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Research Article

Development and Validation of RP-HPLC Method for Simultaneous Estimation of Dapagliflozin and Bisoprolol in Bulk and Pharmaceutical Dosage Form

Samrat Khedkar[1], Mahesh Pingale[2], Shrimant Bidarkote*[3]

[1]Principal, Vidya Niketan College of Pharmacy, Lakhewadi, Pune, Maharashtra, India 413103.
[2]Associate Professor, Vidya Niketan College of Pharmacy, Lakhewadi, Pune, Maharashtra, India 413103.
[3]Vidya Niketan College of Pharmacy, Lakhewadi, Pune, Maharashtra, India 413103

The assay of Dapagliflozin & Bisoprolol was performed with tablets and the % assay was found to be 100.10 & 100.08% which shows that the method is useful for routine analysis. The linearity of Dapagliflozin & Bisoprolol was found to be linear with a correlation coefficient of 0.999 and 0.999, which shows that the method is capable of producing good sensitivity. The acceptance criteria of precision is RSD should be not more than 2.0% and the method show Intraday and Inter-day precision 0.13 and 0.30 % for Dapagliflozin and Intraday and Inter-day precision 0.13 and 0.30 % for Bisoprolol. which shows that the method is precise. Which shows that the method is repeatable when performed in different days also. The total recovery was found to be for Dapagliflozin is 99.45-100.58 % and for Bisoprolol is 99.66-100 %. The validation of developed method shows that the accuracy is well within the limit, which shows that the method is capable of showing good accuracy and reproducibility.

Keywords: Dapagliflozin, Bisoprolol, % RSD, Accuracy.

INTRODUCTION

Diabetes and high blood pressure are becoming more common. Diabetics are more likely to have hypertension than comparable non-diabetics [1]. Patients with both diseases are far more likely to experience early microvascular and macrovascular issues. The likelihood of microvascular and macrovascular issues is significantly reduced by actively controlling blood pressure (BP). Hypertension increases mortality in individuals with diabetes by 7.2 and 37 times, respectively [2]. Strict blood pressure control and early blood pressure treatment significantly reduced microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary artery disease (CAD), stroke, and peripheral vascular disease), according to the Hypertension Optimum Trial (HOT) and the U.K. Prospective Diabetes Study (UKPDS) epidemiological study [3]. For those with diabetes and related heart issues, a combination of dapagliflozin and bisoprolol is used to regulate blood sugar levels while lowering cardiac strain. Bisoprolol is a selective β1-adrenergic receptor blocker that reduces cardiac workload and improves hemodynamic stability. Dapagliflozin, a highly selective inhibitor of the Sodium-Glucose Co-Transporter 2 (SGLT2), reduces renal glucose reabsorption and promotes glycosuria, thereby improving glycemic control in individuals with Type 2 Diabetes Mellitus. Its unique insulin-independent mechanism also offers additional cardiovascular and renal benefits. Dapagliflozin acts through an insulin-independent mechanism by promoting the excretion of glucose via the kidneys, thereby distinguishing its mode of action from that of traditional antidiabetic agents. [4] It selectively inhibits Sodium-Glucose Co-Transporter 2 (SGLT2) over SGLT1, leading to reduced renal glucose reabsorption and improved glycemic control.

Chemically, dapagliflozin is described as (2S,3R,4R,5S,6R)-2-{4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl}-6-(hydroxymethyl) oxane-3,4,5-triol, with a molecular formula of $C_{21}H_{25}ClO_6$ and a molecular weight of 408.873 g/mol. It appears as a white to off-white crystalline powder and is soluble in solvents such as ethanol, methanol, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF). [5] Bisoprolol fumarate (BISO), on the other hand, is a highly selective β1-adrenergic receptor blocker that reduces cardiac output and heart rate by inhibiting sympathetic stimulation of the heart. [6] This pharmacological activity contributes to decreased cardiovascular risk in patients with hypertension and heart failure. Its chemical name is 1-[(propan-2-yl) amino]-3-(4-{[2-(propan-2-yloxy) ethoxy] methyl} phenoxy) propan-2-ol, with a molecular formula of $C_{18}H_{31}NO_4$ and a molecular weight of 325.443 g/mol. It is off-white to white crystalline powder, readily soluble in water and methanol, and moderately soluble in alcohol, glacial acetic acid, and chloroform, but only slightly soluble in acetone and ethyl acetate. [7]

