RESEARCH PAPER

Development and Validation of a Stability-Indicating Analytical Method for Dapagliflozin in Bulk and Pharmaceutical Dosage Form

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ABSTRACT

Dapagliflozin is an efficient and reliable drug. The RP-HPLC technique was created and approved for the quantitative measurement of dapagliflozin in pharmaceutical dosage forms and bulk. Chromatographic separation was accomplished with an appropriate C18 column and an optimized mobile phase composition to guarantee sufficient retention and symmetrical, sharp peaks. Over the chosen concentration range, the approach showed satisfactory linearity with correlation coefficients exceeding accepted validation limits. ICH Q2(R1) recommendations were followed in the assessment of accuracy, precision, specificity, robustness, system applicability, limit of detection, and limit of quantification. The method showed excellent sensitivity and reproducibility, with minimal interference from excipients or potential degradation products. Stress studies confirmed that the procedure is stability-indicating and capable of distinguishing dapagliflozin from its degradation products. All things considered, the established RP-HPLC method is straightforward, quick, and appropriate for regular stability testing and quality monitoring of formulations containing dapagliflozin.

Keywords: RP-HPLC, Hyperglycemia, Dapagliflozin, RSD, precision

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Introduction

A major global public health concern is diabetes mellitus, a chronic metabolic disease. It has a major negative impact on society and the economy in addition to reducing life expectancy and quality of life. concern. In addition to lowering life expectancy and quality of life, it also significantly burdens society and the economy [1]. It acknowledged as one of the top ten causes of death worldwide adults, responsible for an estimated four million fatalities in just 2017. The continuous search for more potent therapeutic strategies has led to the development of novel pharmacological classes, such as sodium glucose co-transporter-2 (SGLT2) inhibitors [2]. The first medication authorized in this class, dapagliflozin, is now a mainstay of contemporary diabetic treatment [3]. The most prevalent underlying cause of end-stage renal disease in the United States is still type 2 diabetic mellitus (T2DM). and over 40% of patients with T2DM also have chronic kidney disease (CKD) [4]. Dapagliflozin has shown benefits beyond decreasing blood sugar. Further advantages, especially in reducing the course of CKD and enhancing heart failure outcomes[5]. However, attaining complete diabetes control continues to be a difficult task. Less than half of T2DM patients are able to maintain appropriate blood pressure, blood glucose, or lipid levels, and less than one in five are able to do so all at once.[6] Hyperglycemia, a high blood glucose level brought on by abnormalities in insulin secretion, action, or both, is a hallmark of diabetes mellitus (DM), a chronic illness[7]. One of our plasma glucose (PG) criteria is used to diagnose diabetes: increased fasting plasma glucose (FPG) (>126mg/dL), (ii)2-hourPG during a

75g oral glucose tolerance test (OGTT) (>200 mg/dL), (iii) random (>200 mg/dL) with typical hyperglycemia signs and symptoms, or (iv) hemoglobin A1 Clevel >6.5%.Oral antidiabetic medications include biguanides, sulfonylureas, meglitinide, thiazolidine dione (TZD), dipeptidyl peptidase4 (DPP4) inhibitors, sodium glucose cotransporter (SGLT2) inhibitors, and glucose idase inhibitor[8] Examining the several analytical techniques that have been developed for identifying antidiabetic medications of the SGLT2 class in bulk and different pharmacological dose forms was the aim of this study[9]. The methodology developed for estimating. This study also took into account medications either alone or in conjunction with other oral hypoglycemic medications[10]. Subtype 2 of the sodium-glucose transport proteins (SGLT2), which is in charge of at least 90% of the kidney's glucose reabsorption, is inhibited by dapagliflozin[11]. When this transporter is blocked, blood glucose has expelled through the urine. Although the effectiveness of this class of drugs is still unknown, dapagliflozin reduces HbA1c by 0.90 percentage points when combined with metformin in preliminary clinical trials[12]. Fig.1 shows Structure of Dapagliflozin.

