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QbD-based optimization of guar gum suspension medium for optimum pourability and sedimentation volume

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A stable, adequately pourable guar-gum suspension medium has been developed by using the QbD approach. For this, the QTPP is defined followed by its subset CMA (guar gum and sucrose concentration). The CQA are viscosity and sedimentation volume. The target range for viscosity is 99 - 101.3 cps and sedimentation volume 0.98-1 for preparing the optimized suspension. To achieve this optimization, the central composite design has been opted which would fit well to the quadratic model. The quadratic equations and the ANOVA results are validated. The analysis phase of graphical and numerical optimization suggested that 0.1g of guar-gum and 20g of sucrose can achieve an optimized viscosity and sedimentation volume suspension. This contour plots and surface plots are utilized to check the combined interaction of the variables. The checkpoint analysis reveal appropriate percentage variance, which signify the predictive ability of the developed model and validated the design for an optimum suspension. Further, scale-up and stability studies will verify the projected promising results which may be scaled up for its applications in pharmaceutical, food and chemical industries.

Keywords: Central Composite Design, Guar gum, Pharmaceutical suspensions, Optimization, QTPP

Natural Gums are polysaccharides that originate naturally from either plants or microbial sources. They can bind with water and form gels. Plant-based gums like exudate gums ooze out from the bark of the tree as a protective mechanism of the plant after giving an external cut. These exudate gums are produced by disintegrating the cellulose in the plants through a process called gummosis like gum arabic, gum karaya etc. Gums are also obtained from the seeds called seed gums, the gums are collected from the embryos of the seed, which is stored in the form of food reserve like guar gum, tamarind gum, locust bean gum, etc. Natural gums are gaining interest as excipients due to their non-toxicity, biodegradability, biocompatibility, easy availability, and economical nature[1]. Galactomannans are one such natural polysaccharides, which are most preferred amongst all mainly because of their viscosity improving property in aqueous solutions in small concentrations. Chemically, they consist of a D-mannose backbone to which D-galactose units are attached as side chains. These gums are characterized by their mannose to galactose (M/G) ratio. Some of the commercially available gums are guar gum (M/G: 1:2), tara gum (M/G: 1:3) and locust bean gum (M/G: 1:4) etc. Out of these, guar gum is the most widely used which is easily available, economical, and extensively researched for its multipurpose applications varying from food, agriculture, paint, pharmaceuticals etc.[2].

Guar gum is obtained from the seeds of plants *Cyamopsis tetragonolobus,* belonging to the Leguminosae family. It consists of 80% of galactomannan with 12% water, 2% acidic insoluble ash, 5% protein, 0.7% ash and 0.7% fat. In recent years, it has gained recognition among researchers because of its wide applications in pharmaceutical industries as well as in agriculture, water purification, paint industry, cosmetic industry, and drug delivery systems. The most desirable property of guar gum is that it has thermal as well as freeze-thaw stability which makes it more convenient to be used in cold prepared frozen foods independent of temperature, to form a stable re-suspensions[3]. It is hygroscopic and dissolves readily in cold water forming viscous solution even in small concentrations. Its viscosity increases with the increase in temperature. Owing to this property, it is used as an excipient by pharmaceutical industry as a binding, stabilizing, emulsifying, suspending, and thickening agent[4].

This study aims to formulate a stable, easily pourable aqueous suspension medium by optimizing the concentration of guar gum and sucrose as both are soluble in water. Considering its rheology, it shows a

typical shear thinning property, which means producing higher viscosity in low shear rates and lower viscosity in high shear rates. When combined with Newtonian fluids, it displays a decrease in the sedimentation rate showing a limited impact of residual particles on its property. Thus, it offers the ability to produce stable suspension with a variety of solid particulate matter suspended in it and allows comparatively static conditions for better shelf life[5]. The stable suspension prepared can not only solve the concerns of many industries mentioned earlier for use of the stable suspending medium but also will make it easily accessible, economical, versatile, non-toxic, non-polar, producing viscous solution even in cold water and will help in particles to remain suspended for a longer duration[6].

