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A NOVEL RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF DAPAGLIFLOZIN AND SAXAGLIPTIN IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT: In the present work, a rapid, specific, accurate and precise Reversed phase high performance liquid chromatographic (RP-HPLC) method has been developed and validated for simultaneous determination of Dapagliflozin and Saxagliptin in bulk and pharmaceutical dosage form. Successful chromatographic separation of Dapagliflozin and Saxagliptin was carried out with Inertsil-ODS, C_{18} column (250 × 4.6 mm; 5 µm) with mobile phase consisted of a mixture of Methanol and Potassium dihyrogen phosphate buffer in the ratio of 45:55 v/v delivered at a flow rate of 1.0 ml/min. The eluents are monitored by PDA detector and peaks values were measured at 210 nm. The retention times for Dapagliflozin and Saxagliptin were 4.707 min and 6.684 min respectively. The present analytical method was validated according to ICH guidelines (ICH, Q2 R1). The linearity study of Dapagliflozin and Saxagliptin was found in the concentration range of 20-70 µg/ml and 20-70 µg/ml respectively and coefficient of variance was 0.999 for both drugs. % recovery was found to be 100.37% and 100.16% for Dapagliflozin and Saxagliptin respectively. LOD was 0.109 µg/ml and 0.58 µg/ml and LOQ was 0.332 µg/ml and 1.77 µg/ml for Dapagliflozin and Saxagliptin respectively. It inferred that the developed method was successfully applied for the simultaneous estimation of Dapagliflozin and Saxagliptin in bulk and its commercial pharmaceutical dosage forms and could be used for the routine analysis of the studied drugs in quality control laboratories.

INTRODUCTION: Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder characterized by absolute or relative insulin deficiency [1]. Expected rise in prevalence of diabetes is mainly due to increased life span because of better healthcare facilities and increase in diabetic risk factors, especially physical inactivity and obesity due to sedentary life style.

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Pancreatic *β*-cell function is gradually deteriorated in patients of T2DM which is reflected into inadequate glycemic control on a long run [2].

Dapagliflozin **Fig. 1** is chemically known as (1s)-1, 5- anhydro- 1- C- [4- chloro- 3- [(4-ethoxyphenyl) methyl] phenyl]-D-glucitol. It has a molecular formula of $C_{24}H_{33}ClO_8$ with molecular weight 408.98 g/mol [3]. Dapagliflozin is selective Sodium Glucose Co Transporter 2 inhibitor (SGLT 2). It acts by reducing the re absorption of glucose by the kidney, leading to excretion of excess glucose in the urine, thereby improving glycemic control in patients with type 2 diabetes mellitus [4]. Saxagliptin **Fig. 2** is chemically known as (1S, 3 S, 5S)-2[(2S)-2- amino- 2- (3- hydroxy- 1- adamantyl) acetyl]-2

azabicyclo hexane-3-carbonitrile) with molecular formula of $C_{18}H_{25}N_3O_2$ and molecular weight of 315.41 g/mol [5]. Saxagliptin is a selective and potent dipeptidyl peptidase (DPP)-4 inhibitor, approved as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus (T2DM). In patients with T2DM, once-daily administration of Saxagliptin before breakfast achieves sustained inhibition of plasma DPP-4 activity and reduction of postprandial hyperglycaemia, including after dinner, associated with an increase in plasma glucagon-like peptide-1 levels [6, 7, 8]. Combination of Dapagliflozin and Saxagliptin is marketed as a Tablet (Qtern) containing 10 mg of Dapagliflozin, 5 mg of Saxagliptin.

Combination of these two drugs is indicated for the treatment of type-2 Diabetes. Using Dapagliflozin leads to heavy glycosuria (glucose excretion in the urine), which can lead to weight loss and tiredness.

Literature survey revealed a variety of analytical methods *viz*. HPLC, LC-MS and, GC has been reported for estimation of Dapagliflozin and Saxagliptin individually or in combination with other drugs. The reported methods are Spectrophotometric [9-15], HPLC [16-35], LC-MS [36-37] and GC [38] method are reported for the simultaneous estimation of DAP and SAX in combined pharmaceutical formulation.