MATERIAL AND METHODS

1.2.1 Instrumentation Chemicals and reagents:

The HPLC system consisted of Agilent connected with PDA detector. Dapagliflozin & Bisoprolol standard gift samples were provided by Aadhaar Life Science Pvt. Ltd. Solapur. Methanol, acetonitrile and water (HPLC grade) were purchased from Merck Chemical Company. Sodium hexane Sulphonic acid, glacial acetic acid (Analytical grade) and 0.22 µm pump Nylon filter were purchased from S.D. Fine Chemicals Ltd., Mumbai. The Whatman filter paper No. 41 was obtained from Modern Science Lab. All other reagents used were analytical grade. All the glassware used were borosilicate glass. Tablet formulations (DapaBiso 10/5) were obtained from the local market.

1.2.2 Chromatographic Conditions:

- Oven Temp: 30°C
- Flow rate: 1 ml/min.
- Mobile Phase: 0.1% O-Phosphoric Acid: Acetonitrile (55: 45, % v/v)
- Preparation of Buffer: In 1000 ml HPLC water, 1ml of Ortho-Phosphoric Acid was added and mixed well and filtered through 0.45-micron membrane filter and sonicated to degas for 10 minutes.
- Runtime: 10 minutes
- Injection Volume**:** 10 µl
- Wavelength**:** 225 nm
- Diluent**:** 0.1% O-Phosphoric Acid: Acetonitrile (50: 50, % v/v)
- Column**:** Phenomenex Kinetex XB-C18 (4.6 x 150mm, 5 µm)

1.3 Standard Preparation:

a. Dapagliflozin Standard Stock solution-I (SSS-I):

i. Prepare a Standard Stock Solution (SSS-I) of by adding 10 mg of Dapagliflozin in 100 ml volumetric flask & add 50 ml diluent, sonicate for 5 minutes and make the volume to 100 ml with diluent. (Conc. of Salbutamol in SSS-I = 100 µg/ml).

b. Bisoprolol Standard Stock solution-II (SSS-II)

ii. Prepare a Standard Stock Solution (SSS-II) of by adding 5 mg of Bisoprolol in 100 ml volumetric flask & add 50 ml diluent, sonicate for 5 minutes and make the volume to 100 ml with diluent. (Conc. of Bisoprolol in SSS-II = 50 µg/ml).

c. Then add 1.0 ml of SSS-I and 1.0 ml of SSS-II in 10 ml volumetric flask and add 5 ml diluent and vortex and make up the volume with diluent. (Conc. of Dapagliflozin = 10 µg/ml and Conc. of Bisoprolol = 5 µg/ml)

1.4 Preparation of Drug Product sample solution:

Tablet were crushed in mortar and pestle, tablet powder equivalent to 1mg Dapagliflozin and 0.5 mg of Bisoprolol was weighed in 10 ml volumetric flask and diluent was added up to the mark and sonicated for 5 minutes. Further the solution was filtered and 1 ml of filtrate was diluted to 10ml.

1.5 Selection of Wavelength:

The sample was scanned from 190-400 nm with DAD detector. The Wavelength selected for analysis chosen

was 225 nm on the basis of appropriate intensity of both peaks.

1.6 Method Validation:

a. Specificity & Assay:

Individual sample of Blank, Dapagliflozin working standard (10 µg/ml), Bisoprolol working standard (5µg/ml), Mixture working standard and Drug product of was prepared and peaks were for identified from Retention Time.

