REVIEW ARTICLE

A Structural Framework for Developing Self-emulsifying Drug Delivery System through Quality by Design Approach

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Abstract

In recent years, drug discovery studies show that more than 40% of new drugs synthesized are having poor aqueous solubility rendering them poorly bioavailable after oral administration. Self-emulsifying drug delivery systems (SEDDS) are the novel lipid-based formulations having the potential to enhance the oral bioavailability of poorly water-soluble drugs which belong to class II and IV of the biopharmaceutical classification system. SEDDS is the isotropic mixtures of oil, surfactant, cosurfactant, and sometimes cosolvent. The presence of surfactant enhances the membrane permeability, whereas medium- and long-chain triglyceride oils promote the lymphatic absorption of the drug. The better performance of SEDDS in terms of improvement in solubility and permeability characteristics has rapidly introduced many SEDDS products into the market and many others in the clinical development phase. Quality by design (QbD) is a regulatory-driven approach, which adopts a multitude of techniques in product development, which lends a controlled and reproducible result, thereby resulting in a formulation which could meet the therapeutic goals. The complexities of the SEDDS formulation and the ingredients involved in the design of experiment and risk assessment techniques based on QbD methodologies are increasingly used in the formulation development of SEDDS. This review provides a summary of the systematic application of QbD concepts in the development of SEDDS for poorly bioavailable drugs.

Key words: Bioavailability, design space, mixture design, quality by design, self-emulsifying drug delivery system

INTRODUCTION

Quality by design (QbD) is a regulatory approach to pharmaceutical development with predefined objectives. QbD emphasizes on product and process control, based on sound pharmaceutical and biomedical sciences and quality risk management. QbD advocates on a thorough understanding of critical factors and process controls affecting the product quality.[1] The critical process parameters (CPPs) and critical material attributes (CMAs) are the factors defining critical quality attributes (CQAs) of the drug product. Design of experiment (DoE) and process analytical technology is the primitive tools that can be used in QbD. In the current scenario, the application of QbD for generic products is wide spread, including identifying and defining the target product profile (TPP), risk assessment, identifying the CQAs of the product, and developing a control strategy for the manufacturing process controls and rigorous monitoring of the process to ensure product quality. Post-process validation, the regulatory filing shall include the defined ranges for all the critical and operating process parameters. Subsequent to the approval, the CQA is monitored to establish the performance of the process which is within the defined ranges and variability.[2] Hence, QbD ensures product quality by controlling the formulation and process variables.[3] The benefits of QbD include improved product design, lowered manufacturing costs, risk assessment, mitigation, and better management of post-approval.

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Received: 11-03-2020
Revised: 18-05-2020
Accepted: 28-05-2020

In recent years, only 60% of the newly discovered drugs were readily soluble in water and remaining are poorly soluble, posing a challenge to formulate them as oral dosage forms, due to their poor dissolution and bioavailability characteristics. The alternative route of administration of these drugs is through parenteral, resulting in increased production cost, poor patient compliance, and toxicity in chronic diseases, and demanding long-term therapy. Self-emulsifying drug delivery system (SEDDS) is a lipid-based drug delivery system (LBDDS) aimed to increase the dissolution of orally administered drugs, majorly biopharmaceutical classification system II class of drugs and to some extent class IV drugs in the gastrointestinal tract (GIT).[4] Ideally, SEDDS is an isotropic mixture of natural/synthetic oil(s), semisolid/liquid surfactant(s), and sometimes cosolvent, which upon introduction into aqueous phase emulsifies to form a fine emulsion.

SEDDS, when released in the GIT, with the aid of GI fluids and the mild agitation of the stomach and intestinal motility, leads to the emergence of fine oil in water (O/W) emulsion.[5,6] The formulations producing oil droplets after emulsification ranging from 100 to 250 nm are referred to as the self-microemulsifying drug delivery system and <100 nm as self-nanoemulsifying drug delivery system, respectively. At present, self-double emulsifying drug delivery systems and supersaturable SEDDS are wide spread in pharmaceutical and agro-based industries. The advances in manufacturing technologies have quickly introduced LBDDS as commercial products into the marketplace with several others in clinical development.[7] The fact that almost 40% of the drugs are poorly soluble implies that SEDDS studies should continue, where many SEDDS formulation is critical to meet the unmet needs in the pharmaceutical market. In the current outlook into the pharmaceutical industry, there is minimal uptake of lipid-based formulations due to empirical development strategies and control process challenges, resulting in few commercially successful drug products in the market. There are various challenges in the lipid-based systems that require more research on the characterization of lipid physicochemical properties and also how lipids minimize plasma profile variability, and formulation categorization framework, understanding typical methodologies by which optimized formulation can be selected for each drug product. Development of SEDDS in a QbD framework will be able to address the challenges in early product development and high-quality SEDDS can be manufactured by the application of mathematical models throughout the manufacturing process.[8,9] Through this review, we made an attempt to understand the concept of QbD and its application in the development of SEDDS for poorly bioavailable drugs.

