Development and Validation of Novel Stability-Indicating LC Method for the Determination of Saxagliptin and Metformin

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ABSTRACT

Aim: Development of a novel precise, selective and sensitive stability indicating RP-HPLC method has been developed and validated for the determination of Saxagliptin hydrochloride (SAX) and Metformin HCl (MET) in bulk drug and pharmaceutical dosage form. **Materials and Methods:** The separation was carried out on a Phenomenex Luna, SCX, 250 x 4.6mm, 10 μm using a mobile phase of ammonium dihydrogen phosphate buffer pH 2.50: methanol [70:30 % v/v]. Quantitation was achieved using UV detection at 210 nm. **Results:** The retention times were about 6.2 min for SAX and about 10.4min for MET. Calibration curves were linear over the concentration range from 5-100μg/mL for SAX and 40-800μg/mL for MET. Peak purity of SAX and MET established in presence of all major degradation product in stressed samples. **Conclusion:** The proposed method of analysis has been validated as per ICH guidelines and proved to be specific, precise, linear, rugged and robust. The effectiveness of the method was demonstrated with marketed pharmaceutical preparation of SAX and MET.

Key words: Saxagliptin, Metformin, Stability indicating, Forced degradation, Pharmaceutical preparation.

INTRODUCTION

Saxagliptin (SAX), (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, (Figure 1a) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) used as oral hypoglycemic drug for the management of type 2 diabetes mellitus. Saxagliptin is indicated as an addition to diet and exercise to get better glycemic control in patients with type 2 diabetes. It is available commercially as Onglyza tablets and also in mixture with Metformin as KOLMBIGLYZE XR tablets.[1] Metformin hydrochloride (MET), N, N-dimethylimidodicarbonimidic diamide hydrochloride [Figure 1b] is an antidiabetic drug in the biguanide class that induces glycolysis in peripheral tissues.[2] Pharmaceutical preparation containing SAX and MET, used in the management of type 2 diabetes.

Literature review reveals that methods are available for simultaneous determination of SAX and MET in combination by using Spectrophotometric[3] and Chromatographic[4-7] technique. Several methods for Metformin HCl alone and in combination with other drugs are also available those includes Spectrophotometric[8] and HPLC.[9-21] There are some chromatographics methods available for SAX.[22-27] some electrochemical methods are also reported for determination of Metformin and Saxagliptin.[28-30]

A stability-indicating method identify and estimates the analytes specifically with good resolution with its degradants in forced degradation study. As per ICH guidelines

it's a prerequisite of development of stability-indicating method. The guidelines clearly require the conduction of forced degradation studies beneath different conditions, like acidic hydrolysis, alkali hydrolysis, photolysis, oxidation, Thermal, etc. and resolution of the analyte from degradant impurities. The chromatographic purity of analyte peak in degradation samples is must for the validation of the any method and this is the most important when development of any stability-indicating method.

In present study, a simple stability indicating method for quantification of SAX and MET has been developed and validated. Stability indicating nature of the method has been established in stressed samples and successfully applied for a pharmaceutical preparation.

MATERIALS AND METHODS

Instrumentation

Agilent 1200 series equipped with quaternary pump, autosampler and DAD detector was used. The data processing was done by using AGILENT Open Lab software. The chromatographic separations were performed on a Phenomenex Luna SCX column (250 x 4.6 mm i.d., 10 μm particle size) as a stationary phase and ammonium dihydrogen phosphate buffer (pH 2.50): Methanol [70:30 % v/v] as mobile phase. A 10 μL sample solutions were injected to chromatographic system using autosampler system. The flow rate of 1.8 mL/min and detection wavelength of 210 nm was taken for analysis. The column temperature and autosampler temperature was kept at 40°C and 10°C respectively.

Denver analytical balance was used for weighing and pH measurement was performed by using Lab India pH meter. Mobile phase filtration was performed by vacuubrand 2°C vacuum pump using 0.45μm nylon membrane filter paper. Specificity was conducted by using heating oven, photo stability chamber and hot plate from Thermolab India.