% Assay was calculated as follows:

b. Repeatability & System Suitability:

A single working standard was prepared as described in section 2 and 6 injections were made from same solution and checked for system suitability. System suitability parameters are as below:

c. Linearity & Range:

5 samples of varying concentrations ranging from 80-120% were prepared. The concentrations are given below

Table: 1 Concentration of linearity Study for HPLC

% Level	Dapagliflozin Conc. (µg/ml)	Bisoprolol Conc. (µg/ml)
80	8	4
90	9	4.5
100	10	5
110	11	5.5
120	12	6

The sample preparations are given as below;

X ml of Dapagliflozin and Y ml of Bisoprolol standard solution was added to 10 ml diluent to make up the concentrations given above:

Table: 2 Standard solution diluent to make up the concentration

X ml of SSS-I	X ml of SSS-II	Diluted to
0.8	0.8	10 ml
0.9	0.9	10 ml
1.0	1.0	10 ml
1.1	1.1	10 ml
1.2	1.2	10 ml

c. Accuracy:

Accuracy was determined by means of recovery experiments, by the determination of % mean recovery of both the drugs in the formulation at three different levels (80-120%).

i. Samples were prepared of 80%, 100% and 120% concentration by spiking the same amount of concentration given in table for Linearity.

ii. Samples were injected in triplicate to calculate % RSD.

iii. % Recovery was also calculated.

d. LOD/ LOQ:

LOD is the lowest amount of analyte in a sample that can be detected but not necessarily quantify under the stated experimental conditions. LOQ is the lowest concentration of analyte in a sample that can be determined with the acceptable precision and

accuracy under stated experimental conditions. Was calculated by using ANOVA technique.

e. Robustness:

To determine the robustness of the developed method, experimental conditions were deliberately altered, and the system suitability parameter retention time and peak area were evaluated.

i) The Robustness was performed by changing the column temperature and Wavelength by ± 2˚C and ± 2 nm.

ii) Each Sample was injected and % RSD of peak area was calculated at each condition.

Table: 3 Robustness Study for HPLC

Condition	Increased	Normal	Decreased
Column Oven Temperature	32˚C	30˚C	28˚C
Wavelength	227 nm	225 nm	223 nm

f) Intra & Inter-day Precision:

i. Single mixture working standard and drug product was prepared and injected twice in a day at different time intervals to evaluate intra-day precision.

ii. Same mixture working standard was analysed on second day to evaluate the inter-day precision.

iii. % RSD of peak was calculated at each interval and stability of solutions were estimated.

RESULT AND DISCUSSION:

i) Selection of analytical wavelength:

The sample was scanned from 200-400 nm with PDA detector. The Wavelength selected for analysis chosen was 225 nm on basis of appropriate intensity of Dapagliflozin.

