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Analytical Quality by Design-Assisted HPLC Method for Quantification of Canagliflozin and Stability Studies

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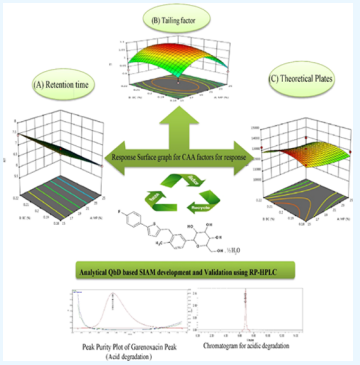
ABSTRACT: The present study is intended to develop the high-performance liquid chromatography (HPLC) method for the analysis of Canagliflozin using the analytical quality by design (AQbD) approach. The key parameters were methodically optimized with the help of factorial experimental design, and contours were plotted when investigated using Design Expert software. A stability-indicating HPLC technique was developed and validated for the quantitative estimation of Canagliflozin, and its stability was assessed using various forced degradation conditions. Successful separation of Canagliflozin was accomplished using a Waters HPLC system with a photo diode array (PDA) detector and Supelcosil C18 column (250 × 4.6 mm, 5 μm) and 0.2% v/v solution of trifluoroacetic acid in water/acetonitrile (80:20% v/v) as the mobile phase maintaining the flow rate at 1.0 mL/min. The detection wavelength was 290 nm, and Canagliflozin got eluted at 6.9 min with a run time of 15 min. Canagliflozin peak purity values in all degradation conditions indicated that the peak is homogeneous, and therefore this method can be considered stability-indicating. The proposed technique was found to be specific, precise (% RSD about 0.66%), linear (12.6−37.9 μg/mL), rugged (overall % RSD about 0.50%), and robust. The standard and sample solutions were stable after 48 h (cumulative % RSD about 0.61%). The developed AQbD-based HPLC method can be used for the assay of Canagliflozin in Canagliflozin tablets of regular production batches and stability samples.



INTRODUCTION

Sodium glucose cotransporter-2 (SGLT2) antagonists are a family of drugs licensed by the FDA to be used in persons with type 2 diabetes mellitus (T2DM) in combination with diet and physical activity to control blood glucose levels. They reduce blood glucose levels by inducing the kidneys to excrete glucose via urination.[1,2] Canagliflozin (CAN) is an SGLT2 blocker that is taken orally, developed to treat T2DM.[3] It was initially authorized by the FDA in 2015 for T2DM therapy and then again in 2018 for a secondary intention of lowering cardiovascular disease (CVD) risks in patients diagnosed with T2DM. CAN is the first oral antidiabetic agent to be licensed for the prophylaxis of CVD in patients with T2DM.[4] The IUPAC name of CAN is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol,[5] and its molecular formula is $C_{24}H_{25}FO_5S$; the structure is shown in Figure 1. The literature review reveals methods for the estimation of CAN in biofluids, humans, and rat plasma by liquid chromatography−mass spectrometry (LC/MS/MS)[6,7] and high-performance liquid chromatography (HPLC)[8−10] and the determination of related substances in CAN.[11] Few methods using HPLC,[12−18] HPTLC,[19] and UV[20,21] methods for the estimation of CAN in bulk or its pharmaceutical form have been documented. The reported conventional methods were tedious and fretful, requiring a large number of experimental runs, and always yielded a narrow robust method that has a high risk of failure during transfer/real-time usage. The analytical quality by design (AQbD) technique is a potential option for reducing experimental time and expense. Pharmaceutical firms have recently begun to use QbD in analytics for trouble-free compilation with FDA and ICH guidelines. The benefits of applying QbD principles to analytical methods include identifying and minimizing sources of variability that may lead to poor method robustness and ensuring that the method meets its intended performance requirements throughout the

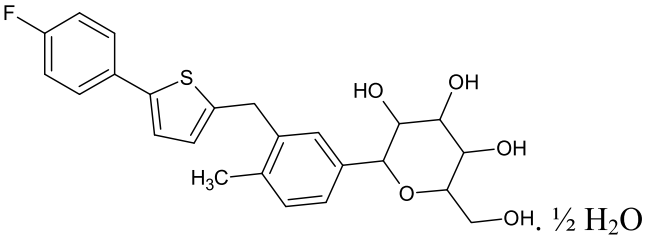


Figure 1. Chemical structure of Canagliflozin hemihydrate.