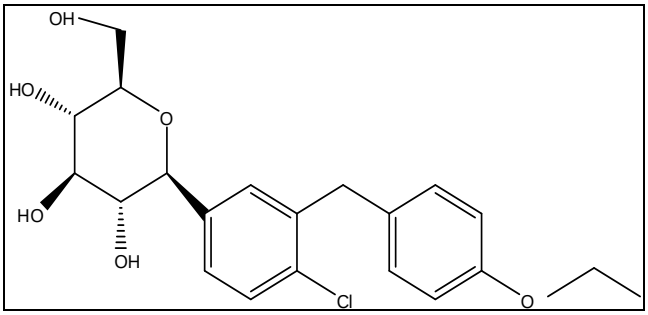

FIG. 1: CHEMICAL STRUCTURE OF DAPAGLIFLOZIN

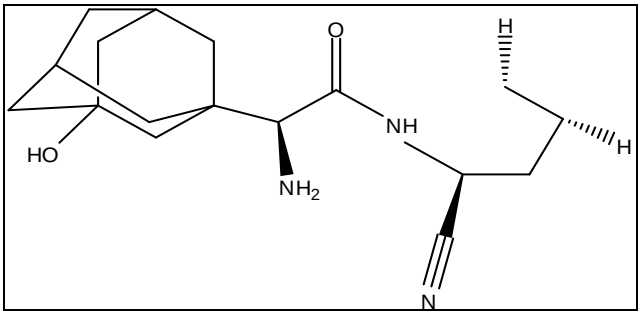

FIG. 2: CHEMICAL STRUCTURE OF SAXAGLIPTIN

The objective of the present study is to develop a novel, simple, accurate, precise, economic method for the simultaneous estimation of Dapagliflozin and Saxagliptin in bulk and pharmaceutical dosage form. Validate the method according to ICH guidelines [39].

MATERIALS AND METHODS:

Chemicals and Reagents: HPLC grade of acetonitrile, water and analytical grade of orthophosporic acid, potassium dihydrogen phosphate was procured from Merck Pharmaceuticals Ltd., Mumbai, India. Standard drug samples of Dapagliflozin and Saxagliptin were obtained as gift samples from Active Pharma Labs, Hyderabad, India. The marketed formulation of Dapagliflozin and Saxagliptin (Qtern) were procured from local Pharmacy store.

Instrumentation: The analysis was performed by using a chromatographic system Water 2690/5 series HPLC comprised of vacuum degas, auto injector, and dual gradient pump with Photodiode Array detector. The HPLC system was equipped with Empower 2 software.

Chromatographic Conditions: Dapagliflozin and Saxagliptin was analysed with Inertsil-ODS C_{18} column (250 × 4.6 mm, 5 µm particle size) for the chromatographic separation. The mobile phase was composed of a mixture of Methanol and Potassium dihyrogen phosphate buffer in the ratio of 45:55 v/v and water was used as diluent and it was delivered at a flow rate of 1.0 ml/min. Injection volume was 20 µl and UV detection was performed at 210 nm. The run time was set 12 min.

Mobile Phase Preparation: Accurately weighed 2.72 g of Potassium dihydrogen phosphate transferred in a 1000 ml clean and dry volumetric flask, add about 900 ml of HPLC water and Sonicated for degassing and then finally make up the volume with water. pH of the buffer was adjusted to 3.4 with dilute Orthophosporic acid. To 450 ml of Methanol, 550 ml of buffer was added in a beaker to give 1000 ml of mobile phase.

Standard Stock Preparation: Accurately weighed and transferred 10 mg Dapagliflozin and 10 mg of Saxagliptin working standards into 100 ml clean dry volumetric flasks, add 70 ml of diluent and

sonicated for 20 min to dissolve it completely and make up to the mark with same diluent and it gives 100 µg/ml of Dapagliflozin and 100 µg/ml Saxagliptin (Stock solution). From the above stock solution, 4.0 ml was pipette out in to a 10 ml volumetric flask and then make up to the final volume with diluent.

Sample Preparation: Twenty tablets (Qtern) were accurately weighed, crushed and mixed in a mortar and pestle. A portion of powder equivalent to the weight of 10 mg was accurately weighed and transferred into 100 ml volumetric flask, add 70 ml of diluent and sonicated for 30 min to dissolve it completely and make up to the mark with same diluent, and then the solution were filtered through a 0.45 µm membrane filter. From the above filtered solution, 4.0 ml was pipette out in to a 10 ml volumetric flask and then make up to the final volume with diluent. Likewise sample was further diluted to get required concentration.

Method Validation: The proposed method was validated according to the ICH guidelines which include system suitability, specificity, linearity, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ) and robustness. Under the validation study, the following parameters were studied.