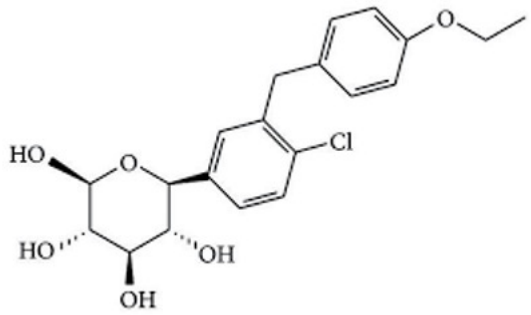

Fig.1 Structure of Dapagliflozin

Chemical description (2S, 3R, 4R, 5S, 6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6 (hydroxyme thyl)oxane-3,4,5-triol[13]. After oral treatment, dapagliflozin is quickly absorbed, with peak plasma concentrations and an oral bioavailability of roughly 78%.
(Tmax) was reached in one to two hours[14]. It can be administered with or without meals because food intake has no effect on its absorption. After absorption, the drug displays a relatively large apparent volume of distribution (~118 L) and is extensively bound to plasma proteins (~91%), mainly albumin. This high binding capacity contributes to its wide distribution throughout the body[15].

Material and Method

Optimization of Detection Wavelength in the High Performance Liquid Chromatographic Method

The sensitivity of the UV-detecting HPLC method depends on the appropriate choice of wavelength of detection. A wavelength that provides a good reaction for the medications to be identified is optimal. A UV detector was used to optimize the wavelength at various wavelengths for a good response. Drug solutions containing 10µg/ml of each dapagliflozin were made in methanol for this investigation. A wavelength of 235 nm was chosen for more research after the drug's UV spectrum was examined[16].

Optimization of Mobile Phase Chromatographic Conditions for DAPA Estimation

To determine DAPA, a quick, easy, and affordable approach has been created. Various factors, including ratio, were changed to optimize the developed RP-HPLC process. of flow rate and mobile phase to produce symmetrical, crisp peaks with superior baseline separation. In order to achieve maximal absorption, the detecting wavelength was set at 220 nm[17].

Choosing a Mobile Phase: Various solvent system combinations based on the type of drug and a wealth of literature survey were conducted to ascertain the ideal circumstances for the successful separation and sample optimization[18].

The mobile phase consisting of
Solvent A – Acetonitrile (90%)
Solvent B – Water (10%)
Solvent C – NA
Solvent D – NA

Chromatographic state:

Column: 4.6x250mm FinepackJasco 5µ 1.0 mL/min is the flow rate.
Column temperature: 30°C ± 5°C
Sample temperature: 25°C ± 5°C
Volume of injection: 20 µl
UV detector at 220nmTen minutes is the run time.
Retention time: Dapagliflozin takes about 4.5 minutes.
Requisites: Mobile Phase (HPLC grade)
Diluent: ACN: Water(90:10) (Mobile Phase/Diluent)
Preparation of test solution:
About 10mg of Dapagliflozin was put into a 10 mL volumetric flask after being precisely weighed. After adding the diluent, the mixture was sonicated for ten minutes in an ultrasonic water bath. After cooling the solution, diluent was added to bring the volume up to par. then passedthrough 0.45 µ syringe filter. The final solution served as the test solution[19].

Procedure:

Five replicates of the standard solution and one duplicate of the test solution were injected. The standard chromatogram described below was used to derive the system appropriateness parameters. Analyte peak theoretical platesNLT 2000 Analyte peak tailing factor: NMT 2.0% RSD for normal duplicate injections: NMT 2

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1.2 Forced degradation study

Forced degradation studies (stress testing) assess a drug's stability by exposing it to extreme conditions to identify degradation products and validate stability-indicating methods. They are classified into acidic, basic, oxidative, thermal, and photolytic degradation [20].

The procedure involves subjecting the drug/substance to each stress condition (e.g., acid/base hydrolysis, oxidation with H_2O_2, heat exposure, UV/light exposure) and analyzing samples using HPLC to detect and quantify degradation products. These studies help determine degradation pathways and ensure the robustness of analytical methods[21].

In acidic degradation, the drug is treated with an acid solution (commonly 0.1–1 N HCl) and heated at a controlled temperature for a specific time, then neutralized and analyzed (usually by HPLC) to assess degradation[22]. Fig. 2 indicated acidic degradation of the drug.

