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Original Article

Formulation and Evaluation of Castor Oil Containing Self-emulsifying Pellets by Using Design of Experiment

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ABSTRACT

Background/Objectives: The objective of the study was to examine the feasibility of extrusion/spheronization techniques for formulation of castor oil loaded self-emulsifying pellets. The study was also aimed at optimization of the self-emulsifying pellet system with design of experiments. **Materials and Methods:** Various surfactants and co-surfactants were tested for their ability to emulsify castor oil. The proportion of components (castor oil, surfactant and co-surfactant) in self-emulsifying pellets was optimized using a D-optimal mixture design. During optimization, the effect of composition of oil(X_1), surfactant(X_2) and cosurfactant(X_3) blend on responses like dispersion time (Y_1), resultant globule size (Y_2) and polydispersity index (Y_3) was studied. The developed self-emulsifying mixture was further loaded on pellet formulation using extrusion spheronization technique. **Results:** The application of D-optimal mixture design resulted in 16 batches, out of which the optimized batch consists of castor oil (30.92%), Cremophore EL (58.56%) and PEG 400(10.51%) having dispersion time of 53 sec, globule size of 242 nm and polydispersity index of 0.243 with desirability value of 1. All the formulation components affected the performance of pellets significantly. Free flowing pellets were obtained with 30% of oil loading. **Conclusion:** The self-emulsifying pellets of castor oil were successfully optimized with mixture design. The developed system containing castor oil can be used for orally for conditions like arthritis or can also serve as a carrier system for any drug or herbal active.

Keywords: Solid self-emulsifying drug delivery system, Castor oil, Self-emulsifying pellets, Extrusion spheronization, Dispersion time.

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INTRODUCTION

Self-emulsifying drug delivery system (SEDDS) or self-micro emulsifying drug delivery system (SMEDDS) is defined as an isotropic combination of oil, surfactant, co surfactant and lipophilic drug. In the GI tract, when diluted with aqueous medium and gently agitated, they form fine oil in water emulsions or microemulsions.[1] They enhance the interfacial area and distribution of drugs in the GI tract.[2,3] SEDDS typically produce opaque emulsion with globule size range between 100 and 300 nm,[4] whereas the globule size produced by SMEDDS is below 100nm. Microemulsions form spontaneously and deliver the drug in a solubilized form. Furthermore, the drug is rapidly dissolved and absorbed across the intestinal membrane due to its large surface area and rapid dissolution.[1]

Since fine oil droplets of emulsion can pass immediately from the stomach and distribute uniformly throughout the GI tract, so they minimize irritation typically experienced during prolonged contact with bulk drugs. Compared to simple oily solutions, SEDDS provide a large surface area between oil and water, which promotes partitioning of the drug between the two phases. These systems may therefore provide more reproducible plasma concentration profiles and improvement in absorption rates for lipophilic drugs whose oral absorption is dissolution limited. SEDDS formulations have also attracted attention for improving the bioavailability of compounds classified as Class II under the Biopharmaceutical Classification System (BCS).[5] The self-emulsification ability of the formulation is determined by various formulation parameters including, concentration of surfactant in mixture, relative proportion of oil to surfactant, polarity of both oil the phases in emulsion, resulting globule size, and charge. Self-emulsification ability in turn determines the efficiency of formulation regarding oral absorption.

For oral administration, generally SEDDS are prepared in the liquid state and then filled in either soft or hard gelatin capsules. In terms of production costs, drug stability, compatibility with capsule shells, leakage, and precipitation, these liquid dosage forms often have some drawbacks.[6] The creation of several solid self-emulsifying (SE) dosage forms, such as self-emulsifying tablets and pellets, have been investigated in order to address

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these problems, including the desirable inclusion of liquid SEDDS into solid dosage form.[7,8]

In pharmaceutical industries, formulation scientists are very interested in pellets due to their advantages over traditional solid dose forms. These benefits include improved bioactive safety and efficacy as well as versatility in developing and optimizing the dosage form. It is the fact that pellets disperse/distribute readily and equally throughout the gastrointestinal tract. As a result, there is an increase in drug absorption, which lowers the fluctuations in plasma levels and reduces the incidence of side effects. Because of this, drug absorption is increased; resulting in decrease in peak plasma fluctuations reducing potential side effects. Pellets, on the other hand, diminish intra- and inter-subject variability of plasma profiles, which increases the safety and effectiveness of the medication. They also reduce differences in gastric emptying rates and overall transit duration.[9] Additionally, taking pellets prevents the dose dumping effect, which is a major factor in high local drug concentrations, as well as discomfort brought on by some active ingredients.[10]

The most widely used techniques for manufacturing pellets in the pharmaceutical industry are extrusion/spheronization, solution-suspension layering, and powder layering. Recent years have seen the preparation of pellets containing self-emulsifying mixture with microcrystalline cellulose and lactose through extrusion/spheronization or wet granulation in high-shear mixers.[11,12] Controlling the *in vitro* release of drugs from such pellets could be achieved by film coating of the pellets with an appropriate polymer.[13] Research on the development of solid self-emulsifying systems is expanding, but there are very few publications on the topic.[11,14,15] Compared to other approaches, the extrusion/spheronization technology has significant technological advantages. Extrusion/spheronization technique results in spherical, uniformly packed pellets with a narrower size distribution, good flow characteristics, and minimal friability.[16] Extrusion/spheronization technique is the preferred way for creating pellet-based dosage forms because of these benefits, and this technology can be successfully used to combine the benefits of SEDDS with pellets. High lipid loads usually make it challenging for formation of self-emulsifying pellets.