To achieve stability, the concentration of the suspending medium and sucrose was varied to get an optimized sedimentation rate of the resultant suspension medium, offering optimum pourability at the same time. The basis of utilizing the Quality by Design approach is as per the ICH recommendation for formulating pharmaceutical products. In this study, to plan the experiment, statistical design of experiments (DOE) is utilized. The response surface methodology (RSM) is a statistical and mathematical approach to observe the effect of parameters affecting the responses of the experiment. The main advantage of using RSM is the ability to avoid the replication of experimental designs and to evaluate the effect of parameters simultaneously[7]. Face Centered Central composite design (FCCD) which is sub part of RSM, is most widely used as optimization tool by researchers nowadays[8]. It allows the experimenter to extract maximum information, and, at the same time it offers an opportunity to perform the ANOVA test for checking the significance of the model as well as the 'lack of fit' test, without creating any confusion with a large number of design points[9].

In the current study, to get an optimized guar gum based suspension formulation, we utilized Central composite design taking guar gum concentration and sucrose concentration as two factors (independent variables)which were varied at three levels (-1, 0 and +1) respectively. Their effect has been studied on responses (dependent variables) viz. sedimentation volume and pourability of suspension medium. The measurement of the viscosity of the suspension estimated its pourability and the sedimentation rate indicate the rate of settling and hence the stability of the suspension. Thus, it was hypothesized to formulate guar gum and sucrose-based suspension medium using QbD and systematic optimization approach for producing optimum physical stability and pourability.

Experimental Section

Materials

Guar gum was procured from Central Drug House (P) Ltd, India. Propyl paraben and methyl paraben were purchased from Arora & co., India. Sucrose was procured from Fisher scientific, India. All the chemicals and reagents were of suitable analytical grade and were used as received.

Software: Design Expert® 11 (Version 7.1.6) was used as the software for performing optimization.

Defining QTPP and identifying CQAs for applying QbD approach

In this QbD based approach to formulate pharmaceutical suspension, the first step is to define quality target product profile (QTPP) which summarizes the quality characteristics of the proposed drug product. The proposed targets were better physical stability of the suspension and optimum pourability of the final formulation. These targets were responsible for serving as the main parameter to design the formulation highlighting the quality, safety, and efficacy of the formulation. The proposed target as QTPP were the type of dosage form, its proposed route of administration, its physical stability, its pourability, colour and appearance etc[10]. After defining the QTPP for this experiment, the next step was defining CQAs which are a subset of QTPP. The CQAs created the formulation and physical attributes. Among the identified QTPPs, the most critical attributes were chosen based on literature search, previous expertise, and knowledge with their appropriate reasons [10].

Design of Experiment (DoE) based optimization of suspension medium

After selecting CMAs, the next step in QbD approach was to apply response surface methodology using Design of Experiment to search the optimum values of selected CMA in the design space. The optimization was performed using a face centered central composite design. The independent variables were the concentration of guar gum and concentration of sucrose taken at three levels i.e. low, medium and high for both critical material attributes (CMA) with coded values as : -1, 0 and +1 ; corresponding actual values were 0.1, 0.15 and 2.0 g/ml for guar gum and 20g/mL, 40 g/ml and 60 g/ml for sucrose respectively

and α = 1. To perform statistical optimization, Design-Expert software (Design Expert 12.0.4, Stat-Ease, Minneapolis, MN) was employed to create design matrix of suspension formulations that suggested a total of thirteen batches including four additional centre points per block.

The formulation parameters suggested the combination of CMAs were developed in triplicate and were analysed for respective CQA (Sedimentation volume and viscosity of suspension). With the help of Design-Expert software, the obtained results were statistically evaluated by ANOVA. The ANOVA test is used to ensure the significance of generated model terms. To generate the polynomial equations, Multiple Linear Regression Analysis (MLRA) was performed. MLRA also establish the interaction effects of CMAs on CQAs. 2D Contour Plots and 3D Response Surface Plots were generated using the software which helped in evaluating the correlation. The target/constraint values for CQAs were defined as per QTPP. Using the desirability approach, both numerical and graphical optimization were performed. As an attempt to get the final optimized suspension formulation, the checkpoint analysis was performed.