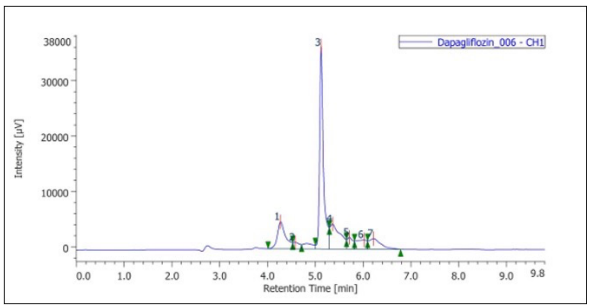


Fig. 2 Acidic degradation

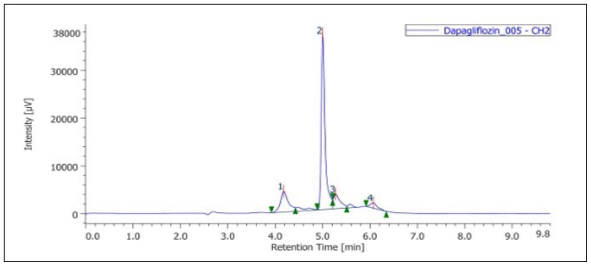


Fig.3 Oxidative degradation

In oxidative degradation, the drug is exposed to an oxidizing agent (commonly 0.1–3% hydrogen peroxide) for a specified time at room or elevated temperature, then analyzed to identify oxidative degradation products[24]. Fig.3 shows oxidative degradation.

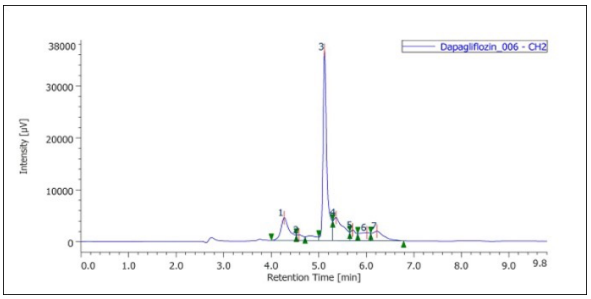


Fig.4 Photolytic degradation

- **In photolytic degradation**, the drug or formulation is exposed to UV and visible light (as per ICH Q1B guidelines) to assess its light sensitivity, and the resulting samples are analyzed for degradation products[25]. Fig.4 indicate Photolytic degradation effect of drug

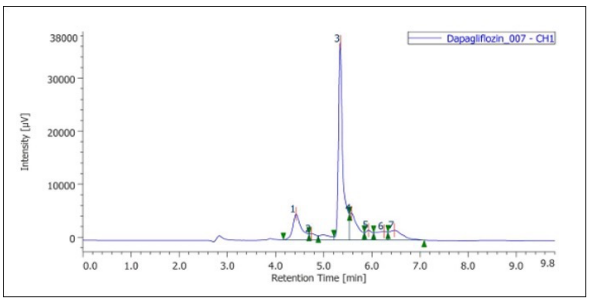


Fig.5 Thermal degradation

- **In thermal degradation**, the drug or formulation is exposed to elevated temperatures (usually 40–80 °C) in dry or humid conditio Fig.5 Thermal degradationns for a defined period, and the samples are analyzed to assess heat-induced degradation[26]. Fig.5 indicate thermal degradation.

Forced degradation type	Actual peak Auc	Degraded peak Auc	% Degradation
Acidic degradation	501244	207978	41.49 %
Basic degradation	501244	207811	41.45 %
Oxidative degradation	501244	218724	43.63 %

Photolytic degradation	501244	204432	40.78 **%**
Thermal degradation	501244	236839	47.25 **%**

Table No.1 Forced degradation

Verification of the Developed RP-HPLC Method

Linearity Process:

The mobile phase and optimum parameters were used to set the chromatographic conditions. was let to reach stationary phase, as the steady baseline showed. Chromatograms were acquired after separate injections of test solutions with varying concentrations. Five 10 ml volumetric flasks were filled with 0.5, 0.6, 0.7, 0.8, and 0.9 ml of the stock solution to create a series of test preparations of dapagliglozin (5 10µg/ml). The final volume was then adjusted with aceteonitrile[27].

Method of Precision Study

Precision within and between days

To conduct an intraday precision research, a test solution with the same concentration was prepared and analyzed twice a day. To measure interday precision, the identical process was used on two separate days. %RSD was used to report the outcome. The accuracy outcome shown a high degree of repeatability, with a relative standard deviation percentage of less than 2[28].

