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Optimization of Self-Microemulsifying Drug Delivery Systems (SMEDDS) Using a D-Optimal Design and the Desirability Function

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ABSTRACT D-optimal design and the desirability function were applied to optimize a self-microemulsifying drug delivery system (SMEDDS). The optimized key parameters were the following: 1) particle size of the dispersed emulsion, 2) solubility of the drug in the vehicle, and 3) the vehicle compatibility with the hard gelatin capsule. Three formulation variables, PEG200, a surfactant mixture, and an oil mixture, were included in the experimental design. The results of the mathematical analysis of the data demonstrated significant interactions among the formulation variables, and the desirability function was demonstrated to be a powerful tool to predict the optimal formulation for the explored system.

KEYWORDS Self-microemulsifying drug delivery systems, Emulsion, D-optimal design, Optimization

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, surfactants, and cosurfactants that form fine oil-in-water emulsions (i.e., SEDDS) or microemulsions (i.e., SMEDDS) when introduced into an aqueous phase under gentle agitation (Constantinides, 1995). Whereas SEDDS typically produce emulsions with particle sizes between 100 and 300 nm, SMEDDS form transparent microemulsions with a particle size less than 100 nm (Khoo et al., 1998). Recently, several studies on oral dosage forms, using a self-emulsifying system, have been performed with the purpose of improving the solubility and bioavailability of poorly water-soluble drugs, which have been reviewed by Gursoy and Benita (Gursoy & Benita, 2004). These formulations can be formulated in soft or hard gelatin capsules to produce a convenient unit dosage system, such as the successful oral pharmaceutical formulation of cyclosporine A.

Pharmaceutical optimization of SEDDS and SMEDDS is often based on the construction of a phase diagram to identify the relevant regions of variables.

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Subsequently, a number of various combinations of excipients are tested, and particle size, as well as visual appearance, is evaluated. These results have been reported in a number of studies (Charman et al., 1992; Amemiya et al., 1998; Khoo et al., 1998; Kawakami et al., 2002a; Kawakami et al., 2002b), presented in large tables, and the formulation is selected based on the judgment of the numbers in these tables without any mathematical interpretation. Recently, Gao and coworkers investigated the application of D-optimal design to minimize one response variable, i.e., the population of large droplets after the emulsification process (Gao et al., 2004). Taha and coworkers have used a Box-Behnken design to optimize the dissolution rate in an SMEDDS formulation (Taha et al., 2005). To our knowledge, no report has been used for a statistical method to optimize a combined number of formulation variables for an SEDDS or SMEDDS formulation. The present study, therefore, deals with the optimization of formulation variables to design the best product under conditions of competitive objectives, because interactive effects via a trial-and-error approach are time-consuming and often unsuccessful. Mathematical optimization by means of an experimental design is most helpful in shortening the experimental time. These experiments will lead to summarizing equations of each dependent variable within the optimum space from which all desired combinations of independent variables may be calculated.

The objective of this study is to evaluate the effect of formulation variables on the substance solubility, capsule compatibility, and the particle size of the formed microemulsion. Furthermore, it is also the objective of this study to optimize the product using mathematical equations, balancing the effects on the responses from the formulation variables.

MATERIALS

Crystalline Lu 28-179 free base (1′-[4–[1-(4-Fluorophenyl)-1H-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3H),4′-piperidine] (Lu 28–179) or Siramesine (see Fig. 1) was synthesized at H. Lundbeck A/S as previously described (Moltzen et al., 1995). Cremophor EL was donated by BASF AG (Ludwigshafen, Germany) and Akoline MCM was donated by Karlshamns AB (Karlshamn, Sweden). Ph.Eur-grade Triglycerides, medium-chain, were purchased from Delios V (Illertissen, Germany). Tween 80 and PEG200 were purchased from Sigma-Aldrich (St. Louis, USA).

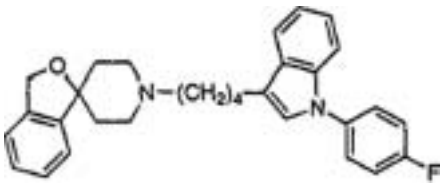

FIGURE 1 Chemical Structure of Lu 28–179.