The effective development of an ideal SEDDS formulation depends on the selection of the constituents, including oil, surfactant, and cosurfactant, and a proportion of these constituents that is well-balanced. The experimental designs have been extensively utilized for developing effective formulations.[17] Based on conventional one-factor-at-a-time methods, the best proportions of SEDDS components have been determined. But these techniques are not only labor-intensive, time-consuming, and ineffective; they frequently also give insufficient information to examine the impact of each component and their potential correlations.[18,19] Statistical optimization tools based on experimental designs including, factorial, Box-Behnken, central composite and mixture designs have been widely used to evaluate the effects of individual variable and their interactive effect on a product or process.[20-22] The D-optimal mixture design is one of the preferred response surface methodologies for optimizing the relative proportion of components within a mixture as it reduces the variance associated with the evaluation of model coefficients and produces the effectively subset by accounting for the criteria for enhancing information matrix determinants.[1,23] Additionally, D-optimal mixture design considers the individual and interactive effect of proportion of components within a mixture keeping fixed weight of total mixture.[1]

The objective of this study was to formulate and optimize the castor oil containing self-emulsifying pellets. The relative proportion of oil, surfactant, and cosurfactant in a self-emulsifying pellet formulation was optimized using D-Optimal Mixture Design. The resulting batches were evaluated for dispersion time, globule size and polydispersity index and design space was obtained to understand the range of critical variables.

MATERIALS AND METHODS

Materials

Castor oil was procured from Research Lab Fine Chem industries, Mumbai. Cremophore EL was received from BASF (Ludwigshanfen, Germany). Lactose, starch and HPMC (E50 LV) was provided from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Pre-formulation studies

Selection of surfactants

Selection of surfactant was done based on its ability to emulsify the castor oil. Castor oil was added dropwise to 15% aqueous solution of tween 80, tween 20 and Cremophor EL by vortexing until turbidity was obtained. The amount of oil required to make the surfactant solution cloudy was compared and the surfactant that can emulsify maximum concentration of castor oil was selected.[24]

Screening of co-surfactant

For the selection of co-surfactant, a method developed in our laboratory was used. Briefly, each co-surfactant (Propylene glycol and polyethylene glycol 400) was mixed with selected surfactant in the ratio of 1:1, 1:2 and 2:1 (Smix). This Smix was blended with oil in ratio 9:1 (Smix: oil). The mixture (0.5 g) was then diluted by 20 ml distilled water using vortexing.Globule size of resulting dispersion was then recorded. The co-surfactant showing lowest globule size (less than 100 nm) was selected for further study.

Table 1: Composition of solid self-emulsifying pellet.

Name of ingredient	Amount (%w/w)	Role
Liquid SEDDS	30	Self-emulsification system
Corn starch	5	Disintegrating agent
Microcrystalline cellulose	37.33	Pelletization aid
Lactose	18.67	Diluent
Hydroxy propyl methyl cellulose	5	Binder
Isopropyl alcohol	q.s.	Solvent

Preparation of castor oil containing self-emulsifying pellet

Preparation of Self Emulsifying Pellets by Extrusion/ Spheronization

Considering the emulsification ability, Castor oil, Cremophore EL, and PEG 400 were selected for preparation of liquid SEDDS. The preparation of liquid SEDDS involved mixing of castor oil (Oil), Cremophore EL (Surfactant) and PEG 400 (Co-surfactant) with magnetic stirring until formation of isotropic mixture. The pellets were prepared by the extrusion spheronization technique. The pellets were formed by mixing fixed proportion of liquid SMEDDS (30%) with other excipients (70%) which were mixture of cornstarch, lactose and Microcrystalline cellulose. The lactose, cornstarch and microcrystalline cellulose were mixed in a mortar and the liquid SMEDDS formulation was adsorbed on this powder blend. Hydroxy Propyl Methyl Cellulose in isopropyl alcohol was used as binder solution for formation of wet mass. The wet mass was passed through sieve no. #16 to obtain extrudates which were spheronized using a cross hatch geometry frictional plate (2mm size) in Shakti Lab Spheronizer (India) at rotation speed of 850 rpm for 5 min.[6] The moist pellets were dried in vacuum oven (Being, DZF-6032) at 50°C for 3 hr. The composition is shown in Table 1.

Experimental design for optimizing castor oil containing self-emulsifying pellets

In a classical mixture design, random selection of levels is not done since it helps to optimize the relative proportion of constituents from all the possible proportion of component within the constraint. The total of all the component in a mixture is one. A computer-aided design method known as D-optimal design increases the definite information matrix while reducing the generalized variance. The levels of constraints of component in mixture were chosen through preliminary tests, which evaluated the mixtures capacity to construct self-emulsifying systems.

For the optimization of composition of Self-emulsifying pellet formulation D-optimal mixture design was used. Three different components were used as independent variables in this design. The concentrations of different component of formulation were set within range viz, 30%–70%, of Castor oil (oil; X_1), 10%–60% of Cremophore EL (surfactant; X_2), and 10%–60% of PEG 400 (cosurfactant; X_3) respectively. In every experiment, the concentrations of these three components added up to 100%. The optimization was carried out based on the responses viz., Dispersion time (Y_1), Globule size (Y_2) and polydispersity index (Y_3). To develop and evaluate experimental run, Design-Expert Software version 10 (Stat-Ease Inc, Minneapolis, MN, USA) was used. Sixteen experimental runs were suggested by design, which included factorial points (high and low level from the constraints on each factor), centers of edges, and an overall center point. Mathematical models were obtained after data processing by application of ANOVA.[1]

Characterization of castor oil containing self-emulsifying pellets

Micromeritic properties

According to USP, standard procedure, different micromeritic characteristics such as bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose of pellet were calculated.[25]

Dispersion time

The time required to disperse 0.5 g pellets in 100 ml HCl at 37 ± 0.5°C to form a solution using magnetic stirrer was noted as dispersion time. The resulting emulsion was further evaluated for globule size and polydispersity index.