Acceptance standards

NMT 2.0 should be the obtained percentage RSD.

LOD and LOQ:

Using the standard deviation of the y-intercept and slope from the linearity curves, LOD and LOQ are calculated using the following formula. where S is the calibration curve's slope and σ is the response's standard deviation[29].

Precision

Typically, samples are prepared in concentrations between 50% and 150% of the nominal sample preparation. These samples are examined, and each sample's recovery is computed. For this investigation, make three preparations at 50%, 100%, and 150% levels, then inject them into the chromatography. Inject from the lowest concentration to the highest concentration.

Determine the percentage RSD, mean recovery, and individual recovery. Acceptance Standards: Both the mean and individual recovery percentages should fall between 98.0% and 102.0%. Repeatability For five consecutive injections of the sample solution from the same homogenous mixture at working concentrations, the %RSD (Relative Standard Deviation) value is less than 2, indicating that the method developed is precise by the test of repeatability and, consequently, it can be understood that the method yields consistently reproducible results Precision[30].

Sturdiness

The robustness of an analytical procedure is an estimate of its capacity to last unchanged by slight but intentional change in the analytical method parameters. To assess HPLC method robustness some measurable factors were intentionally changed. The study was carried out solution (5 µg/mL) by varying the wavelength (230,235, and, 240 nm), flow rate (0.8,1 and 1.2 mL/min) and Temperature (35, 40, and 45 degrees Celsius) respectively[31]. For three consecutive injections of solution (5 µg/mL) by two distinct analysts of the sample solution from the same homogenous mixture at working concentrations, the number for %RSD (Relative Standard Deviation) less than 2 indicates that the method devised is tough[32].

Result and Conversation

Creation of a Dapagliflozin HPLC technique

The purpose of determining dapagliflozin in bulk form, a high performance liquid chromatographic technique was created and verified. Acetonitrile: Water (90:10 v/v) makes up the mobile phase. The resultant chromatogram displays the highest wavelength at which the medication demonstrates a maximum responsiveness of 220 nm.

Standard and Test used for validation studies

1.1 Particularity

The following solutions are injected into the HPLC apparatus to show the assay's specificity.

- As a blank, diluent
- Test Solution

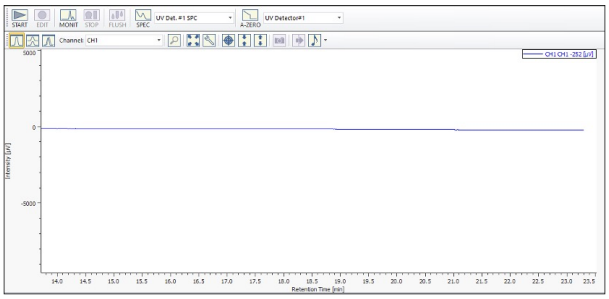


Fig.6 Blank solution's HPLC chromatogram

Fig.6 The chromatogram observed in Blank solution's HPLC.

Sr. No.	Sample name	Analyte name	Purity flag	Specificity

1.	Dapagliflozin	Dapagliflozin	No	Specific

Table. 2 Specificity of sample

Results and evaluation:

1.1 The following assessments were conducted by comparing the chromatograms of the Blank solution, Standard solution, and Test solution. The analyte peak from the blank solution did not co-elute with any signal. During the sample's retention period, no interfering peak was seen from the blank. The sample from the test solution and standard solution did not exhibit any purity flags.

System accuracy

Six replicate injections of the standard were used to assess system precision using the suggested method. In Table 2, the peak area, average, and percentage RSD were computed and tabulated. Accuracy tested in the different six concentration Fig. 1. 02 PPM, Fig. 2. 4 PPM, Fig. 3. 6 PPM, Fig 4. 8 PPM, Fig. 5. 10 PPM, Fig 6. 12 PPM.

