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Research Article

A VALIDATED STABILITY INDICATING RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF DAPAGLIFLOZIN, METFORMIN AND SAXAGLIPTIN IN BULK IN PHARMACEUTICAL ORAL DOSAGE FORMS.

[1]Koppula Sravani, [2]Kanduri Valli Kumari

[1]M. Pharmacy, Department of Pharmaceutical Analysis, Malla Reddy Institute of Pharmaceutical science, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District.

[2]Department of Pharmaceutical Analysis, Malla Reddy Institute of Pharmaceutical science, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District.

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ABSTRACT:

Metformin, Dapagliflozin, and Saxagliptin in solid dose form were estimated simultaneously using a simple, accurate, and exact approach. The chromatogram was conducted on an Agilent C18 150x4.6mm, 5mm. A mobile phase comprising acetonitrile and 0.01N Kh2Po4 in a 70:30 v/v ratio was injected through the column at a flow rate of 1.2mL/min. Buffer pH was adjusted to 3.5pH using Ortho Phosphoric Acid. The temperature was kept at 26 °C. The optimal wavelength for Metformin, Dapagliflozin, and Saxagliptin was 238.0 nm. Metformin, dapagliflozin, and saxagliptin had retention times of 3.598, 2.827, and 3.209 minutes, respectively. The %RSD of system accuracy for Metformin, Dapagliflozin, and Saxagliptin were determined to be 0.7, 0.4, and 0.6, respectively. The %RSD of method precision for Metformin, Dapagliflozin, and Saxagliptin were determined to be 0.7, 0.9, and 0.4, respectively. Metformin, Dapagliflozin, and Saxagliptin showed percentage recovery rates of 100.03%, 100.23%, and 99.64%, respectively. LOD values are derived using regression models for Metformin, Dapagliflozin, and Saxagliptin. The LOQ values for Metformin, Dapagliflozin, and Saxagliptin were 1.62 µg/ml, 0.12 µg/ml, and 0.05 µg/ml, respectively, based on regression models. The regression equation for Metformin was y = 5641.2x + 8389.3. Dapagliflozin was y = 6070.3x + 132, whereas Saxagliptin was y = 5843.6x + 75.1. Retention durations are reduced, therefore the method devised was easy and cost-effective, and it may be used in frequent quality control tests in industries.

Key Words: Dapagliflozin, Saxagliptin, RP-HPLC.

INTRODUCTION

The class of metabolic illnesses known as diabetes mellitus is distinguished by irregularities in either the action or secretion of insulin, or both, leading to persistent elevation of blood glucose levels. Dysregulation of protein, fat, and carbohydrate metabolism arises from the function of insulin as an anabolic hormone. At the level of insulin receptors, the signal transduction system, and/or effector enzymes or genes, these metabolic disorders arise from either insufficient insulin to elicit a substantial response or the resistance of target tissues, particularly the liver, adipose tissue, and skeletal muscles, to insulin.[1-6]

The metabolic syndrome, a group of diseases marked by obesity, insulin resistance, and other cardiovascular risk factors, is frequently associated with type 2 diabetes. A significant development in the treatment of type 2

Address for Correspondence: Koppula Sravani**,** M. Pharmacy, Department of Pharmaceutical Analysis, Malla Reddy Institute of Pharmaceutical science, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District.; **E-Mail:** koppulasravani2410@gmail.com.

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diabetes is the acknowledgement of the necessity for proactive and timely control of insulin resistance, dyslipidaemia, hypertension, and albuminuria. The activity of this medicine is characteristic of a newly developed category of anti-hyperglycemic medications that operate by a distinct mechanism.[7]

Type 2 diabetes is treated with a combination of three drugs called Metformin Dapagliflozin and Saxagliptin. It is marketed as Qternmet XR tablet. It aids in glycemic management for those with diabetes. It is usually administered when other diabetes drugs are not providing enough glycemic control. [8 -14]