COMPONENTS OF QBD

QbD is a science and risk-based approach used in pharmaceutical product development. The recent advancement in the pharmaceutical industry, the traditional end-product testing approach, is overtaken by the formulation by design concept.[10] The systematic approach adopted during the product development identifies the manufacturing and process challenges which need to be monitored to deliver the product with consistent quality. The regulatory benefit of QbD in the current scenario is the approval of pharmaceutical products in less time with reduced audit frequency.[11,12]

The key components of QBD are:

1. Definition of quality TPP (QTPP)
2. Identification of CQAs of drug product
3. Identification of CMA
4. Selection of appropriate production process and identification of CPP
5. Establishment of design space
6. Definition of the control strategy.

QTPP

Quantitative surrogate measure for clinical efficacy and safety of the product can be defined as "A prospective overview of drug product quality characteristics, preferably accomplished to ensure the desire quality, taking into account the drug product safety and efficacy." TPP is the basis for the development of the product; it usually signifies components like the labeled use of the product, its safety, and efficacy. QTTP makes sure that the quality characteristics are adequate to ensure safety and efficacy of the product is as promised by the label [Table 1]. In the case of SEDDS, various quality attributes were identified and they are physical appearance, droplet size, polydispersibility index, transmittance, drug release, and apparent permeability of the drug.[13]

CQAs

QTPP essentially helps to identify the CQAs. These are the physical, chemical, biological, or microbiological characteristics of the product which should be within a particular limit to ensure the desired product quality. Quality characteristics such as sterility, purity, dissolution, therapeutic effect, and other patient-specific features such as the specific population and clinical diagnosis attribute the selection of CQAs. CQAs are of different types of examples, include CQAs based on the nature of the drug substance, excipients, and packing materials. The prime CQAs are identified from QTPP based on the severity of harm that may occur to the patient as a result of product failure. At the initial stages of process validation, the identification of CQAs takes place and it is also called as process design stage. During the process design stage, the acceptance limits and ideal ranges for CQAs will be established along with that protocols for measurement, data collection modes, and data analysis process will be materialized. The CQAs considered in the SEDDS development with the proper justification for each quality parameter with the limits are presented in Table 2.

Table 1: Quality target product profile for SEDDS

QTPP elements	Target	Justification
Dosage form	Tablet/capsule	Ease of administration
Dosage type	Lipid-based formulation	Enhancement of bioavailability
Dosage strength	% w/w, unit dose	For the desired therapeutic action
Route of administration	Oral	Most convenient route for patients
Pharmacokinetic parameters	Tmax, Cmax, area under the curve	For ascertaining the minimum effective concentration at the target site and to ensure the rapid onset and efficacy of the product
Stability	As per the conditions of ICH Q1B long-term stability studies	To assess degradatory pattern of the drug and excipients used in the formulation
Drug product quality attributes		
Physical attributes	Product must meet the compendial quality standards	
Droplet size		
Transmittance		
Polydispersibility index		
Zeta potential		
Emulsification efficiency		
Drug content		
Drug release		
Permeability		
Container closure system	Alu-Alu Blister	Acts as permeation and photo barrier

SEDDS: Self-emulsifying drug delivery systems, QTPP: Quality target product profile

Table 2: Critical quality attributes of SEDDS system with justification

Quality attributes of drug product	Target	Critical quality attribute	Justification
Physical attributes			
Color	Acceptable to patient	No	The physical attributes were not directly related to safety or efficacy of the product
Odor			
Appearance			
Droplet size (nm)	<200 nm	Yes	Smaller and consistent globule size is essential for stability and bioavailability of the formulation
Transmittance (%)	>95%	Yes	Transparency of the product ensures the minimization of the droplet size
Poly dispersibility index	Dimension less value (0.1–1)	Yes	The value close to zero indicates homogeneity in the droplet size and ensures the physical stability of the product
Zeta potential (mEv)	Negative value	Yes	The magnitude of the Zeta potential value indicates the stability of dispersion system
Emulsification efficiency(s)	>20 s	Yes	Spontaneous emulsification ensures the fast release of drug
Drug content	As per the target dose	Yes	Ensures safety and efficacy of the product
In vitro drug release (%)	>80% in the target time	Yes	Dissolution will have direct impact on bioavailability
Permeability in 45 min	>80%	Yes	f ≥80%, important for attaining therapeutically effective concentration of drug in the blood