Preparation method of suspension medium

To prepare the suspension, in 27 mL of heated distilled water, methyl paraben and propyl paraben were added with continuous stirring. Required quantity of sucrose (as per the experimental design matrix) was added to the above solution with continuous stirring at 60°C. The suspension could stand for 15 min till it cools down at 45°C and filtered through filter paper. Guar gum (as per the experimental design matrix) was weighed and added to this syrup. Tween 80 was added to the required amount of distilled water separately and then added to the above solution. Sodium Saccharin was dissolved in 10 ml of distilled water and added to the above solution. It was followed by the addition of menthol crystals and amaranth dye. The solution was continuously stirred to obtain a homogenous suspension. Volume was made up to 50ml by distilled water. The suspensions were observed for 15 days to check their stability (by calculating Sedimentation Volume) and pourability (by observing its viscosity).

Characterization of pharmaceutical suspension

Determination of viscosity of the formulated suspensions

The viscosity of the suspension was determined by using Brookfield Viscometer (BROOKFIELD LVDV-II+P) serial no- 8487828 using spindle number 6 1 at 60 r/min.

Determination of sedimentation volume of the formulated suspensions

The sedimentation volume was determined using the formula:

$$\text{Sedimentation volume} = V_e/V_t$$

Where, V_e is the equilibrium volume and V_t is the total volume of the suspension.

Results and Discussions

Defining QTPP and identifying CQAs for applying QbD approach

The suspension as a dosage form can suspend insoluble solid particles in a liquid solvent and offer better bioavailability than the solid oral dosage forms like tablet and capsules. As recommended by ICH guidelines, the QTPP and related characteristics were defined in Table 1 for the development of suspension medium. QualityTarget Product Profile (QTPP) were identified followed by applying DoE approach. The CQAs which were responsible for accomplishing the defined QTPP are represented in Table 2 along with their suitable description.The dependent variables or critical quality attributes (CQA) were viscosity and the sedimentation volume of the suspension.

DoE based optimization of guar gum-based suspension medium

In the present study, we aimed at preparing an optimized suspension by QbD based approach using central composite design. The experimental variables and levels for the optimization of amounts of guar gum and sucrose are shown in Table 3. As per the design matrix, total of 13 formulations were to be prepared. We successfully formulated 13 batches of suspension (5 centre points, 4 axial points, and 4 factorial points) as suggested by the design matrix of the three-level two-factor central composite design (Table 4). The different formulations prepared were quite stable and checked for the sedimentation volume and viscosity on Day 15. The physical stability of the suspension depends on the viscosity and sedimentation rate, which we tried to achieve in formulation by varying the amount of guar gum and sucrose. Thus, for this study, the concentration of guar gum and concentration of sucrose is considered as the experimental variables which are affecting the preparation of stable suspension. The results obtained for the responses are shown in Table 4. These responses were used for the statistical and mathematical treatment using Central Composite Design (CCD) for evaluating the effects of the factors on responses in such a way that we can

Table 1 —QTPP elements to produce guar gum-based suspension medium.

QTPP elements	Target	Justification
Dosage form/delivery system	Biphasic Liquid dosage form	Offer better drug release than the solid dosage forms like tablet and capsule
Route of administration	Oral	The oral route is the most accepted route by the conscious patients. It does not require any special expertise to administer the dose, easy to carry and if any toxic effects are there, it can be overcome by inducing vomiting etc.
Dosage type	Pharmaceutical suspension medium	The preparation can act as a medium to suspend required compatible drug and will offer better drug release profile than the solid dosage forms like tablet and capsule. Although, the effect of tween 80 and the other excipient are not yet studied in this experiment
Appearance	Transparent pink coloured	The colour of the suspension was due to addition of Amaranth dye which provided it elegance and aesthetic appeal
Stability	The suspension medium was checked for sedimentation volume value	The physical stability of the suspension was checked using sedimentation volume to check whether the medium will be able to preserve the therapeutic potential of the suspended drug during the storage period
Container and closure system	Amber coloured glass bottle	To avoid the exposure to external CO_2, moisture and ensure target shelf-life. The use of bottle will facilitate administration of the suspension via spoon etc. Although, we have not tested the effect of light exposure on the stability of the dosage form