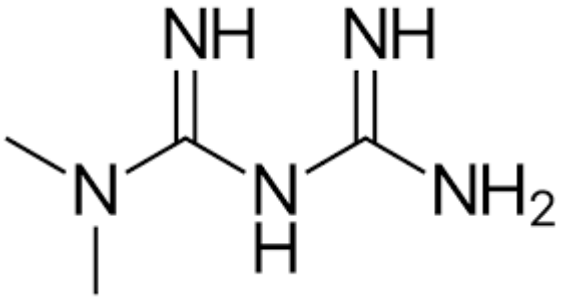

Figure 1 Structure of Metformin

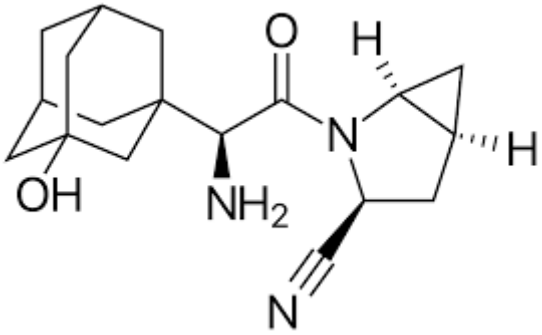

Figure 2 Structure of Dapagliflozin

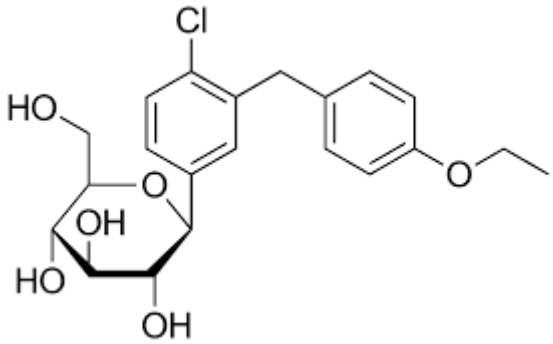

Figure 3 Structure of Saxagliptin

Metformin: Metformin is a biguanide antihyperglycemic agent and first-line pharmacotherapy used in the management of type II diabetes [15,16]

it is chemically known as 1-carbamimidamido-N,N-dimethylmethanimidamide. 17 It is sometimes referred to as a "insulin sensitiser", resulting in a decline in insulin resistance and a clinically significant fall in fasting insulin levels in the blood.16

Dapagliflozin: It is a sodium-glucose cotransporter 2 inhibitor used in the management of type 2 diabetes mellitus. It is Chemically known as (2S,3R,4R,5S,6R)-2-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-6-(hydroxymethyl)oxane-3,4,5-triol. 18 Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule.

Saxagliptin: It is an DPP-4 inhibitor used for the management of type 2 diabetes mellitus. It is Chemically referred as (1S,3S,5S) -2-[(2S)-2-amino -2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile. 19

An extensive literature research has unearthed a multitude of recorded analytical procedures, including the discovery of more economically efficient ways. Nevertheless, there is currently no documented approach for calculating stability studies. Hence, a reliable and cost-effective approach is suggested for assessing the stability

of Metformin, Dapagliflozin, and Saxagliptin, and their medicinal dose form using RP-HPLC.20- 27 must be validated and developed as per ICH guidelines

Materials and Methods

Spectrum pharma Research Solution provide with Metformin, Dapagliflozin, and Saxagliptin pure drugs (API) gift samples and Combination Metformin, Dapagliflozin, and Saxagliptin tablets (Qternmet XR) received from local market. The chemicals and buffers utilized in this estimation were obtained from Rankem, an Indian supplier.

Instrumentation

The development and method validation were conducted using a WATERS HPLC, specifically the model 2695 SYSTEM, equipped with a Photo diode array detector. The system also included an automated sample injector and the Empower 2 software.

Objective:

The primary objective of this study is to provide a highly exact, accurate, sensitive, specific, consistent, and efficient analytical method for the simultaneous quantification of Metformin, Dapagliflozin, and Saxagliptin in their pure form and throughout tablet formation.