Acetonitrile (Labscan, Ireland) for the analysis was HPLC grade. The water used in all experiments was obtained from an Elgastat Maxima water purification system (Elga Labwaters, England). All other chemicals were analytical reagent grade.

METHODS

Preparations of SEDDS and SMEDDS

5 g of each formulation was prepared by the addition of variable proportions of glycerides, surfactants, and cosolvent into a 12-mL teflon-lined, screw-capped glass tube. The components were mixed by gentle stirring.

Determination of the Solubility in the Vehicles

Excess Lu 28-179 free base was weighed into glass tubes with teflon-lined caps containing the mixture for examination. The tubes were flooded with nitrogen, and the contents were rotated by a magnet at ambient temperature for 48 h. The tube was then centrifuged at 1000 g for 10 min, and a 100-mg sample was taken and diluted with the mobile phase and subsequently analyzed by high-pressure liquid chromatography (HPLC). The evaluations of the solubility in the formulation mixtures were performed as single-point determinations, whereas they were conducted in triplicate for the individual components of the formulation.

Analysis of Lu 28-179

For analysis of Lu 28-179 solubility in the predetermined vehicles, 100 mg of the supernatant was added to 100 mL of the mobile phase, and the sample was vortexed for 1 min. After sufficient dilution, the solution was analyzed by HPLC as previously described (Christensen et al., 2004), using a Merck-Hitachi model equipped with a pump (C6200), a UV-VIS detector (L4250), a column oven (L-5025), an autosampler

(AS200A), and the software LaChrom 2000 for analysis of the obtained data.

Droplet-Size Analysis

2 mL of each formulation, saturated with Lu 28-179, was added dropwise to 200 mL of purified water at 37°C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm, using a USP XXIII dissolution apparatus 2 (Erweka, Germany). The particle size of the emulsions formed by this procedure was determined by photon correlation spectroscopy using a Zetasizer 3000 (Malvern Instruments, United Kingdom). Light scattering was monitored at 25°C at a 90° angle after external standardization with spherical polystyrene beads (220 ± 6 nm). The dispersed formulations were either measured directly or after dilution to produce the required count rate (50–300 Kcps) to enable accurate measurement. Purified water was used as the dilution medium.

Hard Gelatin Capsule Compatibility

0.45 mL of the individual formulation was filled into hard gelatin capsules (size 1), which were obtained from Capsugel (France). The capsules were subsequently sealed in the CFS1000 (Capsugel, France) using liquid encapsulated microspray sealing (LEMS) technology. The capsules were then placed in desiccators containing saturated salt solutions in the bottom of the container. 20 capsules were stored at 32% RH ($MgCl_2$) and 54% RH (MgN_2O_6) in an open disc, and the mass was determined every week for four weeks. The relative humidity was controlled by a hygrometer (Testo 608-H2, Testo, Germany) in all the desiccators during the study to confirm the intended humidity.

Experimental Design and the Desirability Function

In a classical mixture design where the composition is the factor of interest, the levels cannot be chosen arbitrarily, as all fractions of the components must sum up to unity (Snee, 1971). In a three-component mixture, all possible combinations may graphically be represented by an equilateral triangle. The range over which the components are varied may be restricted, resulting in a delimited area of interest. Such an area is usually an irregular polyhedron delimited by extreme vertices. The most superior design available in this case is a D-optimal design (Lewis & Chariot, 1991). D-optimal design is referred to as a computer-aided design, where the determinate information matrix is maximized and the generalized variance is minimized.

Preliminary experiments were performed to select the levels of constraints of the formulation variables, which were judged on the mixtures' ability to form a self-microemulsifying system. The mixture study was a three-component system: a mixture of Akoline MCM and medium-chain triglyceride (2:1, w/w) (X_1), a mixture of Cremophor EL: Tween 80 (1:1, w/w) (X_2), and PEG 200 (X_3). Based on preliminary investigations the range of each component was selected as follows:

$$20\% \le X_1 \le 60\%$$
$$10\% \le X_2 \le 60\%$$
$$10\% \le X_3 \le 70\%$$

A design expert software package (Modde, version 7.0, Umetri AB, Sweden) was used to generate the design. The software selected a set of candidate points as a base design. These included factorial points (high and low level from the constraints on each factor), centers of edges, constraint plane centroids, axial check point, and an overall center point. The base design consisted of 15 runs. This design allowed for the fitting of a full quadratic model on the four responses. The D-optimal experimental domain and the observed responses are shown in Table 1 and in Fig. 2. Fitting of the quadratic model to the data was performed with Modde version 7.0 (Umetri AB, Sweden).