Emulsion globule size analysis and polydispersity index

Analysis of globule size and polydispersity of nanoemulsion was performed using particle size analyzer (Horiba, SZ 100, Japan) based on dynamic light scattering. The sample was placed in cuvette and light scattering was observed at a 90° angle at 25°C temperature. The mean globule size and size distribution was obtained along with polydispersity index.

Field Emission scanning electron Microscopy

The morphology of solid pellets for the optimized castor oil containing SEDDS formulation was observed using a field emission scanning electron microscope (Nova NanoSEM NPEP303, Germany) with 10 kV acceleration voltage.

RESULTS AND DISCUSSION

Selection of surfactant

Surfactants play a major role in performance of SEDDS. The formulation should immediately disperse upon dilution by gastrointestinal fluid just by gentle mixing. Considering the non-toxicity of nonionic surfactants and their GRAS status (generally recognized as safe), Cremophore EL, Tween 20 and

Tween 80 were screened. Castor oil was soluble in Cremophore EL at 231±0.83 mg/mL, in Tween 20 at 189±0.650 mg/mL and in Tween 80 at 14.6±0.650 mg/mL as shown in (Figure 1). The results demonstrated greater emulsification ability of Cremophore EL compared to Tween 20 and Tween 80 for the castor oil and hence was selected for the formulation.

Selection of cosurfactant

Selection of cosurfactant was based on its ability to yield a lower globule size. From (Figure 2) it is evident that propylene glycol as cosurfactant in different ratio with surfactant resulted in globule size of 830nm (1:1), 917 nm (1:2) and 1013 nm (2:1) respectively. Polyethylene glycol 400 resulted in globule size 85.8nm (1:1), 356.2 nm (1:2) and 361.9 nm (2:1) respectively. Considering the lower globule size with PEG 400 at 1:1 ratio (S: CoS), it was selected as co-surfactant over polyethylene glycol.

Optimization by D-optimal mixture design

Table 2 indicates various independent variables *viz.* Castor oil (X_1), Cremophore EL (X_2), and PEG 400 (X_3) selected for study. To evaluate performance of self-emulsifying pellets, various responses such as the dispersion time (Y_1), globule size (Y_2) and polydispersity index (Y_3) were selected. Table 3 indicates result of 16 batches from design wherein, the dispersion time (Y_1) ranged from 14 sec to 122 sec, globule size (Y_2) ranged from 94.06 nm-839.73 nm and polydispersity index (Y_3) ranged from 0.2323 to 1.5826. All the responses were fitted to suggested mathematical models for linear regression analysis. Various statistical parameters, including the squared correlation coefficient (R^2), adjusted R^2 values, sequential *p*-value, and lack of fit *p*-value, suggested that the linear model was the most appropriate mathematical model for the dependent variables Y_1 and Y_2, while a cubic model was recommended for the response Y_3. Nearby values of R^2 and adjusted R^2 (difference less than 0.2) suggested good model fit. For Y_1, Y_2, and Y_3, the sequential *p*-values were 0.0594, 0.0351, and 0.0300, respectively. The model terms are considered significant when the sequential *p*-value is less than 0.05. An adequate model fit is indicated by a lack of fit *p*-value >0.1. The responses Y_1, Y_2, and Y_3 had a lack of fit *P*-value was 0.0011, 0.5269, and 0.8340, respectively. In this experiment for dispersion time (Y_1) a sequential *p*-value was greater than 0.05 and lack of fit value was less than 0.1 indicating model terms were not significant. For globule size (Y_2) and polydispersity index (Y_3) model terms were significant. Additionally, the suggested model's suitability was verified and resulted in normal plots of residuals (Figures 3A, 3B and 3C).

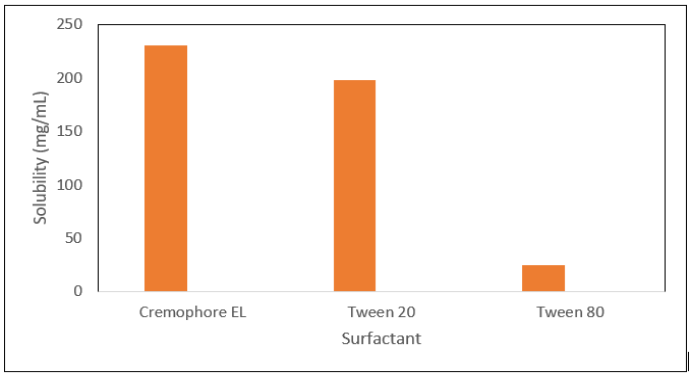

Figure 1: Solubility of castor oil in various surfactant.