System Suitability Test: HPLC system was optimized as per the chromatographic conditions. 20 µL of standard solutions of drugs were injected in triplicate into the chromatographic system. To ascertain the system suitability for the proposed method, the parameters such as retention time, theoretical plates, relative retentions, tailing factor were calculated and compared with standard specification of system.

Specificity: Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. The specificity of method was determined by comparing the chromatograms of blank, standard and sample.

Linearity: Linearity is the ability (within specified range) to obtain test results are directly proportional to the concentration of analyte in the sample. Linearity is evaluated by visual inspection of plot of signal as a function of analyte concentration. If there is a linear relationship test results are calculated by regression line by method of least squares. Calibration curves were constructed by plotting peak area *vs*. concentration of Dapagliflozin and Saxagliptin and the regression equations were calculated. The calibration curves of Dapagliflozin and Saxagliptin were plotted over 6 different concentrations for two drugs.

Accuracy: Accuracy of analytical method is 'measure of how close the experimental value to the true value' accuracy of the method was determined by standard addition method. A known amount of standard drug is added to the fixed amount of pre-analysed injection solution. Percent recovery is calculated by comparing the area before and after addition of the standard drug. The standard addition method is performed at 50%, 100% and 150% level. The solutions are analysed in triplicate at each level as per the proposed method.

Precision: Precision is expressed as the closeness of agreement between a series of measurements obtaining from multiple sampling of the same homogeneous sample. Six replicate injections of a known concentration of Dapagliflozin (40 µg/mL) and Saxagliptin (40 µg/mL), have been analyzed by injecting them into a HPLC column on the same day. The intermediate precision was estimated by injecting samples prepared at the same concentrations on three different days by different operators. The peak area ratios of all injections were taken and standard deviation, % relative standard deviation (RSD), was calculated.

Limit of Detection (LOD) and Limit of Quantification (LOQ): Limit of detection (LOD) and limit of quantification (LOQ) of Dapagliflozin and Saxagliptin were determined by calibration curve method. Solutions of Dapagliflozin and Saxagliptin were prepared in linearity range and injected in triplicate. Average peak area of three analyses was plotted against concentration.

LOD and LOQ were calculated by using the following equations:

$$LOD = 3.3 \times N/B$$
$$LOQ = 10 \times N/B$$

Where N is residual variance due to regression; B is the slope.

Robustness: The standard and samples of Dapagliflozin and Saxagliptin were injected by changing the chromatographic conditions like flow rate of the mobile phase, pH of the buffer and composition of the mobile phase. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

RESULTS AND DISCUSSION: The HPLC procedure was optimised for simultaneous determination of Dapagliflozin and Saxagliptin in bulk and pharmaceutical dosage form by using column Inertsil-ODS C_{18} (250 × 4.6 mm internal diameter; 5 µm particle size) in isocratic mode with mobile phase consisting of Methanol : Buffer in the proportion of 45:55 v/v. The flow rate of mobile phase was 1.0 ml/min and both the components were monitored at 210 nm with PDA detector. Resulted in peaks with good shape and well resolved. The results of optimized HPLC conditions were shown in **Table 1**. The method was linear in the range of 20-70 µg/ml and 20-70 µg/ml for Dapagliflozin and Saxagliptin with correlation coefficient 0.999 for both Dapagliflozin and Saxagliptin. Linear regression data for Dapagliflozin and Saxagliptin were given in **Table 2**, the linearity curves for Dapagliflozin and Saxagliptin were shown in **Fig. 3** and **Fig. 4**.

TABLE 1: OPTIMIZED CHROMATOGRAPHIC CONDITIONS OF DAPAGLIFLOZIN AND SAXAGLIPTIN

Parameter	Condition
Mobile phase	Methanol: Potassium dihydrogen phosphate buffer (45:55% v/v)
pH	3.4 (Adjusted with dil. Ortho phosphoric acid)
Column	Inertsil-ODS, C_{18} Column (250 × 4.6 mm; 5 µm)
Injection volume	20 µL
Column temp	Ambient
Wave length	210 nm
Flow rate	1.0 ml/min
Run time	12 min
Retention time	Dapagliflozin - 4.707 min, Saxagliptin - 6.684 min

TABLE 2: LINEARITY RESULTS OF DAPAGLIFLOZIN AND SAXAGLIPTIN

S. no.	Dapagliflozin		Saxagliptin	
	Conc. (ppm)	Area (AU)	Conc. (ppm)	Area (AU)
1	20	315485	20	605754
2	30	465823	30	903457
3	40	630548	40	1214572
4	50	774655	50	1516471
5	60	926485	60	1824723
6	70	1095354	70	2105355