SEDDS: Self-emulsifying drug delivery systems

CMA

The material attributes mean the physical, chemical, biological, or microbiological properties of any input material. The input materials can be raw material, starting material, reagents, solvents, process aids, or active pharmaceutical ingredients used in the manufacturing of pharmaceuticals. The material attributes are quantifiable and should be within appropriate range or limits to ensure desired characteristics in the product. The small changes in the material attributes leading to poor product performance are considered to be critical and need to be controlled in the product development. SEDDS is the isotropic mixtures of oil, surfactant, and cosurfactant/cosolvent. The ideal proportion of the selected lipid, surfactant, and cosurfactant will influence the quality parameters in the SEDDS. Hence, lipid, surfactant, and cosurfactant are considered as the CMAs and to be factored in the DoE. At the same time, the utmost importance to be given for the selection of appropriate excipients for formulation development through DoE. Oils used in the SEDDS preparation are triglycerides such as short-chain triglycerides (SCT), medium-chain triglycerides (MCT), and long-chain triglycerides (LCT). Among the triglycerides, MCTs and LCTs are preferred than SCTs due to their higher solvent capacity for the drug. MCTs are best preferred in case of preparation of nano-sized SEDDS formulation, whereas LCTs are used for those drugs which need to be absorbed through the lymphatic system.[14] The second important ingredient of the SEDDS system is a surfactant. Surfactants act by reducing the interfacial tension between the oil and aqueous phase. The surfactants selected for SEDDS system ideally should be hydrophilic in nature, having a hydrophilic-lipophilic balance (HLB) of more than 10 are preferred due to self-emulsification of SEDDS in the presence of GI fluids for the formation of oil/water (O/W) nano/microemulsion under the mild agitation provided by the stomach and intestinal motility.[15] The cosurfactant helps in improving the fluidity of the interfacial membrane, thereby reducing the total amount of surfactant required in the formulation of SEDDS. The cosurfactant should be lipophilic in nature, having an HLB value <8 are chosen in the preparation of SEDDS. These are some of the basic criteria to be considered in the selection of SEDDS components and all these characteristics of the excipients are depicted in the Ishikawa diagram [Figure 1].

CPP

CPPs are process variables which have an impact on product quality. To ensure predetermined qualities in the product, all the manufacturing operations should be monitored and controlled throughout the manufacturing. The process parameters having a higher impact on the CQAs are considered as most critical; hence, it needs to be identified and prioritized. The prioritization can be done with the help of prior knowledge and initial experimental data gathered about the entire process. The manufacturer should thoroughly identify such factors and set the acceptable range for the factors. Operating conditions within the desired range considered safe and effective in attaining the CQAs; otherwise, it leads to product failure. In case of SEDDS, the preparation process involves mixing of drug with the preconcentrate of oil, surfactant, and cosurfactant mixture. The CPPs involved in SEDDS manufacturing are stirring time, temperature, and speed utilized during the preparation and further the mixture sonicated to enhance the homogenization process. Stirring and sonication process parameters are presented in the Ishikawa diagram [Figure 1]. Based on the prioritization of risk associated with process parameters will be factored in the design.

Risk assessment

Risk assessment is the structured approach that helps in the identification, assessment, and prioritization of risks involved in the product development.[16] The three main components of risk assessment are (a) risk identification: Based on the prior knowledge or historical data available can be used thoroughly to identify the potential hazards associated with the system; (b) risk analysis: The assessment of the risk associated with the recognized hazards; and (c) risk evaluation: Significance of the risk will be evaluated with the help of qualitative and quantitative scale. Both qualitative and quantitative methods are utilized for the risk assessment. Fishbone or Ishikawa diagram is one of the qualitative tools used for the identification of the main causes and sub causes affecting the product performance. The risk estimation matrix is the qualitative model used to represent the potential risks associated with the material attributes and the process attributes having a

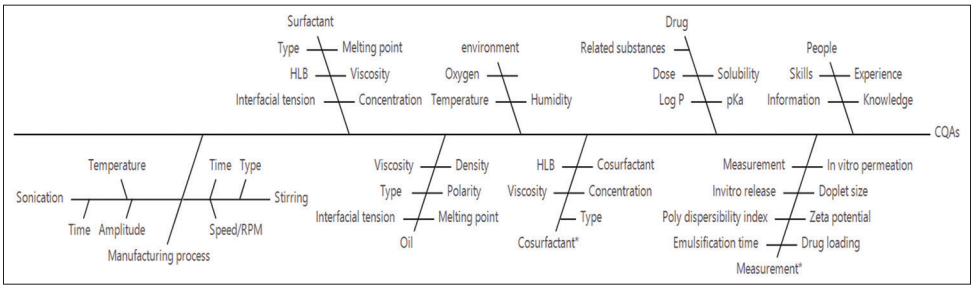

Figure 1: Ishikawa diagram depicting the causes and sub causes affecting quality characteristics of self-emulsifying drug delivery systems

