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RESEARCH

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Evaluating the prediction power and accuracy of two smart response surface experimental designs after revisiting repaglinide floating tablets

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Abstract

Background There is a soar in the figure of companies aiming to achieve efficiency in undergoing experimental processes. Therefore, instead of deploying one-factor-at-a-time, design of experiments is becoming rampantly utilized in order to reduce the resources outflow. There are a copious of different smart designs which could be employed as design of experiments tools. Central composite and d-optimal designs were investigated in this paper. The purpose of this investigation was to compare the two designs and identify the most accurate design at analyzing, interpreting and making predictions with regards to the data offered. The aforementioned purpose was achieved by applying both designs to a preexisting study which sought to prolong the gastrointestinal retention of repaglinide tablets through deploying a full factorial design. Further optimization was performed using Design-Expert software after inducing an outlier point.

Results *R*-squared, adjusted *R*-squared, predicted *R*-squared and adequate precision were computed in addition to acquiring diagnostics figures such as predicted versus actual, residual versus run, Box–Cox, contour plot and 3D surface plots. Model equations were also produced for each design. Results showed that both designs were successful at modeling the data both scoring *r*-squared values > 0.7 and adequate precision > 4 implying high fitting, prediction power and ability to navigate the experimental space using a reduced number of experimental runs. The d-optimal design obtained the least relative error of only 3.81%.

Conclusions In conclusion, the d-optimal design provides a great tool for reduction of experimental testing which in turn diminishes resources consumption. Therefore, this design is favored to be enforced in the pharmaceutical sector.

Keywords Repaglinide, Floating, Optimization, d-optimal, Central composite

Background

The production of pharmaceutical commodities is a sophisticated, time-consuming, expensive and labor-intensive endeavor which necessitates extensive planning and exhaustive testing of products and processes with the aspire of achieving the most optimized process and the superlative quality of the medicine [1]. For this reason, many methods have prevailed with the purpose of coherent optimizing the production of medications [2]. Conventionally, one-factor-at-a-time (OFAT) studies were

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adopted to deduce the optimized formulation of remedies. The one-factor-at-a-time optimization approach adheres to the concept that in order to ascertain the impact of a single factor, it is imperative to keep all other factors constant. In other words, only one factor is altered at a time. This experimental design may not be the most efficient approach when the factors under consideration are interacting or interfering. Due to the proven inefficiency of OFAT, it is now rarely implemented in the pharmaceutical engineering processes. To solve the impracticality of OFAT, a new statistical approach was developed by Sir Ronald Fitcher in the twentieth century [3]. His method was named as "design of experiments (DOE)". This systematic formulation of experiments entails a multifaceted strategy aiming at enhancing the quality of a product through limited experimentation and judicious allocation of resources [4]. The design of experiment (DOE) approach relies on planning and executing the least amount of experiments where variables are altered simultaneously to produce a cause-and-effect relationship, while minimizing errors [5–7]. The steps of DOE deployment are designing, developing, evaluating and finally analyzing the product. The application of design of experiments (DOE) is widely employed for the execution of Quality by Design (QbD) [8]. In this context, Q8 and Q9 are major constituents of QbD where Q8-pharmaceutical development and Q9-quality risk assessment were first introduced in the international conference on harmonization (ICH) in 2009. Quality by Design is a concept which revolves around the notion that attainment of product and process understanding serves as the pivotal factor in ensuring the quality of the end product [9, 10]. This comprehensive apprehension is illustrated by embedding quality in the developing stages of the product and its processes of manufacturing in lieu of testing for quality after the manufacturing process is finalized [11]. Mitigating possible quality hazards is crucially achieved by identifying possible failures that may negatively influence the quality of the product and subsequently actions are put in place to ensure sustainment of product compliance with the quality standards [12]. Possible failures that might prevail could be pinpointed using fishbone diagram, a root cause analysis tool.

There are a multitude of different designs currently employed throughout the pharmaceutical industry. Two of the response surface designs include the central composite and the d-optimal. Central composite designs fundamentally select the upper and lower limits of testing values and extend the space of the experiments beyond both thresholds (alpha + 1 & alpha − 1) [13]. The central composite design is suitable for materials which are insensitive to harsh testing condition. Sensitive materials which should not be implemented in the central composite design include proteins and liposomes. On the other hand, the d-optimal design works by assembling information matrices for all points then deducing their determinants. The points procuring the highest determinants are encompassed in the model [14].

Despite differences, both are concurrently considered smart designs. These types of designs depend on exploiting rich-information points to establish their models. Rich-information points consist of a lower number of points which conceal the space of the experiment effectively.

In the current study, the use of smart response surface designs such as the d-optimal and the central composite was proposed instead of the full factorial in order to optimize pharmaceutical dosage forms aiming for the reduction of number of experiments and therefore saving resources, time and effort. Moreover, the two investigated smart designs were compared regarding the *r*-squared, adjusted *r*-squared, predicted *r*-squared, adequate precision and through different diagnostics tests and finally comparing them regarding the percentage relative error. The design with the lowest relative error was recommended.

To our knowledge, this is the first study that compares these two smart experimental designs in the optimization of pharmaceutical dosage forms. This concept can be projected to the other more sophisticated pharmaceutical processes such as extraction or analysis methods [15, 16] and to optimize advanced drugs carriers and delivery systems such as the lipidic, polymeric and inorganic nanoparticles [17–19] and regarding their different processes of preparation and characterization [20–23].