After the fitting of the mathematical model, the desirability function was used for the optimization. During the optimization of a multivariable formulation, such as an SMEDDS, the responses have to be combined in order to find a product, which the formulator defines as having the desired characteristics. The application of the desirability function combines all the responses into one variable (Harrington, 1965) and leaves the possibility to predict the optimum levels for the independent variable. The individual desirability for each response is

TABLE 1 **Experimental Matrix for the D-Optimal Design and Results**

	Variable factors			Results			
Run	X_1	X_2	X_3	Particle size (nm)	Solubility (mg/g)	Weight change 32% RH (%)[1]	Weight change 54% RH (%)[1]
1	0.2	0.2	0.6	39.1	39.4	3.84	9.78
2	0.2	0.2	0.6	34.5	55.4	3.84	10.07
3	0.6	0.2	0.2	24.8	84.2	1.15	3.55
4	0.2	0.7	0.1	14.9	32.4	0.11	2.55
5	0.2	0.7	0.1	17.7	39.4	0.10	2.54
6	0.6	0.3	0.1	30.7	114.3	0.53	2.43
7	0.2	0.367	0.433	14.5	50.4	2.43	7.10
8	0.2	0.533	0.267	15.0	77.9	1.29	4.98
9	0.333	0.2	0.467	17.6	63.1	2.74	7.36
10	0.467	0.2	0.333	19.2	63.4	1.93	5.47
11	0.333	0.567	0.1	16.4	74.6	0.35	2.60
12	0.467	0.433	0.1	22.6	78.3	0.50	2.52
13	0.4	0.35	0.25	14.6	50.0	1.35	4.32
14	0.4	0.35	0.25	15.3	50.5	1.23	4.23
15	0.4	0.35	0.25	14.5	53.2	1.28	4.32

[1]After four weeks storage at ambient temperature.

normalized by the use of the following methods (Harrington, 1965): the desirability value d_i will have values between 0 and 1. The value of d_i will either be one-sided (calculated after Eq. (1)), or two-sided (calculated after Eqs. (2, 3)):

$$d_i = \frac{Y_{\max} - Y_i}{Y_{\max} - Y_{\min}} \tag{1}$$

$$d_i = \frac{Y_i - Y_{\min}}{C_i - Y_{\min}} \quad Y_{min} \le Y_i \le C_i \tag{2}$$

$$d_i = \frac{Y_i - Y_{\max}}{C_i - Y_{\max}} \quad C_i < Y_i \le Y_{max} \tag{3}$$

where $Y_{\max}$ is the maximum desired value for the response, $Y_{\min}$ is the minimum desired value for the response, Y_i is the experimental result, and C_i is the mean of the upper and lower limit for the two-sided responses.

A desirability value of 0 represents an unacceptable value for the responses, and a value of 1 represents the most desired value for the responses (Harrington, 1965). By maximizing d_i, it is possible to obtain the desirability D of the process and formulation parameters that satisfy the responses.

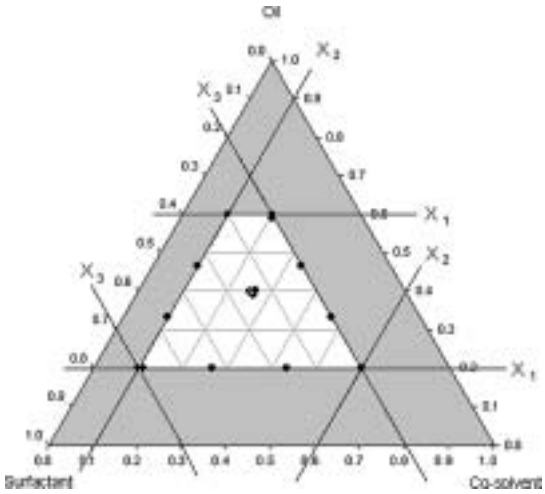

FIGURE 2 **Schematic Presentation of the Experimental Domain (the white area) in the Ternary Diagram, the Constraints, and the Conducted Experiments Within the Domain.**

The cumulated desirability function is defined as the geometric mean of all the d_i and is calculated as shown in Eq. (4):

$$D = \sqrt[n]{d_1 \cdot d_2 \cdot d_3 \cdot \ldots \cdot d_n} \tag{4}$$

The optimum formulation of this study is selected to have a droplet size as small as possible, a solubility ranging between 50 and 150 mg/g, and a weight change at the two storage conditions below 3% to prevent the capsules from sticking together. After the optimization, the validity of the predicted response was investigated by production and evaluation of a SMEDDS with the calculated optimum.