strong influence on the CQAs of the product [Table 3]. Each factor will be assigned risk grades of low, medium, or high as per the priority. Failure mode and effects analysis (FMEA) is a commonly used quantitative risk assessment tool, helps to assess systematically the degree of risk associated with various parameters. Failure modes detect any errors and defects related to the process, material, design, or equipment. It also helps to rank these based on their importance. The risk priority number (RPN) obtained through the FMEA helps in determining which failure mode requires corrective action and which risks are acceptable. The RPN calculated by multiplying severity by occurrence and detectability. The prioritization of the risk is done through the size of the RPN number obtained [Table 4]. FMEA model utilizes ranking values ranging from 1 to 10. Product knowledge, clinical, and non-clinical expertise regarding product quality is essential for making these assessments. Once the significant material attributes and process parameters are identified, the high level of process understanding can be done through the DoEs or with the help of mathematical models.

DoE

DOE is the structured statistical concept applied successfully in pharmaceutical product development. The key steps involved in the DoE are presented in Table 5. The regulatory guidelines from Food and Drug Administration, International

Table 3: Risk estimation matrix

		Drug product CQAs							
		Droplet size	**Transmittance**	**PDI**	**Zeta potential**	**Emulsification efficiency**	**Drug content**	**Drug release**	**Permeation flux**
Material attributes	**Drug**								
	Dose	Low	Low	Low	Low	Low	High	High	High
	Solubility	Medium	Medium	Low	Low	Low	High	High	High
	Log P	Medium	Low	Low	Low	Medium	Medium	Medium	High
	pKa	Medium	Medium	Low	Low	Medium	Medium	Medium	High
	Oil/Lipids								
	Interfacial tension	Medium	Medium	High	High	High	Medium	High	High
	Polarity	Medium	Medium	High	High	High	Medium	High	High
	Lipid concentration	High	High	High	High	High	High	High	High
	Viscosity	Medium	High	Low	Low	Medium	Low	Medium	Low
	Lipid composition	High	High	High	High	High	High	High	High
	Surfactant								
	Concentration	High	High	High	High	High	High	High	High
	Viscosity	Medium	High	Low	Low	High	Low	Low	Low
	HLB	High	High	High	High	High	High	High	High
	Melting point	Low	Low	Low	Low	Low	Low	Low	Low
	Cosurfactant								
	Viscosity	Medium	Medium	Low	Low	Medium	Low	Low	Low
	Concentration	High	High	High	High	High	Medium	Medium	Medium
	HLB	High	Medium	Medium	Medium	High	Medium	Medium	Medium
Process parameters	**Stirring**								
	Time	High	Medium	High	Medium	High	High	Medium	Medium
	Speed	Medium	Medium	High	Low	Medium	High	Medium	Medium
	Temperature	Medium	Medium	Medium	Low	Medium	High	Medium	Medium
	Sonication								
	Time	High	High	High	Low	High	High	Medium	Medium
	Temperature	Medium	High	Medium	Low	High	High	Medium	Medium
	Amplitude	Medium	High	Medium	Low	Medium	Medium	Medium	Medium

Table 4: FMEA variable with the score

FMEA variables	Frequency of incidence	RPN score
Severity	Very low impact	1
	Unimportant failure	2–3
	Average importance for the failure	4–6
	Critical failure and causes harm to patient	7–8
	Significant harm to patient because of critical failure	9–10
Occurrence	Very less possibility	1
	Failure might happen	2–3
	Failure happens time to time	4–6
	Recurrent failure	7–8
	Failure will occur	9–10
Detection	Failure detection is ensured	1
	High probability of failure detection	2–3
	Failure detection very not certain	4–6
	Low possibility of failure detection	7–8
	Failure detection is highly unlikely	9–10

Risk priority number = Severity X occurrence X detectability

Table 5: Different steps in DoE

Key steps in DoE	Description
Describe	The CMAs, CPPs along with that CQAs (responses) to be identified to determine the actual goal of the experiment. The main goal of the experiment is to construct a predictive model.
Specify	Assumed model to be specified and contains all the effects which need to be estimated and describe the relationship between variables.
Collect	The experiments will be conducted to collect the required data. Generated data help to fit the model. Based on the goal, the model helps to identify the active effects as well as the optimal settings.
Fit	The experimental data to be fit to the assumed model and, if required, refine the model.
Predict	The refined model can be used to address the experimental goals. The factors having a strong influence on the response are identified and their levels will be identified to optimize the response.

