipient with solubilizing, emulsifying, and pH-modifying characteristics that may enhance the microenvironment for drug dispersion. Benzyl alcohol, a slightly aromatic alcohol, is known for its solvent properties and compatibility with lipid-based systems. The inclusion of these components in the solubility screening broadens the design space for SNEDDS by enabling the identification of novel combinations that may produce superior nanoemulsifying behavior and drug-loading capacity. Moreover, their regulatory acceptance and biocompatibility further justify their selection as candidate oils or oil-phase enhancers in the formulation stage of SNEDDS development.

Vehicles were chosen based on their ability to solubilize PLH effectively, ensuring safety and compatibility with the drug. Benzyl alcohol (BA), likely attributed to PLH's ability to form hydrogen bonds with the hydroxyl group, shows high solubility with a value of 6.93 ± 0.05 mg/g. Similarly, surfactants and cosurfactants, such as Tween 20 and Span 20, exhibited high solubilization capabilities for PLH [17]. Therefore, BA was chosen as the oil phase Tween 20 (8.32 ± 0.04 mg/g), and Span 20 was selected as surfactant/cosurfactant as they demonstrated the best solubility for PLH.

3.2. Pseudoternary phase diagram construction

The diagrams were developed to determine the microemulsion area and optimize the concentrations of oil, cosolvent, and S/CoS based on the results from the experiments on solubility, as indicated in **table 1**. As shown in **figure 1**, a combination of TEA/BA (1:2) efficiently optimized the nanoemulsion region [18].

Table 1 Solubility of PLH in various surfactants and oils

Vehicle	Solubility (mg/g)
Oils	
PG	0.65 ± 0.02
PEG 400	3.15 ± 0.05
Triethanolamine	4.32 ± 0.26
Benzyl alcohol	6.93 ± 0.05
Surfactant/cosurfactant	
Kolliphor	0.06 ± 0.01
Labrasol®	3.12 ± 0.02
Tween 80	2.66 ± 0.38
Span 20	5.58 ± 0.01
Tween 20	8.32 ± 0.04

Every value presents the mean ±SD (n=3)

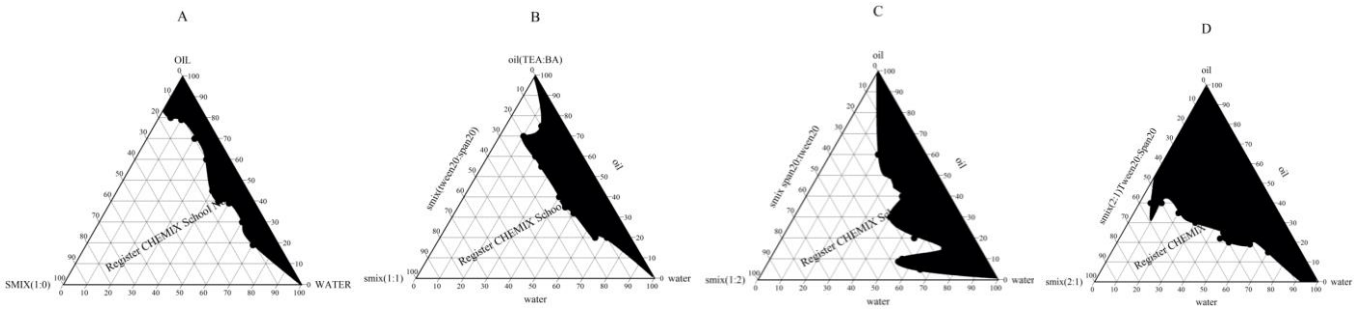

Figure 1. Pseudoternary phase diagram of the SNEDDS formulation (the black region presents the nanoemulsion phase)
A: water-oil (TEA/BA)(1:2)-smix (1:0)(Tween 20/span 20) B: water-oil(TEA/BA)(1:2)-smix (1:1)(Tween 20/span 20)
C: water-oil(TEA/BA)(1:2)-smix (1:2)(Tween 20/span 20) D: water-oil(TEA/BA)(1:2)-smix (2:1)(Tween 20/span 20)

3.3. Design of experiment (DoE) and optimization of SNEDDS

We utilized a mixture design to optimize the composition of pranlukast-loaded SNEDDS, employing the trial version of Design Expert software. It was observed, as detailed in the table, that 16 trial runs were established based on the design, incorporating two center points, as shown in **table 2**. The ranges for Y1 varied from 60.21 to 66.28 nm, Y2 from 18.69 to 20.63 mg/g, and Y3 from 90.69 to 94.33%.