Table 1: Chromatographic Conditions

Mobile phase	Acetonitrile: 0.01NKh2Po4 (70:30 v/v)
Flow rate	1 ml/min
Column	Agilent C18(4.6 x 150mm, 5µm)
Detector wave length	238 nm
Column temperature	26°C
Injection volume	10µL
Run time	5.0 min

Preparation of Standard stock solutions: Accurately weighed 250mg of Metformin, 2.5 mg of Dapagliflozin and 1.25mg of Saxagliptin and transferred to three 50ml volumetric flasks separately. 25ml of Diluent was added to flasks and sonicated for 20mins. Flasks were made up with Water: Acetonitrile (60:40 v/v) and labeled as Standard stock solution 1, 2 and 3. (5000µg/ml of metformin, 50µg/ml of Dapagliflozin and 25µg/ml of Saxagliptin).

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipette out and taken into a 10ml volumetric flask and made up with Water: Methanol (50:50 v/v) (500µg/ml of metformin, 5µg/ml of Dapagliflozin and 2.5µg/ml of Saxagliptin).

Preparation of Sample stock solutions: 5 tablets were weighed and calculate the average weight of each tablet then the weight equivalent to 1 tablet (1285.6 Avg wt) was transferred into a 100 mL volumetric flask, 75mL of diluent added and sonicated for 50 min, further the volume made up with diluent and filtered. (10000µg/ml of metformin, 100µg/ml of Dapagliflozin and 50µg/ml of Saxagliptin).

Preparation of Sample working solutions (100% solution): From the filtered solution 0.5ml was pipette out into a 10 ml volumetric flask and made upto 10ml with diluents. (500µg/ml of metformin, 5µg/ml of Dapagliflozin and 2.5µg/ml of Saxagliptin).

System suitability parameters: The system suitability parameters were determined by preparing standard solutions of 500µg/ml of metformin, 5µg/ml of Dapagliflozin and 2.5µg/ml of Saxagliptin and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should be not more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Table 2: System suitability results

	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Dapagliflozin	2.827	14694	9476	1.36	
2	Saxagliptin	3.209	30764	5464	1.14	3.0
3	Metformin	3.598	2817364	6946	1.45	2.6

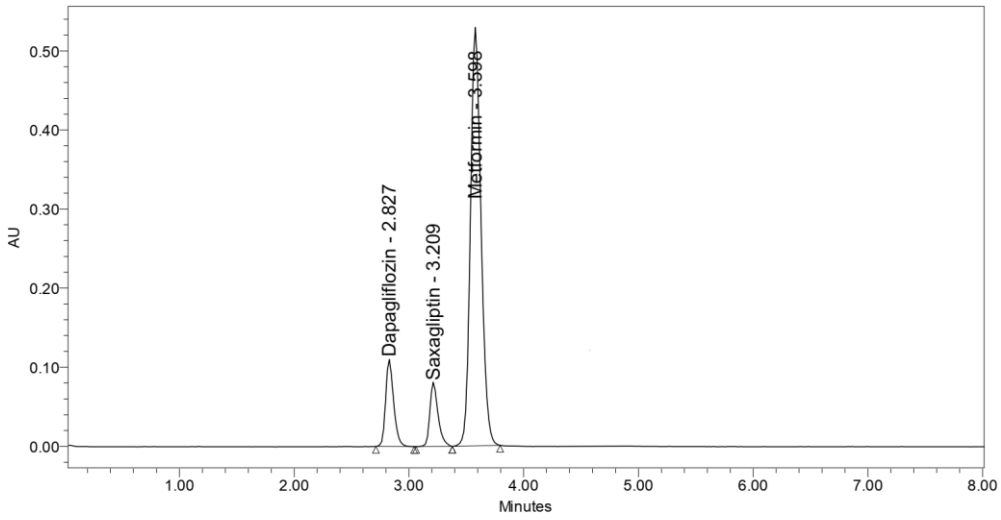

Figure 4: system suitability Chromatogram

Table 3: Specificity data

Sample name	Retention time(mins)	Area
Dapagliflozin	2.827	514889
Saxagliptin	3.209	768301
Metformin	3.598	