CMAs: Critical material attributes, CPPs: Critical process parameters, CQAs: Critical quality attributes, DoE: Design of experiment

Conference on Harmonization (ICH), encourage statistical concepts to product quality and conformity. The ICH guideline Q8 (R2) has described the science-based approach to product development. DOE describes mathematically the relationship between the independent factors (X) affecting the dependent variables (Y) and expressed as $Y = f(X_n)$. Figure 2 depicts the systematic development of high-quality SEDDS system by understanding the design. DOE takes into account of all the input variables simultaneously, methodically, and proficiently for the development and optimization of the product. DOE enables the identification and quantification of input variables alone as well as interaction effects of multiple variables and their significant effect on the output variables.[17] In a QbD-based DoE development, screening design, response surface design, and mixture designs are employed. Experimental planning with the screening design enables to evaluate a large number of factors in a small number of experimental runs. In these designs, all the factors are tested to find out the most influencing factor among various CMAs and CPPs. Various screening experimental designs used, such as fractional factorial, Plackett–Burman, are usually used. After the screening experiments, the significant variables having a prominent influence on the product CQAs are explored in the optimization stage and identify the optimal ranges for CMA and CPP. The optimization can be done by various experimental designs such as response surface design, central composite design, and Box-Behnken design. Table 6 summarizes some of the research work related to SEDDS development by the application of DoE concept.[18-27]

Mixture design

Pharmaceutical formulations are prepared by blending two or more ingredients together. Proportions of each ingredient must be determined to attain the optimal desired product characteristics. Mixture design is a type of response surface method that applies statistical concepts to design experiments with an objective to optimize the response for obtaining the required quality.[28] It is effective in determining the proportion of ingredients necessary for the blend. The standard mixture designs used in pharmaceutical product development are Simplex lattice design and Simplex centroid design.[29] When factors are subjected to additional constraints such as minimum and maximum value for each component of the mixture, the design is referred to as constrained mixture design or extreme vertices design.[30]

Assumptions and purpose of mixture design

The design assumes, the response depends on the relative proportions of the ingredients present in the mixture and not on the total amount of the mixture. It can be used to predict the response for any mixture or combination of ingredients empirically.[31,32] The influence of each component singly and in combination with other components on the response can be obtained. In a mixture, experiment factors cannot be varied

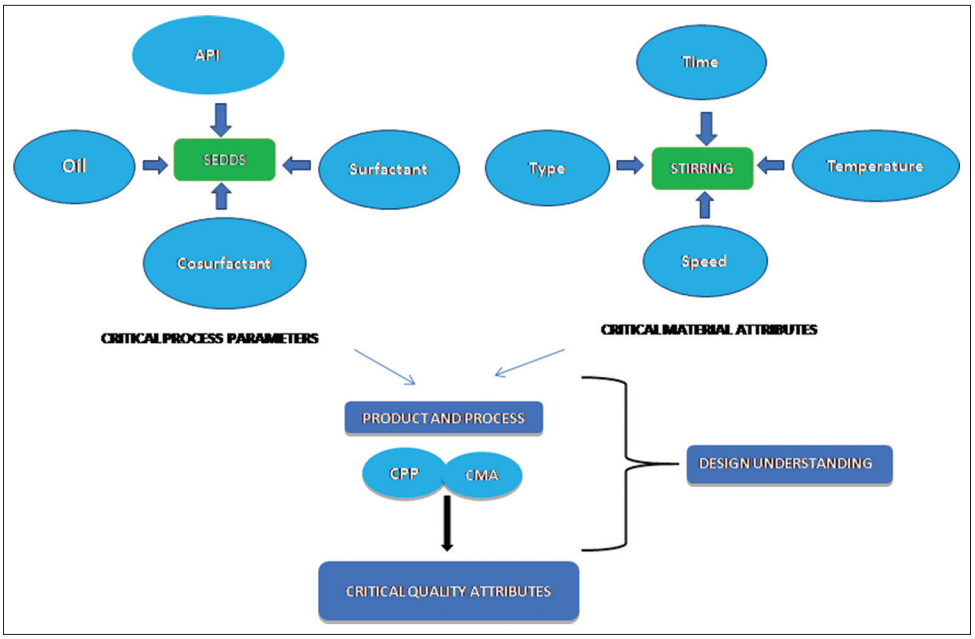

Figure 2: Design understanding – systematic representation for the development of self-emulsifying drug delivery systems

