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ANALYTICAL QUALITY BY DESIGN APPROACH FOR DEVELOPMENT AND VALIDATION OF UV-SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF CANAGLIFLOZIN IN BULK AND FORMULATION

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AQbD (Analytical quality by design), Canagliflozin, Central composite design-Spectrophotometric method

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ABSTRACT: The present work deals with the development and validation of a novel, robust, precise, and accurate UV-spectrophotometric method for the estimation of canagliflozin in bulk and formulation using the principle of Analytical Quality by Design (AQbD). A central composite design (CCD) was employed for initial parameter screening and method optimization. Different statistical parameters were evaluated to decide the appropriateness of experimental data. Canagliflozin shows an absorption maximum at 290 nm using methanol and water. Factor screening slit width and sampling interval were identified as critical method variables, which were further evaluated by a CCD. Design Expert (Version 12.0.6.0, Stat-Ease Inc., Minneapolis, MN USA) software was used for the method optimization and generation of design space Good linearity was obtained for canagliflozin in the range of 5-25 µg/mL with R2> 0.9989. The method was found to be accurate with good average % recovery. The developed method was validated as per ICH guidelines. Based on AQbD development of the Spectrophotometric method ensured that quality is built into the method. The method was robust and can be applied for determination of the canagliflozin in a pharmaceutical dosage form. The developed method was also cost-effective as it employs combination of water and methanol as solvent system.

INTRODUCTION: Canagliflozin is the first oral antidiabetic drug approved for the prevention of cardiovascular events in patients with type 2 diabetes. The Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. Canagliflozin is chemically (1S)-1, 5-anhydro-1-[3-[[5-(4- fluorophenyl)-2-thienyl] methyl]-4-methylphenyl]-Glucitol and belongs to the class of SGLT2 inhibitors [1, 2].

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The structure is shown in **Fig. 1**. It is white to off white powder, soluble in many organic solvents (ethanol, methanol, tetrahydrofuran, acetone), but insoluble in aqueous media. The log P of the drug substance is [3].

44 at 20 ºC and pH=7 [3]. There is no pKa in the physiological pH range. The molecular weight of Canagliflozin is 453.53 g/mol, and formula is $C_{24}H_{25}FO_5S$ [4, 5]. It is used in the treatment of type-2 diabetes. Canagliflozin inhibits the reabsorption of glucose from kidneys and lowers the renal glucose threshold by inhibiting sodium-glucose transport protein (SGLT2) [6]. By blocking SGLT2, Canagliflozin decreases reabsorption of filtered glucose and reduces the renal threshold for glucose (RTG), thereby elevating the urinary glucose

excretion (UGE) and reducing raised plasma glucose in patients with type-2 diabetes [7]. Urinary glucose excretion induced by canagliflozin leads to an osmotic diuresis, which can be associated with caloric loss and reduction in weight. The drug is commercially available in various forms of once-daily oral dosage formulations. Canagliflozin can be used as monotherapy or multi-therapy in the treatment of type-2 diabetes [8].

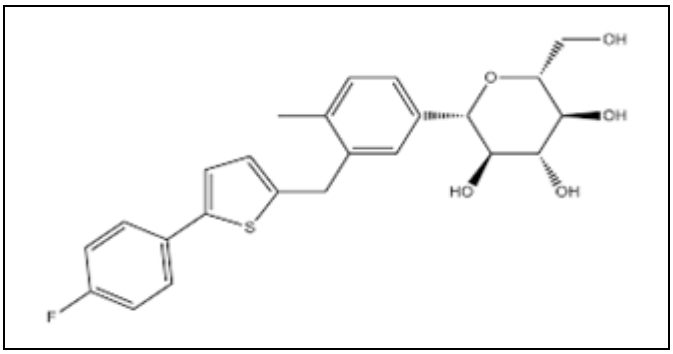

FIG. 1: STRUCTURE OF CANAGLIFLOZIN

The concept of quality by design was elaborately given by the quality expert Joseph M. Juran. QbD principles are widely applicable in various fields like the food and automobile industries. The Toyota automobiles were the initiator for the application of these principles, and later it is now adopted by the pharmaceutical industries also. Recently the novel approach has been used by USFDA for the whole pathway of drug discovery, development, and manufacturing [9, 10]. Nowadays, AQbD has become a very important aspect of the pharmacy and International Conference on Harmonisation (ICH) guidance on pharmaceutical development as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [18]. Currently, QbD approach has been successfully implemented in generic formulation development.

Equivalent to process QbD, the outcome of AQbD is well understood and fit for intended purpose with robustness throughout the lifecycle [11, 12, 13, 14]. AQbD life cycle has different tools, which are further discussed. As already widely discussed in the scientific literature applying the Analytical quality-by-design (AQbD) concept to analytical methods ensures a controlled risk-based development of a method where quality assurance will be guaranteed [15, 16, 17]. The literature survey revealed that few analytical methods were reported for estimation of the drug-like HPLC, UV, LC-MS and HPTLC analysis [19, 20, 21, 22, 23]. The recent Quality by design and analytical quality by design topics were not discussed. In the present study an attempt was made for utilization of analytical quality by design approach for method development and validation so that the quality of method is maintained throughout the lifecycle. The main idea is the implementation of the recent AQbD approach on HPTLC method development and validation and focuses on every step of AQbD approach is understood in-depth to ensure optimum method performance over the lifecycle of the product.