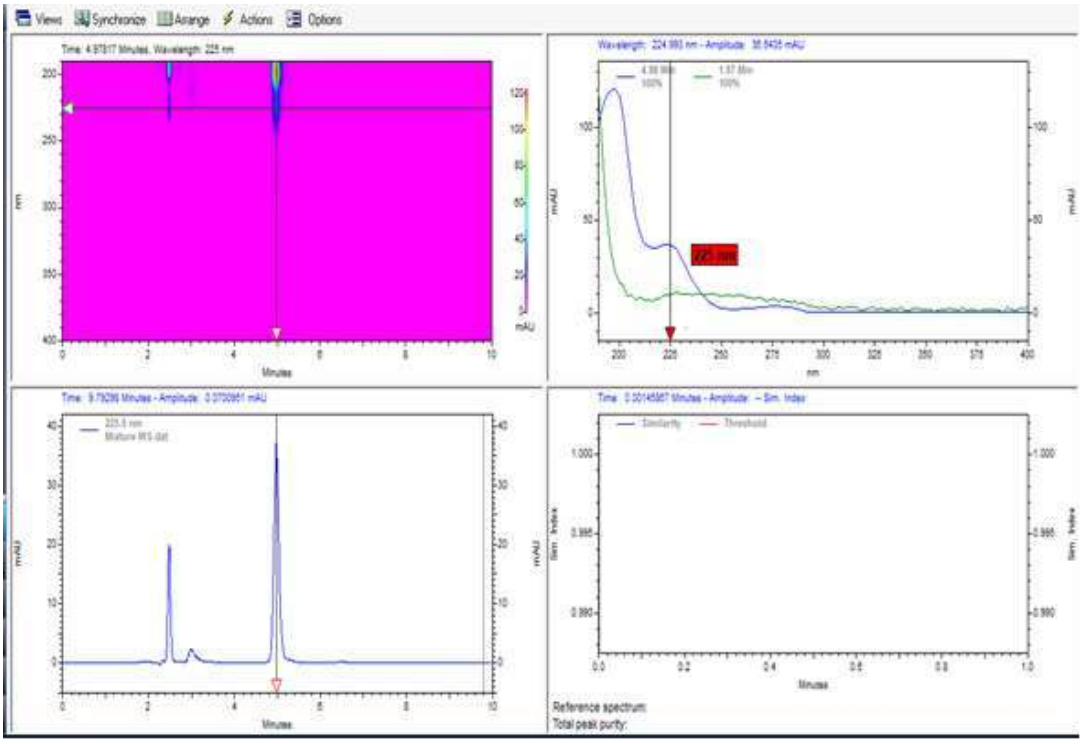

Figure 1: Spectrum of Dapagliflozin & Bisoprolol between 200-400 nm in mobile phase.

Dapagliflozin RT 4.96 min and Bisoprolol RT 2.49 min show the maximum absorbance at 225 nm. Hence, HPLC analysis was carried out at 225 nm.

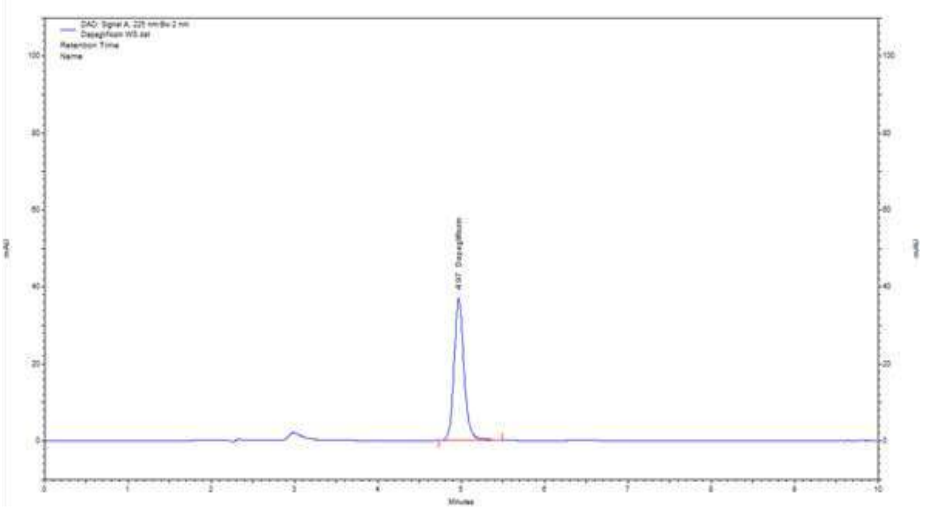

Figure 2: Chromatogram of Standard Dapagliflozin.