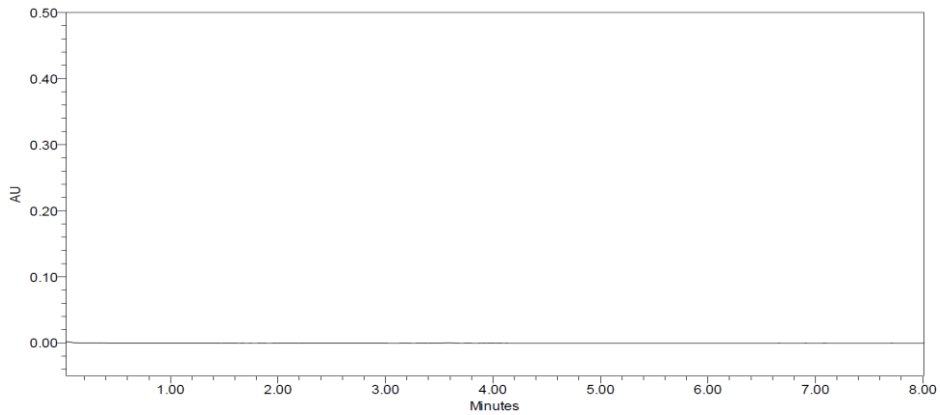

Figure 5: Blank

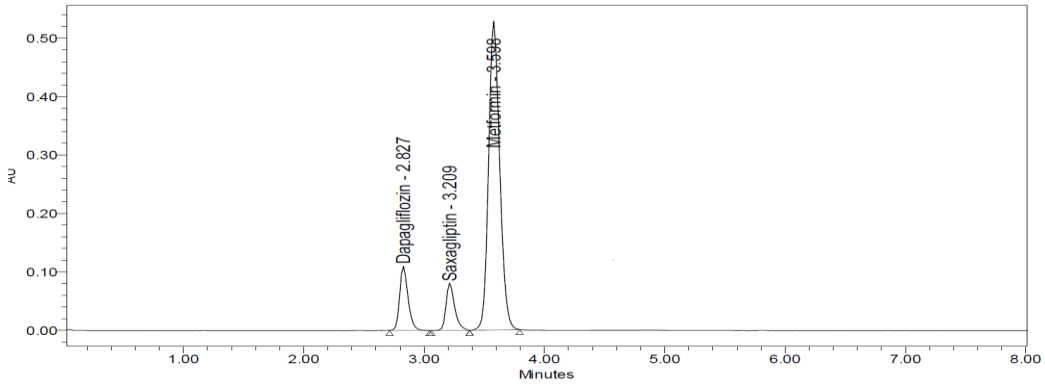

Figure 6: Specificity of Metformin, Dapagliflozin, and Saxagliptin

Linearity:

Calibration data is given in table 4 and regression data in table 5 and calibration curve in figure 7, 8, 9

Table 4: Calibration data of Metformin, Dapagliflozin, and Saxagliptin

Metformin		Dapagliflozin		Saxagliptin	
Conc (µg/mL)	Peak area	Conc (µg/mL)	Peak area	Conc (µg/mL)	Peak area
0	0	0	0	0	0
125	706691	1.25	7648	0.625	3671
250	1422964	2.5	15215	1.25	7429
375	2128465	3.75	22840	1.875	10964
500	2855600	5	30790	2.5	14706
625	3484136	6.25	38360	3.125	18584
750	4260601	7.5	45286	3.75	21795