Influence of independent variables on dispersion time

Equation 1 was obtained from multiple regression analysis and indicates the relationship between proportions of components and dispersion time (Y_1). Table 4 shows the findings of the analysis of variance for dispersion time (Y_1).

$$\textbf{Dispersion Time } (Y_1) = +23.19*X_1+53.46*X_2+84.24*X_3 \text{ (Eq. 1)}$$

As shown in (Figure 4 A Y_1; left panel) a 3D response surface plot explained the effect of each component and its mixture on dispersion time extrapolated using the plot. As a *p*-value for X_1 and X_2 component was greater than 0.1, it indicated non-significance of effect on dispersion time whereas for X_3, *p*-value less than 0.05 indicated significant increase in dispersion with increase in co surfactant concentration.

The two component mixture graphs in (Figure 4 B; left panel) illustrate the results of altering the ratio of X_1 and X_2 with a constant amount of X_3. With an increase in X_1 (oil) and a reduction in X_2, the dispersion time decreased (surfactant).

A value of desirability 0 denotes an undesired response value, while 1 denotes the response value that is desirable as shown in (Figure 5 A).

Table 2: Variable used in D-optimal Mixture design.

Component	Range (%)	
	Minimum	Maximum
Castor oil	30	70
Cremophore EL	10	60
PEG 400	10	60

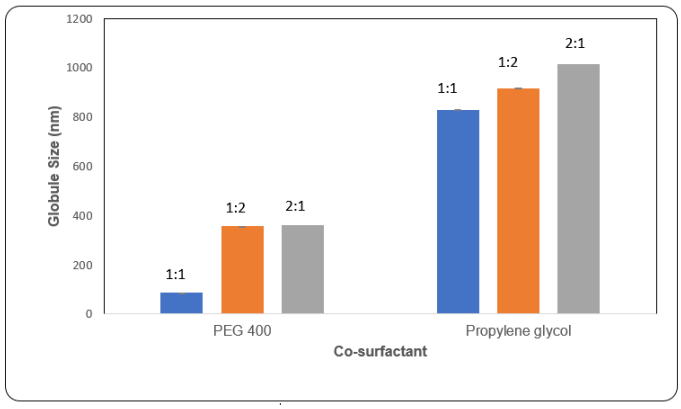

Figure 2: Selection of different co-surfactant on the basis of globule size.

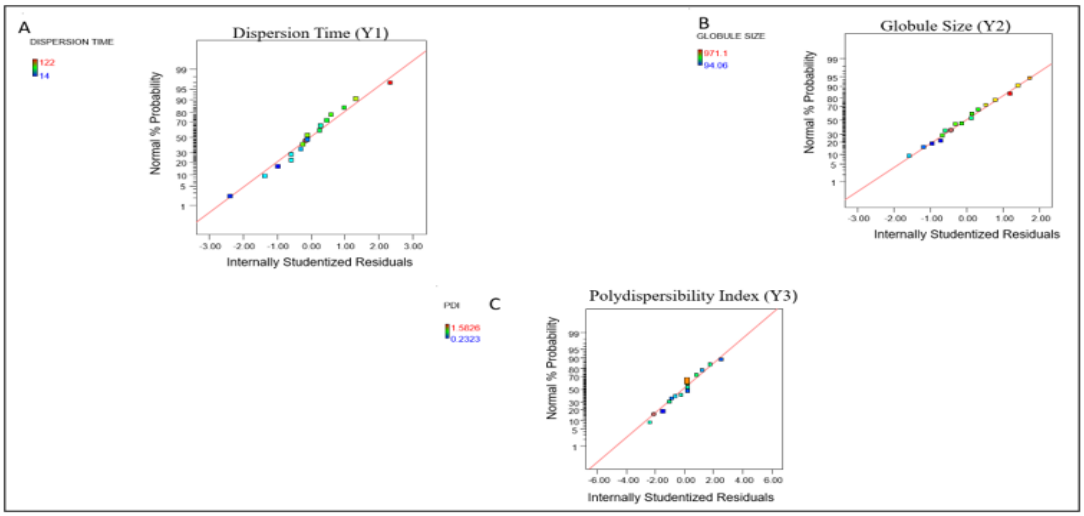

Figure 3: Adequacy of the model for checking the normality of residuals and outliers of the responses dispersion time (A), globule size (B) and polydispersity index (C).