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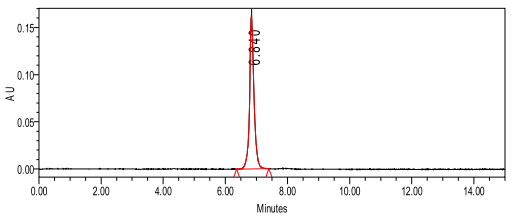

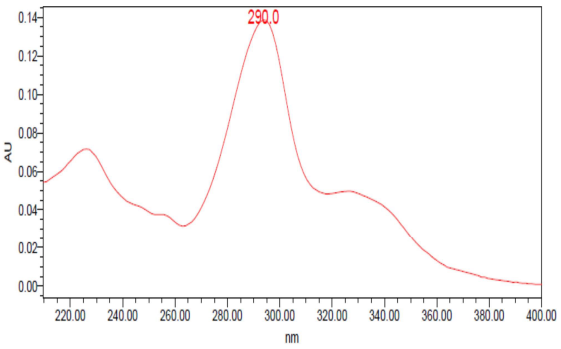

S.No	Name	RT (min)	Area	TF	TP count
1	CAN	6.840	1610147	1.09	13173

Figure 2. Chromatogram and UV spectrum of Canagliflozin standard solution (210−400 nm).

Table 1. System Suitability Test (SST) for QbD—Evaluation of CAN 100 mg Tablets[a]

parameters	set I	set II	set III	set IV	set V
retention time (min)	6.840 ± 0.006	6.916 ± 0.009	6.654 ± 0.033	7.701 ± 0.001	7.251 ± 0.004
capacity factor	1.443 ± 0.002	1.470 ± 0.003	1.376 ± 0.012	1.751 ± 0.000	1.590 ± 0.001
theoretical plate count (USP)	13173 ± 172	10897 ± 127	11744 ± 105	14387 ± 125	9237 ± 116
tailing factor	1.09 ± 0.005	1.07 ± 0.004	1.03 ± 0.004	1.50 ± 0.008	1.05 ± 0.011
area (mean)	1,610,147 ± 6577	1,657,059 ± 5101	1,586,934 ± 4650	1,599,501 ± 4300	1,766,557 ± 7254
% RSD of five replicate injection	0.41	0.31	0.29	0.27	0.41

[a]Set I, control (optimized method); set II, buffer concentration variation (+0.2 mL/L); set III, buffer concentration variation (−0.2 mL/L); set IV, stationary phase variation (BDS Hypersil C18, 250 × 4.6 mm, 5 μ); and set V, use of other buffer (OPA).

Table 2. Confirmation of Solution 1 of 100 Response[a]

solution 1 of 100 response	predicted mean	predicted median	std dev	*n*	SE pred	95% PI low	95% PI high
RT	8.26255	8.26255	0.667269	1	0.744873	6.50121	10.0239
TF	1.19306	1.19306	0.0794532	1	0.0886936	0.983329	1.40278
TP	4329.59	4329.59	371.766	1	415.002	3348.27	5310.92

[a]Two-sided, confidence = 95%.

product and method lifecycle. The major objective of AQbD has been to identify failure modes and establish a robust method operable design region or design space within meaningful system suitability criteria and continuous lifecycle management. If an AQbD approach has been implemented in the development stage, the flexibility of an analytical method is granted without the need for revalidation or regulatory review.[22−27] Stability testing is required to reveal the intrinsic stability properties of active pharmaceutical ingredients, according to the ICH guidelines for stability testing.[28] The proposed chromatography technique is distinct from the literature following analytical method development through the QbD approach for quantitative estimation of CAN in API/pharmaceutical dosage form with the enactment of stability studies. The optimized technique was verified in accordance with ICH standards[29−31] and its latest international convention.

MATERIALS AND METHODS

Canagliflozin hemihydrate (CANH) was obtained from Rainbow Lab (% purity: 98.8% w/w on as-is basis). Acetonitrile (ACN, HPLC grade), hydrochloric acid, hydrogen peroxide, sodium hydroxide, and trifluoroacetic acid (TFA) of AR grade were purchased from Merck Chemicals, Hyderabad. Water (HPLC grade) was purchased from Rankem. In-house formulations of CAN 100 mg tablets were utilized (Label Claim; each film-coated tablets contain: CANH, equivalent to CAN 100 mg).