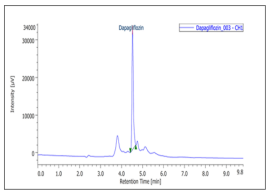


Fig. 1. 02 PPM

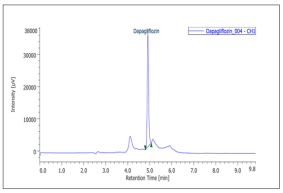


Fig. 2. 4 PPM

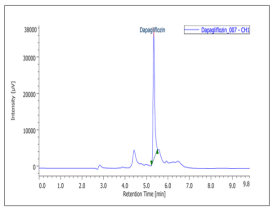


Fig. 3. 6 PPM

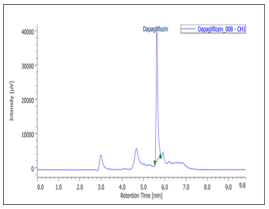


Fig 4. 8 PPM

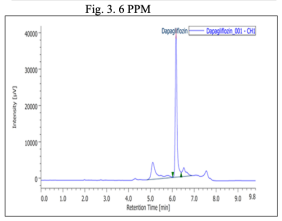


Fig. 5. 10 PPM

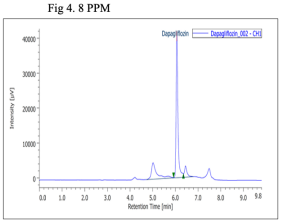


Fig 6. 12 PPM

Inject. No	**Dapaglifliozin Peak Area**
1	151090
2	159795
3	156962
4	154931
5	154846
6	156378
Mean	155667
% RSD	1.848%

Table.3 System Precision of Dapagliflozin

Acceptance Criteria:

The following ranges should apply to the relative standard deviation: % RSD for Empagliflozin Area < 2.0%

Results and evaluation:

The precision of the system is shown by the percentage RSD observed within the permitted limit.

Method accuracy

Intermediate precision-

The six test solutions were prepared separately. Each was analyzed as per proposed procedure. The % assay, average and % RSD was calculated and tabulated in the Table 3 and 4.

Name of Analyte	**Time interval**	**Intraday**	**Time interval**	**Interday**
Dapagliflozin	Morning	73.31	Today	73.29
	Afternoon	74.42	Tomorrow	71.11
	Evening	74.16	Day after tomorrow	71.36
	Average	73.96		71.92
	% RSD	0.785 %		1.659 %

Table. 4. Interday and intraday Dapagliflozin

Acceptance Criteria:

The following ranges should apply to the relative standard deviation from analyses 1 and 2.

The total percentage RSD for the intraday and interlay dapagliflozin assay should be less than 2.0%.

Results and evaluation:

For intraday and interday analysis, the percentage RSD of the test findings from three to three determinations falls within the acceptable range

Linearity

The sample's peak area response was found to be linear between 2 and 12 ppm of working concentration. Six distinct known concentrations of the sample's stock solutions were diluted. Concentration (as x-value) versus area (as y-value) was shown on a graph. The The regression's slope, y-intercept, and correlation coefficient (r2) were computed and tabulated in Tables 5 and 6.The linearity of method evaluated in different levels Fig.1. 02 PPM, Fig.2. 4 PPM, Fig.3. 6 PPM, Fig.4. 8 PPM, Fig.5. 10 PPM, Fig.6. 12 PPM.

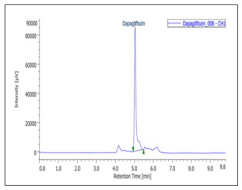


Fig.1. 02 PPM

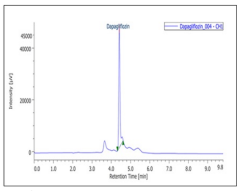


Fig.2. 4 PPM

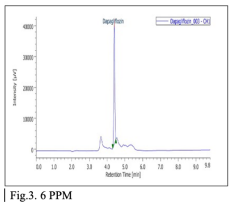


Fig.3. 6 PPM

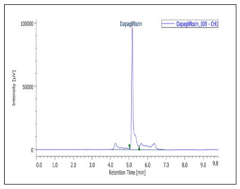


Fig.4. 8 PPM

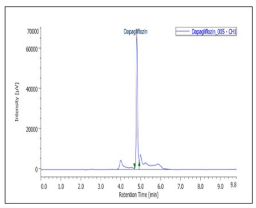


Fig.5. 10 PPM

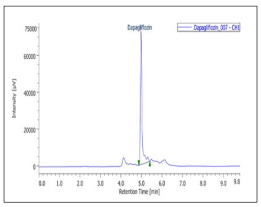


Fig.6. 12 PPM

Conc. of Sample (ppm)	Average Peak area
02	134912
04	209240
06	306410
08	400722
10	501244
12	610306
0.997	

