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Original Article

Optimizing Encorafenib Validation: A Quality by Design Approach Empowered by Green Chemistry

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ABSTRACT

Background: Green chemistry, also known as environmentally sustainable chemistry, is an area of study within a field of chemistry with the main goal of reducing the negative effects associated with chemical reactions and outcomes. Main aim is for fostering development of environmentally conscious as well as sustainable therapies by reducing/eliminating the employment of harmful chemical substances, limiting creation of dangerous substances and conserving energy and resources.**Materials and Methods:** In this investigation, linearity was observed for Encorafenib (ENFB) at concentrations ranging from 2 to 12 µg/mL. The technique of solving simultaneous equations was applied in order to determine the drug concentrations. **Results and Discussion:** The estimated recovery percentage from the chosen dosage form, capsules, with a sample size of six, was 100.4% with a Standard Deviation of ±0.028 (SD). The recovery rates of accuracy study, on average, fell between 99.8 and 101.05%. Throughout intra-day assessments, the observed percentage relative standard deviation, or %RSD, was continuously less than 2%, demonstrating a high level of accuracy in this recommended methodology. The outcome of validation process and the statistical analysis of these recommended methodologies show that the suggested processes can be implemented in the stimulated quality control laboratories. **Conclusion:** The current method is regarded to be adequate for evaluating ENFB in capsule dosage formulation quantitatively since it successfully eradicates any possible interference from regularly used excipients. As a result, such procedure is applicable to a wide range of analytical purposes.

Keywords: Drug concentrations, Encorafenib, Green Chemistry, Quality by design, Statistical analysis, Validation.

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INTRODUCTION

Because of the increased advancement of scientific and technological developments, revenue generation is currently occurring all over the world. However, this prosperity also adds to ecosystemic degradation, as indicated by problems like ozone holes, climate change and the buildup of non-invasive organic toxins throughout the natural world (Joshi and Adhikari, 2019). In an effort towards lessen the harm that chemicals produce and release into the environment, a multidisciplinary strategy entitled "green chemistry" has been established. In order to reduce waste, save resources and increase the use of organic products, the principal objective of this investigation is to find ecologically friendly alternatives to existing chemical-based techniques (Sharma *et al*., 2019).

The IUPAC (International Union of Pure and Applied Chemistry) formula for ENFB is 1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)] methyl N[(2S)-1-(-1-(propan-2-yl)1-H-pyrazol-4-yl][amino)propan-2-yl pyrimidin-2-yl]carbamate (Figure 1) (Augustyna *et al*., 2023). This innovative compound belongs to one class of medications known as BRAF inhibitors, designed to disrupt the activity of mutated BRAF protein which are often present in melanomas. By precisely targeting these aberrant proteins, ENFB aims to impede the proliferation of cancer cells and undermine their ability to metastasize, ultimately conferring improved outcomes and enhanced quality of life for afflicted individuals (Mishra *et al*., 2023). ENFB's physiology of action highlights its role as a targeted medication in the management of cancers driven by mutated BRAF proteins, offering a promising approach for combating advanced melanoma and potentially other malignancies in which BRAF mutations are implicated (Balamurugan and Mishra, 2020).

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ENFB as solid dosage formulations and biologically active specimens are assessed employing HPLC, LC-MS technique, UV-visible Spectroscopy (Bhatt *et al.*, 2018). Although the described UV spectrophotometric method, has certain disadvantages, it includes linearity range within a limit, absence of Sandell's sensitivity, as well as there is no molar extinction coefficient to be displayed. As a consequence, the Quality-by-Design (QbD) method was implemented for creating developed and novel UV spectrophotometric method for quantifying ENFB via capsule preparation (Reddy *et al.*, 2018).

QbD is an integrated approach that combines excellence in all aspects for the operation in order to ensure the intended inference is attained. QbD, an organising principle for creativity which adheres with the guidelines established by ICH (International Council for Harmonisation) regarding technical requirements for medications with human use systematically; specifically, ICH-Q8-(R2) (Mishra *et al.*, 2024). Such a plan starts with goals that are well-defined and emphasises comprehending and maintaining the structure as well as the end result. The technique used in this plan is founded on sound scientific principles and includes risk-reduction measures to ensure the accuracy and dependability of the outcomes. QbD was introduced in 2002, after the FDA's "Pharmaceutical Current Good Manufacturing Practises (cGMPs) for the 21st Century" initiative. The process includes six steps concerned with utilising the quantitative investigation, QbD Perspective as well as establishing reliable along with high-quality analyzed technique having a higher level of resilience.