Instrumentation. The investigation was carried out with a Waters-2695 (Model alliance) HPLC with a PDA detector, Empower Software version 2, an analytical balance (Mettler Toledo), a pH meter (Lab India), and an ultrasonicator. The Supelcosil C18 column (250 × 4.6 mm, 5 μm) with a flow rate of 1 mL/min (isocratic) was used.

Preparation of Solutions. *Preparation of Trifluoroacetic Acid Buffer (0.2% v/v).* Two milliliters of trifluoroacetic acid (TFA) was taken in a volumetric flask and diluted to 1000 mL with water (HPLC grade).

Preparation of the Mobile Phase. TFA (800 mL) and 200 mL of acetonitrile (ACN) were accurately measured and mixed (TFA/ACN = 80:20% v/v) and degassed for 10 min in an ultrasonicator before filtering with a 0.45 μ membrane filter under vacuum filtration.

Preparation of Diluents. ACN and water were combined in a ratio of 75:25 (% v/v).

Preparation of Standard Solution. Precisely 101 mg of CANH was taken in a 200 mL volumetric flask. Subsequently, 140 mL of diluent was introduced and agitated for 10 min in a sonicator with intermittent stirring for dilution and blended well. The mixture was filtered (with a 0.45 μm filter), and 5 mL of the mixture was pipetted out; the volume was adjusted to 50 mL by adding the diluent (50 ppm).

Test Assay Preparation Analytical Target Profile (ATP). One hundred milligrams of CAN tablet powder was measured

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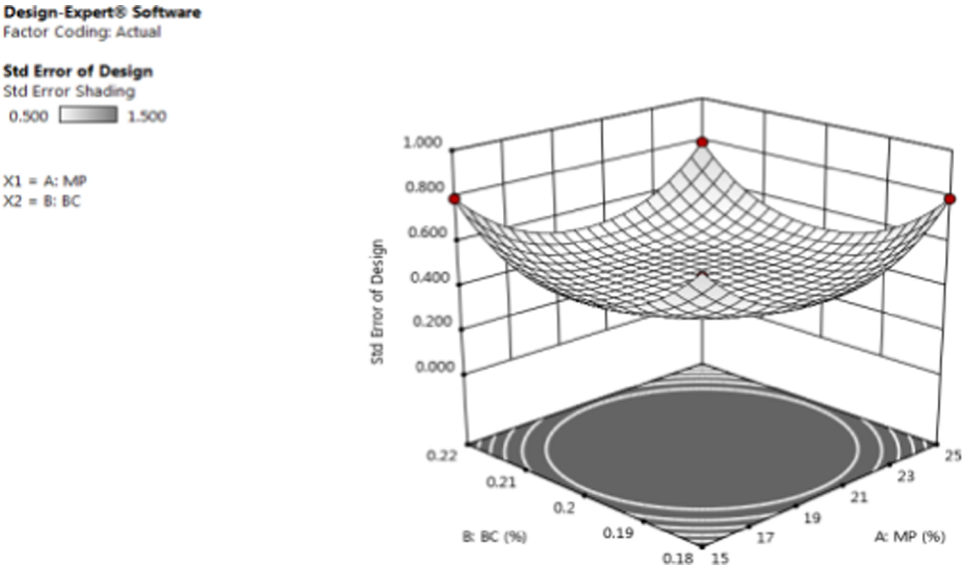

Figure 3. Response surface plot for standard error of design: the CAN 100 mg tablet assay method.