Table. 5. Linearity of Dapagliflozin

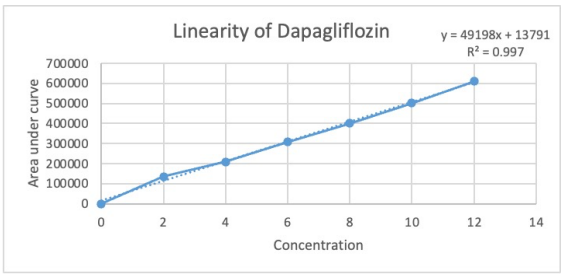


Fig. 7. Calibration curve of Linearity Dapagliflozin

Acceptance Criteria:

The Correlation coefficient (r^2) > 0.9967

Results and evaluation:

Since the correlation coefficient is within the acceptable range, the method is regarded as linear.

Sturdiness

To show the method's resilience, the effects of slightly altered chromatographic conditions were examined in accordance with ICH criteria. The tests are performed by injecting blank and standard solutions while changing the chromatographic settings listed below.

Sr. No	Parameters	Working parameter	- changes	+ changes
2	Wavelength	220 nm	218 nm	222 nm

Table.6 Robustness parameter

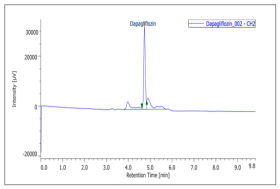


Fig.1. Wavelength +2 nm

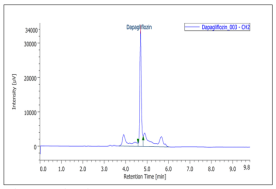


Fig.2. Wavelength +2 nm

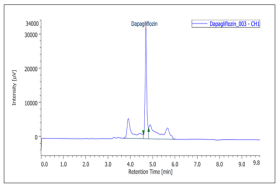


Fig.3. Wavelength +2nm 2nm
Fig.5. Wavelength +2nm

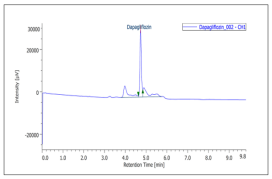
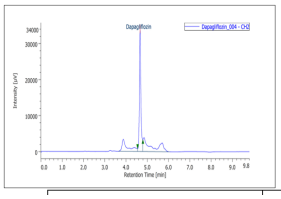
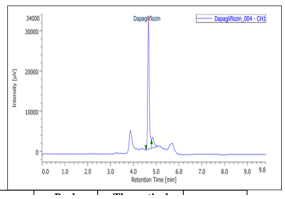


Fig.4.Wavelength +2nm
Fig.6.Wavelength +2nm





Robustness parameters		% RSD	Peak tailing	Theoretical plates	Remark
Sample					
Wavelength (+2 nm) and (-2 nm)	172266	0.599%	-	24129	Pass
	170232		-	24142	Pass
	171033		-	23609	Pass
	155965	1.728%	-	25152	Pass
	152321		-	23378	Pass
	150823		-	25351	Pass

Table.7 Robustness of Dapagliflozin

Acceptance Criteria:

The system suitability requirements should be met and the percentage RSD of peak area response resulting from three replicate injections of the sample solution should be less than 2.0%.

Results and evaluation:

For findings obtained under various chromatographic settings, the system suitability parameters and percentage RSD are within acceptable bounds. As a result, the approach is determined to be reliable.

Conclusion:

- Chromatographic comparison demonstrated the specificity of the HPLC test for assay, and the procedure was determined to be specific.
- The correlation was used to determine the linearity of the suggested method.

coefficient and the technique was discovered to be

linear and to fall between 50 and 150% of working concentration.

- Concentration studies were used to calculate the method's precision, and the proposed method was determined to be accurate because all of its parameters fulfilled the acceptance criteria.

Data statement

The paper contains all relevant data supporting the development and validation of the RP-HPLC technique for dapagliflozin. This study did not create or analyze any publically accessible datasets.

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