The use of QbD methodology additionally reduces the time essential to establish a dependable analytical method, additionally it is regarded as an economically advantageous plan for guaranteeing quality throughout the beginning stages of methodology development. QbD, or Design of Experiments (DoE), is widely recognised as a critical technique for establishing the ideal configuration arena for method efficiency and incorporating it into the paradigm. The key objective of this work is the use of stringent experimental designs; the overall objective is for reducing the quantity of changes those happens with regards the spectrophotometric aspect of ENFB. The principal objective is to pick the best options. Investigations starts with a component, screening analysis that used FFD; Fractional Factorial Design to identify essential technique variables having impact on performance (Krishnan and Mishra, 2020). Following that, Central Composite Design (CCD) was used for upgrading the process, assuring the durability as well as success in meeting predefined goals. The study's purpose was to develop a new UV Spectrophotometric approach which was comprehensive as well as dependable to detect the quantity of ENFB as capsule dosage formulation. We had the opportunities for achieving such goal by effectively applying QbD principles across the method development process, followed by ICH-compliant validation.

MATERIALS AND METHODS

Reagents and standards

Trident Pharma of Maharashtra, India provided an ENFB standardised sample that had a purity of more than 99.5%. Merck Ltd. of Jamshedpur, India supplied MeOH, Methanol used in manufacture of our medication along with reagent solution. Because the commercial capsule formulation of ENFB (75 mg) was available, it was procured and tested implementing the approved techniques.

Instrumentation and optical characteristics

One microprocessor-controlled single beam system and the LI-285 UV spectrophotometer (produced by Lasany, India) having 10 mm calibrated quartz cuvettes were employed for performing the spectrum analysis. The adoption of a high-precision analytical device allowed for accurate reagent measurements. One method utilised to influence a certain dosage form's disintegration was ultrasonication (Enertech, India).

Incorporating the analytical-target profile

The only comprehensive evaluation of academic text sources that are currently in existence and an analytical target profile was created using drug profiles that include both chemical and physical attributes. This explanation offers a concise synopsis of the quality standards connected to an analytical technique. The final objective of this effort was to create an analytical technique for figuring out the concentration of ENFB in capsule dosage form that is both accurate and economical (Mishra *et al.*, 2020). Therefore, a UV spectrophotometric technique has been used to enable the quick determination of ENFB in line with the main objective of this work (Balamurugan *et al.*, 2019). The simplicity and efficiency of the UV spectrophotometric methodology made it the preferred method over more complex analytical techniques when it came to drug analysis (Balamurugan *et al.*, 2018).

Incorporation of cause-effect relationship along with risk management

One of the easiest ways to visualise the relationships between many factors that could impact a method's efficacy is Ishikawa fish-bone diagram (Sarangi *et al.*, 2020). To have a better understanding of how these factors can impact ENFB's UV spectrophotometry properties, an Ishikawa diagram was made. Utilising Control-Noise-Experimentation (CNX)-based Cause-Effect Risk Assessment Matrixes, the researchers identified which parameters are extensive to impact statistical characteristics of the investigation. Many CMVs (Critical Method Variables) were found in the study and they were associated with higher final scores and they are suggested as high-risk factors (Panigrahy and Reddy, 2015). General configuration of such CMVs changes based on the sample integrity, sampling intensity, scan rate, solvent used and pH of the sample. In order to identify the crucial method

parameters, a screening approach was established and the CMVs were further studied (Dekervel and Petrillo, 2024). Gradually, the response surface was optimised using an appropriate design of experiments.

CMVs screening by FFD

To screen essential factors, Design Expert 13 software, version 13.0.14, USA, FFD, was utilised and identify those with high risk. Several elements were identified as critical technique variables after comparing spectrum design, accuracy and absorbance. Prioritisation investigations were conducted using what had previously been determined and the sample integrity, solvent type and detection wavelength had been determined using the Ishikawa fish-bone diagram. These features were then examined by direct observation. In order to assess the procedure variables of MeOH concentration (A) and sample pH (B), FFD experimentation having a minimum of five trials; one acting as a centre point and was conducted using Design Expert software. After evaluating the parameters at both higher and lower levels, the technique was applied to find CMVs that change the response variables' absorbance (Y). By comparing actual and predicted values and using the prediction equation, pareto chart and fitting summary plots, significant parameters were found.