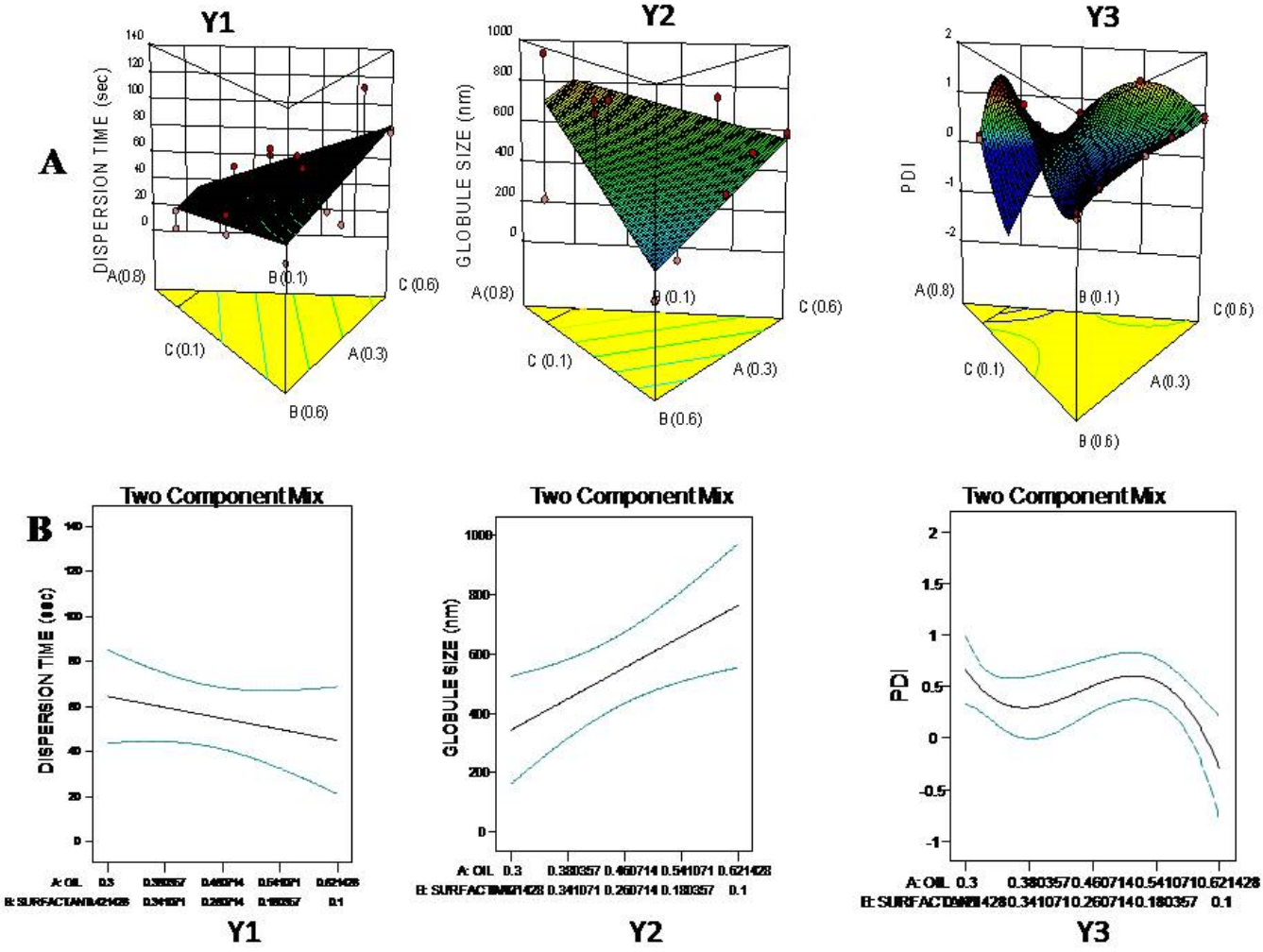

Figure 4: Effect of SEDDS component on response Y1, Y2 and Y3.