Chemicals and Reagents

Pharmaceutical grade SAX was supplied by VerGo Pharma, Goa, India. While MET was supplied by Soham Healthcare Ltd India. Saxagliptin HCl 5mg and Metformin HCl 1000mg combination tablets were used for method verification which were purchased from Indian local market. All solutions were prepared with milli-Q-water. Acetonitrile was HPLC grade, Merck. Orthophosphoricacid was AR grade, Merck. Hydrochloric acid and sodium hydroxide pellets were GR grade, Merck. Hydrogen peroxide solution (30% w/v), SDFCL India.

Preparation of Diluent: (2:20:78 water: acetonitrile: methanol % v/v)

Mixed 20mL water, 200mL of acetonitrile and 780mL of methanol and sonicated.

Preparation of Standard

Saxagliptin Standard solution stock: Weighed and transferred Saxagliptin HCl equivalent to 50 mg of saxagliptin into a 50 mL flask and made up to volume with Diluent.

Standard solution of saxagliptin and Metformin: -10 mL of above standard stock transferred into a 100 mL volumetric flask in which added about 40 mg of metformin and made up to volume with Water.

Tablet test sample Preparation

Weighed 10 tablets to a 500 ml volumetric flask to that added 10 ml of water vortex for 5 min to dissolve the coating of tablets, added 100 mL acetonitrile vortex for 5 min checked for proper dispersion of tablets further added 300 mL of methanol and sonicate it for 10 min with vigorous shaking. Allow to equilibrate at room temperature and diluted to volume 500mL with methanol. Centrifuged at 5000 RPM for 5 mins. Supernatant solution used as sample for Saxagliptin assay analysis and for Metformin analysis 2.0 ml of centrifuged sample was transferred to 100mL flask and made up to mark with water.

Validation of developed Method

The validation of developed method was done as per ICH guidelines.[19]

System Suitability Parameters

According to USP[20] system suitability is an important part of chromatographic method. It's useful to confirm the reproducibility of the developed method. The system suitability parameters like % RSD of five replicates injections, Theoretical plates and tailing for peaks were recorded which were found to be acceptable. The results are shown in Table 1.

Specificity

To show the good separation of SAX and MET from their impurities an experiment was conducted. To make sure the efficient separation of degradant peaks of excipients at the retention time of SAX and MET degradation of excipients was carried out. Formulation and placebo samples were separately exposed to various stress conditions to bring degradation. The formulation was exposed to alkaline hydrolysis by refluxing sample solution in 0.1 N sodium hydroxide at room temperature for 1 hr. Similarly the acidic hydrolysis was conducted

by refluxing sample solution in 5N hydrochloric acid at 60°C for 24 hr. The hydrolysis with water conducted by refluxing sample solution at temperature of 60°C for 24 hr. Oxidation was conducted by exposing sample to 30% hydrogen peroxide solution at 60°C for 2 hr. For Photo stability study, formulation kept in Petri-plates and was exposed to sunlight and UV light for 7 days. Humidity stress was conducted separately by exposing Formulation to humidity at 25°C, 90% RH for 7 days. Thermal stress was conducted by heating formulation at 105°C for 24 hr. Placebo samples were also prepared like a formulation and exposed to condition same as formulation. Forced degradation placebo and samples were all injected into the chromatographic condition as per test method to show the spectral peak purity of peaks. Table 2 shows forced degradation data for SAX and MET.

Accuracy

Accuracy of method was performed by recovery study. Sample solutions were prepared by solid spiking at about 50 %, 100% and 200% of test concentration level into placebo and it was then injected into developed method. The %RSD for the tablet analysis was not more than 2.0% which shows a good accuracy. Recovery results tabulated in Table 3.

Precision

System precision

System precision is the measure of how closeness of agreement between a series of measurement under the same analytical condition. Mixed standard solution prepared was injected for six times. The % relative standard deviations were found to be 0.1% and 0.1% for SAX and MET respectively.