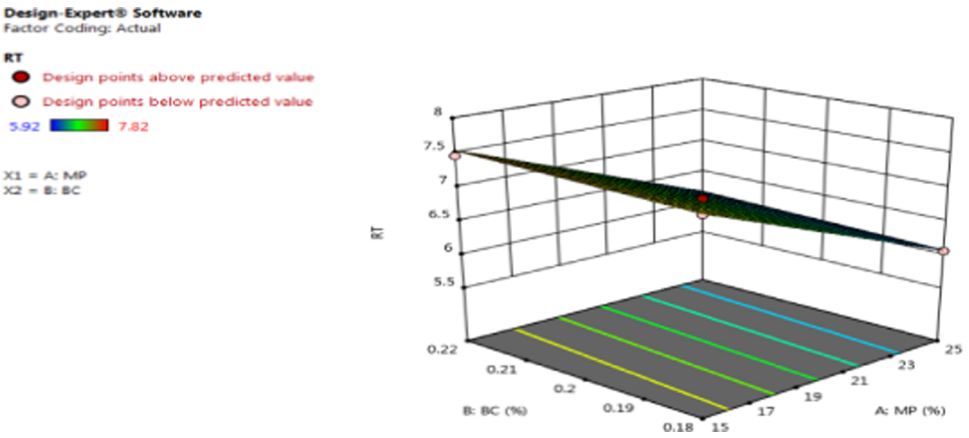

Figure 4. Response surface graph for CAA factors for response (A) retention time (RT).

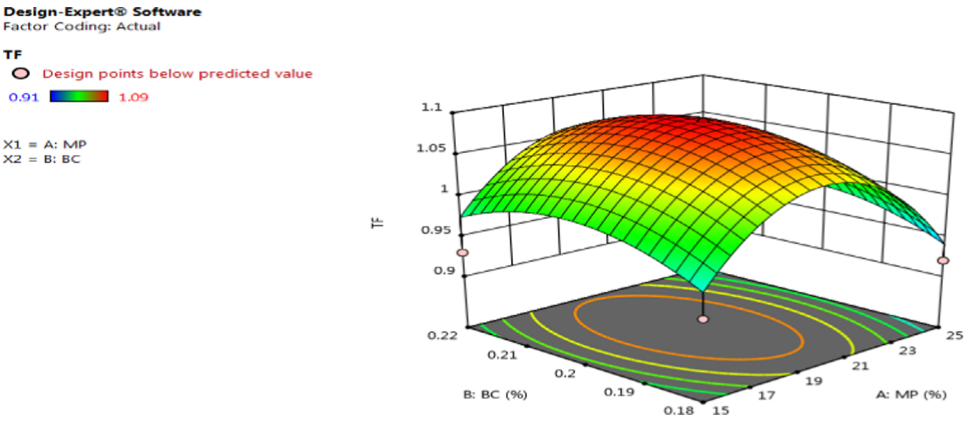

Figure 5. Response surface graph for CAA factors for response (B) tailing factor (TF).

and transferred accurately to a 200 mL measuring flask. The diluent (140 mL) was poured into the flask and sonication was carried out for 30 min with intermittent shaking for dilution and agitated well. The mixture was sieved (through a 0.45 μ filter), 5 mL of the mixture was pipetted out, and the volume was adjusted to 50 mL using a diluent (50 ppm).

Analytical Target Profile. This study used a risk-based approach based on the principles of the QbD in accordance with the ICH Q8 and Q9 and was supplied for both ruggedness and robustness evaluation. According to ICH Q8 standards, robustness can be defined as a method's ability to endure material variability and changes of the process and equipment without the adverse effects.[31] Identifying the ATP

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includes selecting method requirements, including the target analytes (both drug and its impurities), analytical method type, and product specifications. The target was CAN API (Active Product Ingredient), while the selected technique was the determination of CAN. The proposed work had method requirements that included diluents, the mobile phase composition, and the column as per the HPLC.

Chromatography Conditions. The AQbD approach was applied for the chromatography method development of CAN. The separation of CAN was performed using the Waters HPLC system (described above). Further, QbD was studied with the help of Design Expert software version 11 [Central Composite Design, CCD]. CCD has been employed to find out the significant factors as well as optimize the chromatography parameters with the fewest possible runs. Two variables (buffer concentration and mobile phase) were selected for the DOE for optimization, whereas retention time (RT), tailing factor (TF), and theoretical plates (TP) were selected as the governing variables. A degasified mixture of 0.2% v/v TFA and ACN in 80:20 (% v/v) serves as the mobile phase. A flow rate of 1 mL/min and a run time of 15 min were maintained. The temperature of the column was fixed at 30 °C. The detection wavelength was chosen as 290 nm with 10 μL as the sample injection volume.