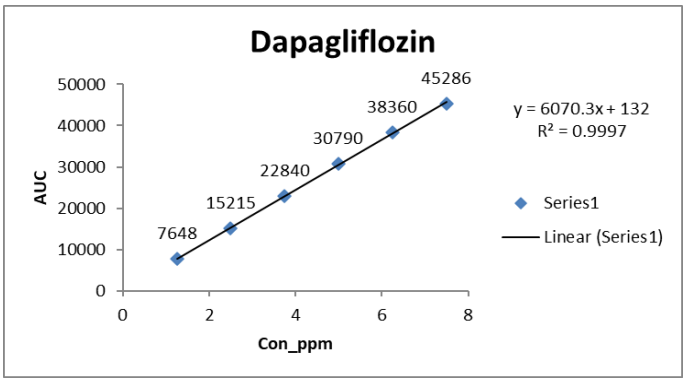

Figure 7 Calibration curve of Dapagliflozin

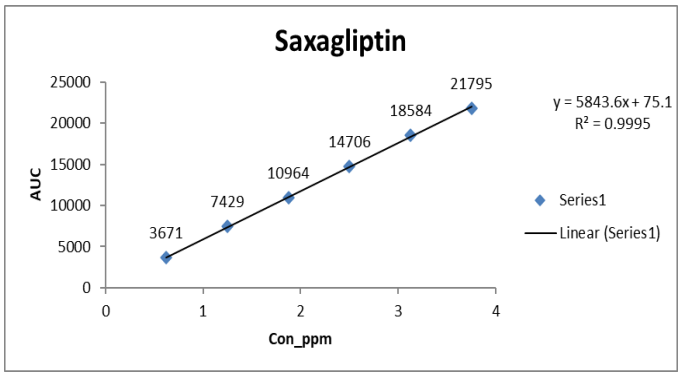

Figure 8 Calibration curve of Saxagliptin

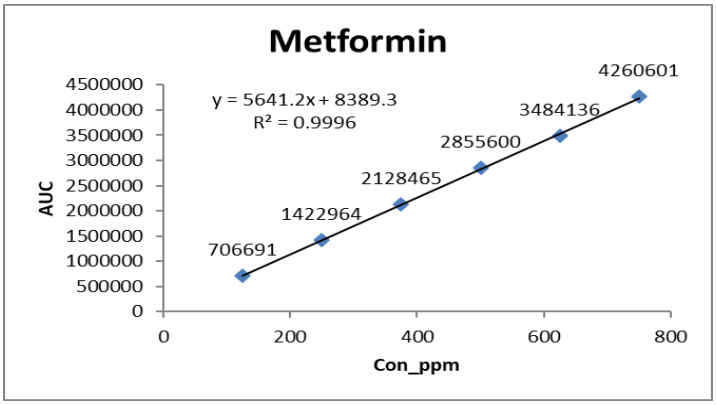

Figure 9: Calibration curve of Metformin

Table 5: regression data

Parameter	Metformin	Dapagliflozin	Saxagliptin
Conc range (µg/mL)	125-750µg/ml	1.25-7.5µg/ml	0.625-3.75µg/ml
Regression Equation	y = 5641.2x + 8389.3	y = 6070.3x + 132	y = 5843.6x + 75.1
Co-relation	0.999	0.999	0.999

Accuracy:

Recovery data shown in table 6

Table 6: recovery data of Metformin, Dapagliflozin, and Saxagliptin

	Metformin			Dapagliflozin			Saxagliptin		
% Level	**Amot Spiked (µg/mL)**	**Amt recovered (µg/mL)**	**% Recovery**	**At Spiked (µg/mL)**	**Amt recovered (µg/mL)**	**% Recovery**	**Amt Spiked (µg/mL)**	**Amt recovered (µg/mL)**	**% Recovery**
50%	250	250.9	100.38	2.5	2.48	99.19	1.25	1.24	99.28
	250	251.4	100.58	2.5	2.51	100.51	1.25	1.24	99.27
	250	251.6	100.65	2.5	2.53	101.35	1.25	1.25	99.92
100%	500	497.3	99.46	5	4.97	99.44	2.5	2.48	99.12
	500	504.3	100.85	5	4.97	99.35	2.5	2.48	99.11
	500	498.9	99.79	5	4.98	99.50	2.5	2.54	101.66
150%	750	747.1	99.62	7.5	7.57	100.93	3.75	3.72	99.31
	750	744.1	99.21	7.5	7.58	101.02	3.75	3.73	99.55
	750	748.0	99.73	7.5	7.56	100.82	3.75	3.73	99.53
% recovery	100.03			100.23%			99.64		