Robustness study implementing CCD and Method optimization

The CCD was used to ensure the accuracy of the method for determining the optimal process circumstances. The screening studies resulted in 13 simulated runs, with at least five central spots selected using CCD to obtain the best CMVs, such as pH (B) and MeOH (A) values. The results of the experiment were analysed using absorbance at 294 nm as the response variable. All tests used the normal ENFB concentration of 10 µg/mL.

Multiple Linear Regression Analysis (MLRA) is a mathematical technique used to fit experimental data into a mathematical model utilising expert software. This model has the potential to examine both the primary and interaction effects. In evaluating the model, polynomial equations were constructed employing only one significant coefficient (p-value<0.05) from ANOVA and parameters like R2, modified R2 and Predicted Residual Sum of Squares (PRESS) were analysed. A number of profilers, including three-dimensional response surface profilers, projection profilers and reciprocal profilers, were used to estimate the model's feasibility. By weighing the several factors, we were able to identify the ideal solution by employing numerical desirability function. Intended area was then drawn appropriately.

Method control strategy

The DoE methodology's design space was employed to guide the development of control techniques for the methodology, which were able to maintain the method's resilience despite minimal modifications to method performance.

Formulation of SSS (Standard Stock Solution)

To prepare ENFB SSS (1000 µg/mL), dilute 10 mg of ENFB in 10 mL of MeOH. 5 mL of the aforementioned stock solution were then transferred to a volumetric flask having a 50 mL capacity and the contents were then filled with water to form 50 mL, in order to produce the 100 g/mL standard solutions.

Dosage form analysis with Response to capsule

The label for Braftovi Capsule/Pierre Fabre states that the ENFB capsule formulation contains 75 mg. To make a solution, dilute 10 mg of ENFB equivalent weight with 10 mL of methanol; MeOH. Once the solution was formed, 5 mL of the solution were added into a volumetric flask having 50 mL capacities and filled with water to reach 50 mL. Dilute 10 mg of ENFB in 10 mL of MeOH to create ENFB SSS (1000 µg/mL). 5 mL of the aforementioned stock solution were then transferred to a volumetric flask having a 50 mL capacity and the contents were then filled with water to form 50 mL, in order to produce the 100 g/mL standard solutions (Mishra *et al.*, 2024).

METHOD VALIDATION

The specificity

The evaluation of drug incorporation into formulation excipients was used to gauge the specificity of the UV-spectrophotometric technique. The purpose of analysing the spectrums was to see if the excipients may have caused any notable interference (Krishnan and Mishra, 2020).

Linearity

Many aliquots of the ENFB working standard solution were collected and placed in various 10 mL volumetric flasks before being diluted with H_2O at the end of the procedure, resulting in a concentration scale ranging from 2 to 12 g/mL (Mishra *et al.*, 2020). UV absorbance was measured at 294 nm. Plotting the absorbance and concentration (in g/mL) on the Y and X axes, respectively, enabled for the building of a calibration curve, which was used to assess the data's linearity.

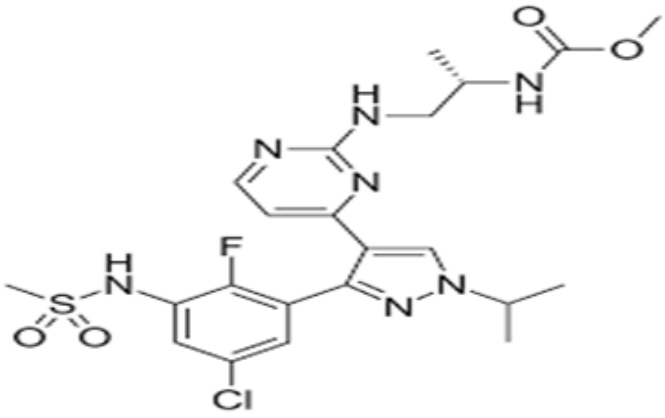

Figure 1: The structure of ENFB.

Precision and Accuracy

Recovery tests were conducted using the usual dilution strategy at 3 different levels; 80%, 100% and 120% of ENFB test solution (10 µg/mL) in order to verify the accuracy of the methodology. For every degree, recovery studies were conducted twice (Balamurugan *et al.*, 2019). Using a plotted calibration curve, the standard medication, ENFB in combination with the recovery solution, was determined. 6 duplicates of the above constant concentration of ENFB (10 µg/mL) were analyzed on one single day in order to evaluate intra-day precision and the %RSD values were computed.