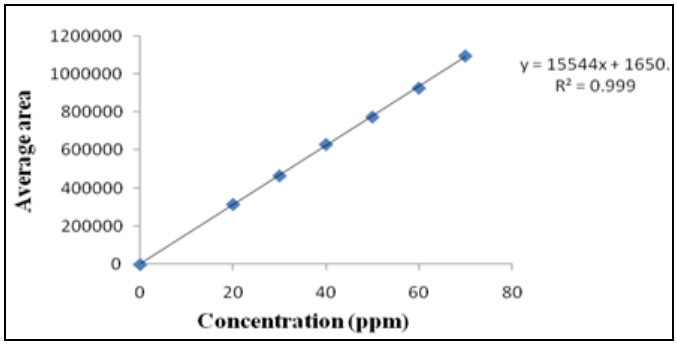

FIG. 3: LINEARITY GRAPH OF DAPAGLIFLOZIN

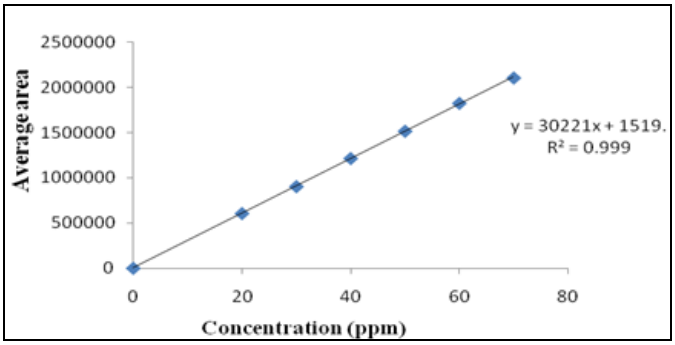

FIG. 4: LINEARITY GRAPH OF SAXAGLIPTIN

The mean % recoveries of Dapagliflozin and Saxagliptin were found to be 100.37 % and 100.16 % respectively. Which indicate the method was accurate. The accuracy results were shown in Table 3. The % RSD values of method precision are 0.155% and 0.0601% for Dapagliflozin and Saxagliptin respectively and % RSD values of system precision are 0.143% and 0.361% for Dapagliflozin and Saxagliptin. The % RSD values of reproducibility for Saxagliptin and Dapagliflozin were found to be < 2%, reveal that the proposed method is precise. The precision results were shown in **Table 4** and **Table 5**.

The retention times of Dapagliflozin and Saxagliptin was 4.707 min and 6.684 min respectively. The number of theoretical plates calculated was 10768 for Dapagliflozin and 9573 for Saxagliptin and tailing factor was 1.155 for Dapagliflozin and 0.892 for Saxagliptin, which indicates efficient performance of the column. The LOD for Dapagliflozin and Saxagliptin were found to be 0.109 µg/ml and 0.58µg/ml respectively. The LOQ for the Dapagliflozin and Saxagliptin were found to be 0.332 µg/ml and 1.77 µg/ml respectively, which indicates the sensitivity of the method.

The % RSD values of robustness studies were found to be < 2% reveal that the method is robust enough was shown in **Table 6**. Results of system suitability and validation parameters of Dapagliflozin and Saxagliptin were shown in the **Table 7**. Validated method was applied for the determination of Dapagliflozin and Saxagliptin in commercial formulations. The % assay was found to be 101.36% and 100.35% for Dapagliflozin and Saxagliptin respectively. Typical chromatogram of standard Dapagliflozin and Saxagliptin was shown in **Fig. 5**. These data show that the proposed method is specific and sensitive for the determination of Dapagliflozin and Saxagliptin.