Table 2 — Identified CQAs responsible to accomplish defined QTPP

CQA	Target	Justification
Viscosity	In range 20-150 cps	It was considered highly critical due to its importance in pourability of the suspension. Too low viscosity suspension will flow like water and cannot be measured easily using teaspoon etc. Too high viscosity of the suspension may not allow the suspension to come out of the bottle in which the suspension is packed. So, optimum viscosity should be in range from 20-150 cps (Kumar and Yagnesh, 2016).
Sedimentation volume	To achieve ideally 1 and the range 0.89-1	It was considered critical as the suspension should be able to keep insoluble solid particles suspended in the suspension. If settle too fast, may make the suspension non-compliant by the patient. If deflocculated, will form a hard cake which may not be re-dispersed. So, ideally the value should be near to 1 when all particles will be suspended in the suspension medium

Table 3— Experimental variables and levels for the optimization of amounts of guar gum and sucrose.

S. No.	Factor	Unit	Level +1	0	-1
1	Sedimentation Volume	gm/mL	20	40	60
2	Viscosity	gm/mL	0.1	0.15	0.2

study the effect of independent factors alone as well as in combination, meaning thereby individual as well as interaction responses. This is quite promising approach as compared to the conventional one-factor-at-a-time (OFAT) method.

The modeling was performed using the Design Expert Software by fitting different mathematical models such as linear, quadratic, and cubic, etc so as to generate the 2-D and 3-D response surface in an attempt to predict any relationship(s) between the

Critical Quality Attributes (sedimentation volume and viscosity of formulated suspension) and Critical Material Attributes (the concentration of guar gum and sucrose). The software suggested the quadratic model after a polynomial analysis for both the responses, without any transformation.

The results obtained from the experimental design have been presented in Table 5 in terms of ANOVA variance analysis with 95% confidence. The significance was defined by $p<0.05$ and is verified by F- test i.e. the obtained F value of 6.05 at a low probability ($p < 0.0176$) and F- value of 21.11 with a low probability of ($p < 0.0004$) respectively for the model of two responses shows the significance of model. Furthermore, the p value of A ($p < 0.0040$), A^2 ($p < 0.0237$) and B^2 ($p < 0.0109$) are considered as significant model terms.

The significance was also evaluated by lack of fit which shows whether the developed model is suitable for the fitting the experimental data or not. The p value of lack of fit ($p < 0.0916$), ($p < 0.0021$) for both the responses respectively shows that the developed model is suitable for the experimental data. It was observed that the adjusted R^2 and predicted R^2 values for both CQA were in reasonable agreement. It indicates that the mathematical model was efficient enough to describe the date satisfactorily.

Table 4 — Design layout of all 13 formulations suggested by the software

S. No.	Factor 1 (A)	Factor 2 (B)	Response 1	Response 2
1	0	0	0.9	121.3
2	0	-1	0.96	115
3	1	0	0.96	196.1
4	-1	1	0.96	195
5	1	-1	0.98	115
6	0	0	0.92	121.1
7	-1	0	0.98	115
8	0	0	0.89	113
9	-1	-1	0.98	96
10	0	0	0.89	114
11	0	0	0.91	117
12	1	1	0.98	260
13	0	1	0.96	185

Analysis of response surface plots

The response surface plots are known to study the interaction between the experimental variables/factors and the responses and their relationships. The plots were created for the two responses which can be seen from (Fig. 1 (a), 1 (b) and Fig. 2 (a), 2 (b).

Response analysis through polynomial equation

Response 1 (R1): Effects of sedimentation Volume

The sedimentation volume was found to range from 0.89 to 0.98. The model F value (6.05) and model terms were found to be significant ($p = 0.0176$) (Table 3) and the lack of fit was found to be insignificant ($p = 0.0916$). The R^2 value was found to be 0.8122.