Quadratic, linear, cubic, and special cubic models were applied to all the dependent variables. After assessing various statistical parameters, for example, standard deviation, squared correlation coefficient (R2), lack of fit P-value, and adjusted R2 values, the cubic model was determined to be the most suitable mathematical model for both Y1 and Y2, as shown in **table 3** [19, 20, 21].

Figure 2 depicts normal probability plots for residuals, showing a linear pattern, suggesting that the error distribution follows a normal distribution, confirming the suitability of the cubic model assumed. Residuals are centered on the midpoint of the line, indicating that experimental outcomes are normally distributed. This figure helps identify externally studentized residuals exceeding three or falling below -3.

Table 2 Experimental matrix data and observed responses from randomized trials in the D-optimal Mixture Design

Run	A: Benzyl alcohol mg	B: Tween 20 mg	C: Span 20 mg	Droplet Size nm	Saturated solubility mg/g	Drug release %
1	16.5303	56.2271	27.2425	63.25	20.46	91.63
2	5	62.4168	32.5832	60.21	18.89	94.21
3	15	75	10	62.36	19.86	90.98
4	22.4406	67.5594	10	65.99	20.59	90.69
5	5	72.5	22.5	60.23	18.73	91.28
6	25	35	40	66.24	20.62	94.31
7	8.39678	51.6032	40	61.54	19.46	94.32
8	16.5303	56.2271	27.2425	63.52	20.22	92.35
9	25	46.2261	28.7739	66.25	20.72	94.12
10	8.39678	51.6032	40	61.58	19.31	94.33
11	15	75	10	62.36	19.72	90.98
12	5	72.5	22.5	61.25	18.69	91.42
13	15.0356	65.4542	19.5102	63.24	20.14	91.23
14	16.5303	56.2271	27.2425	64.29	20.21	93.98
15	17.2091	44.1143	38.6765	65.98	20.48	94.28
16	25	59.4397	15.5603	66.28	20.63	91.21

Table 3 Summary of statistical analysis outcomes and cubic model equations corresponding to the measured responses

Response	Standard deviation	P-Value Lack of fit	R^2	Adjusted R^2
Droplet size Y1	0.4405	0.6228	0.9839	0.9599
Saturated solubility Y2	0.1042	0.6306	0.9913	0.9784
Drug release Y3	0.7069	0.7110	0.9152	0.7879