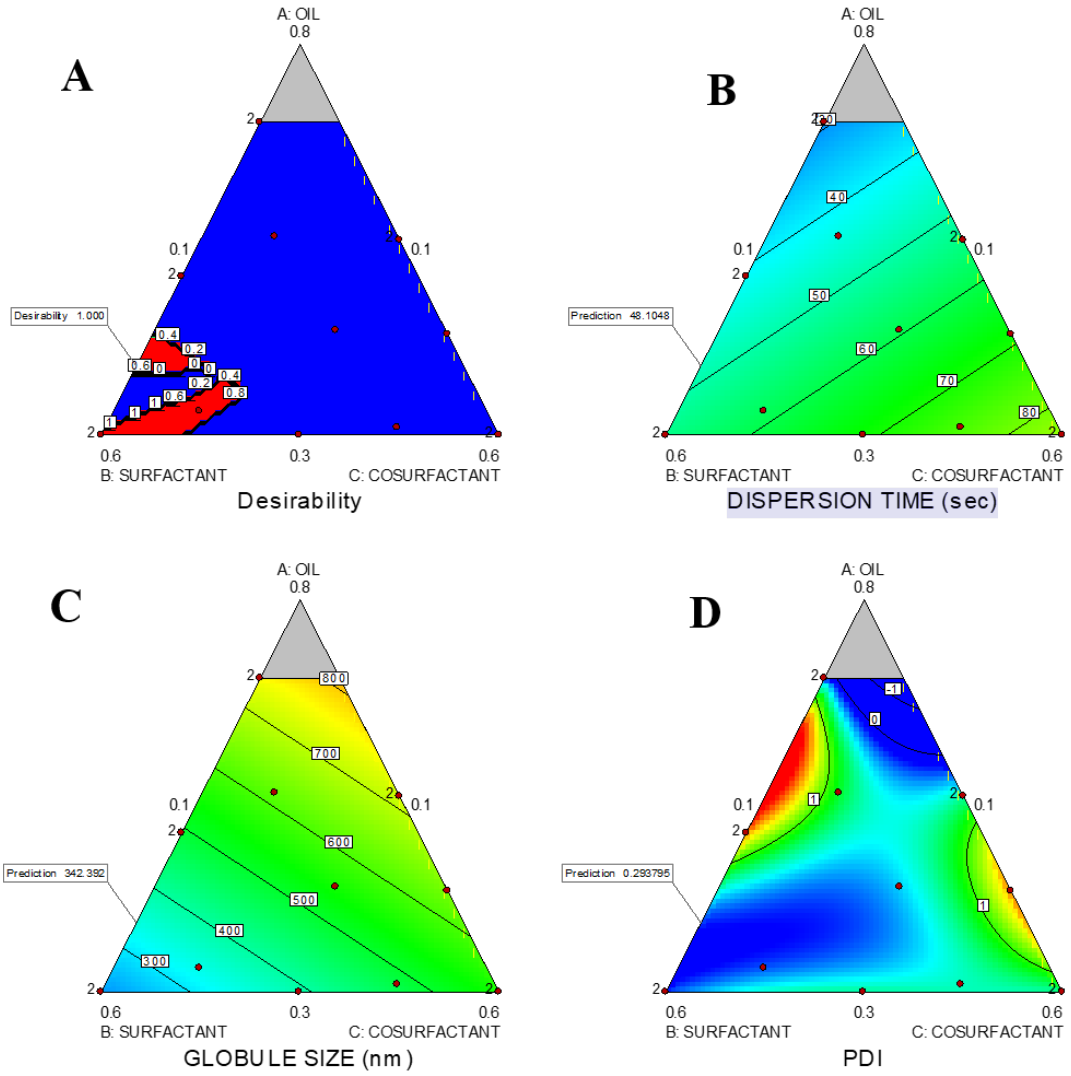

Figure 5: Contour plots for the effect of oil, surfactant and co surfactant on responses. (A-desirability; B-Dispersion time (sec); C-globule size (nm) and D-polydispersity index).

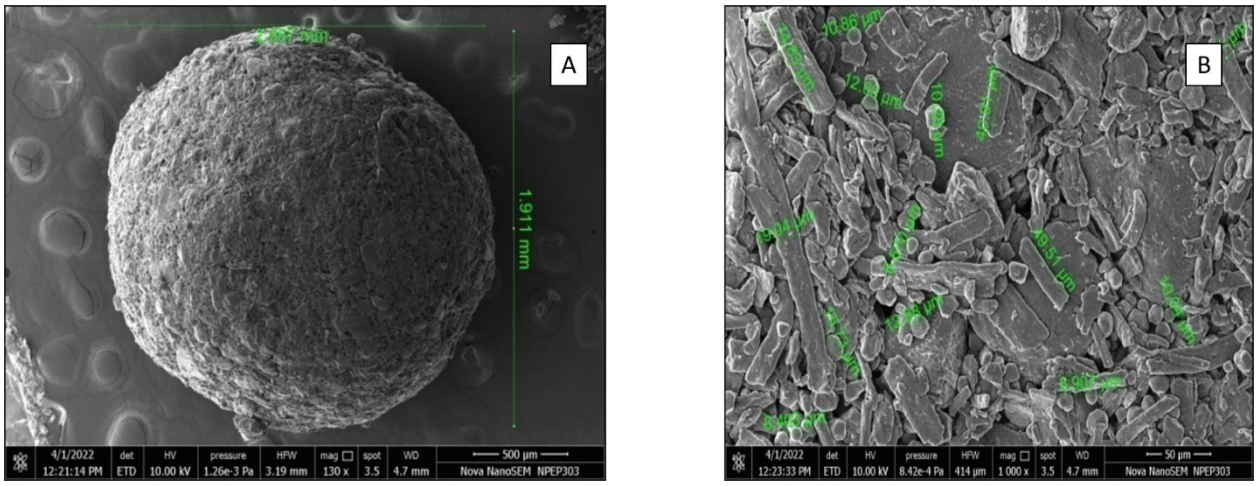

Figure 6: FE-SEM micrographs of the surfaces and cross-section of the castor oil self-emulsifying pellet formulation. (A) (130x) and (B) (1000x).

Table 3: Experimental Matrix for the D-Optimal Design and Results.

Run	Variable			Results		
	Castor oil (%;X1)	Cremophore EL (%;X2)	PEG 400 (%;X3)	Dispersion Time (Sec;Y1)	Globule size (nm;Y2)	Polydispersity index (Y3)
1	42.89	10	47.11	18.9±0.1	745.5±3.2	1.405±0.23
2	30	10	60	79.1±3.1	582.9±4.6	0.782±0.07
3	43.40	23.79	32.79	74.2±2.5	426.3±2.8	0.514±0.13
4	30.97	22.29	46.73	122.1±8.3	544.9±3.8	0.671±0.08
5	70	20	10	14.2±0.1	971.3±9.3	0.447±0.02
6	30	10	60	82.4±0.3	570.1±4.2	0.717±0.18
7	33.05	46.09	20.84	88.2±1.2	180.3±2.3	0.341±0.17
8	54.95	10	35.04	60.1±2.6	582.5±2.9	0.648±0.09
9	30	35.09	34.90	38.2±0.7	418.0±2.7	0.661±0.26
10	70	20	10	27.1±2.1	275.2±6.3	0.380±0.46
11	50.27	39.72	10	34.2±0.2	839.7±8.9	1.582±0.19
12	55.38	25.46	19.15	67.1±1.4	781.1±3.5	0.852±0.45
13	30	60	10	41.3±0.3	94.1±0.9	0.232±0.07
14	30	60	10	41.2±0.8	98.6±1.3	0.353±0.39
15	50.27	39.72	10	48.4±0.2	780.3±2.3	1.213±1.23
16	54.95	10	35.04	65.5±2.3	598.6±4.2	0.726±0.60

Table 4: Analysis of variance for model of the measured responses.