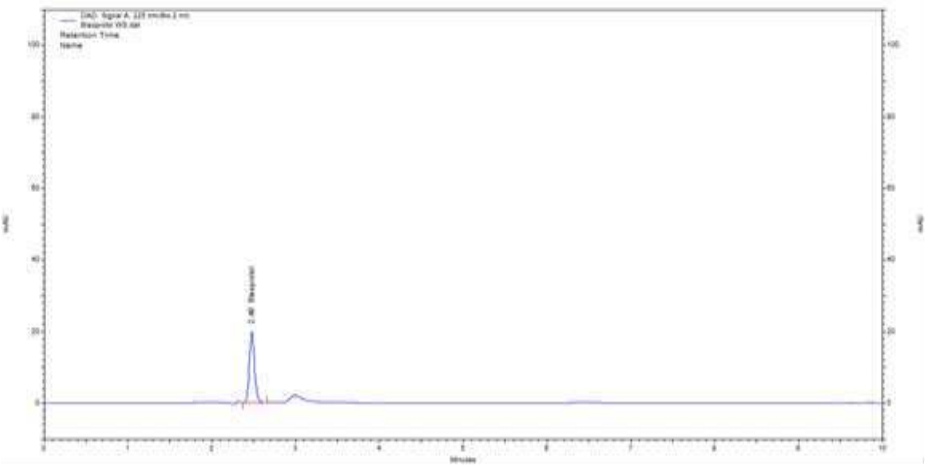

Figure 3: Chromatogram of Standard Bisoprolol.

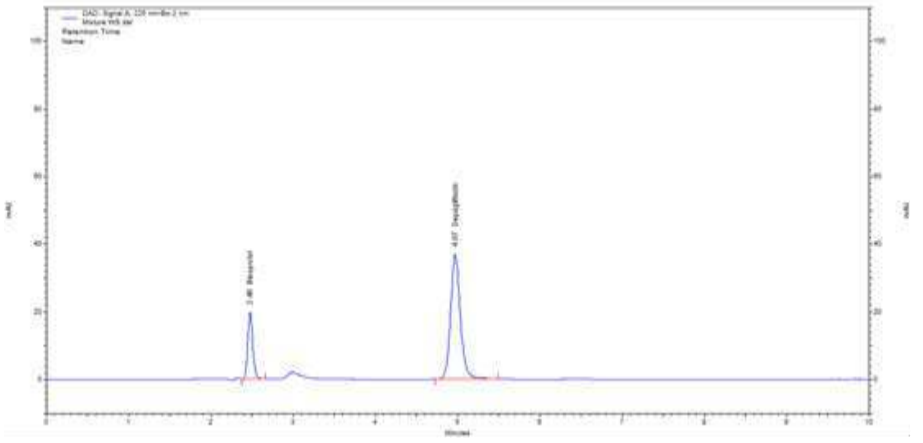

Figure 4: Chromatogram of Standard Mixture of Dapagliflozin & Bisoprolol in optimized chromatographic conditions.

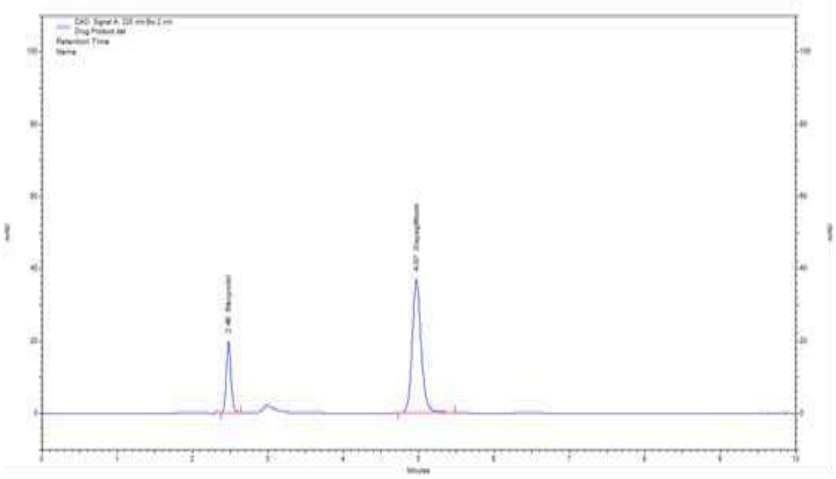

Figure 5: Chromatogram of Sample of Dapagliflozin & Bisoprolol in optimized chromatographic conditions.

iii) Analysis of tablet formulation: -

Table no. 4 Analysis of Marketed formulation.