MATERIALS AND METHODS:

Reagents and Instrument: The standard drug sample was obtained as a gift sample from Zydus pharma, Ahmedabad, Gujarat, India. Invokana (Canagliflozin 100 mg) film-coated tablets were used for the assay manufactured by Janssen CilagSpA, Latina Italy, and marketed by Johnson & Johnson Pvt. Ltd. Mumbai, India. Methanol was procured from Sisco Chem Pvt. Ltd., Andheri Mumbai, and distilled water was collected from distillation assembly. A spectrophotometric scan was carried out on 'Shimadzu' double beam UV-Visible spectrophotometer (UV-1800) with 1 cm quartz cell. Digital weighing balance of Denver SI234, Germany, was used.

TABLE 1: ATP FOR CANAGLIFLOZIN API AND TABLETS

Quality attributes	Target	Criticality
Dosage form	Tablet	Not applicable
Potency	100 mg	Not applicable
Physical description	Solid powder	Not applicable
Appearance	White crystalline powder, or colorless crystals	Critical
Identity	Positive	Critical
Impurities	Hydroperoxide, sulfone, dimer,5-iodo2-methyl benzoic acid	Critical
Heavy metals	LT 31 ppm	Critical
Clinically Relevant Nonmedicinal Ingredients	Lactose, Iron oxide yellow and titanium dioxide	Critical
Route of Administration	Oral	Not applicable

Analytical Target Profile (ATP): The analytical target profile is the necessary tool for product and method development, as it is outlined in the ICH Q8 R (2) guidelines. It defines the method requirements which are expected to be measured that direct the method development process i.e.it is a combination of all performance criteria required for the proposed analytical application shown in **Table 1**.

Critical Quality Attributes (CQA), Critical Material Attributes and Critical Method Attributes (CMA'S): The ICH Q8 guidelines describe CQA as the chemical, microbiological, physical, and biological properties of a drug. These properties should be within the constraints to guarantee that the end product is of desirable quality. Critical method parameters (CMP's) are divided into three types *viz.* parameters regarding analyte, parameters regarding instrument and parameters regarding operation conditions.

1. Critical Quality Attributes: Dosage form, Potency, Physical description, appearance, identity, assay, impurities, content uniformity, heavy metals, clinically Relevant Non-medicinal Ingredients, Route of Administration, Melting point.

2. Critical Material Attributes: Reagent grade, manufacturing and expiry date of reagent, storage conditions, purity, maximum limit of impurities, boiling point or melting point, non-volatile matter.

3. Critical Method Attributes: Sample concentration and diluent, sample solution stability, sample preparation process (dilution process and sonication time, *etc.*), filter or centrifuge, detection category, detection wavelength, solvent cut off, scanning speed, scanning rate, detection mode, baseline correction, auto-zero, baseline correction and autozero, calibration status, slit width, cuvette characteristics, resolution power, baseline flatness, Data Acquisition, and Control System.

2.4. Primary Method Scouting: With the CQA goals defined, method scouting can begin, classically with the literature survey, physical and chemical properties of the moiety, flowcharts, and decision trees to guide the analyst to begin with among the choices. Automation in scouting experiments is ideal procedure shown in **Table 2**.

TABLE 2: REPORTED METHODS FOR ESTIMATION OF CANAGLIFLOZIN BY UV-SPECTROPHOTOMETRY

S. no.	Title	Specification
1	Development and Validation of a Stability-Indicating UV Spectroscopic Method for Determination of Canagliflozin in Bulk and Pharmaceutical Dosage Form	Calibration Curve Range-5,6,7,8,9,10µg/Ml Solvent-Methanol Λ_{max} -290 Nm
2	Simultaneous estimation of canagliflozin and metformin hydrochloride in tablet dosage form by UV spectrophotometry	Calibration Curve Range-2.5,5,7.5,10,12.5,15µg/Ml Solvent-Methanol Λ_{max} -290 Nm
3	Development and validation of UV-spectrophotometric method for estimation of canagliflozin and metformin	Calibration Curve Range- 10,15,20,25,30µg/Ml Solvent-Methanol And Water Λ_{max} -290 Nm
4	Comparison of UV Spectrophotometric and HPLCMethod for Estimating Canagliflozin in Bulk and a Tablet Dosage Form	Calibration Curve Range-5-50µg/Ml Solvent-Methanol Λ_{max} -290 Nm
5	Analysis of canagliflozin, review	Calibration Curve Range- 5,6,7,8,9,10µg/Ml Solvent-Methanol Λ_{max} -290 Nm
6	Development and Validation of UV-Visible Spectroscopic Methods for Simultaneous Estimation of Canagliflozin and Metformin in Pharmaceutical Formulation.	Calibration Curve Range- 1,2,3,4,5µg/Ml Solvent-Methanol Λ_{max} -291 Nm

Risk Assessment: Risk Assessment can be performed from the initial stage of method development to continuous method monitoring. AQbD approach involves the risk identification at the early stages of development followed by appropriate mitigation plans with control strategies that will be established, shown in **Table 3**.

TABLE 3: CQA AND CMA'S ALONG WITH RISK ASSESSMENT.