Methodology

Software

The models and plots for the d-optimal and central composite designs that were provided in this paper were produced using Design Expert v.7.0. software (Design-Expert software, Stat-Ease Inc., MN).

The investigated work

For the purpose of comparing the d-optimal and central composite designs, a paper was selected as a basis for application of both designs [24]. Subsequently, comparing and contrasting the two models was conducted. The chosen paper was entitled "Design expert supported mathematical optimization of repaglinide gastroretentive floating tablets: in vitro and in vivo evaluation" [24]. Repaglinide is an oral agent that falls under the meglitinide class, serving as an anti-hyperglycemic medication. It necessitates regular administration prior to meals due to its brief half-life, which lasts only one hour. Consequently, the medication can result in adverse effects,

including discomfort in skeletal muscles, headaches, and gastrointestinal disturbances [25]. The investigation presented in the selected paper aimed to prolong the absorbance of Repaglinide tablets by optimizing the critical quality attributes (CQAs) entailing the floating lag time response. This was accomplished using a three-factor three-level full factorial design (usually called 33 full factorial design). Three different components concentrations were altered: Okra gum (OG), HPMC (hydroxypropyl methylcellulose) K15M and xanthan gum. In QbD, the factors contributing in the CQAs are the CPPs (critical process parameters) and the material and formulation parameters.

Other than the factors included in the investigated study, some factors also representing CPPs of the prepared tableting process included subjecting the granules to adjusted conditions of a temperature range of 55–60 °C for approximately 120 min, while ensuring that the moisture content remained within the range of 3–5%. The powder was administered through an 80-mesh (0.177 mm pore size) after initial mixing. A 30-mesh (0.595 mm pore size) was used after adding a portion of the granulating medium. A 30-mesh (0.595 mm pore size) was used once more to sift the granules following drying. Furthermore, the compression force was adjusted to maintain the hardness of the tablets within 5 to 8 kg/cm^2.

The material and formulation parameters comprised other numerous crucial excipients satisfying various concentrations, including 2 mg of repaglinide, 10% sodium bicarbonate, 5% citric acid, 7% ethyl cellulose, 2% magnesium stearate, 1% talc in addition to lactose with a quantity sufficient to produce a 200-mg tablet. The granulation medium comprised 8% PVP K30 in 80% ethanol [24].

The use of central composite and d-optimal designs to reoptimize the results

Both central composite and d-optimal designs were used to further optimize the generated gastroretentive tablets regarding the floating lag time response instead of the three-level three-factor full factorial design which originally consisted of 27 experimental runs.

A total of 20 points were used to produce the central composite design model; six of the design points were center points.

On the other hand, a total of 25 points were used to build the d-optimal design model. The 25 points comprised 10 model points, 5 replicate points, 5 points to estimate lack of fit and 5 additional center points. The "Model use" was adjusted to point exchange prior to execution.

Table 1 demonstrates the used factors (the investigated material and formulation parameters) accompanied with their tested ranges.

Table 1 The investigated factors associated with their used ranges

Factors	Ranges of values (%)		
	High (+1)	Medium (0)	Low (−1)
Concentrations of OG	35	22.5	10
HPMC K15M	15	7.5	0
Xanthan gum	10	0	0

Induction of an outlier

The results of the new embraced design points were produced from the equation that was generated in the extensively examined paper [24]. An outlier central point result was introduced for all the central points of both of the newly adopted designs. Accordingly, the floating lag time for coded points corresponding to (0, 0, 0) for OG, HPMC K15M and xanthan gum, respectively, was altered to a value of 90 s instead of 45.

Analysis of results

It is necessary to document the process by which the models were generated which were both quadratic. To empirically ascertain the significance of the model, ANOVA analysis was performed. This statistical test permits the assessment of differences underlying groups and provides valuable insights into the overall effectiveness and sturdiness of the model. Moreover, in order to affirm the reliability and accuracy of the results, an assortment of values was computed including; *R*-squared, adjusted *R*-squared and predicted *R*-squared. *R*-squared value reflects the fitting of the model, adjusted *R*-squared reflects the model's *R*-squared value after insignificant terms are excluded and the predicted *R*-squared represents the model's accuracy at predicting the floating lag time [1]. Additionally, the adequate precision of the model was also determined. This measure provides a quantitative assessment regarding the signal to noise ratio [26]. Moreover, to further appraise the validity and precision of the model and identify any potential flaws or inefficiencies that could be ameliorated, a series of diagnostic tests were conducted. These tests including Box–Cox, residual versus run and predicted versus actual provide a valuable insight regarding the validity of the model and notifies for any necessary adjustments or modifications [27]. Finally, in order to visually portray the model and facilitate a deeper understanding of its underlying relationships, contour and 3D surface plots were obtained. These plots provide a graphical representation of how the change in the compositions of (OG, xanthan gum and HPMCK15) contributes to the

response and highlights how the variation in these variables are reflected upon the outcome of the CQA (floating lag time). Furthermore, contour and 3D surface plots clarify the observation of the optimum quadrants of the model and allow for a more intuitive interpretation of the findings. Overall, the process of generating the model, determining its significance, calculating the different values and adequate precision, performing diagnostic tests, and obtaining contour and 3D surface plots were essential elements for ensuring the validity and consistency of the findings presented in this study.