Method Precision

Method precision study was performed on six sample preparation as per test method. The % Relative Standard Deviation (RSD) found for SAX and MET were not more than 2.0% signifying high level of precision. Results tabulated in Table 4.

Stability of solution

Standard solution and sample were prepared and injected into chromatographic condition at initial and after 24 hr fresh standard and same sample were injected to check the stability. The % RSD for peak areas was determined and found to be less than 2.0 % which shows that stability of the solution at bench top.

Filter Compatibility

Sample solutions were prepared in triplicate as per the methodology. Filtered the sample solution with 0.45μm

Table 1: System Suitability Parameters.			
Parameter	Limit	SAX	MET
% RSD of area of six injections	≤ 2.0	0.2	0.4
% RSD of retention time of six injections	< 2.0	0.3	0.2
Theoretical plates number (N)	> 2000	5246	6458
Tailing Factor	≤ 2	1.1	1.3
Resolution	≤ 1.5	--	4.68
Capacity Factor	1 to 10	2.4	4.7
Selectivity Factor	> 1	--	1.93
HETP	Value should be smaller	0.0477	0.0387

Table 2: Forced Degradation Data for Saxagliptin phosphate (SAX) and Metformin Hydrochloride (MET).						
Sample	% Assay		% Degradation		Peak Purity	
	SAX	MET	SAX	MET	SAX	MET
Control	100.5	100.6	-	-	1.00	1.00
Acid	97.9	99.8	2.1	0.2	1.00	1.00
Base	89.7	97.7	10.3	2.3	1.00	1.00
Oxidative	90.6	89.1	9.4	10.9	1.00	1.00
Thermal	85.6	99.8	14.4	0.2	1.00	1.00
Photolytic	94.5	97.5	5.5	2.5	1.00	1.00

mdi PVDF syringe filter, 0.45μ mdi Nylon 66 syringe filter and analyzed by method and calculated results against the standard. The relative standard deviation was calculated for obtained results and it was found to be less than 2.0 % which shows suitability of filter.

Linearity and Range

Linearity was conducted from 10% to 200% of standard concentration. The standard stock solution was diluted from 10% to 200% concentration and the final solution for linearity of SAX prepared was 10 to 100 μg/ml. Final solution for linearity of MET prepared was 40 to 800 μg/ml. Injected 10 μL of each level solution in duplicate into chromatographic condition. Calibration curve was plotted by response peak area versus the drug concentration at each level. The observations are shown in Table 5.

Limit of Quantitation (LOQ) and Limit of Detection (LOD)

The LOQ and LOD were estimated based on the calibration curves data. The residual standard deviation and slope from calibration data and were used in calculating as below formulae.

$$LOD = 3.3 \times \sigma / S$$
$$LOQ = 10 \times \sigma / S$$

Where, σ = standard deviation
S = slope
The LOD for SAX and MET were observed to be 0.354 and 2.546 μg/mL respectively. The LOQ for SAX and MET were observed to be 1.125 and 7.243μg/ml.

Robustness

The robustness was conducted by making small deliberate changes in the developed method parameters

Table 3: Results of Recovery Study.

Drug	Label Claim (mg/tab)	Concentration μg/mL	Recovery level %	% Recovery Estimated Mean (a) ± SD (b)	% RSD (c)
SAX	5	50	50	99.2 ± 0.3456	0.32
		100	100	99.6 ± 0.5466	0.78
		200	200	99.5 ± 0.6485	0.61
MET	1000	200	50	99.6 ± 0.3564	0.32
		400	100	100.2 ± 0.2456	0.18
		800	200	99.9 ± 0.4561	0.39

(a): Average of Three Determinations (b): Standard Deviation (c): Relative Standard Deviation

Table 4: Results of Method precision.

Sample No.	% Assay	
	SAX	MET
1	99.2	99.5
2	99.8	100.5
3	100.2	99.7
4	98.9	100.2
5	99.5	99.3
6	99.6	98.9
Mean ± SD	99.5 ± 0.4546	99.7 ± 0.5879
% RSD	0.5	0.6

Table 5: Linearity Study of SAX and MET.