Source	Y1(Dispersion time)			Y2 (Globule size)			Y3 (Polydispersity index)		
	SS	F	*p*-value	SS	F	*p*-value	SS	F	*p*-value
Model	4354.06	3.48	0.00435	4.327	4.47	0.033	2.15	17.13	0.0013
X_1	-	-	0.0649	-	-	0.0287	-	-	-
X_2	-	-	0.8512	-	-	0.0145	-	-	-
X_3	-	-	0.0275	-	-	0.8170	-	-	-
X_1X_2	-	-	-	-	-	-	0.14	33.44	0.0012
X_1X_3,	-	-	-	-	-	-	0.47	22.25	0.0033
X_2X_3	-	-	-	-	-	-	0.31	1.55	0.2593
$X_1X_2X_3$	-	-	-	-	-	-	0.022	24.72	0.0025
X_1X_2 (X_1 - X_2),	-	-	-	-	-	-	0.35	11.14	0.0157
$X_1X_3(X_1-X_3)$-	-	-	-	-	-	-	0.16	0.16	0.7073
$X_2X_3(X_2-X_3)$	-	-	-	-	-	-	2.167	0.68	0.4424
Residual	68.83	-	-	6.293	-	-	9.443	-	-
Lack of Fit	7944.19	24.89	0.132	3.850	0.99	0.5322	0.084	0.049	0.8340

Notes: X_1- oil; X_2-surfactant; X_3-cosurfactant.
Abbreviations: SS, sum of squares.Effect of independent variable on globule size

In (Figure 5B) shows the contour plot for the dispersion time which indicates lower dispersion time (quick dispersion) at higher concentration of oil, lower concentration of co surfactant and medium concentration of surfactant within a mixture.

Notes: (A) Three-dimensional response surface plot for the effect of the component. (B)Two-component mixture plot for the effect of varying ratio of two components with a fixed amount of the other component.

Table 5 shows the findings of the analysis of variance for globule size (Y_2). Globule size (Y_2) was affected by each component of self-emulsifying pellets formulation. Three-dimensional response surface plots show the relationship between the independent variables schematically (Figure 4 A Y2; middle panel). These

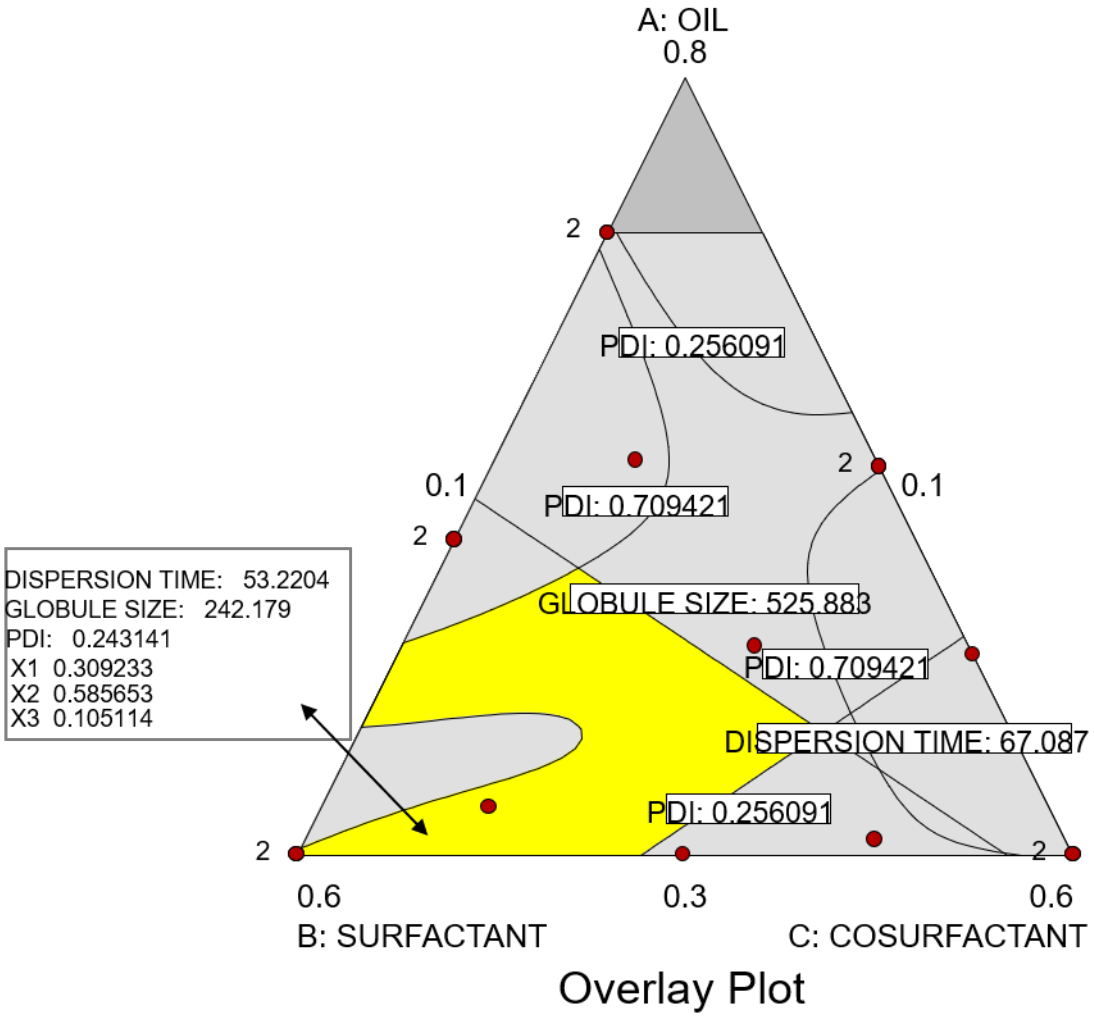

Figure 7: Overlay plot of the optimized castor oil containing self-emulsifying pellets.

findings led to the development of the following linear equation for the globule size: (Y_2).