Critical Test Parameters/Attributes and Initial Risk Assessment. In QbD, experiments were conducted to discover the link between critical test parameters (CTP) and the reaction or qualities of the technique or product (critical quality attributes) (CQAs). The data were then utilized to accomplish the process/test or product quality target test profile (QTTP). The CTPs used in this study were 0.2 mL/L TFA in the mobile phase, a different type of C18 column, and a mobile phase containing orthophosphoric acid (OPA) instead of TFA (same pH and pK_a range). The significance of the design was determined by the evaluation of statistical parameters, i.e., analysis of variance (ANOVA) method and good fit evaluation. The optimization of the method parameters was done on the basis of the response surface method.

RESULTS AND DISCUSSION

The chromatogram and UV spectrum of CAN are shown in Figure 2.

Design of the Experiment (Method Optimization and Development). In QbD approaches, the CTPs passed all of the system suitability parameters with a % RSD of 0.27−0.41% (Table 1). The chromatograms are shown in Supporting Information Figures S1−S4.

Critical Test Parameters/Attributes and Initial Risk Assessment. A factorial design was conducted with Design Expert software v11 (CCD) and applied for observing the effect of two independent variables, buffer concentration (BC %) and organic ratio of the mobile phase (MP %), on three responses, retention time (RT), tailing factor (TF), and theoretical plate (TP), as parameters for optimization of the proposed method. The CCD matrix for screening of method variables using Design Expert software v11 for the CAN tablets assay method is presented in Table S1. The chromatography conditions and ranges fixed for selected variables are given in Table 2. The response surface plot for standard error of design for the CAN 100 mg tablet assay method (Figure 3) shows a precise response. The responses of the variable are represented in the Supporting Information (Figures S5−S10).

Table 3. QBD Data Statistical Analysis Using ANOVA for Responses: Assay of CAN 100 mg Tablet

response	SS	DF	MS	standard deviation	mean	CV %	R_2	adjusted R_2	predicted R_2	adequate precision	F-value	P-value	significance
RT	3.73	2	1.87	1.87	6.81	0.963	0.9886	0.9863	0.9762	61.1407	433.92	0.0001	significant
TF	0.0696	5	0.0139	0.0139	1.01	3.56	0.8552	0.8033	0.1839	8.4499	10.80	0.0035	significant
TP	4.950×10^6	5	9.899×10^5	9.899×10^5	12860.23	4.07	0.7203	0.5205	0.9892	6.8616	3.60	0.0623	not significant

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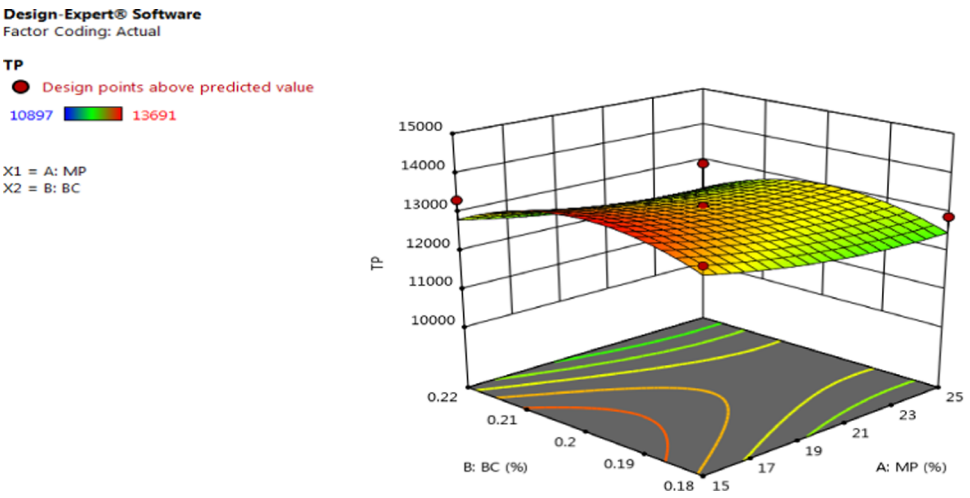

Figure 6. Response surface graph for CAA factors for response (C) theoretical plates (TP).