Sr. No.	Critical Quality Attributes (Cqa), Critical Material Attributes snd Critical Method Attributes (Cma's)	Risk Assessment		
		Low	Medium	High
1	Baseline correction and auto zero			✓
2	Solvent cut off			✓
3	Sample concentration and diluent			✓
4	Detection wavelength			✓
5	Sample solution stability	✓		
6	Sample preparation process (dilution process and Sonication time *etc.*)		✓	
7	Calibration status		✓	
8	Slit width			✓
9	Cuvette	✓		
10	Resolution power		✓	
11	Baseline flatness			✓
12	Scanning speed, rate and mode		✓	
13	System suitability parameters selection with limits		✓	

Method Optimization and Design of Experiments: Once the potential and critical analytical method variables are defined with initial risk assessment, then DoE can be performed to confirm and refine critical method variables based on statistical significance. Design of Experiments approach (DoE) can be used to determine one variable at time design or multi variables designs and their relations and responses. The multifactorial design provides a chance to screen number of conditions in minimum experiments, and then the critical method variables were identified with the aid of statistical data and the method operable design space.

UV-Spectrophotometric Method Optimization:

• **Preparation of Canagliflozin Standard Stock Solution (1000 µg/ml):** Accurately weighed 10mg of canagliflozin was transferred into 10ml volumetric flasks, dissolve and diluted up to mark with Methanol to get stock solution having a concentration of canagliflozin 1000 µg/ml.

• **Preparation of Working Standard Solution (100 µg/ml):** 1 ml of standard stock solution of canagliflozin was transferred to 10 ml volumetric flask and diluted to 10 ml with methanol to get canagliflozin working standard solution of 100 µg/ml.

• **Selection of Detection Wavelength:** The sensitivity of the method with UV detection depends upon the proper selection of detection wavelength. An ideal wavelength is one that gives good response for the drugs that are to be detected. Canagliflozin showed maximum absorption at 290 nm and it was selected as detection wavelength for UV-Spectro-photometric analysis shown in **Fig. 2**.

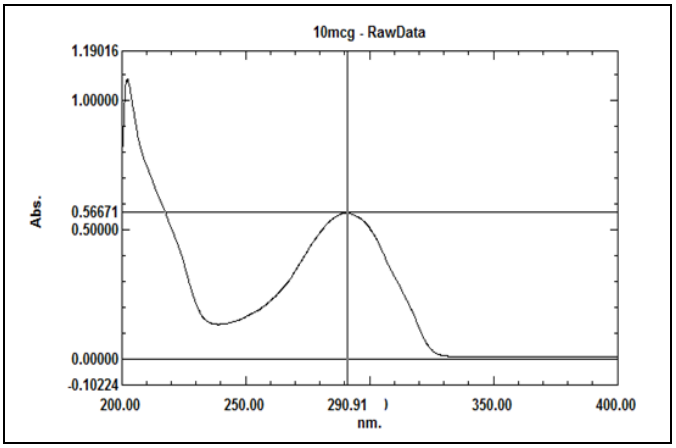

FIG. 2: UV SPECTRUM OF 10 µG/ML CANAGLIFLOZIN SHOWING MAXIMUM ABSORBANCE AT 290 NM

Design of Experiments: A Central composite design was applied to evaluate the various effects of the independent variables. Application volume, temperature (ambient), saturation time, development time, detection and scanning wavelength were selected as constant chromatographic conditions.

Experiments were conducted by applying the standard solution containing canagliflozin, peak area and retardation factor were determined using Design Expert (Version 12.0.6.0, Stat-Ease Inc., Minneapolis, MN USA). The data are shown in **Tables 4** and **5**.

TABLE 4: LEVELS SELECTED FOR CENTRAL COMPOSITE DESIGNS

Name	Units	Low	High	-Alpha	+Alpha	Name
methanol	ml	4.5	5.5	4.5	5.5	methanol
water	ml	4.5	5.5	4.5	5.5	water

TABLE 5: MATRIX OF CENTRAL COMPOSITE OPTIMIZATION DESIGN AND RESPONSES FOR UV-SPECTROPHOTOMETRIC METHOD

	FACTOR 1	FACTOR 2	RESPONSE 1	RESPONSE 2
Run	A: methanol	B: water	Absorbance	λ_{max}
1	4.5	5.5	0.50383	290
2	5	5	0.65704	290
3	5.5	4.5	0.58276	290
4	5	4.5	0.63778	290
5	4.5	5	0.60123	290
6	5.5	5.5	0.51123	290
7	5.5	5	0.46996	290
8	5	5.5	0.51948	290
9	4.5	4.5	0.58851	290

Method Operable Design Region (MODR) and Establishment of Design Space: FDA has suggested conducting MODR to gather with method validation as most recommended. Method operable design region (MODR) is used for the establishment of a multidimensional space based on method factors and settings; MODR can provide suitable method performance.

TABLE 6: OPTIMIZED CHROMATOGRAPHIC PARAMETERS FOR UV-SPECTROPHOTOMETRY.