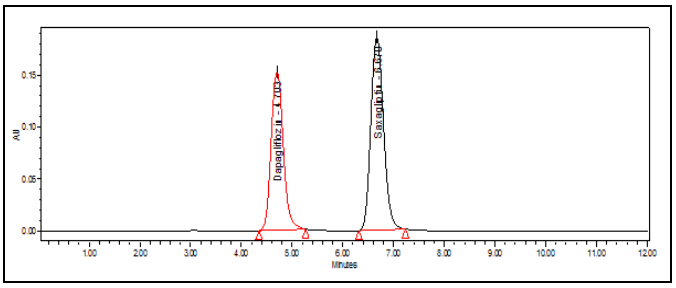

FIG. 5: OPTIMIZED CHROMATOGRAM OF DAPAGLIFLOZIN AND SAXAGLIPTIN

TABLE 3: ACCURACY RESULT OF DAPAGLIFLOZIN AND SAXAGLIPTIN

	Dapagliflozin				Saxagliptin			
Spike Level	Amount added (µg/ml)	Amount found (µg/ml)	% recovery	mean % recovery	Amount added (µg/ml)	Amount found (µg/ml)	% recovery	mean % recovery
50%	20	20.18	100.94	100.95	20	19.98	99.92	99.94
50%	20	20.21	101.09		20	19.99	99.96	
50%	20	20.16	100.80		20	19.98	99.92	
100%	40	40.39	100.97	100.99	40	40.13	100.34	100.10
100%	40	40.32	100.80		40	39.95	99.89	
100%	40	40.47	101.19		40	40.02	100.06	
150%	60	59.49	99.16	99.19	60	60.32	100.54	100.45
150%	60	59.48	99.14		60	60.28	100.47	
150%	60	59.48	99.14		60	60.20	100.34	

TABLE 4: METHOD PRECISION RESULTS OF DAPAGLIFLOZIN AND SAXAGLIPTIN

S. no.	Dapagliflozin (40 ppm)		Saxagliptin (40 ppm)	
	Peak Area	% Assay	Peak Area	% Assay
1	632495	101.46	1212110	100.14
2	632992	101.54	1213700	100.27
3	631828	101.35	1211851	100.12
4	631098	101.23	1212255	100.15
5	630289	101.10	1213283	100.24
6	631322	101.27	1212349	100.16
Mean	631670	101.328	1212591	100.18
Std. Dev	980.68	0.157	729.26	0.0603
% RSD	0.155	0.155	0.0601	0.0602

TABLE 5: SYSTEM PRECISION RESULTS OF DAPAGLIFLOZIN AND SAXAGLIPTIN

S. no.	Dapagliflozin (40 ppm)		Saxagliptin(40 ppm)	
	Peak Area	% Assay	Peak Area	% Assay
1	634753	101.82	1213541	100.26
2	633261	101.58	1214284	100.32
3	633298	101.59	1215341	100.41
4	632221	101.41	1223784	101.11
5	633636	101.64	1213300	100.24
6	632221	101.41	1223784	101.11
Mean	633433	101.61	1216050	100.46
Std. Dev	908.344	0.146	4395	0.361
% RSD	0.143	0.143	0.361	0.363

TABLE 6: ROBUSTNESS STUDY (CHANGE IN FLOW RATE) FOR DAPAGLIFLOZIN AND SAXAGLIPTIN

Drug	Change in flow rate (±0.2ml)	Change in flow rate		
		Average	SD	% RSD*
Dapagliflozin	0.8 ml/min	620425	754.0018	0.086
	1.0 ml/min	634663	1100.917	0.184
	1.2 ml/min	602444	599.8833	0.09
Saxagliptin	0.8 ml/min	1273638.6	3301.369	1.041
	1.0 ml/min	1205763.2	392.1635	0.19
	1.2 ml/min	166277.6	582.9758	0.35

*(n = Standard area of 6 injections)

TABLE 7: RESULTS OF SYSTEM SUITABILITY AND VALIDATION PARAMETERS

S. no.	Parameter	Results	
		Dapagliflozin	Saxagliptin
1	Linearity range (µg/ml)	20-70	20-70
2	Slope (m)	15544	30221
3	Intercept (c)	1650	1519
4	Correlation coefficient (R^2)	0.999	0.999
5	Retention times (min)	4.707	6.684
6	Theoretical plates (N)	10768.34	9573.997
7	Tailing factor	1.155	0.892
8	Repeatability (% RSD)	0.143	0.361
9	LOD (µg/ml)	0.109	0.58
10	LOQ (µg/ml)	0.332	1.77
11	Resolution (Rs)	4.91	

CONCLUSION: It can be concluded that the proposed method is fully validated and is found to be specific, simple, sensitive, accurate, precise and relatively inexpensive giving an acceptable recovery of the analyte. The advantage of this method is short retention time and run time over the other method to give better result. This method can be used as better analytical tool for simultaneous estimation of Dapagliflozin and Saxagliptin in bulk drugs and its pharmaceutical formulations.

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CONFLICT OF INTEREST: Nil

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