Table 4. Forced Degradation and Peak Purity Data

stress conditions	assay (% w/w)	calculated degradation % w.r.t. control	% assay by area normalization	CAN peak	
				purity angle	purity threshold
standard solution	NA	NA	100.0	**0.405**	**0.535**
control sample	100.1	NA	100.0	**0.399**	**0.509**
acidic degradation (HCl) (50 °C for 4 h)	88.8	11.3	98.3	**0.444**	**0.977**
alkali degradation/1N sodium hydroxide (50 °C for 4 h)	91.4	8.7	98.2	**0.366**	**0.854**
oxidation degradation (H_2O_2) (50 °C for 4 h)	93.8	6.3	98.1	**0.359**	**0.841**
thermal degradation (50 °C for 5 days)	89.6	10.5	95.5	**0.259**	**0.781**
photolytic degradation (1.2 million lux hours)	97.4	2.7	97.1	**0.409**	**0.801**
humidity degradation (25 °C/92% RH for 5 days)	98.5	1.6	98.4	**0.364**	**0.914**

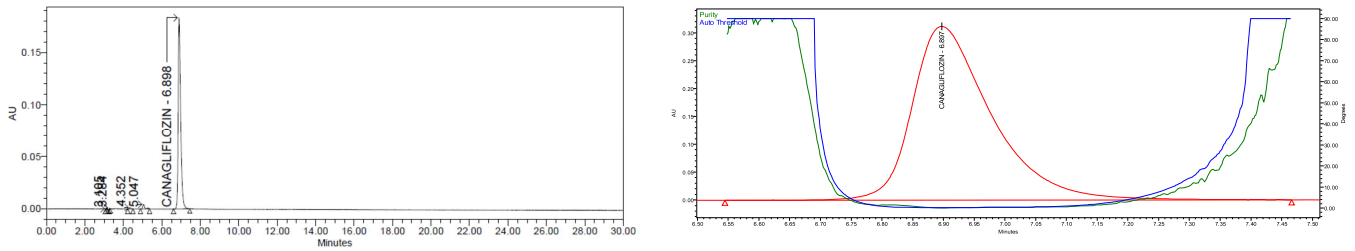

Figure 7. Chromatogram and peak purity plot of Canagliflozin peak (acid degradation sample).

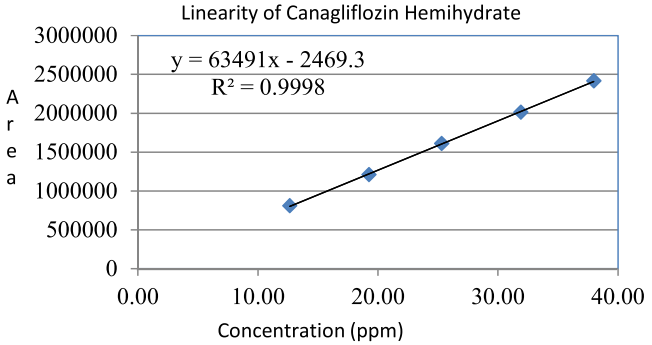

Figure 8. Linearity of Canagliflozin hemihydrate.

Critical Analytical Attributes. The AQbD testing was conducted with Design Expert software v11 (CCD) for the two CAA factors buffer concentration (BC %) and organic ratio of the mobile phase (MP %) for three responses: RT (in min), TF, and TP. The probabilities of the three responses were found to be below 1 (Tables S2−S4), which indicates the significance of the method. According to the three-dimensional (3D) response surfaces and quadratic model equation, it is observed that both variables A and B have a positive effect on RT (Figure 4), TF (Figure 5), and TP (Figure 6). Hence, it shows that the relationship between factors and response is linear; although one or more than one factor is altered simultaneously, it results in a similar grade of responses (Figures S11 and S12).

Statistical Analysis. ANOVA was used to analyze the QbD data (Table 3). From Table 3, the predicted R-squared for all responses R_1 (0.9762), R_2 (0.1839), and R_3 (0.9892) is in reasonable agreement with the adjusted *R*-squared values of 0.9863, 0.8033, and 0.5205, respectively, i.e., the difference was less in each case. These models can be used to navigate the design space. The results of ANOVA for responses R_1, R_2, and

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R_3 showed that the model F-value of 433.92, 10.80, and 3.60, respectively, implies the models are significant. The p-values for the model terms showed that both variables A and B are significant. These models can be used to navigate the design space. Equations for the three responses retention time, tailing factor, and theoretical plates with reference to coded factors and actual factors are provided below (eqs 1−6).