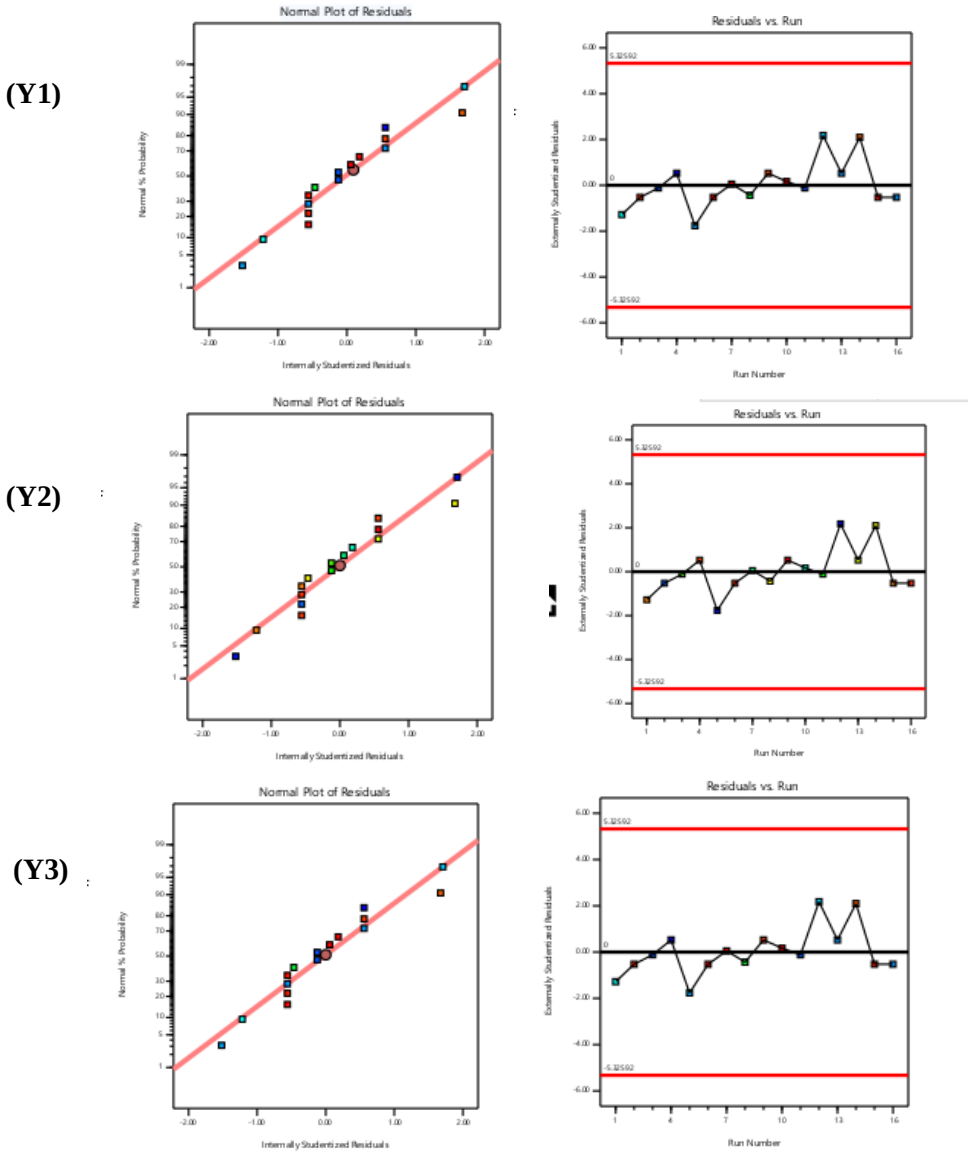

Figure 2. The cubic model adequacy in evaluating the normality of the residuals and Y1, Y2, and Y3 response outliers.
A. Probability plot of normal percentages against internal studentized residuals
B. Plot of external studentized residuals against a run number

The impact of varying component ratios on droplet size, saturated solubility, and drug release is elucidated by the equations below:

The fitted model equation for Droplet size:

-571.83A+64.62B+138.64C+1187.23AB+1059.30AC-160.28BC-1089.42ABC+675.89 AB(A-B) +884.09 AC (A-C) +81.49 BC (B-C)

Saturated solubility:

-81.45A+18.56B+30.11C+192.49AB+174.26AC-20.83BC-172.52ABC+99.56AB(A-B) +139.31AC (A-C)+12.41BC(B-C)

Drug release:

-233.22A+92.57B+123.46C+589.33AC+569.33AC-50.82BC-610.90ABC+321.49AB(A-B)+481.77AC(A-C)+6.66 BC(B-C)

Where:

A=Concentration of benzyl alcohol

B= Concentration of Tween 20

C= Concentration of Span 20

Three-dimensional response surface plots and two-dimensional contour plots were utilized better to understand the relationships between the independent and dependent variables, as depicted in **figures 3** and **4**.

These plots are beneficial for understanding how the change will influence the effect of one factor at the level of another factor.**figure 3** illustrates the impact of Benzyl alcohol (A), Tween 20 (B), and their effect measure modification on Y1 at the 0 level of Span 20 (C). At the -1 level of Tween 20, Y1 increased with an increase in the concentration of BA, whereas at the +1 level of Tween 20, Y1 decreased with an increase in A.