Parameters	Optimized Conditions
Instrument type	UV-1800 series
Measuring mode	Absorbance
Scan speed	Fast
Wavelength range	400-200 nm
Initial baseline correction	Water: Methanol (50:50v/v)-for spectrum mode
Autozero	Water: Methanol (50:50v/v)-for photometric mode
Absorbance scale	0.00A – 4.00A
Software	UV-Probe
Sampling interval	0.2
Slit width	1.0 mm
Auto sampling interval	enabled
Scan mode	single
Light source change wavelength	340.0 nm
S/R exchange	normal

It is also used to establish meaningful method controls such as system suitability. The term design space is well put forward in ICH Q8 guideline, which states that it is "the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality". From the outcome of the above DoE, MODR is selected as follows. The chromatographic condition is presented in **Table 6**. By performing the central composite design, the absorbance obtained was reported in the table. The entire model was fitted well for optimization. The following graphs were obtained from the design expert software.

Response surface and contour plots were studied to visualize the effect of factor and their interaction to develop design space for a robust method. The contour plot is a two-dimensional (2D) representation of the response plotted against combinations of numeric factors and/or mixture components. There could be different combinations, which may give several feasible solutions for a robust process. Out of these combinations, whichever is the most desirable from the point of proper absorbance range can be selected as a robust process. This contour space is called design space in products and method operable design (MODR) in analytical works. The MODR that controls the variation in responses obtained from contours a two-dimensional plot. It was also noted that the optimized use of water and methanol composition gives significant results, which are not affected by the other factors. Hence, it was kept as final for method validation, which

offered several method advantages. From the graphs, it was observed that all the results were falling in the graphical areas denoted by the red points in the different graphs and the color of the contour plots shows the operable design region for each run. The green area in the contour plot shows the best region in which the method can be operable, giving accurate results. Moving within design space (green area region) is not considered as a change by the regulatory bodies.

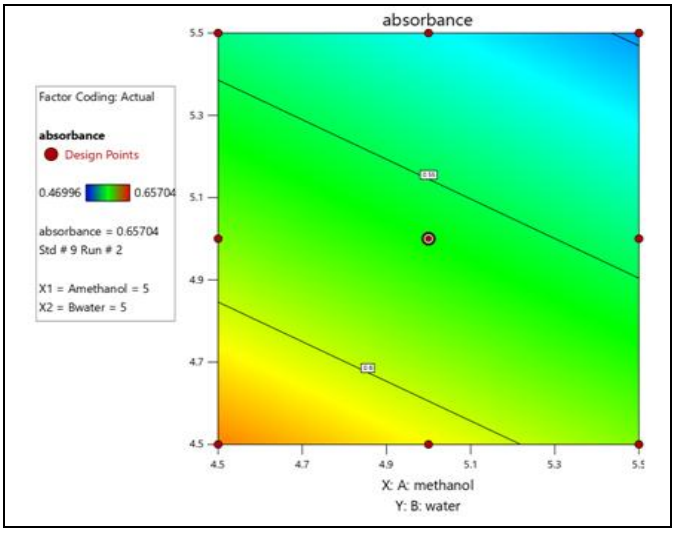

FIG. 3: CONTOUR PLOT OF RUN-2(MIDDLE),RUN-1,8,6 (UPPER SIDE FROM LEFT TO RIGHT),RUN-5 (IN CENTER OF LEFT AXIS), RUN-7(IN CENTER IF RIGHT AXIS) AND RUN- 9,4,3 (BOTTOM SIDE LEFT TO RIGHT)

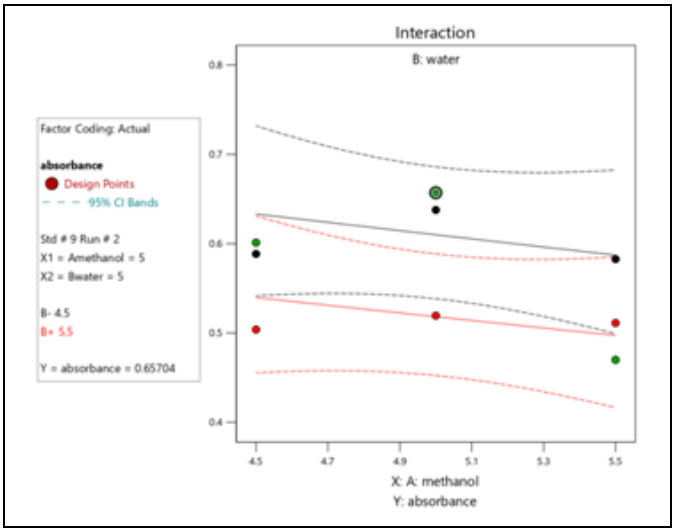

FIG. 4: INTERACTION PLOT SHOWING ALL RUNS IN ONE GRAPH HIGHLIGHTING RUN 2

The run 2 gives the results which were within the most appropriate space and can be considered in the design space.

The standard concentration of 15 µg/ml was used for all the runs. The p-value was found to be less than 0.05; hence model was found to be significant for prediction of responses, shown in **Fig. 3** and **4**.

Control Strategy: The control strategy is defined for the attributes which have low risks and can be accomplished. This control strategy is defined and entails the suitable process appropriateness check and verification consistently. The attributes that are at high risks, like sampling solution concentration, application volume, scanning rate, speed, and wavelength are critically monitored. The attributes that are at high risks like sampling solution concentration, baseline correction, scanning rate, speed, and wavelength are given additional consideration. Use of all analytical grade reagents is appreciated, and take care about the proper storage conditions. Rinse all the volumetric flasks used with the methanol prior of an experiment. Slit width, scanning speed, and scanning wavelength are to be critically checked every time. The control strategy need not be different from the conventional procedure it can be as simple as providing caution notes on the standard testing procedures such as precaution comments like usage of a particular grade of reagents, method sensitivity with respect to pH, organic ratio in the mobile phase. By controlling all the optimized chromatographic conditions noted in the table in the MODR section, the following graph as in **Fig. 5** of standard error of design was obtained showing the least error(lightest shade of grey) in run – with the good retardation factor and peak area.