RESULT AND DISCUSSION

Fitting of the Model to the Data

The obtained particle size, the solubility, and the weight change (%) at two different relative humidity levels are presented in Table 1. The relationship between the experimental values for the four responses and the formulation variables were determined by using partial least squares and projection to latent structures (PLS), which allow quantitative relations to be established between multiple variables (Wold et al., 1993). Terms with insignificant *t*-values were excluded, and the effect on the model was judged by the cross-validated correlation coefficient (Q^2). If the value decreased, the descriptor in question was deselected, resulting in a simpler model. This improved the prediction of the four different responses investigated in this study. The resultant equations are given below:

$$\begin{aligned}\text{Droplet size (nm)} = {} & 1.16 + 0.40X_1 + 0.38X_2 \\ & - 0.25X_3 + 1.35X_1^2 + 0.66X_2^2 \\ & + 2.29X_3^2 - 1.09X_1X_2 \\ & - 2.78X_1X_3 - 0.09X_2X_3\end{aligned} \quad (5)$$

$$\begin{aligned}\text{Solubility(mg/g)} = {} & 6.14 - 51.14X_1 + 22.39X_2 \\ & + 50.48X_3 + 331.17X_1^2 \\ & - 169.74X_1X_2 + 207.18X_2X_3\end{aligned} \quad (6)$$

$$\begin{aligned}\text{Weight change 32\% RH (\%)} = {} & 0.76 - 1.12X_1 \\ & - 1.90X_2 + 4.44X_3 \\ & + 2.27X_3^2 + 2.89X_1X_2 \\ & + 0.45X_2X_3\end{aligned} \quad (7)$$

$$\begin{aligned}\text{Weight change 54\% RH (\%)} = {} & 4.40 - 3.64X_1 \\ & - 3.06X_2 + 10.11X_3 \\ & - 0.64X_1^2 - 0.13X_2^2 \\ & + 3.42X_3^2 + 2.37X_1X_2 \\ & - 1.28X_1X_3 - 3.43X_2X_3\end{aligned} \quad (8)$$

where X_1 is the fraction of Akoline MCM:medium-chain triglyderide (2:1, w/w) in the formulation, X_2 is the fraction of a surfactant mixture consisting of Cremophor EL and Tween 80 (1:1, w/w), and X_3 is the fraction of PEG200. The models for particle size and weight change at 54% RH were relatively complex. Table 2 lists the model summary statistics for the four response variables.

Analysis of the Fitted Data

A mean droplet size between 14–39 nm was obtained with these test formulations, demonstrating the formation of very fine emulsions upon dilution. Visually, all the formulations appeared as clear solutions with a slightly bluish appearance within 1 min, indicating the formation of microemulsions. Sensitivity between the formulation components and the droplet size was obtained. However, as the equation for calculating the mean particle size (Eq. (5)) demonstrated, this relationship was relatively complex. As a SMEDDS formulation is a relatively complex formulation system, this finding is not surprising. Taha and coworkers have recently made a relatively complex mathematical description of the droplet size formed after dispersion of an SMEDDS formulation consisting of soybean oil, Capmul MCM-C8, and Cremophor EL (Taha et al., 2005). On the other hand, Gao and coworkers reported a failed attempt to find an adequate mathematical description between the droplet size and an SEDDS formulation consisting of glycerol dioleat, glycerol monooleate, Cremophor EL, and PEG400 (Gao et al.,

TABLE 2 Model Summary Statistics

Response	R^2	R^2-adjusted	Q^2
Particle size	0.913	0.864	0.800
Solubility	0.729	0.559	0.536
Weight change at 32% RH	0.998	0.997	0.994
Weight change at 54% RH	0.997	0.995	0.983

2004). Based on the calculated model for the mean droplet size, the contour plot is shown in Fig. 3. The shape of the 3-D response suggests that the highest sensitivity of the obtained droplet size originates from variations in the fraction of the oil mixture and PEG200, whereas the surfactants, in the range explored, have a more limited effect.