The model suggested the following quadratic

Table 5 — ANOVA results for the data of CCD design for optimizing the amounts of guar gum and sucrose

S.No	Response	Source	Sum of squares	df	Mean square	F value	P value	
1.	Sedimentation volume	model	0.0128	5	0.026	6.05	0.0176	Significant
		A – Concentration of sucrose	0.0000	1	0.0000	0.0000	1.000	
		B – Concentration of guar gum	0.0001	1	0.0001	0.1582	0.7027	
		AB	0.0001	1	0.0001	0.2372	0.6411	
		A^2	0.0050	1	0.0050	11.79	0.0109	Significant
		B^2	0.0029	1	0.0029	6.88	0.0342	Significant
		Residual	0.0030	7	0.0004			
		Lack of fit	0.0023	3	0.0008	4.45	0.0916	
		Pure error	0.0007	4	0.0002			
		Cor Total	0.0157	12				
		R^2 – 0.8122						
2.	Viscosity	Model	27105.86	5	5421.17	21.11	0.0004	Significant
		A – Concentration of sucrose	4543.0	1	4543.0	17.69	0.0040	Significant
		B – Concentration of guar gum	16432.67	1	16432.67	63.99	<0.0001	Significant
		AB	529.0	1	529.0	2.06	0.1944	
		A^2	2128.43	1	2128.43	8.29	0.0237	Significant
		B^2	1362.45	1	1362.45	5.31	0.0547	
		Residual	1797.69	7	256.81			
		Lack of fit	1737.79	3	579.26	38.68	0.0021	Significant
		Pure error	59.91	4	14.98			
		Cor Total	28903.5	12				
		R^2 – 0.9378						

equation for sedimentation volume:

Sedimentation Volume =

$$0.9093+0.0000*A-0.0033*B+0.0050*AB+0.424*A^2+0.0324*B^2$$

The A^2 and B^2 were found to be the significant terms (Table 3). The 2D contour plots and the 3D responses were obtained from the software. A. The 2D and 3D plot showed the effect of sedimentation volume with respect to the concentration of sucrose as 'X' variable and guar gum as 'Y' variable is shown in Figs 1(a) and 1(b). e.g. at concentration levels (1,-1), (-1,0), (-1, -1); and (1,1), the value of sedimentation volume is 0.98. The colour intensity of the response graph shows that value is ranging from 0.89 to 0.98. The plots reveal that the sedimentation volume value is minimum (0.89) when both the concentration levels were at middle level (0 level of concentration of guar gum and 0 level of concentration of sucrose). The value was maximum at many levels of the interaction of the concentration levels of guar gum and sucrose (i.e., 1, -1; 1, 1; -1, -1 and -1,0).

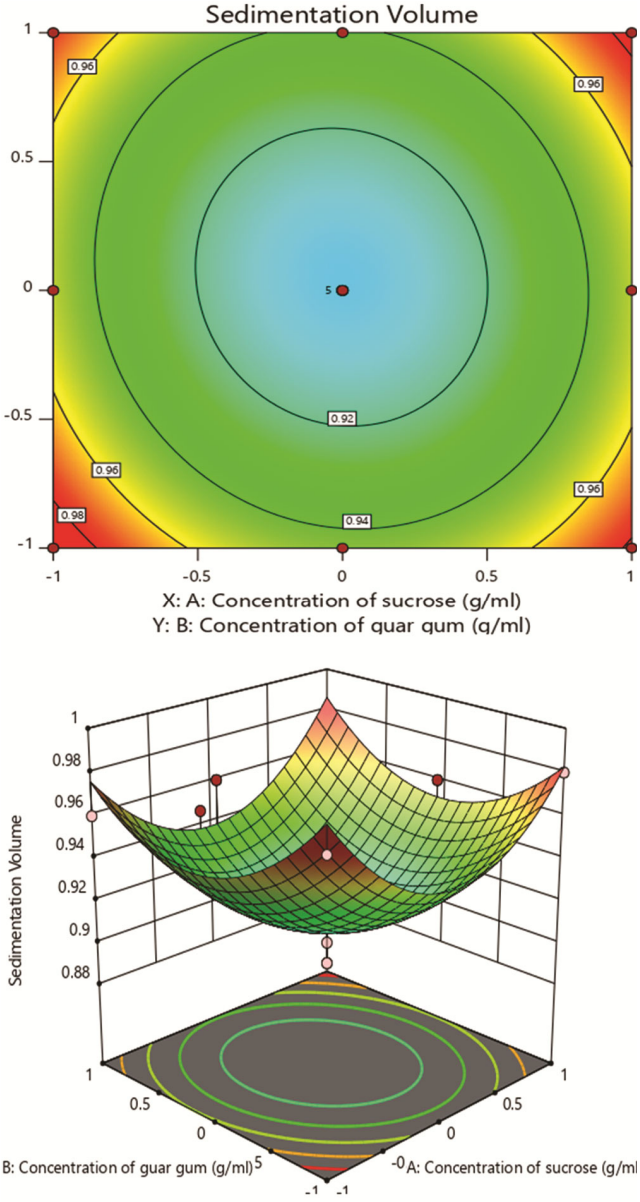

Fig. 1— Digital image of effect of concentration of sucrose and guar gum on sedimentation volume in contour plot (a) and 3D image (b)