System precision was performed and the data was shown in table 7

Table 7: System precision of Metformin, Dapagliflozin, and Saxagliptin

S. No	Area of Metformin	Area of Dapagliflozin	Area of Saxagliptin
1.	2846646	30474	14444
2.	2854466	30474	14653
3.	2848364	30585	14694
4.	2817364	30764	14694
5.	2803636	30634	14637
6.	2847376	30474	14637
Mean	**2836309**	**30568**	**14627**
S.D	**20643.5**	**118.0**	**93.1**
%RSD	**0.7**	**0.4**	**0.6**

The % RSD for the peak areas of Metformin, Dapagliflozin, and Saxagliptin obtained from six replicate injections of standard solution was within the limit.

Method Precision: The precision of the method was determined by analyzing a sample of Metformin, Dapagliflozin, and Saxagliptin and shown in table 8.

Table 8: method Precision

S. No	Area of Metformin	Area of Dapagliflozin	Area of Saxagliptin
1.	2843746	30547	14673
2.	2846366	30143	14726
3.	2837366	30746	14736
4.	2886464	30943	14663
5.	2843746	30636	14637
6.	2837464	30846	14774
Mean	**2849192**	**30644**	**14702**
S.D	**18622.1**	**283.2**	**52.0**
%RSD	**0.7**	**0.9**	**0.4**

From the above results, the % RSD of method precision study was within the limit for Metformin, Dapagliflozin, and Saxagliptin .

Robustness: Robustness conditions like Flow minus (1.1ml/min), Flow plus (1.3ml/min), mobile phase minus (85B:15A), mobile phase plus (95B:5A), temperature minus (21°C) and temperature plus(31°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

Table 9: Robustness data for Metformin, Dapagliflozin, and Saxagliptin .

Condition	%RSD of Metformin.	%RSD of Dapagliflozin	%RSD of Saxagliptin
Flow rate (-) 0.7ml/min	0.9	0.1	0.8
Flow rate (+) 0.9ml/min	0.8	1.4	1.1
Mobile phase (-) 65B:35A	0.9	0.2	0.2
Mobile phase (+) 75B:25A	0.2	0.7	0.4
Temperature (-) 27°C	0.4	0.1	0.4
Temperature (+) 33°C	1.5	0.7	0.2

Sensitivity:

Table 10: sensitivity of Metformin, Dapagliflozin, and Saxagliptin

Molecule	LOD	LOQ
Metformin	0.54 µg/ml	1.62 µg/ml
Dapagliflozin	0.04 µg/ml	0.12 µg/ml
Saxagliptin	0.02 µg/ml	0.05 µg/ml

Force Degradation Studies: table 11 shows degradation conditions and table 10 shows the obtained degraded data and purity plot chromatogram in figure 10, 11, 12

Table 11: degradation conditions

Stress condition	Solvent	Temp(^{0}C)	Exposed time
Acid	2N HCL	60^{0}c	30 mins
Base	2N NAOH	60^{0}c	30 mins
Oxdation	20% H_2O_2	60^{0}c	30 mins
Thermal	Diluent	105^{0}c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^{0}c	

Table 12: degradation data

Type of degradation	Metformin		Dapagliflozin		Saxagliptin	
	% Rccovered	% Degraded	% Rccovered	% Degraded	% Rccovered	% Degraded
Acid	96.38	3.62	96.23	3.77	95.42	4.58
Base	94.91	5.09	94.27	5.73	94.48	5.52
Peroxide	99.55	0.45	99.49	0.51	99.25	0.75
Thermal	99.00	1.00	98.39	1.61	99.58	0.42
Uv	99.66	0.34	98.45	1.55	99.51	0.49
Water	99.66	0.34	98.84	1.16	98.83	1.17