With respect to coded factors (eqs 1−3)

$$\mathrm{RT} = 7.80 - 0.5834A - 2.76B + 0.1000\mathrm{AB} - 0.6687A^2 + 0.3563B^2 \quad (1)$$

$$\mathrm{TF} = 1.20 + 0.0416A - 0.1203B - 0.0125\mathrm{AB} + 0.0063A^2 + 0.2688B^2 \quad (2)$$

$$\mathrm{TP} = 4592.00 - 267.62A + 214.54B + 90.00\mathrm{AB} - 534.62A^2 - 1048.13B^2 \quad (3)$$

With respect to actual factors (eqs 4−6)

$$\mathrm{RT} = 42.91177 + 265.20685A - 1.79284B + \mathrm{AB} - 1671.87500A^2 + 0.014250B^2 \quad (4)$$

$$\mathrm{TF} = 18.81036 + 3.95527A - 0.871553B - 0.12500\mathrm{AB} + 15.62500A^2 + 0.010750B^2 \quad (5)$$

$$\mathrm{TP} = -72631.89096 + 2.17932 \times 10^5 A + 3306.90861B + 900.00\mathrm{AB} - 1.33656 \times 10^6 A^2 - 41.92500B^2 \quad (6)$$

where A and B are BC % (in mL/L) and MP % (% methanol), respectively.

Method Validation. *Specificity.* The purity of the CAN peaks was assessed by evaluating the sample according to the procedure. The purity values for the CAN peak indicated that it is homogeneous.

Placebo Interference. Placebo solution was formulated according to the test procedure and introduced into the HPLC column (in the placebo chromatogram, CAN peak was not seen).

Forced Degradation Studies. The following settings were used to test the degradation of CAN tablets (100 mg) (Table 4). CAN drug product (100 mg tablets) was subjected to stress degradation under acidic (Figure 7), alkali, peroxide, thermal, photolytic, and humidity conditions. The detailed conditions and their figures are summarized in the Supporting Information (Figures S13−S17).

Injections of forced degradation samples were monitored for a run time of 20 min. Using a photo diode array detector, the peak purity of CAN peak was generated for all of the abovementioned degradation condition samples. From the peak purity data (purity angle less than purity threshold) of the CAN peak, it was concluded that the CAN peak was homogeneous (Table 4) and had no co-eluting peak. This indicates that the proposed RP-HPLC method is specific and stability-indicating.

Precision. *System Precision.* Into the HPLC column, five injections of reference solution were introduced. The area response and % RSD of the CAN peak are shown in Table S5, which indicates an appropriate degree of precision for the HPLC technique. (As per acceptance criteria, RSD must be less than 2%).

Method Precision. The % RSD obtained from the method precision was 0.37%, which indicated an acceptable level of

Table 5. System Suitability Parameters for Robustness[a]

parameters	set I	set VI	set VII	set VIII	set IX	set X	set XI	set XII	set XIII
retention time	6.840 ± 0.006	7.910 ± 0.002	5.845 ± 0.002	7.426 ± 0.004	6.056 ± 0.006	6.828 ± 0.007	6.840 ± 0.007	7.2316 ± 0.007	6.311 ± 0.007
capacity factor	1.443 ± 0.002	1.825 ± 0.001	1.087 ± 0.001	1.652 ± 0.002	1.163 ± 0.002	1.439 ± 0.002	1.443 ± 0.002	1.583 ± 0.002	1.254 ± 0.002
theoretical plate count (USP)	13,173 ± 172	13,995 ± 116	12,846 ± 120	13,329 ± 140	12,903 ± 27	13,505 ± 158	13,330 ± 113	13,329 ± 128	12,903 ± 158
USP tailing factor	1.09 ± 0.005	0.94 ± 0.004	1.09 ±. 004	0.93 ± 0.011	0.92 ± 0.004	1.09 ± 0.004	1.09 ± 0.004	0.93 ± 0.005	0.92 ± 0.004
average area	1,610,147 ± 577	2,081,822 ± 8016	1,499,188 ± 4916	1,925,262 ± 5556	1,559,587 ± 5025	1,499,188 ± 5001	1,741,256 ± 4050	1,925,262 ± 6124	1,579,888 ± 3050
% RSD of five replicate injection	0.41	0.39	0.33	0.29	0.32	0.33	0.23	0.32	0.19

[a]Set I, control (optimized method); set VI, variation in low rate (−0.2 mL/min); set VII, variation in flow rate (+0.2 mL/min); set VIII, variation in organic content in the mobile phase (−5%); set IX, variation in organic content in the mobile phase (+5%); set X, variation in wavelength (λ = 288 nm); set XI, variation in wavelength (λ = 292 nm); set XII, column oven temperature (−5 °C); and set XIII, column oven temperature (+5 °C).