In **figure 4**, the effect of BA (A) and Span 20 (C) and their effect measure modification on Y2 at 0 level of Tween 20 (B=55mg) is depicted. At the -1 level of A, increasing the C amount led to an increase in Y2 and vice versa. This observation aligns with the earlier results of specific solubility tests, which revealed a solubility sequence of pranlukast: Span 20 > Tween 20 > Benzyl Alcohol. Thus, it can be inferred that Span 20 primarily contributed to the drug's solubility in the formulation. **Figure 4** demonstrates the effects of Tween 20 (B) and Span 20 (C) and their effect measure modification on Y3 at the 0 level of Benzyl Alcohol. Increasing the amount of B at a -1 level of C enhances the percentage of drug release.

Figures 5 and **6** illustrate that the actual responses closely align with the predicted ones. In the triangle image, areas not colored grey represent the smallest droplet size, highest saturated solubility, and maximum drug release.

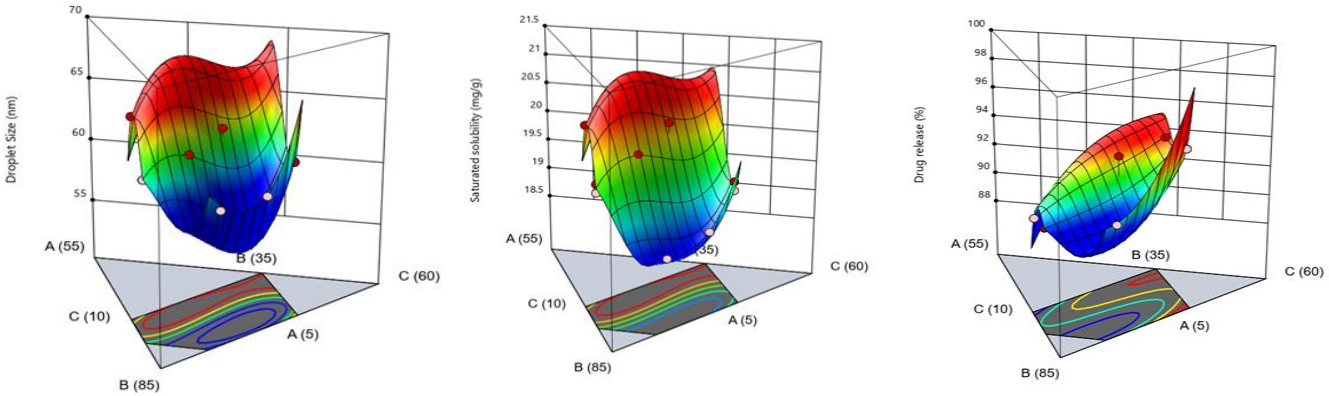

Figure 3. 3D response plot for a Droplet size b Saturated solubility c Drug release