RESULTS

To determine the amount of ENFB in a capsule formulation, the Ultraviolet Spectrophotometric (UV Spectrophotometry) method was developed for this study. The QbD approach was used to determine the variable parameters required to generate the final spectrophotometric settings (Balamurugan *et al.*, 2018). Utilising a standard Ishikawa fish-bone diagram, the technique factors were identified. A physical evaluation of the technique's related variables was carried out. It was noted that ether or acetone would not cause the medication to disintegrate. In water, ENFB was soluble. The wavelength employed for detection was 294 nm, as the standard ENFB solution has a maximum absorption (λ_{max}) in water at that point (Figure 2).

The melting point test confirmed that the sample integrity was good (Sarangi *et al.*, 2020). Nevertheless; more investigation is needed to determine the effects of sample PH, scan speed and sampling interval on process robustness. Based on sample pH, MeOH content and scan speed, FFD streamlined the CMV screening process. Charts showing actual vs. predicted data proved how fit the model was. The model's suitability was indicated by its *p*-value (0.0013), R^2 (0.9138) and RMSE (Root Mean Square Error) (0.0118). An adjusted R^2 of 0.8769 and an expected R^2 of 0.6878 are displayed in the summary of fit.

The CCD was utilised to determine the effect of the CMVs on the absorbance of the response. Thirteen trials were performed in a random order using a UV spectrophotometer in an effort to get a bias-free result with a minimum of 5 centre points. Table 1 displays the spectrophotometric range that was studied in addition to the outcomes of each experiment.

For the *p*-value, the null Hypothesis (H0) has been accepted at the designated significance level of 0.05. The CCD model was carefully studied utilising number of statistical analytic techniques; alike parameter estimations, ANOVA, as well as a prediction profiler, in order to draw worthy end points (Panigrahy and Reddy, 2015).

Plots showing the expected models' perturbations, the effect of independent components on a particular response and all other parameters maintained constant at a reference point are displayed in Figure 3(A). A slope or curve's degree of inclination indicates how sensitive it is to a particular element (Dekervel and Petrillo, 2024). According to the provided study, which is depicted in Figure 3(A), sample pH was found to have a greater significant impact on absorbance than factor B, the sampling interval. The baseline model is shown as blue dots on the actual vs. predicted graph (Figure 3(B)), which also shows that the experimental data line falls evenly within the accuracy interval parameters. The observed data was highly similar to the expected data, indicating that the model was effective in explaining data variation and refuting the null hypothesis (Mishra *et al.*, 2023).

The response surface is displayed against the pH and MeOH concentration in Figure 4. (The pH is displayed in relation to the MeOH concentration). An examination of perturbation and response plots from optimising models revealed that the parameter significantly affected the analytes' absorbance (Bisson *et al.*, 2024).

Moreover, a *p*-value of less than 0.0005 was found by Analysis of Variance (ANOVA), suggesting that, the model is appropriate for explaining the flexibility shown in the data. Furthermore, the observations suggest that the null hypothesis has to be disproved. Moreover, the lowest value observed when PRESS was anticipated validated the adequacy of the model (Gautam *et al.*, 2024).

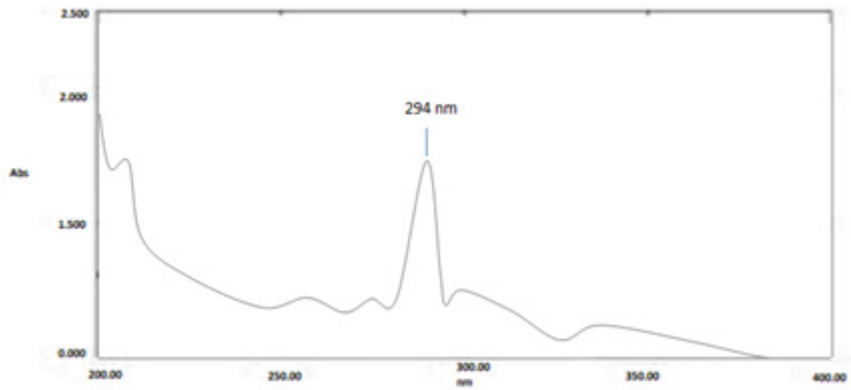

Figure 2: Typical UV absorption spectrum of ENFB.

Table 1: Experimental design matrix Interpreting range studied for robustness study and obtained responses spectrophotometrically.