Calculation of the percentage relative error (% relative error)

The percentage relative error was calculated by utilizing the following equation [24]:

$$\text{Relative error}(\%) = \frac{\left|\text{Predicted value} - \text{Actual value}\right|}{\text{Predicted value}} \times 100.$$

Results

Tables 2 and 3 demonstrate the different runs (points) generated as rich-information points of the central composite and the d-optimal designs, respectively, accompanied with the results of these runs as calculated from the generated equation of the used work of Naveen et al. [24] utilizing a three-level full factorial design to optimize the floating lag time of repaglinide floating tablets.

Table 4 illustrates the significance of both models ($P < 0.001$) [28]. The type of the two generated models corresponding to the two adopted designs was a quadratic function. Furthermore, the *R*-squared, adjusted *R*-squared and predicted *R*-squared differences were within 0.2 increments for both models and all of them scored values above 0.7 implying acceptable and reliable models. For the central composite model, the discrepancy between the *R*-squared and predicted *R*-squared was 0.0056 which is a minimal value, while for the d-optimal model, the discrepancy was higher (0.1289). The adequate precision exceeded a value of 4 as counseled for both models (adequate precision for d-optimal was 14.161 and for the central composite was 122.830). Furthermore, the parameter "lack of fit" was favorably insignificant in both models.

It is highly visible by observing Fig. 1 that the points present in the predicted versus actual plot of the central composite model were closer to the 45-degree line (indicating the close values of the predicted results to the actual counterparts). Hence, the model floating lag time predictions were closer to the actual values. Also obviously, the predicted versus actual plot of the d-optimal model acquired values that seemed relatively distant from the 45-degree line; yet, they were still considered close.

Table 2 The central composite generated design points associated with their calculated results

Experiment number	OG concentration	HPMCK15M	Xanthan gum	Floating lag time
1	0	0	0	90
2	−1	1	1	71.34
3	0	−1.68	0	141.39
4	0	0	−1.68	74.71
5	−1	−1	−1	72.18
6	1	1	1	69.84
7	1	1	−1	94.78
8	1	−1	−1	177
9	0	0	0	90
10	−1	1	−1	52.28
11	−1.68	0	0	77.72
12	0	0	1.68	79.02
13	0	1.68	0	46.27
14	0	0	0	90
15	−1	−1	1	102.24
16	1	−1	1	163.06
17	0	0	0	90
18	0	0	0	90
19	0	0	0	90
20	1.68	0	0	164.60

Table 3 The d-optimal generated design points associated with their calculated results

Experiment number	OG concentration	HPMCK15M	Xanthan gum	Floating lag time
1	− 1	1	− 1	52.28
2	− 1	0	1	70.21
3	0	0	− 1	56.24
4	0	0	0	90
5	0	0	0	90
6	− 1	1	1	71.34
7	0	0	0	90
8	0	0	0	90
9	− 1	− 1	1	102.24
10	0	1	0	35.24
11	1	− 1	− 1	177
12	− 1	1	− 1	52.28
13	1	− 1	1	163.06
14	1	1	− 1	94.78
15	1	− 1	− 1	177
16	0	− 1	− 1	98.35
17	0	0	0	90
18	1	1	1	69.84
19	− 1	− 1	0	76.63
20	0	− 0.5	0.5	69.20
21	1	− 1	1	163.06
22	1	0	0	99.01
23	1	1	− 1	94.78
24	1	1	1	69.84
25	− 1	− 1	− 1	72.18

Table 4 The generated model analysis results

Design type	Central composite	D-optimal
Significance	Significant	Significant
	$P < 0.0001$	$P < 0.0001$
Model type	Quadratic	Quadratic
R-squared	0.9991	0.9210
Adjusted *R*-squared	0.9984	0.8736
Predicted *R*-squared	0.9935	0.7921
Adequate precision	122.830	14.161
Generated equation	Floating Lag Time = −7828.09234	Floating Lag Time = +76.99172
	+ 1007.19857 * OG concentration	+ 26.21690 * OG concentration
	+ 880.39460 * HPMC K15M	− 27.47543 * HPMCK15M
	+ 1364.29190 * Xanthan Gum	+ 1.21784 * Xanthan Gum
	− 15.58000 * OG concentration * HPMC K15M	− 16.51078 * OG concentration * HPMCK15M
	− 11.00000 * OG concentration * Xanthan Gum	− 10.24740 * OG concentration * Xanthan Gum
	− 2.75000 * HPMC K15M * Xanthan Gum	− 2.74859 * HPMCK15M * Xanthan Gum
	+ 4.43181 * OG concentration^2	+ 17.47349 * OG concentration^2
	− 43.99831 * HPMC K15M^2	+ 4.43398 * HPMCK15M^2
	− 125.72119 * Xanthan Gum^2	− 1.65511 * Xanthan Gum^2