Name	SAX	MET
Range in μg/mL	10-200	40-800
Regression Equation	Y = A + B*C	
Slope (B)	13141.636	43772.483
Intercept (A)	11225.237	226013.036
Correlation coefficient (r)	0.9990	0.9993

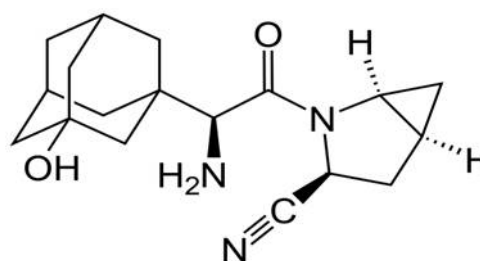C: Concentration in μg/ml Y: Unit of Response Factor a: Standard Error

Figure 1a: Saxagliptin.

like pH ± 0.2 units, mobile phase composition ratio ± 5%, column temperature ± 5 units and flow ± 0.2mL/min. There was no considerable change in percentage recoveries of drugs. The outcome of the robustness study shows that the method is robust as it is unaffected by small variations.

RESULTS AND DISCUSSION

An objective of this study was to develop an improved simple, selective, accurate, reproducible and sensitive stability indicating HPLC assay method for SAX and MET in bulk and pharmaceutical formulation. The reversed phase chromatography was selected for method development of SAX and MET. Ammonium dihydrogen phosphate salt selected for buffer preparation. Phenomenex Luna SCX column selected as stationary phase for retention of MET as MET do not retain in C_{18} column without using ion pair reagent in mobile phase. SCX column has modified stationary phase bonded with ion pair reagent which retains the analytes. Different buffer pH, flow rate, column temperature and different composition of buffer: methanol and buffer: Acetonitrile with different ratios such as 55:45, 60:40, 70:30, 80:20 v/v were tried to separate SAX and MET the best retention and separation was got by using buffer pH 2.50: methanol (70:30, v/v) with a flow rate of 1.8 mL/min and column temperature 40°C. Flow rate was kept 1.8mL/min so as to elute fast the analytes and reduce the run time of method. Column temperature kept at 40°C for better resolution, better peak shape of saxagliptin and metformin. Column temperature 25°C shows less resolution and late elution of peaks than 40°C column temperature. SAX elutes at about 6.2 min while MET elutes at about 10.3 min. Late elution kept so as to separate any degradation placebo peak or impurity peaks. Figure 2-3(a –k) shows typical of blank, placebo, standard and samples of SAX and MET. The retention times of SAX and MET were 6.3 and 10.4 min, respectively. Forced degradation studies were also studied in that acid stress, alkali stress, peroxide, heat, UV treatment given to SAX and MET. Chromatogram of base degradation of saxagliptin shown in Figure 3j and 3k. Peak purity of MET and SAX established in presence of all major degradation product in stressed samples. The calibration plot curve was linear over the range 10 to 200 μg/ml and 40 to 800 μg/ml for the detection of SAX and MET respectively. The correlation coefficients (r) found was not less than 0.99 which shows method is linear statistically. Calibration curve shown in Figure 3h and Figure 3i for saxagliptin and metformin respectively. The recovery at three different level concentrations of SAX and MET was performed, the relative standard deviation values of were less than 2.0%.

The results obtained after analysis of SAX and MET by the developed methods were statistically compared with results of the reported methods.[27] Statistical comparison

Table 6: Statistical comparison obtained by proposed method and reported method.