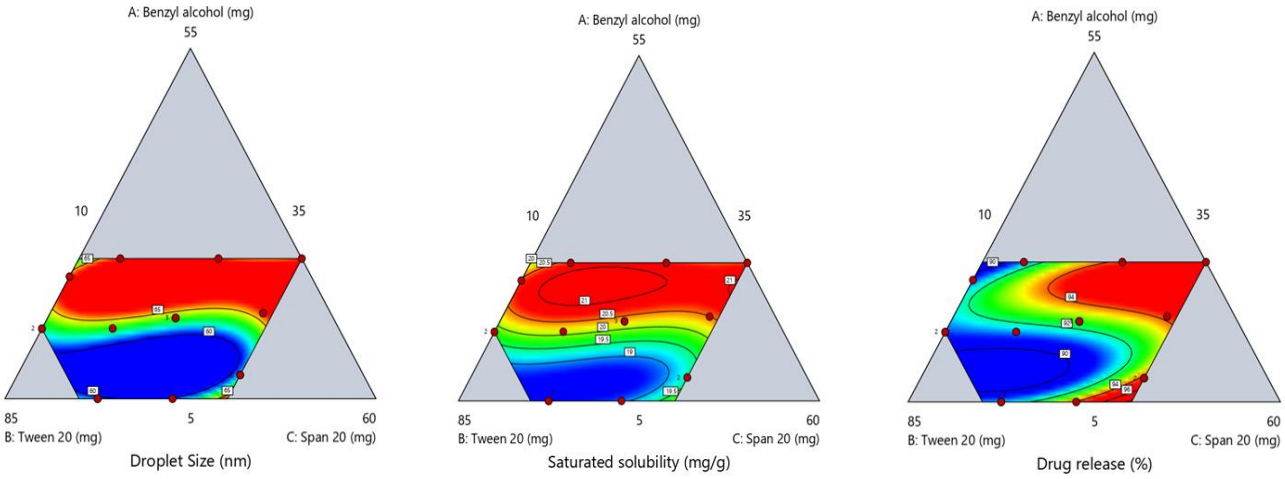

Figure 4. 2D contour plots for a Droplet size b Saturated solubility c Drug release

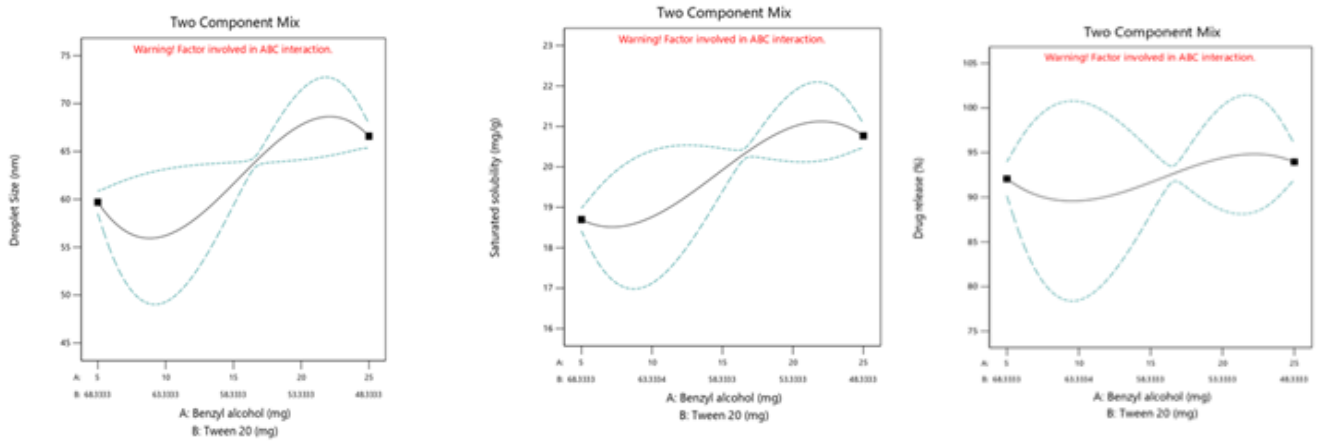

Figure 5. Prediction profile a Droplet size b Saturated solubility c Drug release