Globule Size (Y_2) = +879.73.4*X_1+226.78*X_2+553.99*X_3 (Eq.2)

Equation 2 demonstrated a significant effect of all the components of mixture on globule size (Y_2) as evident from *p* value (Table 4). From the contour plot (Figure 5C) and two-component mixture plot (Figure 2B; middle panel) it is evident that showed that the globule size decreased with increase in surfactant concentration and with decrease in oil and co surfactant concentration.

Effect of independent variable on polydispersity index

Table 4 shows analysis of variance for polydispersity index (Y_3). For polydispersityindex, cubic model was found to be the best fit. Three-dimensional response surface plots (Figure 4 A Y_3; right panel) shows the relationship between independent variables. In order to verify the relationship between the independent variables and Y_3, following equation was created on the basis of the analysis of variance.

Polydispersity Index (Y_3) = 4.31*X_1+0.29*X_2+0.75*X_3+15.26*X_1*X_2+10.00*X_1*X_3+0.61*X_2*$X_3$33.65*X_1*X_2*X_3+14.83*X_1*X_2*(X_1-X_2)-0.65*X_1*X_3*(X_1-X_3)+0.93*X_2*X_3*(X_2-X_3)(Eq. 3)

p-value (Prob>F) less than 0.05 indicate significance of model and individual model terms (Table 4). Two component mixture plot (Figure 4B, right panel) and counter plot (Figure 3 D) demonstrated lower polydispersity index value at higher surfactant and oil concentration and lower co surfactant concentration in a mixture.

Characterization of castor oil containing self-emulsifying pellet

Micromeritic Properties of the Pellets

Table 5 indicates micromeritic properties of pellet formulations. The Hausner ratio and compressibility index showed that all

Table 5: Values of micromeritics properties of castor oil containing self-emulsifying pellets.

Run	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Housner Ratio	Angle of Repose (°)
1	0.65±0.01	0.714±0.03	12.46	1.14	26.01
2	0.63±0.02	0.71±0.02	10	1.11	27.31
3	0.56±0.07	0.618±0.02	9.38	1.10	28.32
4	0.55±0.03	0.666±0.01	16.66	1.23	28.27
5	0.58±0.01	0.612±0.02	4.91	1.05	26.45
6	0.62±0.03	0.714±0.04	13.16	1.15	30.65
7	0.58±0.02	0.714±0.03	17.64	1.21	28.31
8	0.52±0.01	0.625±0.02	15.84	1.18	31.12
9	0.58±0.06	0.666±0.02	11.81	1.83	28.13
10	0.51±0.01	0.55±0.01	7.27	1.07	26.31
11	0.67±0.03	0.732±0.02	8.46	1.09	25.23
12	0.62± 0.09	0.769±0.01	12.75	1.23	30.89
13	0.62± 0.03	0.714±0.02	12.46	1.14	26.23
14	0.53±0.06	0.632±0.01	13.52	1.36	28.36
15	0.58±0.01	0.666±0.03	11.81	1.13	28.23
16	0.58±0.2	0.714±0.02	17.64	1.21	29.13

Table 6: Experimental and predicted values for the optimized self-emulsifying drug delivery system.

Response	Experimental Value	Predicted Value	Prediction error (%)
Dispersion time (Sec;Y_1)	51.1±1.96	53.2	-4.35
Globule size (nm;Y_2)	263.2±1.99	242.1	7.92
Polydispersity index (Y_3)	0.251±1.67	0.243	3.18

pellet formulations had good flow properties and compressibility characteristics.

The Field emission scanning electron microscopy

The Field emission scanning electron microscopy analysis for castor oil containing pellets is shown in (Figure 6). The pellets were spherical in shape with rough surface.

Selection of optimized self-emulsifying pellet formulation using desirability function

The criteria of selection of optimized formulation, minimum dispersion time, less globule size and less polydispersity index. The optimization was carried out for Y_1, Y_2, and Y_3 after obtaining the polynomial equations showing the relationship between the responses and independent variables. The overlay plot for the effect of various variables on the three responses is shown in (Figure 7). Overlay plot revealed design space indicating working concentration of independent variables to obtain desired design response. The optimized batch was selected from design space with concentration of 30.92% of X_1, 58.56% of X_2, and 10.51% of X_3 respectively, with the desirability value of 1. The validation of the model was performed by formulating the optimized batch and comparing experimental results with predicted values. To evaluate accuracy and reliability, prediction error values were calculated from predicted and experimental values. The prediction error of less than 10% confirmed model validation (Table 6). Thus, this result demonstrated the accuracy and reliability of the D-optimal mixture design approach, which was used to optimize the castor oil containing self-emulsifying pellet.

CONCLUSION

The D-optimal mixture design was successfully used to develop and optimize castor oil containing self-emulsifying pellet formulation. The optimized castor oil containing SEDDS included 30.92% castor oil (oil; X_1), 58.56% cremophore EL (surfactant; X_2) and 10.51% PEG 400 (co-surfactant; X_3). Model prediction and experimental value showed good agreement with various responses such as, dispersion time (Y_1), globule size (Y_2) and Polydispersity index (Y_3). The optimized formulation resulted in low dispersion time (53 sec), globule size (242 nm) and polydispersity index (0.243). The validation of model confirmed the robustness of formulation to achieve desired result. Extrusion spheronization process was effectively utilized to load up to 30% of self-emulsifying formulation on pellets. Thus, this study provides the basis for further studies wherein the developed system can effectively utilized for delivery of actives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PEG 400: Polyethylene glycol 400.

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