Run No.	Conc. of Methanol in ml (A)	pH (B)	Absorbance (Y)
1	1.37868	5	0.327
2	3.5	5	0.342
3	3.5	5	0.342
4	3.5	5	0.342
5	3.5	5	0.342
6	2	3	0.268
7	3.5	7.82843	0.386
8	3.5	2.17157	0.322
9	2	7	0.357
10	5	3	0.366
11	3.5	5	0.342
12	5	7	0.349
13	5.62132	5	0.391
Range	Low	High	
MeOH	2	5	
pH	3	7	

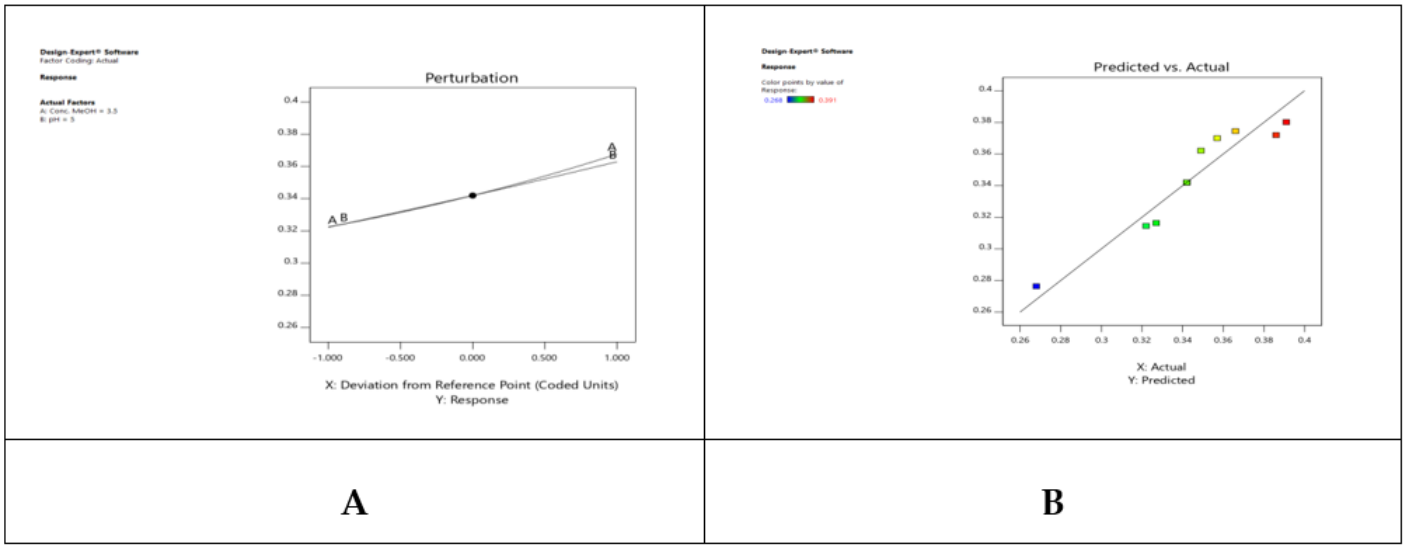

Figure 3: (A): Plot. (B): Predicted vs. Actual Plot.

When estimating the risk of variability from different factors, the evaluation of parametric estimates is essential. The existence of a non-zero slope is confirmed by a *p*-value of less than 0.05.

Sampling interval×pH (B) and conc. of MeOH (A) became the greatest impacting method variable.

()=0. 3402+0.0226 +0.0203 -0.0265 +0.0031 2+0.0006 2

Table 2 displays the optical characteristics related with the spectrophotometric approach. Devised approach exhibited both selectivity and specificity by proving that there is no interaction between the commonly used formulation additives in the chosen dosage forms and the planned operation. On a concentration range ranging from 2 to 12 µg/mL, the drug demonstrated linearity. The linearity data's regression analysis produced a respectable degree of overall goodness of fit. The statistical metrics R^2, adjusted R^2 and predicted R^2 yielded values of 0.9138,