Response 2 (R2): Effects on Viscosity

The value of viscosity of the suspensions ranged from 96 to 260 cps. The model F value (21.11) and model terms were found to be significant (p = 0.0004) (Table 3) and the lack of fit was found to be significant

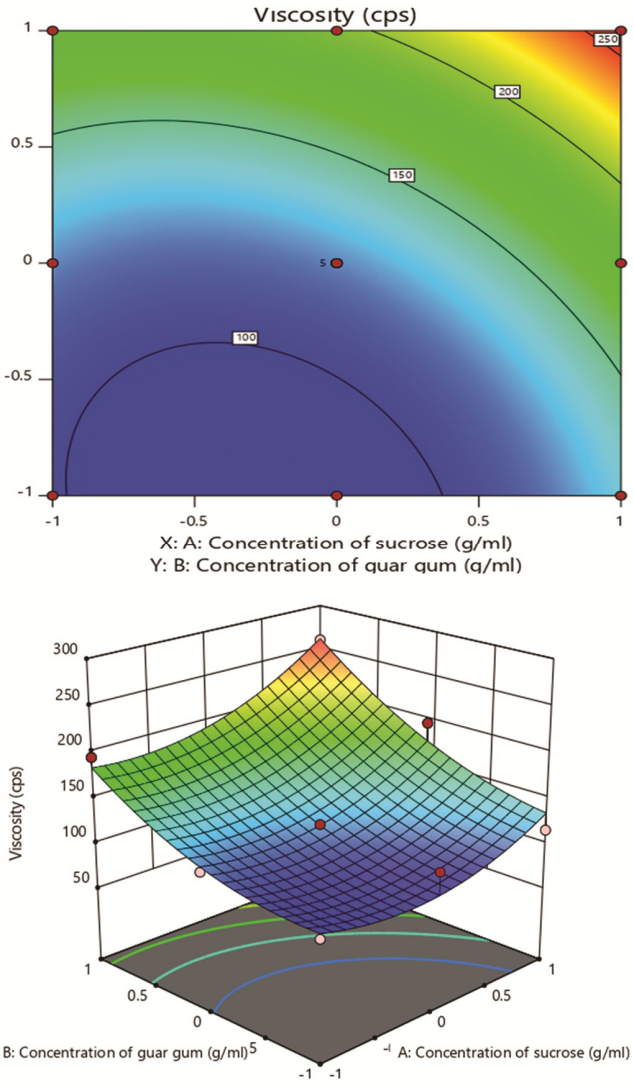

Fig. 2 — Digital image of effect of concentration of sucrose and guar gum on viscosity in contour plot (a) and 3D image (b)

($p = 0.0021$). The R^2 value was found to be 0.9378.

The model suggested the following quadratic equation for viscosity:

$$\text{Viscosity} = 120.28+27.52*A+52.33*B+11.50*AB+27.76*A^2+22.21*B^2$$

The terms A, B and A^2 were found to be significant terms (Table 3). The effect of two variables (concentration of guar gum and concentration of sucrose) on viscosity was studied and is shown as 2D and 3D plot in Figs 3(a) and 3(b). The colour intensity variation represents the range of the response values. The plots reveal that the viscosity value is minimum when both the concentration levels were minimum (-1 level of concentration of guar gum and -1 level of concentration of sucrose). The value was maximum when both the concentration levels were maximum (+1 level of concentration of guar gum and +1 level of concentration of sucrose).