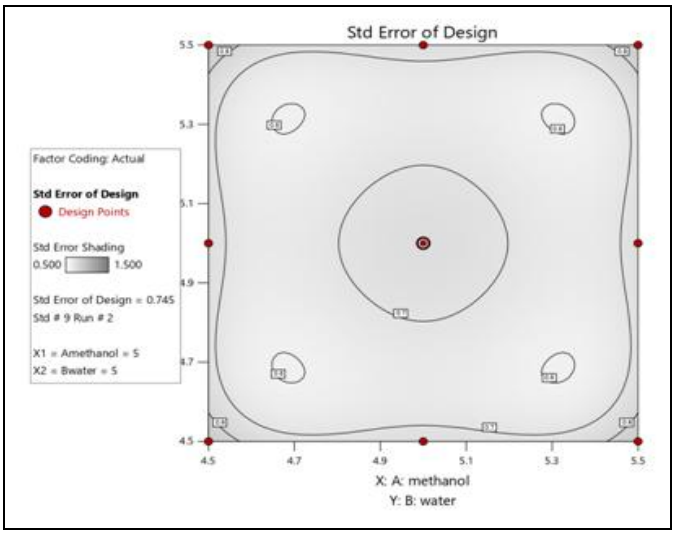

FIG. 5: CONTOUR PLOT FOR STANDARD ERROR OF DESIGN

Method Validation: Method validation entails clarifying that the chosen method will provide information that meets the guidelines of the ATP, in the predicted conditions. Subsequently, the attribute presentation requirements must be put in place before the predicted presentation of the analytical development process. AQbD method validation approach is the validation of analytical method over a range of different API batches. It uses both DoE and MODR knowledge for designing method validation for all kinds of API manufacturing changes without revalidation. The approach provides the required ICH validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach requires fewer resources than the traditional validation approach without compromising quality.

Linearity and Range: Transfer 0.5, 1, 1.5, 2, and 2.5 ml of CF from standard working solutions into a 10 ml volumetric flask and diluted up to the mark with methanol and water (5:5 v/v) to get the concentration range 5-25 µg/ml for CF. The calibration standards were analyzed by the proposed method. The absorbance of CF was measured. The calibration curve for CF was constructed by plotting the absorbance against respective drug concentrations. A linear regression analysis was performed.

Precision:

• **Repeatability:** The precision of the instrument was checked by measurement of the absorbance of solutions (n = 6) of CF (15 µg/ml) without changing the other parameters of the proposed method.

• **Intermediate Precision:**

a) Intraday Precision: The intra-day precisions of the proposed method were determined by analyzing corresponding responses in triplicate on the same day for 3 different concentrations of standard solutions of canagliflozin (10, 15 and 20 µg/ml).

b) Interday Precision: The inter-day precisions of the proposed method were determined by analyzing corresponding responses in triplicate on 3 different days over a period of 3 days for 3 different concentrations of standard solutions of CF (10, 15, and 20 µg/ml).

Accuracy: To the pre-analyzed sample (10 µg/ml was the basic sample concentration), a known amount of standard solution of pure drug CF was studied for accuracy at four different levels (0%, 80%, 100%, and 120%).

The sample was spiked with 0, 8, 10, and 12 mg of standard CF solution to obtain a final concentration range of 10, 18, 20, and 22 µg/ml for CF, and the absorbance was noted. The amount of the drug was calculated by employing corresponding calibration curve equations. The average recovery obtained at all 3 levels was reported as % recovery.

Sensitivity: The sensitivity of measurement of canagliflozin using the proposed method was estimated in terms of Limit of Detection (LOD) and Limit of Quantitation (LOQ).

The LOD and LOQ were calculated by equation and visually. Based on the standard deviation of the response and the slope, LOD and LOQ were estimated using the formulae:

$$LOD = 3.3\ \sigma/S$$

$$LOQ = 10\ \sigma/S$$

Where, σ = the standard deviation of the response, S = the slope of the calibration curve

Specificity: The standard CF was assessed by comparing their respective spectra with formulation to check the specificity.

Robustness: The robustness of the method was ascertained by deliberately altering the chromatographic conditions. Changes in wavelength were selected as parameters and were varied separately, whereas all other conditions were held constant as described in the method.

Assay of Canagliflozin: Weigh and powder 10 tablets. Weigh accurately a quantity of tablet powder equivalent to 10 mg of canagliflozin in 100 ml volumetric flask, add 50 ml of methanol in it and sonicate for 30 mins. dilute up to 100 ml with methanol. Take 1 ml of above solution in 10 ml volumetric flask and dilute up to 10 ml with methanol to get the final concentration of 10µg/ml. Also prepare 10 µg/ml of standard CF from the stock solution and scan both the solution and % purity was calculated.