The solubility (mean ± s.d., $n = 3$) of Lu 28-179 in the unmixed vehicle components at 25°C is presented in Table 3. Based on these data, it seems difficult to obtain the desired solubility of 100 mg/g. The solubility data in Table 1, however, demonstrate that the use of statistical design and mathematical tools may be beneficial when optimizing complex formulation systems such as SMEDDS, as synergistic effects and interaction between excipients can be identified and evaluated. Gao and coworkers studied the solubility of cyclosporine A and they reported a significant decrease in the solubility when the proportion between the Cremophor EL and Transcutol was changed (Gao et al., 1998). A similar effect was not observed for the formulation system evaluated in this study. Based on the calculated model for the solubility of Lu 28-179 in the formulation, the contour plot is shown in Fig. 4. The oil mixture provides the largest contribution to the solubility of Lu 28-178. The two other formulation components have more limited effects on the solubility of Lu 28-178.

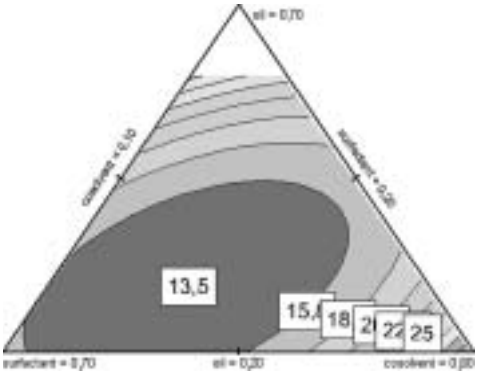

FIGURE 3 2-D Contour Plot of Mean Droplet Size (nm) of the Mixture Study Result.

TABLE 3 Solubility of Lu 28-179 (mean ± s.d.,*n* = 3) in the Pure Excipients Used in the Optimized SMEDDS

Excipient	Solubility (mg/g)
Medium chain triglyceride	49.0 ± 2.7
Akoline MCM	72.5 ± 3.6
Cremophor EL	47.5 ± 2.0
Tween 80	53.0 ± 2.7
PEG 200	21.7 ± 1.0

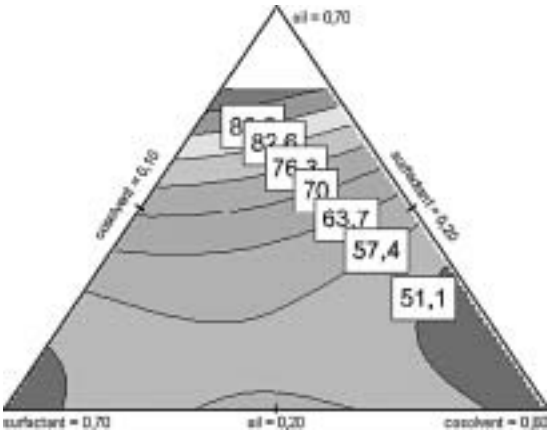

FIGURE 4 2–D Contour Plot of the Solubility of Lu 28–179 of the Mixture Study Result.

The compatibility between the formulation and the hard gelatin capsule was determined as previously suggested by Cadé and Madit (Cadé & Madit, 1996). The relationship between the weight changes of the stored capsules, which is assumed to be equal to the change of water content in the gelatin, is presented in Eqs. (7, 8), and the two contour plots, based on the calculated model, are shown in Figs. 5 and 6. The most hygroscopic excipient in the formulation is PEG200, which is also the formulation component with the most pronounced impact on the weight change of the capsule and hence its stability. As a consequence of this effect, the content of PEG200 should be minimized to avoid changes in the

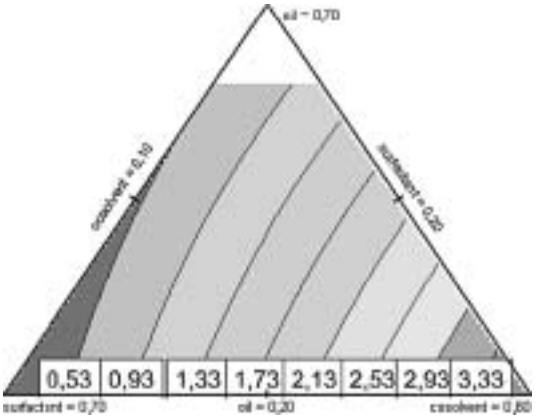

FIGURE 5 2-D Contour Plot of the Weight Change (%) of the Hard Gelatin Capsules Stored at 32% RH for Four Weeks of the Mixture Study Result.