Sample ID	Bisoprolol			Dapagliflozin		
	RT	Area	% Assay	RT	Area	% Assay
BSP WS	2.48	175113	-	-	-	-
DPG WS	-	-	-	4.97	643083	-
MIX WS	2.48	175212	-	4.97	643165	-
Drug Product	2.48	175345	100.08	4.97	643784	100.10

Amount of drug present in the marketed formulation was calculated using RP-HPLC. Amount of Dapagliflozin & Bisoprolol was found to be 100.10 & 100.08 % respectively. This method can be employed for routine analysis of Dapagliflozin & Bisoprolol.

I. Linearity:

Different concentration of solution prepared for Linearity of both Dapagliflozin & Bisoprolol are shown in respectively.

1.8 Validation of RP-HPLC Method: [8-13]

Table No. 5 Linearity dilutions for Dapagliflozin.

Dapagliflozin		
% Level	Conc. (µg/ml)	Area
80	8	518051
90	9	577866
100	10	643083
110	11	698784
120	12	768073

Table No. 6 Linearity dilutions for Bisoprolol.

Bisoprolol		
% Level	Conc. (µg/ml)	Area
80	4	140273
90	4.5	157698

100	5	175113
110	5.5	192888
120	6	209716

According to ICH guideline linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration of an analyte Linearity was studied by plotting a graph of area v/s concentration. A series standard solution of Dapagliflozin & Bisoprolol were prepared in the concentration range of 8 µg/ml to 12 µg/mL and 4 µg/mL to 6 µg/mL respectively with linearity range 80-120% for both the drug. The regression coefficient (r^2) of Dapagliflozin was found to be 0.999 & for Bisoprolol regression coefficient (r^2) was found to be 0.999. The equation of regression line for Dapagliflozin was found to be y=62096x+20209 for Bisoprolol was found to be y=34815x+1061.6 Linearity graph of Dapagliflozin & Bisoprolol shown in figure 6 & 7 respectively.

II. Precision:

The Precision study of Dapagliflozin & Bisoprolol are shown in Table 5 respectively**.**

Table No. 7 Precision of Dapagliflozin & Bisoprolol.

Dapagliflozin				
Condition	**Sample ID**	**RT**	**Area**	**% Assay**
Morning	WS	4.97	643165	-
	DP	4.97	643784	100.10
Evening	WS	4.97	643762	-
	DP	4.97	642755	99.84
% RSD				**0.18**
Day 2	WS	4.97	642689	-
	DP	4.97	641674	99.84
% RSD				**0.15**

Bisoprolol				
Condition	**Sample ID**	**RT**	**Area**	**% Assay**
Morning	WS	2.48	175212	-
	DP	2.48	175345	100.08
Evening	WS	2.48	175423	-
	DP	2.48	175235	99.89
% RSD				**0.13**
Day 2	WS	2.48	174234	-
	DP	2.48	173346	99.49
% RSD				**0.30**

The accuracy of an analytical process used to determine intra-day and inter-day variation. The percentage relative standard deviation (RSD) for Intraday and Inter-day precision was 0.13 and 0.30 % for Dapagliflozin and Intraday and Inter-day precision 0.13 and 0.30 % for Bisoprolol. The obtained findings are less than 2% suggests a high level of precision.

III. Accuracy:

The accuracy study of Dapagliflozin & Bisoprolol are shown in Table 6 and 7 respectively**.**

Table 8 Accuracy Study of Dapagliflozin.