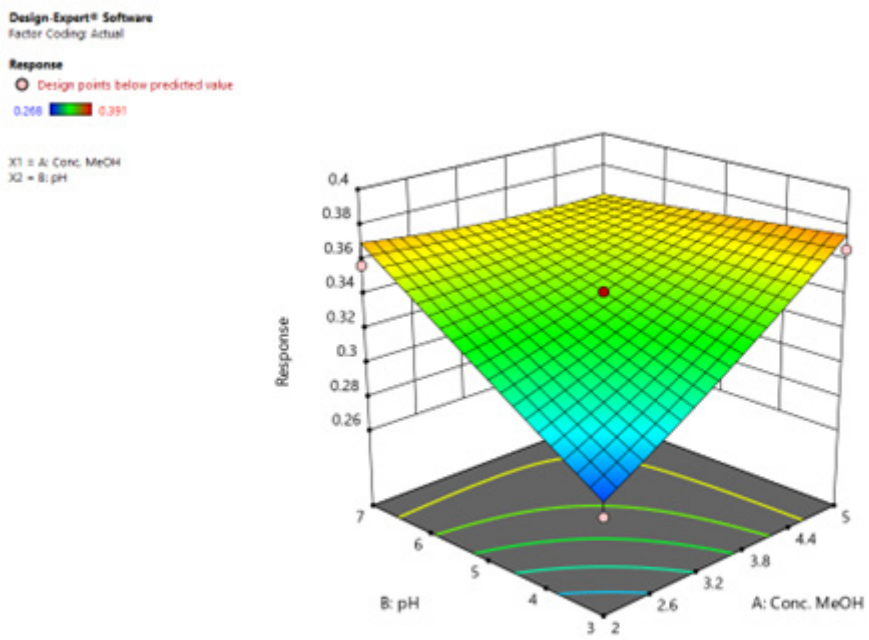

Figure 4: 3-d response surface plot for Absorbance vs. Conc. of MeOH Vs. pH.

Table 2: Optical Characteristics and Summary of validation variables.

Variables	Obtained Values
Correlation coefficient (R2)	0.998
Linearity Range (µg/mL)	2-12
Wavelength (nm)	294
Molar extinction coefficient (ltr/ mol.cm)	$1.998*10^4$
Precision (% R.S.D., *n*=6)	1.90004
Regression equation (Y=ax+b)*	0.0364x+0.0133
Accuracy (% Recovery±S.D.)	
80%	2.437303±0.01633
100%	4.413495±0.3266
120%	1.967462±0.01633
% Range of error	
99% confidence limits	±0.23
95% confidence limits	±0.17

R.S.D.: Relative Standard Deviation; S.D.: Standard Deviation; A.U.: Absorbance Units; Y=ax+b, where Y=absorbance, a=slope, b=intercept and x is the concentration, † is average of three determinations at each level.

0.8522 and 0.3868, respectively. A significant *p*-value of less than 0.05 statistically indicated that such an approach used to analyse the linearity of the data in the ANOVA was adequate. Based on six samples, the recommended dosage form (capsule dose form) had a recovery rate of 99.8% with a standard variation of ±0.0068 (Mishra *et al.*, 2023).

DISCUSSION

The accuracy investigation yielded recovery rates ranging from 99.8 to 101.9%. The percentage RSD for intraday evaluations was found to be much less than 2%, pointing out a high degree of precision with regards to the methodology that was suggested. The inferences produced from the implemented strategy occur within the predetermined range, highlighting that the availability of additives has not affected the methodology.

CONCLUSION

The QbD methodology made it possible to quantify ENFB precisely using a UV spectrophotometric method. The application of QbD guaranteed a high degree of analysis. The researcher had to be very mindful of the pH and MeOH concentration when designing control strategies for the method and organising follow-up experiments to enhance its efficacy. The approach seems to be innovative, straightforward, precise and accurate based on the data. Quality control labs can make use of the proposed strategy, which is based on statistical analyses of method validation data. Despite problems with widely used fillers, this method can be utilised to calculate the ENFB, capsule dose form. Thus, in particular, this methodology is appropriate for general analytical objectives.

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Jharkhand, for providing them with access to the essential research facilities.

CONFLICT OF INTEREST

The investigators do their research work without having any conflicting interests. There are no experiments on humans or animals that any of the investigators performed that are mentioned in the article.

ETHICAL APPROVAL

For this experiment, there is no need of any ethical approval as no human or animal experiments are conducted.

ABBREVIATIONS

ENFB: Encorafenib; **QbD:** Quality by Design; **RSD:** Relative Standard Deviation; **SD:** Standard Deviation; **SSS:** Standard Stock Solution; **MeOH:** Methanol; **IUPAC:** International Union of Pure and Applied Chemistry; **DoE:** Design of Expert; **ICH:** International Council for Harmonisation; **CMV:** Critical Method Variable; **FFD:** Fractional Factorial Design; **CCD:** Central Composite Design; **CNX:** Control-Noise-Experimentation; **MLRA:** Multiple Linear Regression Analysis; **PRESS:** Predicted Residual Sum of Squares; **RMSE:** Root Mean Square Error; **ANOVA:** Analysis of Variance; **H_2O:** Water.

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