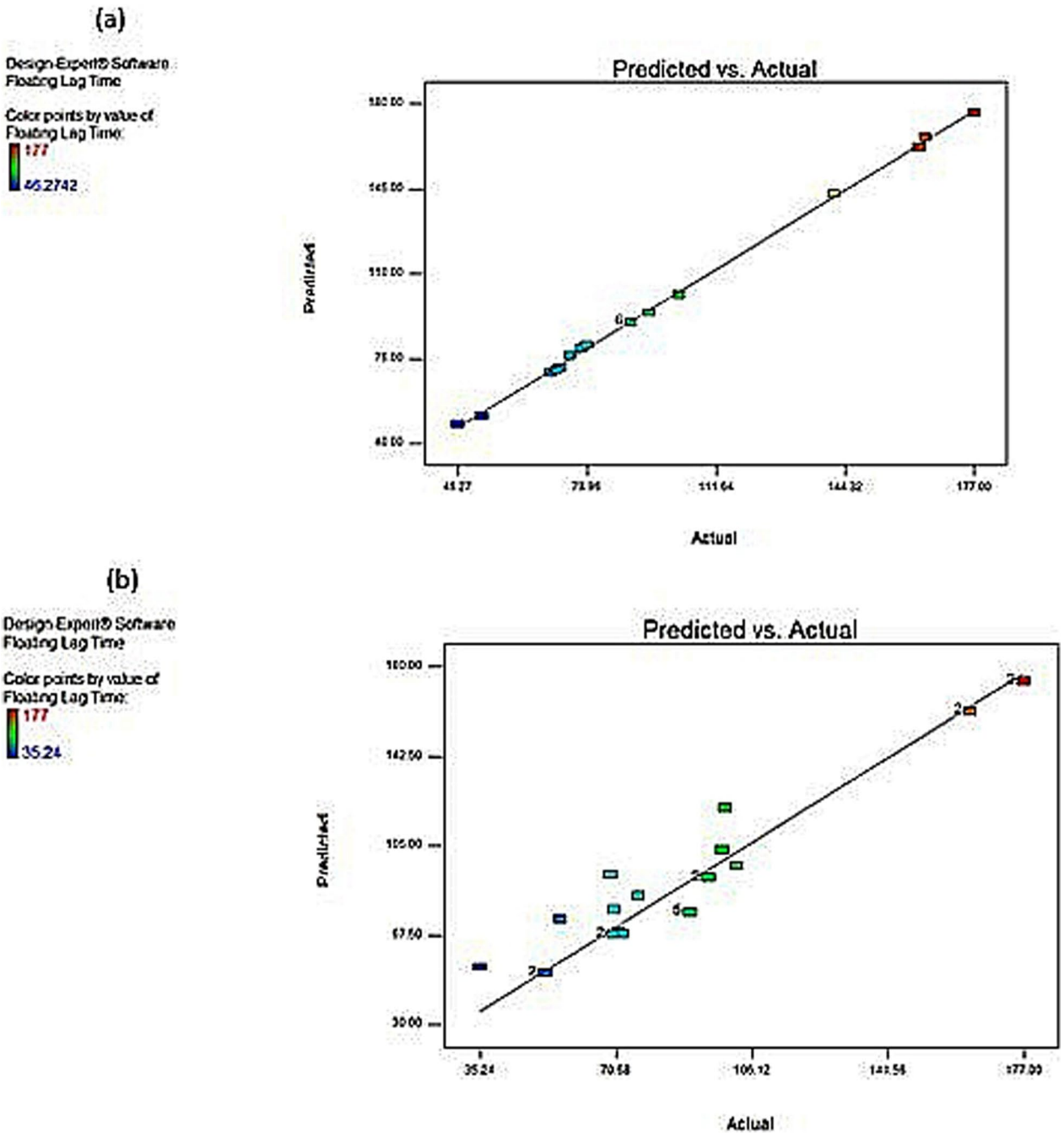

Fig. 1 Predicted versus actual plots for **a** central composite and **b** d-optimal designs

As inferred from Fig. 2, the points representing the different runs of the two investigated models were evenly scattered around the zero line of the Design-Expert® generated plots of both designs and represents the models functions. Moreover, for the residual versus run point distribution of the central composite model, 40% of the points were situated above the zero line, approximately 30% were situated on the zero line, and 30% were situated under the zero line. On the other hand, for the residual versus run point distribution for the d-optimal model, 60% of the points were situated above the zero line, 8% of the points were approximately situated on the zero line, and 32% of the points were situated under the zero line.