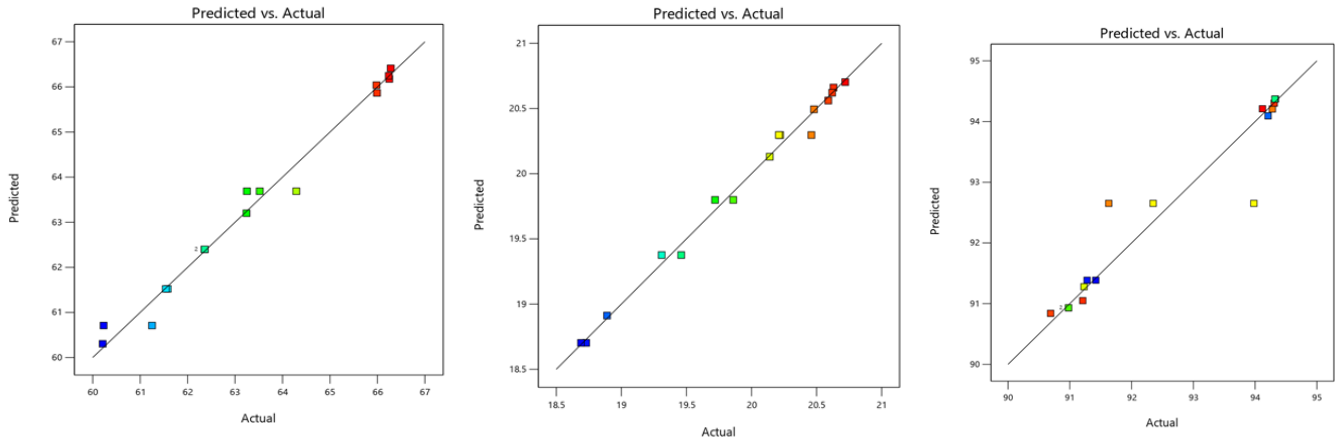

Figure 6. Actual vs. predicted graph for a Droplet size response b Saturated solubility c Drug release

The general linear scale desirability function, suggested by Derringer and Suich [22, 23], was utilized to enhance optimization further. This function aims to pinpoint an optimal and balanced point within the design space that achieves the set objectives for the dependent factors. A desirability value of 1 indicates the optimal performance of the factors under investigation, while 0 indicates an undesirable response, as shown in **figure 7**. An overlay plot depicted in **figure 8** illustrates the impact of various variables on the two responses. The optimal formulation of pranlukast-loaded SNEDDS includes 22.44 mg of Benzyl alcohol, 67.55 mg of Tween 20, and 10 mg of Span 20, resulting in a droplet size of 65.866 nm, a saturated solubility of 20.56 mg/g, and a drug release of 90.84%, achieving a desirability index of 1.