Continued Method Monitoring and Improvement: CMM is the final step in AQbD life cycle; it is a continuous process of sharing knowledge gained during the development and implementation of design space. This includes results of risk assessments, assumptions based on prior knowledge, statistical design considerations, and a bridge between the design space, MODR, control strategy, CQA, and ATP. Once a method validation is completed, the method can be used for routine purposes, and continuous method performance can be monitored. This can be performed by using control charts or tracking system suitability data, method-related investigations, and so forth. The following points should be continuously monitored during the whole process: Solubility, reagent grade, manufacturing and expiry date of reagent, storage conditions, reagent purity, mobile phase composition and saturation time, stationary phase, detection wavelength, development distance of plate, sample concentration and diluent, sample solution stability, sample preparation process (dilution process and sonication time *etc.*), plate type(particle size, dimensions, and thickness), data resolution and types of lamps, scanning mode, speed and rate, software used, band length and no. of bands, sample application volume, spray rate and position, syringe volume and size, scanning wavelength, the distance between tracks, slit dimensions. Once a method validation is completed, the method can be used for routine purposes and continuous method performance can be monitored. This can be performed by using control charts or tracking system suitability data, method-related investigations, and so forth CMM allows the analyst to proactively identify and address any out-of-trend performance.

Life Cycle Management: Life Cycle Management is a form of continuous assessment that is necessary to establish of an analytical method for quality control or routine testing over time to ensure that the analytical method remains compliant with the goal described ATP. The adaptation of the previous concepts and the existing concept is used in the verification of the analytical process to support the consistency of the product that is to be examined. And for the development of the reliability of the analytical method throughout the increasing of the understanding and decreasing of the variability. This is done to ascertain that the analytical process correlates with the planned objectives specified in the analytical process. The lifecycle concept is an addition of the existing advantages of the AQbD concept shown in **Fig. 6**.

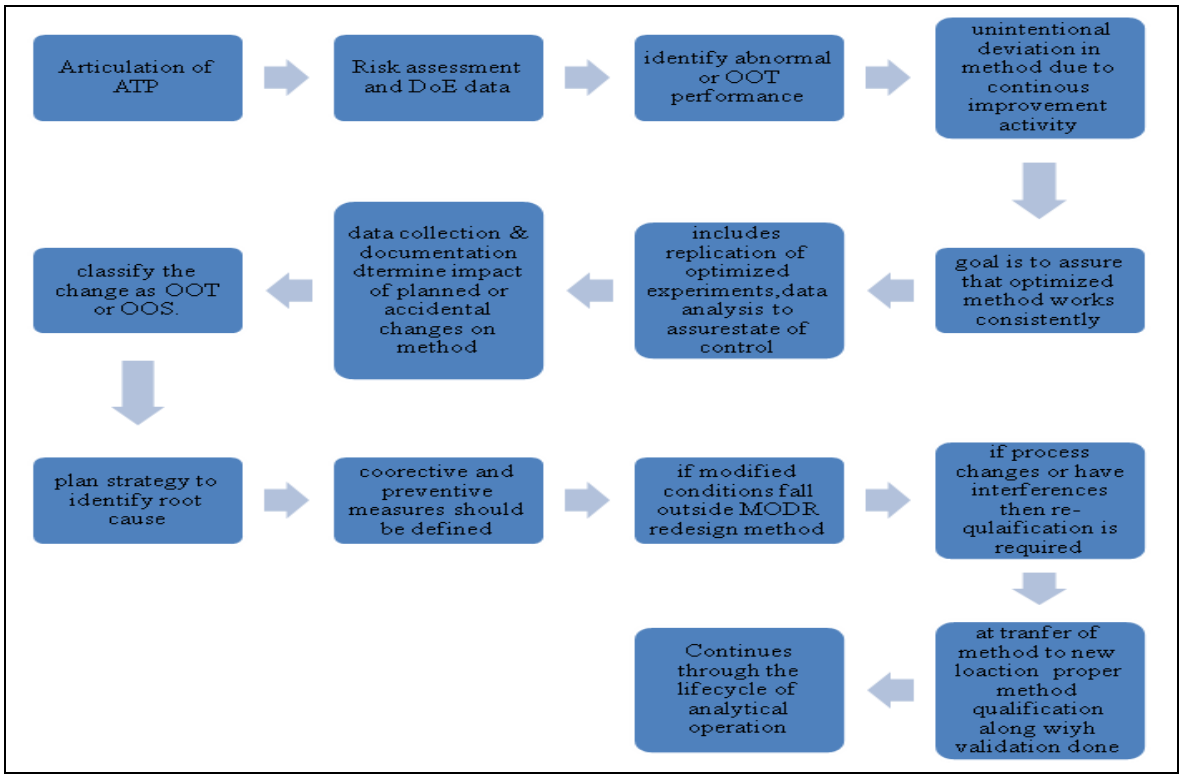

FIG. 6: LIFE CYCLE MANAGEMENT FOR AQBD APPROACH FOR METHOD DEVELOPMENT

RESULTS AND DISCUSSION:

Linearity and Range: The linearity of an analytical method is its ability to elicit test results that are directly proportional to the concentration of analyte in a sample within a given range. The linearity is express in terms of the correlation coefficient of linear regression analysis. Linear regression data for the calibration plots revealed good linear relationships between absorbance and concentration over the ranges 5-25 µg/ml for CF. The linear equations for the calibration plots were y = 0.0314x + 0.1636 with Regression (r2) being 0.9989 for CF at 290 nm. **Table 7** show the Linearity data of CF. The calibration curve and Overlay spectra of CF at 290 nm was as shown in **Fig. 7** and **8,** respectively. The range for CF was found to be 5-25 µg/ml from the linearity studies.