Table 6: Examples of DoE application in the development of SEDDS

Formulation	Experimental design	Independent variables	Dependent variables	References
Docetaxel SEDDS	4-factor,2-level D-Optimal design	Capryol 90,Vit E TPGS, Gelucire 44/M, Transcutol HP	Solubility mg/ml, mean droplet size in nm	[18]
Etodolac SNEDDS	Box-Behnken design	Phosal 53 MCT, Labrasol, PEG 400	Emulsification time in seconds, % transmittance, relative turbidity	[19]
Nelfinavir mesylate-SMEDDS	D-Optimal mixture design	Maisine 35-1, Tween 80, Transcutol HP	Droplet size in nm, PDI, Self-emulsification time in seconds, viscosity, firmness	[20]
Lovastatin S-SNEDDS	Taguchi design and face-centered cubic design	Nikkol-HC050, Lutrol-F127, Capmul MCM	Droplet size in nm, Emulsification time in seconds, % drug release in 15 min	[9]
Docetaxel S-SEDDS	D-optimal design	Oleic acid, tween 80, PEG 400	Emulsification time in seconds, % cumulative drug release at 30 min	[21]
Tadalafil SNEDDS	Full mixed factorial design	Tween 80, labrasol, span 80,transcutol, Labrafil M199	% transmittance	[22]
∞-tocopherol Self emulsified adjuvant system	Mixture design	Polysorbate 80, squalene, ∞-tocopherol	Mean droplet size in nm, PDI	[23]
Lovastatin- stabilized SEDDS	3-level factorial design	Sodium alginate, hydroxypropyl methylcellulose	% drug encapsulation efficiency	[24]
β carotene SNEDDS	Simples lattice design	Olive oil, Tween 80, PEG 400	Emulsification time, transmittance	[25]
Apigenin-SMEDDS	Simplex Lattice Design	Cremophor EL, Tween 80, Transcutol HP	Solubility of Apigenin in SMEDDS mg/ml, mean droplet size in nm	[26]
SNEDDS with monoacyl phosphatidylcholine and Kolliphor RH 40	D-optimal design	Medium-chain glycerides fraction, Lipoid S LPC 80, Kolliphor RH 40, ethanol fraction	Mean droplet size in nm	[27]

DoE: Design of experiment, SEDDS: Self-emulsifying drug delivery systems

independently of one another. The mixture components are the proportion, which eventually sums to one; hence, the feasible region of the mixture design takes the form of a simplex. The 3-factor designs can be observed through 2-D triangular graph and 4-factor designs can be visualized with 3-D tetrahedron. The selection of appropriate mixture design depends on the number of factors and interactions to be studied, the statistical validity and effectiveness of each design, and the ease of execution and cost and time constraints associated with each design.

Variables in mixture design

Mixture design is used in pharmaceutical product development when the factors are a proportion of blend and expressed as fractions which sum to 1 or 100%. SEDDS is the homogenous mixture of different proportions of oil, surfactant, and cosurfactant system. The independent variables [Table 7] to be factored in the design are CMAs such as oil, surfactant, and cosurfactant.[33] The CPPs and their impact on the dependent variables cannot be devised through the mixture design and they were not considered in the model design because the method of preparation of SEDDS is simple; hence, CPPs will be having minimal contribution toward the product variability as evidenced by risk assessment. The dependent factors considered in the design are mean droplet size in the nanometer range, emulsification time in seconds, and % transmittance. Using mixture design, the magnitude of the impact of each independent variable on the dependent variables can be estimated and expressed numerically. Each independent variable will be tested at high and lower levels on the responses.

Efficiency of the design/design diagnostic

The design evaluation platform provides the diagnostics for existing experimental design and it asses the strength and limitations of the design in different ways. The design evaluation explores the design in terms of its power to detect the effects, its prediction variances, its estimation efficiency, its aliasing relationships, and the correlations between the effects through the color map.

Color map on correlation

The color map [Figure 3] depicts the suitability of the design for obtaining a formulation with all the predetermined standard quality characteristics. The color map is efficient in providing absolute correlations among effects. It is used to establish effectively the influence of each factor (independent variables) alone or in the combination of other factors on the responses (dependent variables). The bright red areas represent the most effective combination, whereas the deep red, gray, and blue colors are programmed in the descending order of effectiveness in attaining the responses.[34]

Table 7: Variables in the experimental domain

Independent variables	Levels	
	Low	High
Critical material attributes		
Oil	−1	1
Surfactant	−1	1
Cosurfactant	−1	1