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Table 6. Summary of Validation Parameters

s.no	validation parameters		Canagliflozin tablets	acceptance criteria
1.	specificity		no peak observed in the main peak RT	no peak should be observed in the main peak RT
2.	precision (% RSD of area)	system precision	0.41	% RSD NMT 2.0
		method precision	0.66	
3	accuracy (% w/w)	50%	100.2	between 98 and 102%
		100%	99.8	
		150%	99.8	
4	linearity		r^2 = 0.999	$r^2 \geq 0.99$
5	range		12.6−37.9 μg/mL	
6	LOD		4.03	NLT 3
7	LOQ		15.61	NLT 10
8	ruggedness		% RSD-0.50	% RSD NMT 2

precision. The method and results are presented in the Supporting Information (Table S6).

Accuracy. The accuracy of CAN (50, 100, and 150% level) was analyzed, and the % mean recovery of accuracy values was found to be 100.4, 100.5, and 99.8%. The % RSD was found to be 0.59% (Table S7).

Linearity of Response. A proportionate correlation between area response and concentration of the sample over a working concentration range should be used to demonstrate the method's linearity.

This gave assurance that the response is proportional to concentration, allowing calculations to be done with the help of a single reference/working standard solution instead of a calibration line equation. The linearity of response for CAN was found to range between 12.6 and 37.9 micrograms per milliliter. Data are tabulated in Table S8, and its graphical representation is given in Figure 8, which indicates that the method is linear across the recommended range. (As per acceptance criteria, the correlation coefficient must be more than 0.99).

Ruggedness. Ruggedness was determined by analyzing six samples of the same batch of CAN 100 mg tablets separately in two sets. Days of the experiment, individuals performing them, and equipment/column used should be different from each other. The overall standard deviation and % RSD for obtained data are tabulated in Table S9. The mean of two RSD values was found to be 0.50, which is within the accepted limit and hence proved that the method is rugged.

Stability in Analytical Solutions. Stabilities of reference and sample solutions in analytical solutions (at about 25 °C) were studied after 48 h. (As per acceptance criteria, RSD must be less than 2%.)

Robustness. The method's robustness was studied by deliberately modifying the experimental settings, including flow rate (±0.2 mL/min), MP % (±5%), the detection wavelength (±2 nm), and temperature of column (±5 °C). Under each set, standard solutions were pumped into the HPLC column (5 injections) under each condition, and the system suitability variables (RT, TP, TF, % RSD) were calculated as shown in Table 5.

The current method was novel, precise, sensitive, stable, and cost-effective. Also, the mobile phase used was cost-effective with less consumption of organic solvents compared to the reported methods. The summarized results of method validation as per ICH guidelines are presented in Table 6 and found that all of the parameters were within the acceptance criteria.

CONCLUSIONS

The QbD approach to analytical method development was used for a better understanding of method variables with different levels. The CCD experimental design describes the interrelationships of buffer concentration and organic ratio of the mobile phase at three different levels, and the responses to be observed were retention time, theoretical plates, and tailing factor with the help of the Design Expert 11.0 version. This approach offers a knowledge understanding that helps for the development of chromatography optimization that can be used in the future. In the AQbD-based RP-HPLC method, the peak purity of CAN peak was studied with the help of a PDA detector (for all degradation products, control sample, and reference solution), and the developed technique is validated in accordance with USP and ICH criteria. The innovative stability-indicating RP-HPLC analytical technique uses an LC−MS-suitable volatile buffer for preparing the mobile phase. The automated QbD method development approach using the Design Expert software has provided a better-performing more robust method in less time compared to manual method development. The statistical analysis of data indicates that the method is reproducible, selective, accurate, and robust. This method will be used further for routine analysis for quality control in the pharmaceutical industry. The suggested approach was effectively used for the quantification of marketed CAN 100 mg tablets (Invokana 100 mg, Batch No: IEZ0I00, % Assay: 99.8% w/w).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06038.

Additional information on design of the experiment (critical test parameters/attributes and initial risk assessment, critical analytical attributes), results of forced degradation study, and method validation (PDF)

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Notes

The authors declare no competing financial interest.

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