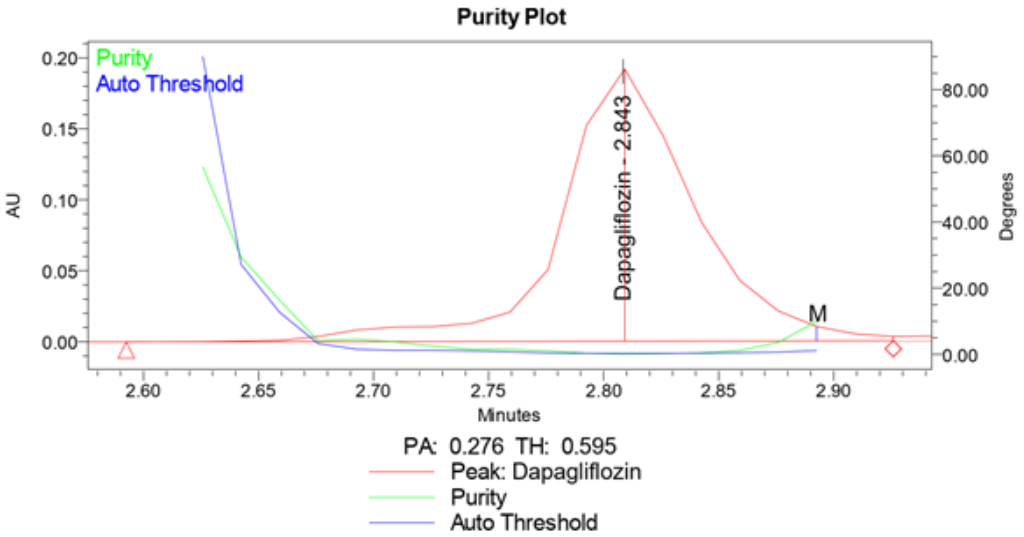

Figure 10: Purity plots for Acid Condition for Dapagliflozin

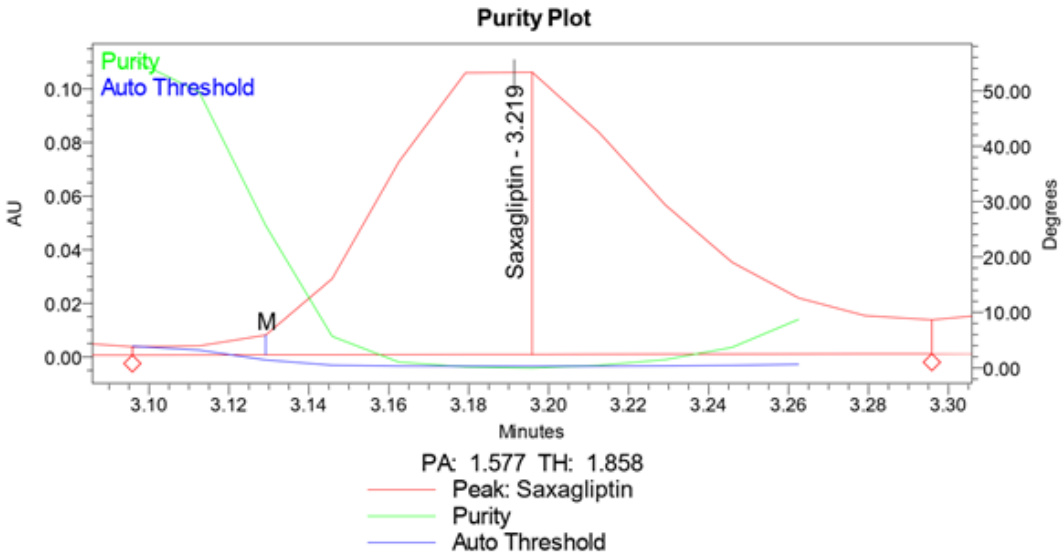

Figure 11: Purity plots for Acid Condition for Saxagliptin

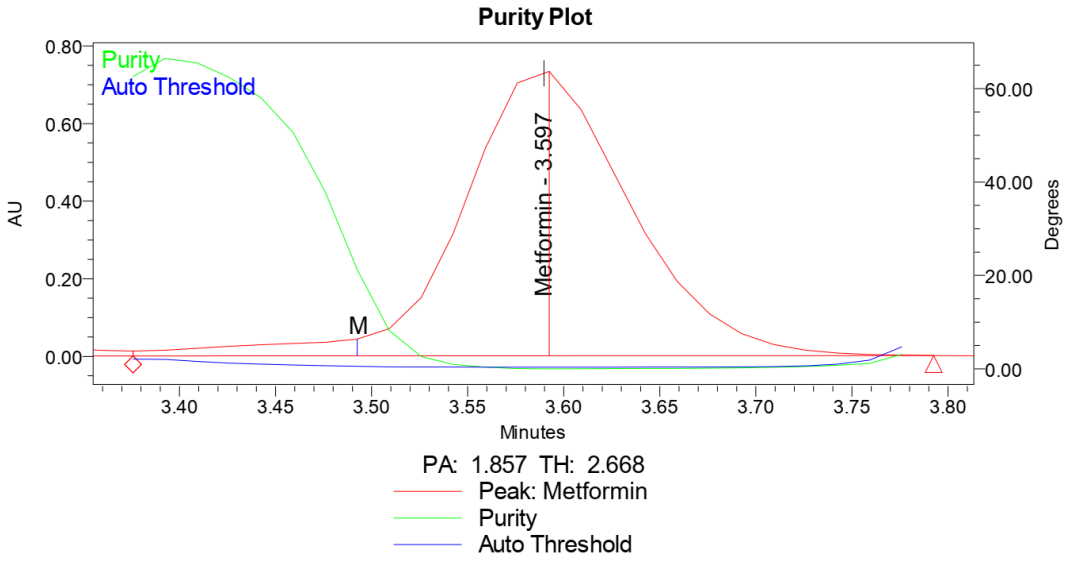

Figure 12: Purity plots for Acid Condition for Metformin.

Assay: Qternmet XR Tablet, bearing the label claim Dapagliflozin 10mg Metformin 1000mg Saxagliptin 5mg. Assay was performed with the above formulation. Average % Assay for Metformin, Dapagliflozin and Saxagliptin. Obtained was 100.25%,100.05% and 100.41% respectively.

Table 11: assay data

	Metformin			Dapagliflozin			Saxagliptin		
S.no	**Std Area**	**Sample area**	**% Assay**	**Std Area**	**Sample area**	**% Assay**	**Std Area**	**Sample area**	**% Assay**
1	2846646	2843746	100.06	30474	30547	99.73	14444	14673	100.22
2	2854466	2846366	100.15	30474	30143	98.41	14653	14726	100.58
3	2848364	2837366	99.84	30585	30746	100.38	14694	14736	100.65
4	2817364	2886464	101.56	30764	30943	101.03	14694	14663	100.15
5	2803636	2843746	100.06	30634	30636	100.02	14637	14637	99.97
6	2847376	2837464	99.84	30474	30846	100.71	14637	14774	100.91
Avg	**2836309**	**2849192**	**100.25**	**30568**	**30644**	**100.05**	**14627**	**14702**	**100.41**
Stdev	**20643.5**	**18622.1**	**0.655**	**118.0**	**283.2**	**0.92**	**93.1**	**52.0**	**0.355**
%RSD	**0.7**	**0.7**	**0.7**	**0.4**	**0.9**	**0.9**	**0.6**	**0.4**	**0.4**

Assay was calculated by the formula:

$$\%\ \text{Assay} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{10} \times \frac{100}{1} \times \frac{10}{1} \times \frac{P}{100} \times \frac{FV}{L.C} \times 100$$

AT	Average Peak area of sample in test solution
AS	Mean peak area of sample in standard solution
WS	Weight of drug working standard taken in mg
P	Assay of drug working standard in % on dried basis
L.C	Label Claim

Figure 13 Assay formula

Conclusion:

The study's results will help a lot with checking the quality of affordable medications that contain Metformin, Dapagliflozin, and Saxagliptin . This might be because the study used a simple way to prepare the samples, which only needed a short analysis time and a small amount of mobile phase. After testing two medicines together in a single dose, the data showed that the newly developed analysis method was very close to being 100% effective.

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