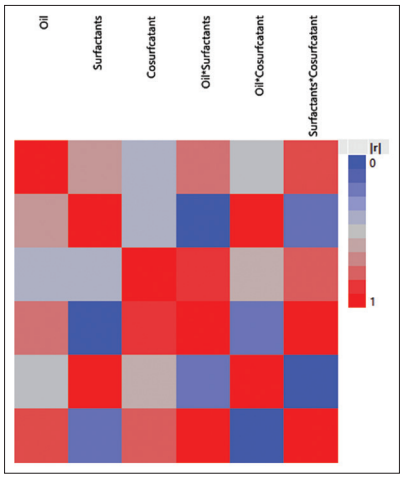

Figure 3: Color map on correlations

Model fitting

Statistical regression approaches used to describe the relationship between the dependent variable and independent variable. The curve fitting methods include multiple linear regression (MLR), partial least square, logistic regression (LR), and artificial neural networks (ANN). MLR is the most common type of linear regression analysis. MLR describes the numerical relationship between two or more dependent and independent variables by fitting into a linear equation for the experimental data. It will explain the variance in the dependent variable in relation to the independent variable and expressed as R^2. Thus, the independent variable selected should have proper theoretical justification to avoid any over-fit model. The independent variable selected must be continuous or categorical. The main function of MLR is (a) identify the strength of effect of independent variable on dependent variable, (b) calculate the impact of changes, and (c) identifies the point estimation and predicts the trend. PLS is not for understanding the relationship between the variables. PLS is used for constructing the predictive model when the number of independent variables is more than the number of data points. LR models are used when the dependent variables are categorical. LR is a predictive analysis and it is used to describe the data and explain the relationship between the independent variable and dependent variable which is binary. ANN is a mathematical model used to check the nonlinear relationship between variables and the possible interaction among the variables. Where it fails to

estimate the significant effect of factors on the responses. The major difference between ANN and regression model is that it provides a generalized relationship between variables without any specific numerical function.

Design verification through ternary mixture profiler

The mixture profiler helps in visualizing and optimizing the responses (CQAs) resulting from the mixture experiments. The mixture profiler report displays the mixture profiler plot, factor setting and control, and response settings and control. For the mixture models, the response contours will be displayed on a ternary plot, where the three or more factors in the model are the components of a mixture. A ternary plot is a two-dimensional display of three components that sum to 1 or 100%. Each vertex of the triangle represents the pure blend of a single component (factor in the mixture) is 1 (100%); the remaining components will be zero. In case of constrained factors, the feasible mixtures are represented by the portion of the ternary plot. The shaded area of the plot represents the infeasible portion and the feasible region will be unshaded. The model ternary mixture plot for SEDDS system is presented in Figure 4. The experimental batches will be prepared as per the ternary mixture profiler and characterized to confirm with the predetermined quality characteristics. The lack of difference in the variance of observed and predicted responses indicates better goodness of fit.

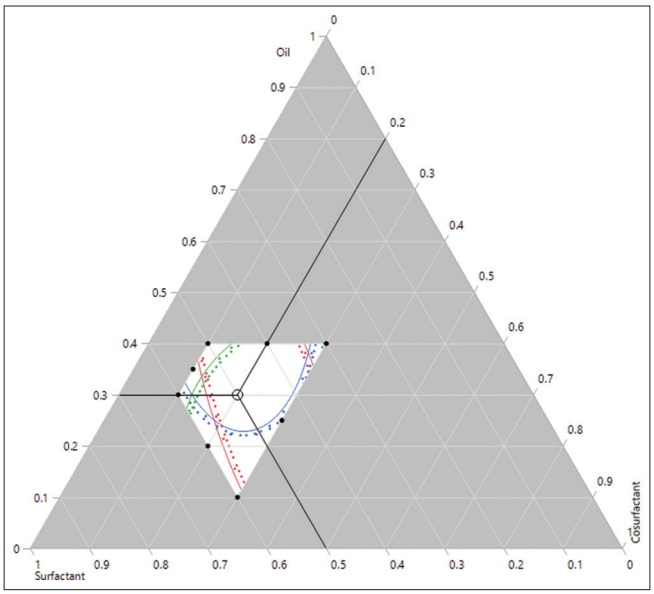

Figure 4: Ternary mixture plot

Model optimization by contour profiler and prediction profiler

The mixture models are interpreted visually by inspecting the contour plots [Figure 5] of the response surface and the simple optimization can be done with the help of these plots. The contour profiler report contains contour plot, surface plot for individual responses, independent factor settings and control, and dependent factor settings and its control. The individual surface plots will be obtained for each response. The contour plots help in concluding the intra- and inter-mixture behavior of the two mixtures. The other most popular approach used for simultaneous optimization of the formulation is the desirability function approach. The desirability function approach utilizes prediction profiler [Figure 6], whereas the optimization is performed by attaining global desirability function for the respective responses considered in the design. The global desirability function value generated is assigned with a value ranging from 0 to 1. The value close to one indicates