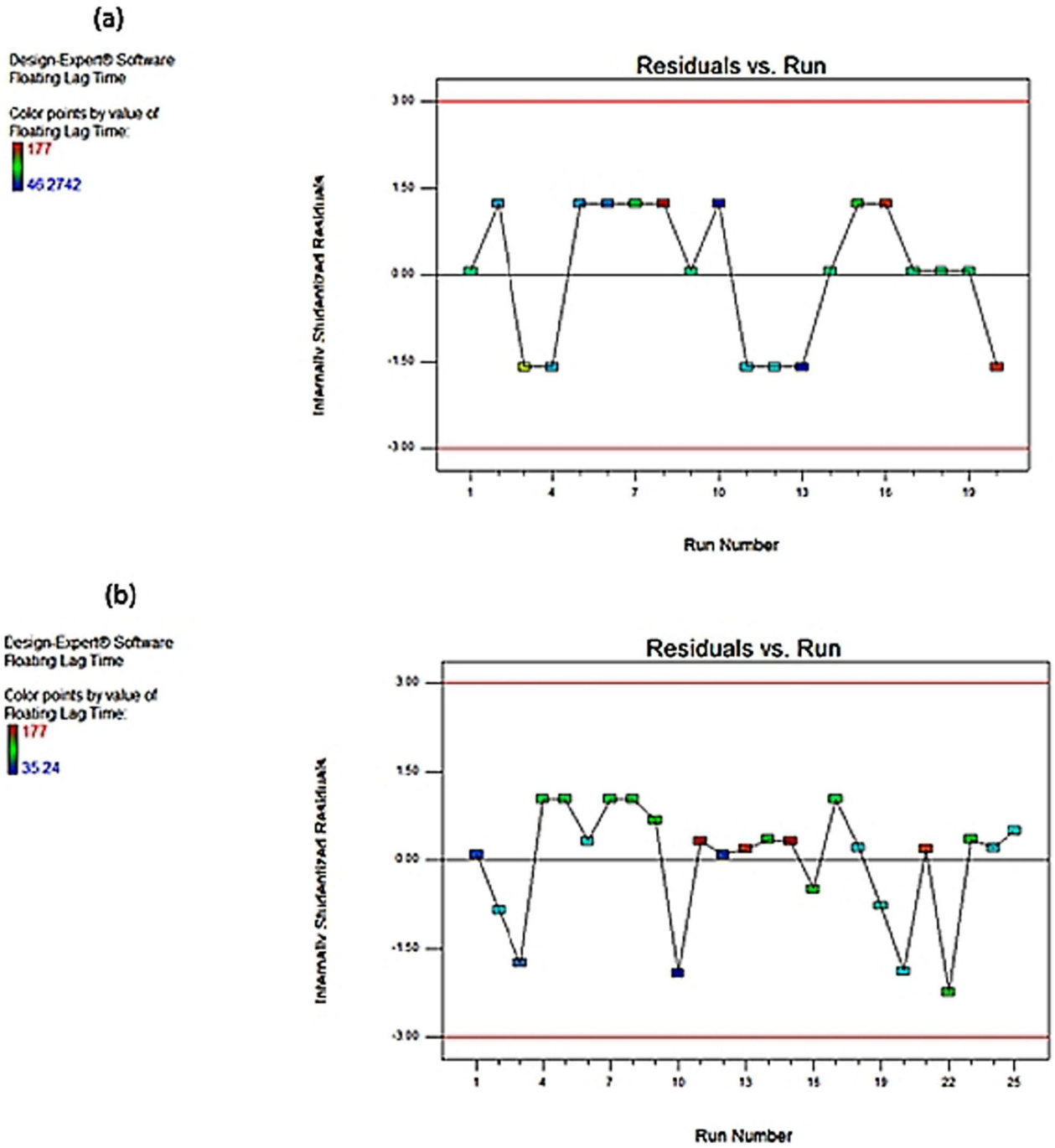

Fig. 2 Residual versus run plots for **a** central composite and **b** d-optimal designs

As obvious from Fig. 3, both models powers lied within the confidence interval ranges of the Box–Cox diagnostic and validating test generated from the utilized software while acquiring power correspondents of lambda = 1 [2].

Contour plots use varied gradients of colors to represent segments which occupy high and low floating lag time responses as depicted in Fig. 4.

3D surface plots are similar to contour plots in that they show areas where the response is at different