Sample ID	Reps	Spiked Conc. (µg/ml)	Area	Amount Recovered (µg/ml)	% Recovery	AVG	STDEV	% RSD
80%	Rep 1	7.99	518051	8.04	100.58	100.58	0.000918	0.00
	Rep 2	7.99	518053	8.04	100.58			
	Rep 3	7.99	518044	8.04	100.58			
100%	Rep 1	9.99	643083	9.98	99.88	99.89	0.014988	0.02
	Rep 2	9.99	643075	9.98	99.88			
	Rep 3	9.99	643246	9.98	99.91			
120%	Rep 1	11.99	768073	11.92	99.41	99.45	0.030657	0.03
	Rep 2	11.99	768513	11.92	99.47			
	Rep 3	11.99	768445	11.92	99.46			

Table 9. Accuracy Study of Bisoprolol.

Sample ID	Reps	Spiked Conc. (µg/ml)	Area	Amount Recovered (µg/ml)	% Recovery	AVG	STDEV	% RSD
80%	Rep 1	4.00	140273	3.99	99.97	100.00	0.084208	0.08
	Rep 2	4.00	140456	4.00	100.10			
	Rep 3	4.00	140235	3.99	99.94			
100%	Rep 1	5.00	175113	4.99	99.84	99.88	0.042085	0.04
	Rep 2	5.00	175235	4.99	99.90			
	Rep 3	5.00	175246	4.99	99.91			
120%	Rep 1	5.99	209716	5.97	99.64	99.66	0.032154	0.03
	Rep 2	5.99	209745	5.97	99.65			
	Rep 3	5.99	209845	5.98	99.70			

The method's accuracy defines how close the method's results are to the true value. The results of the accuracy testing revealed that the technique is accurate within acceptable ranges. When the % RSD for Dapagliflozin & Bisoprolol is calculated, all of the results are within acceptable bounds. A maximum RSD of 2.0% indicated acceptable accuracy within the range. According to the Accuracy research, the percent recovery of Dapagliflozin is 99.45-100.58 % and Bisoprolol is 99.66-100 %, both of which are within the ICH standards.

iv. Limit of Detection (LOD) and Limit of Quantification (LOQ):

The LOD and LOQ of Dapagliflozin & Bisoprolol are shown in Table 8.

Table 9. The LOD and LOQ of Dapagliflozin & Bisoprolol.

Sr. No	Name of drug	LOD (µg/mL)	LOQ (µg/mL)
1.	**Dapagliflozin**	0.57	1.72
2.	**Bisoprolol**	0.07	0.22

Sensitivity of the method was determined with respect to limit of detection (LOD) and the quantification limit of an individual analytical procedure is the lowest amount of an analyte in a sample which can be quantitatively determined with the suitable precision and accuracy. LOD and LOQ value for Dapagliflozin was found to be 0.57 µg/mL and 1.72 µg/mL, LOD and LOQ value for Bisoprolol was found to be 0.07 µg/mL and 0.22 µg/mL respectively.

iv. System suitability:

System suitability data of Dapagliflozin & Bisoprolol given in below Table 9 and 10.

Table 10 System suitability or Repeatability parameter of Dapagliflozin.

Dapagliflozin					
Sample ID	**Area**	**RT**	**TP**	**Asymmetry**	**Resolution**
100% Rep 1	643083	4.97	8839	1.13	15.46
100% Rep 2	643214	4.97	8845	1.14	14.60
100% Rep 3	643225	4.97	8871	1.16	14.58
100% Rep 4	643289	4.97	8823	1.12	15.01
100% Rep 5	643397	4.97	8894	1.08	15.56
100% Rep 6	643143	4.97	8812	1.11	14.32
AVG	643841	4.97			
STDEV	110.1715	0			
% RSD	0.02	0.00			

Table11 System suitability parameter of Nortriptyline hydrochloride.