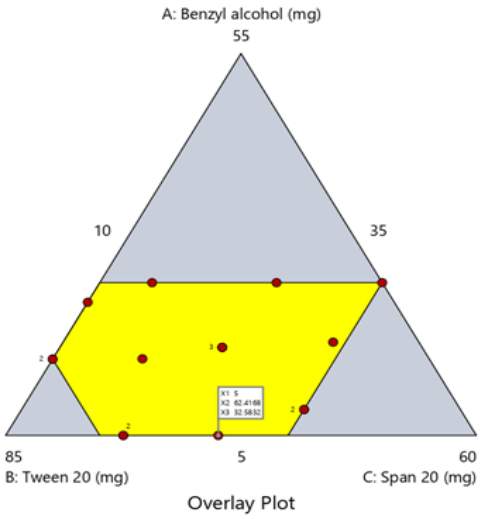

Figure 8. Overlay plot of the optimized PLH-loaded SNEDDS

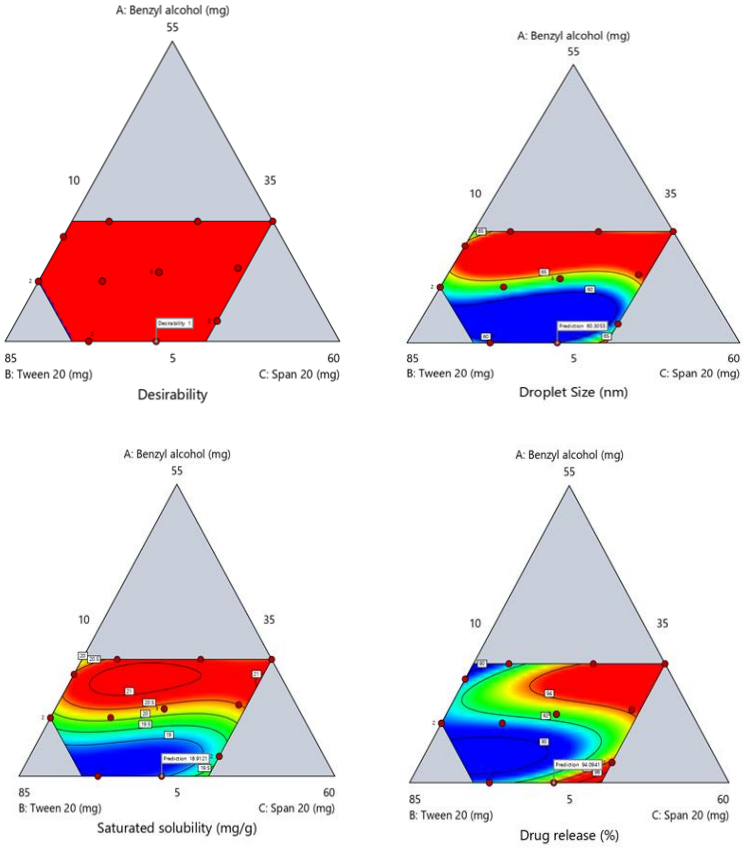

Figure 7. Desirability index for formulation optimization.

3.4. Globule size

The PLH-loaded SNEDDS formulation was characterized to assess its particle size distribution, homogeneity, and colloidal stability. Dynamic light scattering (DLS) analysis revealed a Z-average droplet size of 66.28 nm, suggesting successful nanoscale emulsification. However, intensity-weighted size distribution indicated a bimodal pattern, with a predominant peak at 759.3 nm (71% intensity) and a secondary peak at 5000 nm (29% intensity), as shown in **figure 9**. This distribution reflects the coexistence of nanosized droplets and larger aggregates, likely due to partial coalescence or insufficient emulsification energy. The polydispersity index (PDI) was recorded as 0.839, indicating significant size heterogeneity and a lack of monodispersity. Zeta potential measurements further supported these findings, with the formulation exhibiting a value of –19.7 mV. While this value suggests moderate electrostatic repulsion, it is below the threshold of ±30 mV and is typically associated with stable colloidal dispersions. The combination of high PDI and modest zeta potential highlights the formulation's suboptimal stability and the need for further optimization to ensure long-term homogeneity.

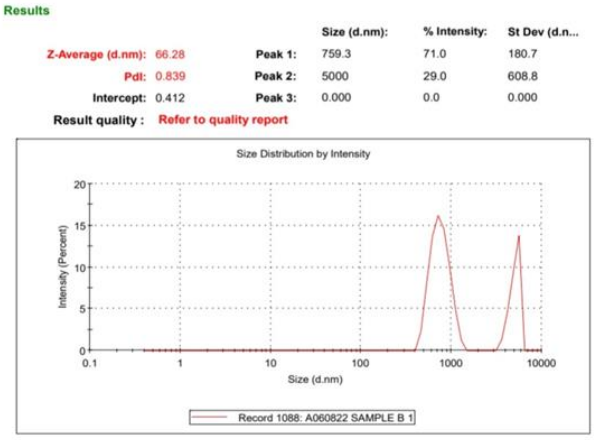

Figure 9 PDI and Globule size of optimized formulation

Despite these limitations, the current findings offer valuable insight into the formulation behavior of SNEDDS and underscore critical variables that can be refined to enhance system stability. These characterization results are a rational foundation for iterative development using statistical optimization techniques such as D-optimal design.

Conclusion

A successful and optimized PLH-loaded SNEDDS formulation was created using a D-optimal mixture design. The optimized formulation of pranlukast loaded SNEDDS, comprising 22.44 mg of Benzyl alcohol, 67.55 mg of Tween 20, and 10 mg of Span 20, resulted in a 65.866 nm droplet size, saturated solubility of 20.56 mg/g, and drug release of 90.84%, with a desirability index value of 1. There is a correlation between the observed and predicted values for all the dependent and independent variables. The optimized formulations exhibit a globule size, indicating that the emulsion droplets are in the nanometric range, specifically 66.28 nm, and a PDI value below 0.5, demonstrating uniform globule size distribution. Additionally, the zeta potential is measured at -19.7 mV.

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Authors' contribution

Kaveri Raja Jagadish gathered details of manuscript and contributed to writing the manuscript regarding this work. Saranya Palavalasa contributed for the collection of information from various resources. Paravastu Venkata Kamala Kumari analyzed these data and necessary inputs were given towards the designing and drafting of the manuscript.

Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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