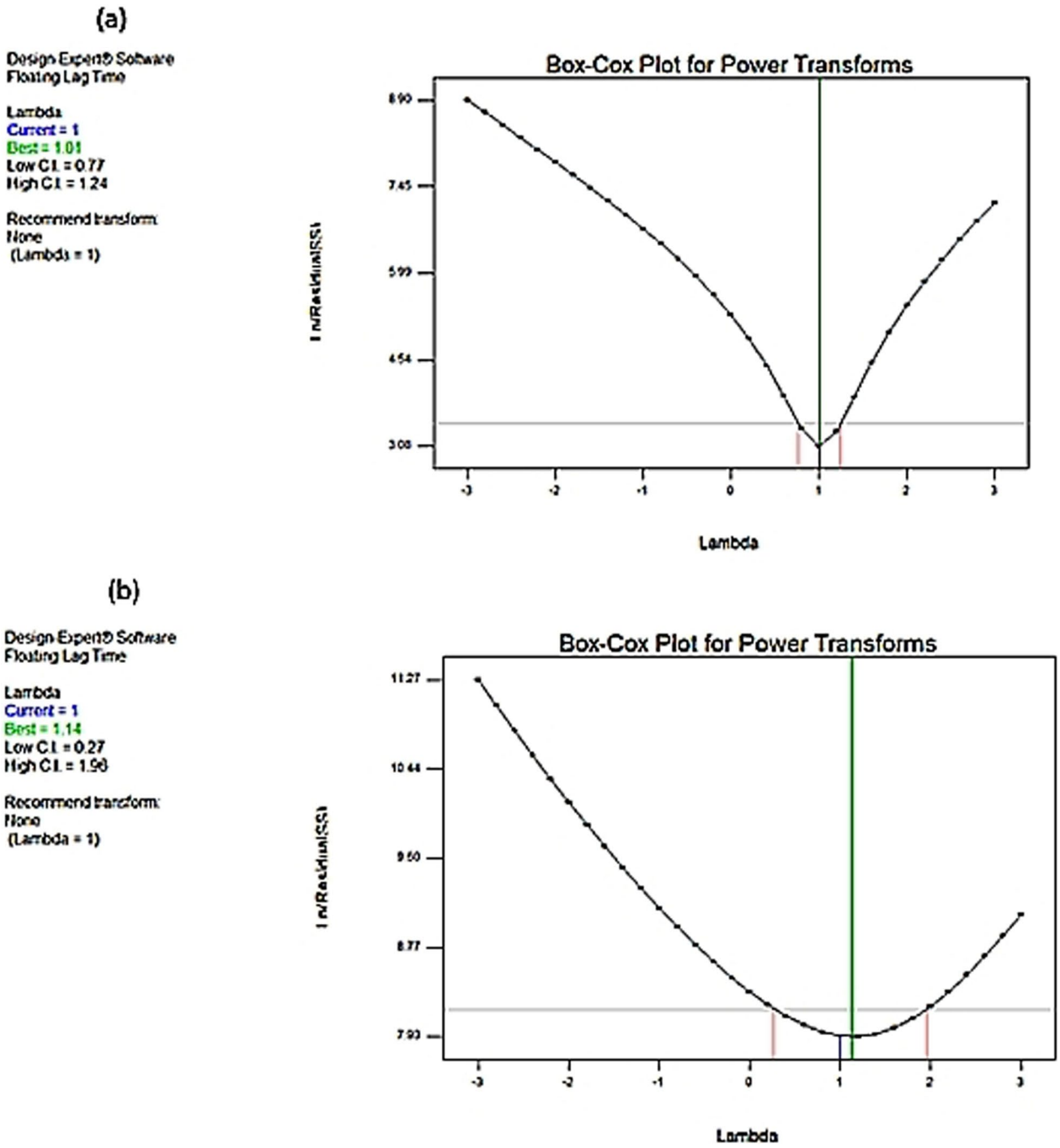

Fig. 3 Box–Cox plots for **a** central composite and **b** d-optimal designs

values but with a three-dimensional viewing facet. The peak response occurred at the red areas while the lowest response occurred at the blue areas [29]. It is obvious from Fig. 5 that the peak floating lag time response was present at coded values of (1, 0, − 1) corresponding to OG, xanthan gum and HPMCK15 concentrations, respectively.

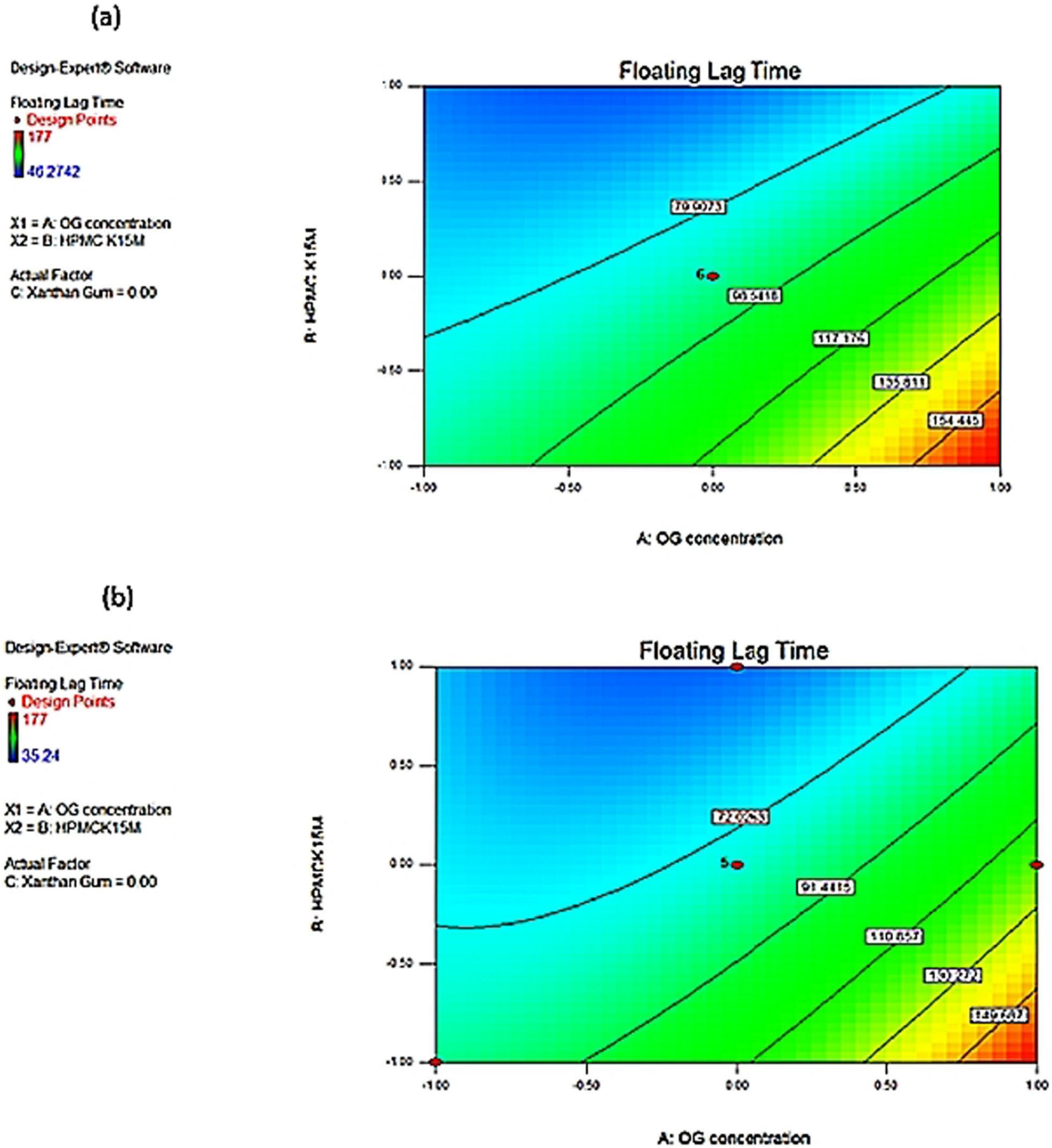

Fig. 4 Contour plots for **a** central composite and **b** d-optimal designs at a constant xanthan gum (at its middle level, code = 0)

The d-optimal design had a lower relative error compared to the central composite design by a difference of 0.7556% for the coded point: 0.66 OG concentration, HPMC K15M and 0.85 xanthan gum, in spite of inducing an outlier critical point (Table 5).