Bisoprolol					
Sample ID	**Area**	**RT**	**TP**	**Asymmetry**	**Resolution**
100% Rep 1	175113	2.48	7983	1.11	0.00
100% Rep 2	175442	2.48	7975	1.19	0.00
100% Rep 3	175441	2.48	7963	1.00	0.00
100% Rep 4	175682	2.48	7855	1.10	0.00
100% Rep 5	175438	2.48	7943	1.12	0.00
100% Rep 6	175296	2.48	7974	1.12	0.00
AVG	175402	2.48			
STDEV	188.4537	0			
% RSD	0.11	0.00			

The system, method, and column performance were validated by testing system suitability features. Six times, a standard solution of Dapagliflozin & Bisoprolol was injected into the system, and the system's suitable features were evaluated. Method is having repeatability because % RSD is within limit i.e. below 2.

V. Robustness: Robustness data of Dapagliflozin & Bisoprolol given in below

Table 12 Robustness parameter of Dapagliflozin.

Variation in Column temperature (Dapagliflozin)							
Condition	**Sample ID**	**RT**	**Area**	**% Assay**	**Average**	**STDEV**	**% RSD**
28˚C	WS	4.97	643115	-	100.03	0.054476	0.05
	DP	4.97	643152	100.01			
30˚C	WS	4.97	643165	-			
	DP	4.97	643784	100.10			
32˚C	WS	4.97	643724	-			
	DP	4.97	643714	100.00			
Variation in Column temperature (Dapagliflozin)							
Condition	**Sample ID**	**RT**	**Area**	**% Assay**	**Average**	**STDEV**	**% RSD**
223 nm	WS	4.97	643197	-	100.03	0.057235	0.06
	DP	4.97	643154	99.99			
225 nm	WS	4.97	643165	-			
	DP	4.97	643784	100.10			

227 nm	WS	4.97	643765	-			
	DP	4.97	643774	100.00			

Table 13 Robustness parameter of Bisoprolol.

Variation in Column temperature (Bisoprolol)							
Condition	**Sample ID**	**RT**	**Area**	**% Assay**	**Average**	**STDEV**	**% RSD**
28˚C	WS	2.48	175423	-	100.03	0.043991	0.04
	DP	2.48	175422	100.00			
30˚C	WS	2.48	175212	-			
	DP	2.48	175345	100.08			
32˚C	WS	2.48	175321	-			
	DP	2.48	175321	100.00			
Variation in wavelength (Bisoprolol)							
Condition	**Sample ID**	**RT**	**Area**	**% Assay**	**Average**	**STDEV**	**% RSD**
223 nm	WS	2.48	175135	-	100.02	0.045603	0.05
	DP	2.48	175124	99.99			
225 nm	WS	2.48	175212	-			
	DP	2.48	175345	100.08			
227 nm	WS	2.48	175321	-			
	DP	2.48	175322	100.00			

Robustness was investigated using various deliberate alterations in chromatographic settings, such as changes in column Condition like 28˚C, 30˚C and 32˚C**.** RSD was shown to be less than 2% in the Dapagliflozin & Bisoprolol robustness studies. As a result, it is strong and adheres to ICH criteria.

CONCLUSION:

The method achieved the best separation of Dapagliflozin & Bisoprolol simultaneously in gradient mode, both the drugs are well separated in shorter time, which reduce overall analysis time and solvent consumption. According to ICH criteria, all validation parameters were determined to be within the permitted ranges. Regardless of the excipients used, it was discovered that the proposed technique was easy, precise, accurate, robust, and specific to the drugs of interest. This method demonstrated its capability for detecting and quantifying pharmaceuticals at lower concentrations by providing adequate figures of merit, such as excellent linearity, precision, and accuracy, and low LOD and LOQ. These results highlight the effectiveness of the method for routine analysis in pharmaceutical settings. Furthermore, the simplicity of the isocratic approach allows for easier implementation in laboratories, making it a valuable tool for researchers and quality control analysts alike.

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