TABLE 7: RESULT OF CALIBRATION READING FOR CANAGLIFLOZIN *(N=6)

Concentration of CF (µg/ml)	Mean absorbance ± SD	%RSD
5	0.3172±0.003	0.99
10	0.4678±0.005	1.10
15	0.6554±0.005	0.78
20	0.7823±0.008	1.07
25	0.9498±0.0010	1.04

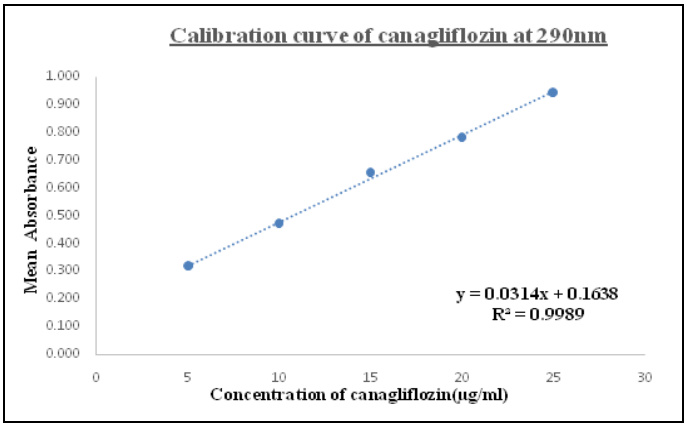

FIG. 7: CALIBRATION CURVE OF CANAGLIFLOZIN AT 290 NM

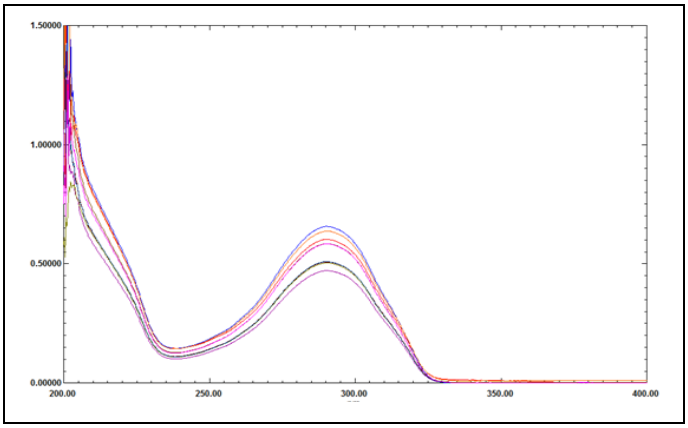

FIG. 8: OVERLAY SPECTRA SHOWING LINEARITY OF CANAGLIFLOZIN AT 290 NM

TABLE 8: REPEATABILITY STUDY OF CANAGLIFLOZIN *(N=6)

Concentration (µg/ml)	Absorbance at 290 nm
15	0.6578
15	0.6698
15	0.6587
15	0.6543
15	0.6533
15	0.6532
Mean	0.6575
SD	0.005
%RSD	0.81

Precision: Repeatability-The %RSD values for CF was found to be 0.81% at 290 nm shown in **Table 8**, which is following ICH guidelines. Low relative standard deviation indicates that the proposed method is repeatable.

Intermediate Precision-Intraday Precision and Interday Precision: Results were reported in terms of % RSD. The precision of the method was expressed as relative standard deviation (%RSD). The %R.S.D. values for intra-day precision study for CF was 1.15-1.22% and for inter-day study 1.17-1.31%. The % RSD values listed in **Table 9** were <2.0%, confirming that the method was sufficiently precise as per ICH guidelines.

TABLE 9: INTRA-DAY AND INTER-DAY STUDY OF CANAGLIFLOZIN *(N=3)

Concentration (µg/ml)	Intra-Day Area Mean ± SD	%RSD	Inter-Day Area Mean ± SD	%RSD
10	0.4376±0.006	1.19	0.4132±0.006	1.17
15	0.6609±0.010	1.15	0.6789±0.010	1.21
20	0.7634±0.007	1.22	0.7808±0.009	1.31

Accuracy: When the method was used for accuracy and subsequent analysis for both drug and pharmaceutical dosage form and spiked with 0, 80, 100, and 120% of additional pure drug, the recovery was found to be 98.15-99.45 % for CF shown in **Table 10**. The closeness of the result nearly to 100 % assured the accuracy of the developed method for the purpose.

TABLE 10: DETERMINATION OF ACCURACY FOR CANAGLIFLOZIN *(N=3)

Concentration of Sample taken (µg/ml)	Concentration of pure API spiked (µg/ml)	Total Concentration (µg/ml)	Mean total Concentration Recovered (n=3) (µg/ml)	%Recovery Mean (n=3)
10	0	10	9.98	99.18
10	8	18	17.77	99.26
10	10	20	19.63	98.15
10	12	22	21.87	99.45

Sensitivity: LOD and LOQ were determined from the standard deviations of the responses for six replicate determinations calculated by the equation as in **Table 11** and determined visually also as in **Fig. 9**.