Discussion

Both of the discrepancy values between the adjusted *r*-squared and the predicted *r*-squared of the two investigated designs were considered low. Hence, the models

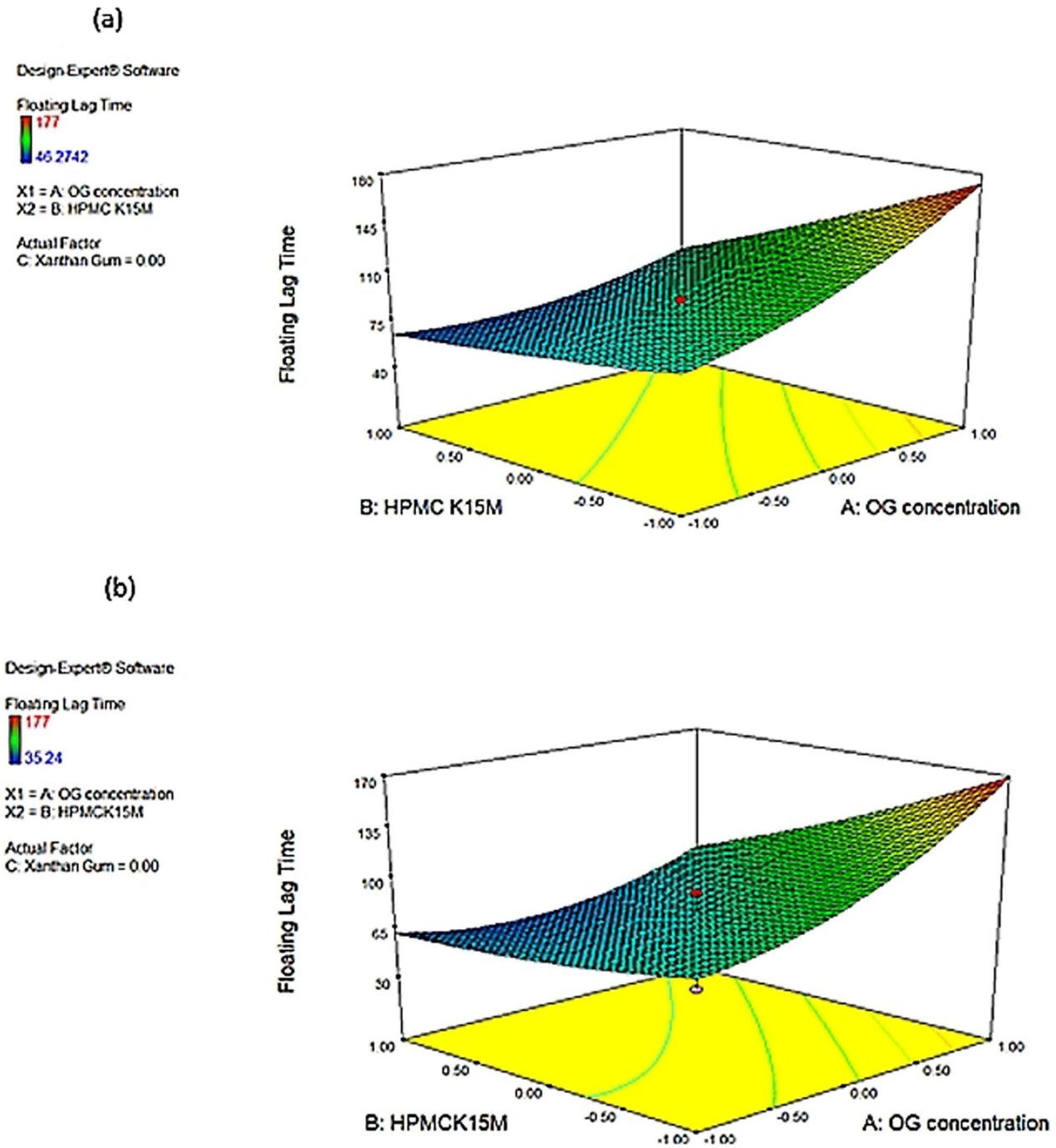

Fig. 5: 3D surface plots for **a** central composite and **b** d-optimal designs at a constant xanthan gum (at its middle level, code = 0)

Table 5 Percentage relative error obtained between the predicted and actual values for the coded point: 0.66 OG concentration, 1.00 HPMC K15M and 0.85 xanthan gum

Design	Relative error (%)
Central composite	4.5699
d-optimal	3.8143

were sufficient in predicting the results of un-carried experiments and to fully navigate the experimental space.

The values of adequate precision of both designs indicated a very high signal to noise ratio. Therefore, the differences in the acquired results for the floating lag time were a consequence of real signals and not due to random

outcomes and both models are considered successful in navigating the space of the investigated experiment [1].