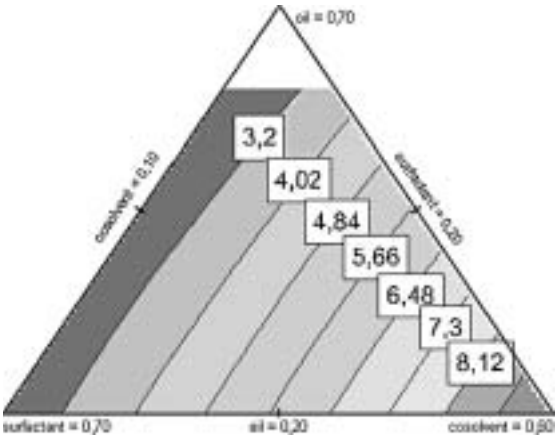

FIGURE 6 **2-D Contour Plot of the Weight Change (%) of the Hard Gelatin Capsules Stored at 54% RH for Four Weeks of the Mixture Study Result.**

composition of the gelatin capsules during the storage period, leading to brittle or sticky capsules.

Optimization of the Formulation Using the Desirability Function

The aim of the optimization of pharmaceutical formulations is generally to find the levels of the variable that affect the chosen responses and determine the levels of the variable from which a robust product with high-quality characteristics may be produced. All the measured responses that may affect the quality of the product should be taken into consideration during the optimization procedure. Furthermore, some of these responses have to be minimized. In this case, these responses comprise the particle size and the weight change of the hard gelatin capsules. Some responses, such as the solubility of Lu 28-179, have to be maximized in order to produce a product of desired characteristics. Using the desirability function, all the defined responses can be combined into one overall response, the overall desirability. As presented in Figs. 3–6, the optimum for different responses varies within the defined formulation range. After the mathematical optimization, the formulation can be characterized further by small-angle X-ray scattering (SAXS) or pulsed field gradient NMR–which is not easy to make, qualitatively–to ensure that the optimized system behaves in a satisfactory manner.

The defined optimum formulation for Lu 28-179 should have a droplet size as small as possible, a solubility ranging between 50 and 150 mg/g, and a weight change at the two storage conditions below 3% to prevent the capsules from sticking together. The results of the desirability analysis are presented in Table 4. Based on Eqs. (5–8), this should give a droplet size of 19.4 nm, a solubility of Lu 28–179 on 75 mg/g, and a weight change of 0.5% and 2.5% at 32% RH and 54% RH, respectively. These calculated values were in close accordance with the experimental results obtained. The experimental results led to a droplet size of 14.2 nm, a solubility of 77.5 mg/g, and a weight change, after four weeks of storage, of 0.5% and 2.5% at 32% RH and 54% RH, respectively. We conclude that these results demonstrate the power of this optimization technique for a complex SMEDDS formulation.

TABLE 4 **Optimum Levels for the Formulation Variables**

Formulation variable	Optimum values (%)
Oil mixture	0.467
Surfactants	0.433
PEG200	0.1

CONCLUSIONS

This study demonstrates a mathematical/statistical approach that can be used to obtain a superior experimental mixture design when the experimental factor space is not a simplex space. In this study, four different responses were measured, including the dispersion characteristics of the formulations upon dilution, the solubility of the compound in the mixtures, and the compatibility of the formulations with the hard gelatin capsule upon storage at two different relative humidity levels. Significant interactions among the formulation components are revealed on the different responses, which, in combination, dictate the total characteristics of the SMEDDS formulation.

Taking the needed compromise for the four different responses into account, the optimal formulation was predicted by the use of the desirability function. This was shown to be a useful approach for optimizing the SMEDDS formulation in question.

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