TABLE 11: LOD AND LOQ FOR CANAGLIFLOZIN* (N=6) (BASED ON EQUATION)

	Canagliflozin (µg/ml)
LOD	1.6652
LOQ	4.6789

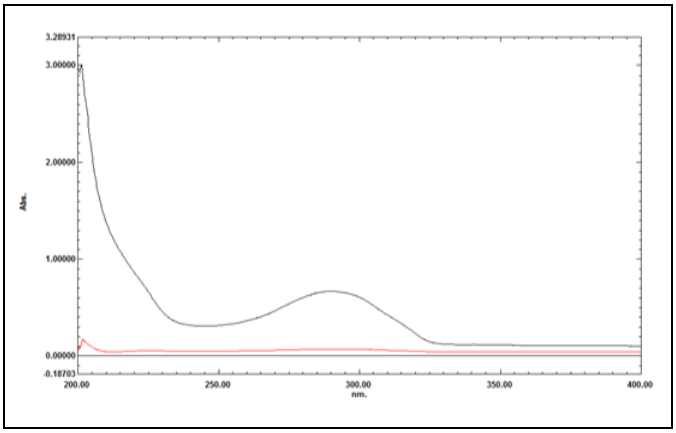

FIG. 9: SPECTRUM OF 2 AND 5 µG/ML OF CF (LOD AND LOQ DETERMINED VISUALLY)

Specificity: The standard CF was assessed by comparing their respective spectra with formulation to check the specificity. The following overlay was obtained as shown in **Fig. 10**.

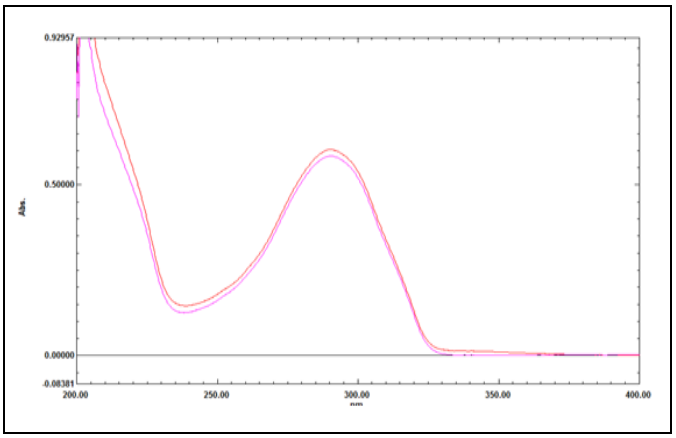

FIG. 10: OVERLAY SPECTRA OF STANDARD CF AND FORMULATION SHOWING SPECIFICITY

Robustness: The proposed method was found to be robust enough (% RSD < 2) to withstand such deliberate changes and allow routine analysis of the sample as in **Table 13**.

TABLE 13: ROBUSTNESS STUDY OF CANAGLIFLOZIN*(N=3)

Parameters	Change control	Concentration (µg/ml)	Mean absorbance	%RSD
wavelength	289	15	0.3746	1.11
	291	15	0.3867	1.14

Assay of Canagliflozin: When the assay of canagliflozin was performed, it gave sharp and well-defined peaks when scanned at 290 nm.

The results in **Table 14** indicate that there was no interference from the excipients. The % purity was 98.26 % for canagliflozin.

TABLE 14: ASSAY RESULT OF SYNTHETIC MIXTURE *(N=3)

Parameters	CF
Actual Concentration (µg/ml)	10
Concentration Obtained (µg/ml)	9.7486
%Purity	98.26
%RSD	1.11

CONCLUSION: A simple, accurate, and precise method has been developed, optimized, and validated using AQbD approach for the estimation of canagliflozin in bulk and formulation. Firstly, all the targeted parameters were studied out accordingly to their criticality. The separation of CQA and CMA's help to focus more on the crucial attributes of the drug and method both. A brief method of scouting assists in choosing the ratio of various UV-Spectrophotometric parameters, which can be worked out with ease for further method development, optimization, and validation. The risk-bearing parameters are thoroughly assessed in accordance with high, medium, and low risk, and

further control strategies are established. Design of experiment was effectively used for method optimization, use of central composite design for optimization generate the design space. Moving within the design space is not considered as a change according to the regulatory bodies. The factors studied were the mobile phase composition while the response was noted for peak area and retardation factor; all other parameters were kept constant for optimization.

The contour plot and 3-D response surface graph were obtained from Design expert software showing the relationship between mobile phase composition and retardation factor. All the validated parameters are found to be within the given criteria as per in ICH guidelines. The validated method was linear, accurate, specific, sensitive, robust, and precise for the determination. Based on the ATP, CQA, CMA, design of experiment, and risk assessment, a control strategy was developed to define and risk management was done.

Implementation of the AQbD approach resulted in a more robust method and can produce consistently reliable and quality data throughout the process. Continuous method monitoring was done by giving critical checks on parameters relating to method and drug.

Continuous assessment of the whole was done by planning a proper lifecycle management strategy which includes all the steps performed throughout the process lifecycle. The developed method is suitable for the analysis of quality control samples of canagliflozin in bulk and formulation in the pharmaceutical industry.

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