The predicted versus actual plots mainly evaluate the accuracy of the model at making predictions regarding actual experimental values through depicting how close the predicted values are to the actual ones [2]. This is implemented by using the 45-degree line as a reference. The closer the points are to this line, the higher the capability of the model at making accurate predictions. Despite the fact that the points in both predicted versus actual plots were relatively close to the 45-degree line, these results implied the high predictive ability of the two investigated designs-generated models.

Residual versus run plots usually identify the errors present in the model. The required ideal situation is that the total distances from the points above the zero line, which represents the model, are approximately equal to the total distances of the points under the same line so that the errors even out [30]. This was approximately obtained for both models. As a conclusion, the points in both models were moderately and favorably scattered around the zero line.

The Box–Cox test primarily aims to accommodate the model response (CQA) with the optimum numerical power. The response is raised to different powers and the power with the best fitting is recommended. Usually, the power which presents the optimum fitting lies in the area between the high and low confidence intervals. The confidence intervals are manifested by the red lines. If the value of the power (lambda) requires altering, then the recommended value should be applied through the transformation tab of the adopted software. Therefore, it was concluded that the power transformation was not required for both of the generated models.

The alteration of color gradients in the contour and the 3D surface plots is correlated with the change of compositions of the factors contributing to the response [14].

The peak floating lag time response scored at coded values of (1, 0, − 1) corresponding to OG, xanthan gum and HPMCK15M concentrations, respectively, may be attributed to the higher swelling index of okra gum (260% [31]) as compared to the other constituents (xanthan gum and HPMCK15M which only reached a maximum of < 250% [32]) contributing to its significant positive effect on the floating lag time.

It could be interpreted from the current study figures and tables that both designs have been successfully leveraged to produce models with excellent qualities. Despite that the central composite scored better *R*-squared, adjusted *R*-squared, predicted *R*-squared and adequate precision values, the d-optimal design was slightly more accurate at predicting the floating lag time response The high accuracy of both models generated from the two utilized smart surface response designs at predicting the floating lag time response is related to a statistical perspective where DoEs utilizing designs such as the central composite and the d-optimal create response models by reducing the maximum variance of the predicted responses and minimizing the error in the estimated coefficients of the model. This approach offers benefits when employing disproportionate shapes and incorporating additional design points [28]. Moreover, the superiority of the d-optimal design at predicting the response for experimental points which were not included as design points (as inferred from the calculated value of the percentage relative error) comes back to the statistical element of building the design through choosing rich-information points that originate from an information matrix possessing the highest determinant which allows handling of a larger experimental space [33]. Although the CCD resulted in excellent and slightly higher *R*-squared values, this may be ascribed to the problem of overfitting that sometimes occur with experimental designs, wherein the model excessively coincides with and conforms to the existing data points. This phenomenon results in a perfect or ideal coinciding of the actual experimental design points with the generated model predictions. It usually happens with higher order functions (above linear, quadratic, cubic, etc.) possessing high curvatures aiming to reduce residuals of the generated model results [34]. This was obviously noticed in the predicted versus actual figure corresponding to the CCD results (Fig. 1). It is worth-noting that the limitation of this paper lied on the use of only one check point (experimental external validation point) in calculating the percentage relative error of the two investigated statistical experimental designs. Nevertheless, that was a forced limitation because this point was solely conducted in the originally experimental paper that the current paper was based on.

Conclusion

The current study aimed to compare the central composite and the d-optimal statistical experimental designs in optimizing the floating lag time response of repaglinide gastroretentive tablets.

The findings of this study showed that:

- Both smart designs extensively discussed in the paper have been successfully utilized to further optimize the tablets with a very high accuracy similar to a previous optimization implemented using a three-level full factorial design despite the induction of an outlier point representing the central critical point of both designs.

- After computing the percentage relative error, it was concluded that the d-optimal design is more robust in predicting the accurate result values of actual experiments of points not included in the designs built.
- The adopted work drew the attention to the problem of overfitting which may lead to decrease the predictivity power of the statistical experimental designs.

Based on the aforementioned conclusions, integrating both smart surface response designs and more specifically the d-optimal design into the routine of experimental activities, companies can excel the effectiveness of testing in addition to reducing expenses by considerable margins. The use of the investigated smart statistical experimental designs accompanied with its assessment can be projected to any dosage form design and conventional or advanced drug delivery systems aiming of reducing the number of runs and experiments conducted and hence saving resources, efforts and time.

One important contribution of this paper is that it provides a guide or an assist to companies and especially pharmaceutical entities when choosing the smart design, they seek to adopt.

Moreover, another contribution of this paper toward the pharmaceutical industry is that it could guide users on how to calibrate design expert software efficiently to produce the d-optimal and central composite designs and their generated models. Future studies should compare the d-optimal design with other smart counterparts.

Abbreviations

OFAT	One-factor-at-a-time
DoE	Design of experiments
GIT	Gastrointestinal TRACT
QbD	Quality by design
ICH	International Conference on Harmonization
GMP	Good manufacturing practices
CQAs	Critical quality attributes
CPPs	Critical process parameters
OG	Okra gum
HPMC	Hydroxypropyl methylcellulose
ANOVA	Analysis of variance
3D	Three-dimensional

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RMH contributed to conceptualization; TE and RMH provided methodology; RMH performed formal analysis and investigation; TE performed writing—original draft preparation; RMH contributed to writing—review and editing, resources, and supervision.

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Availability of data and materials
The data are available upon request.

Code availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable for this work.

Consent for publication
The authors declare no conflict of interest.

Competing interests
The authors declare that they have no competing interests.

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