Search for optimum formulation based on desirability approach and checkpoint analysis

The desirability approach was utilized to perform both numerical and graphical optimization. Once the prediction checkpoint analysis has been successfully performed to predict the final optimized formulation. The solution with the highest desirability (as predicted by the Design expert software) was selected among the solutions proposed by the numerical optimization. These plots were further subjected graphical method. The ranges were entered and a desirability overlay plot was obtained (Figure 3). The goal of the study was to get sedimentation volume value near to 1 and with the range 0.89-1. Thus, the target was to maximize sedimentation value and it was given three plus point importance. In case of viscosity, the goal was to achieve viscosity in the range 20-150cps[11]and was given three plus point importance.

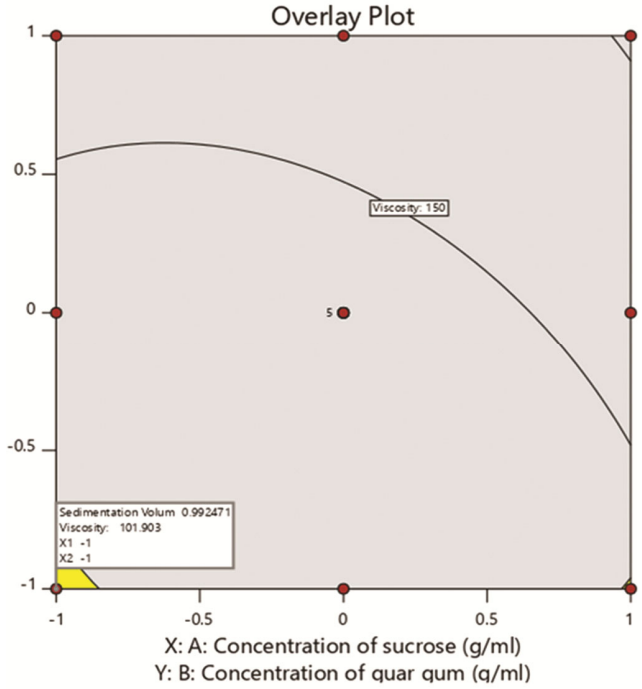

Fig. 3 ─ Overlay plot suggested by the software to get the solution after putting the desired ranges. The goal of the study was to get sedimentation volume in the range 0.89-1 for maximum stability and target was to maximize it; and to get the viscosity value in the range (20-150cps) for best pourability of the suspension.

As an overlay plot, the software suggested the optimized formulation to be using -1 level of X1 i.e., 0.1 gm/mL for guar gum and -1 level of X2 i.e. 20gm/mL for sucrose respectively. The predicted value of sedimentation volume was 0.9992471 and for viscosity, it was 101.903 cps as suggested by the software. The CQAs were obtained at suggested levels of CMAs according to desired target.

To verify the reproducibility, the suspension was prepared using the suggested values. The actual values of responses were 0.97 for sedimentation volume and 99 cps for viscosity respectively, using the software-based suggestions after formulating the suspension medium by taking both independent variables at -1 and-1 level. The percentage variance was calculated using the formula:

$$\text{Percentage variance} = (\text{Actual} - \text{Predicted})/\text{Actual}*100$$

With reference to the predicted values, the percentage variance of the observed values was found to be 1.256% for sedimentation volume and 5.79% for viscosity, which were quite feasible; reproducible; represented predictive ability of the model; and validated the generated design for formulation of optimized guar gum-based suspension medium.

The optimized formulation is expected to offer reduced expenditure of resources; improved time of the product to reach the market; offer limited number of product recalls and rejects; and a faster regulatory product review process[12].

Conclusion

In this experiment, a QbD driven development and optimization of guar gum based pharmaceutical suspension has been carried out for optimum CQAs i.e., physical stability and pourability. The central composite design is found to be an efficient tool for

optimization to generate relevant data for the prediction of pharmaceutical suspension formulation. The central composite design enabled the mapping of responses based on pre-set objective(s) within the design space. Both the CMAs, i.e., the quantities of guar gum and sucrose used in the formulation are found to affect the sedimentation behaviour and pourability of pharmaceutical suspension, which is optimized using the Design Expert software (Version 7.1.6). The optimized formulation prepared shows the maximum stability and can be used as a standard formulation for incorporating the active ingredient for various applications. Thus, this approach can be used to fulfil the needs of the many industries with economical, versatile, and stable suspending medium having better shelf life for their products. However, further pre-clinical study; clinical trials; long term stability studies are also required to validate these results.

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