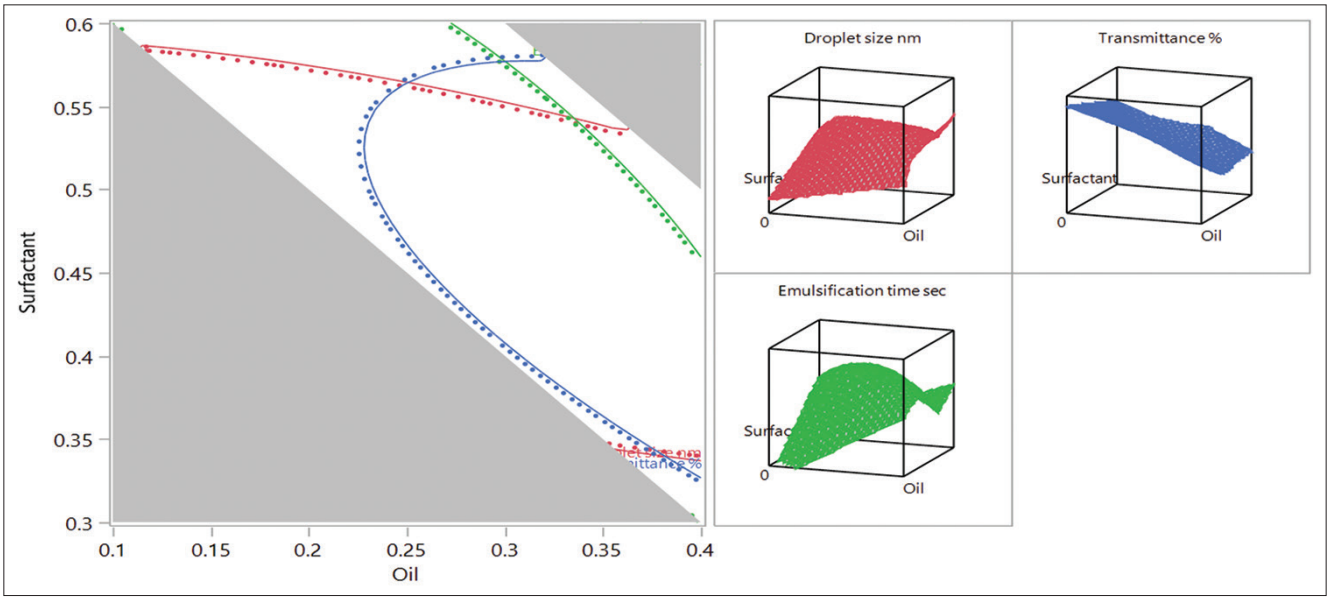

Figure 5: Contour plot

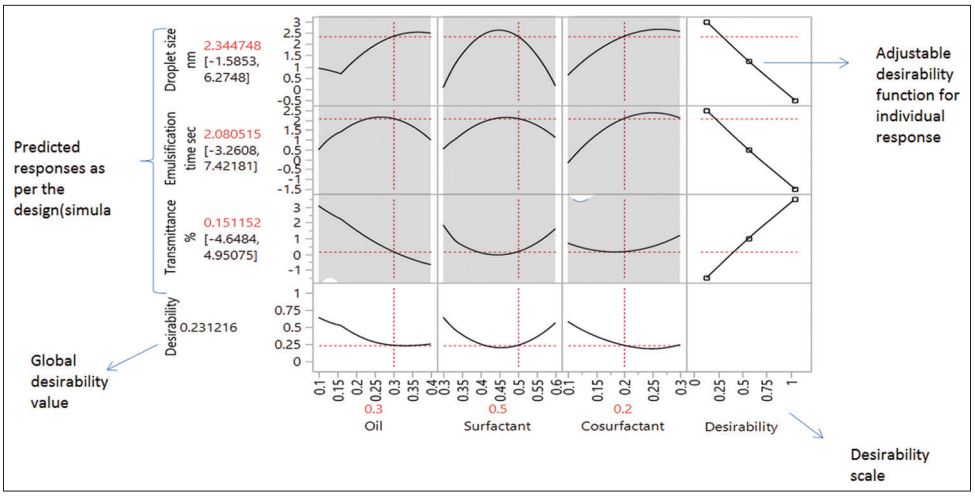

Figure 6: Prediction profiler

the maximization of desirability. The overall desirability will be obtained from the individual desirability.

CONCLUSION

QbD is the global regulatory initiative used to understand the factors and their interaction effects on the predetermined quality characteristics of a product by running the desired set of experiments. The development of SEDDS by the application of QbD concept could be a desirable approach in attaining the therapeutic and the formulary goals. Mixture design could be the choice of design for the development of SEDDS among various experimental designs, where it is able to present maximum effectual information from the minimum number of experimental runs and successfully evaluates the interaction among variables.

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Source of Support: Nil. **Conflicts of Interest:** None declared.