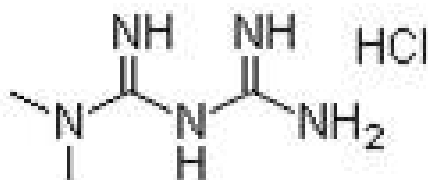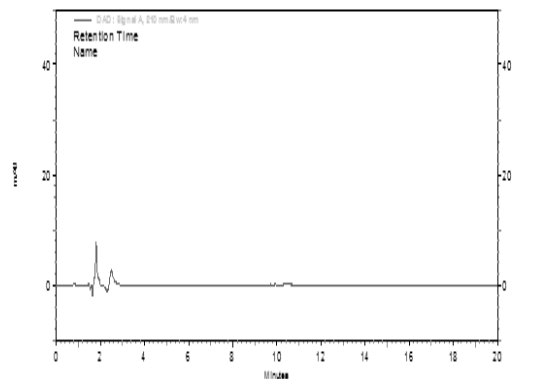| Parameters	Proposed method		Reported method[27]	
Name	SAX	MET	SAX	MET
Mean	99.5	99.7	99.92	100.17
Standard deviation	0.4546	0.5879	1.158	0.996
Variance	0.2066	0.3456	1.341	0.992
n	6	6	7	8
Student *t* test	-0.8834	0.426		
F value	0.1541	0.3484		

Figure 2: Chromatogram of Blank.
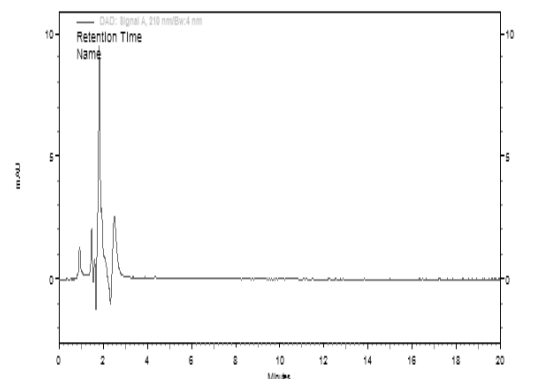

Figure 1b: Metformin HCl.
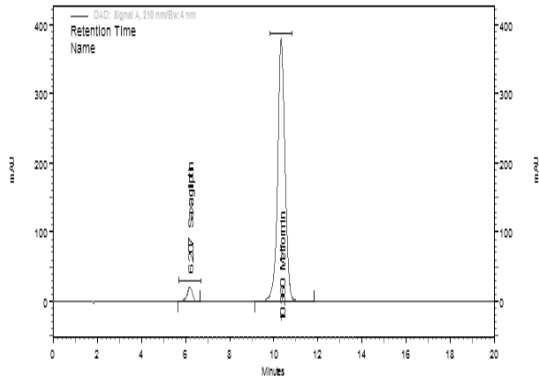

Figure 3a: Chromatogram of Placebo.

Figure 3b: Chromatogram of Standard solution Saxagliptin (100μg/mL) and Metformin (400μg/mL).
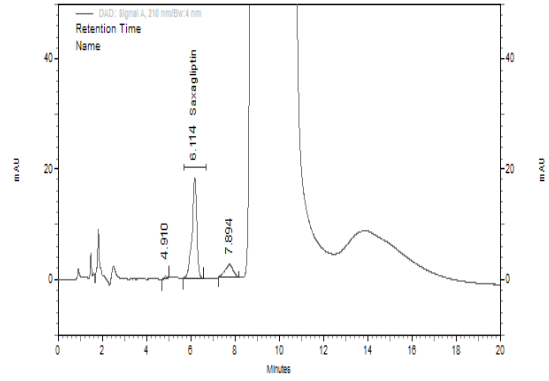

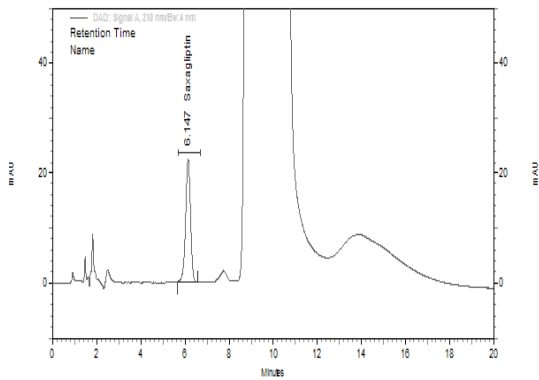**Figure 3e: Chromatogram of Base Degradation for Saxagliptin.**

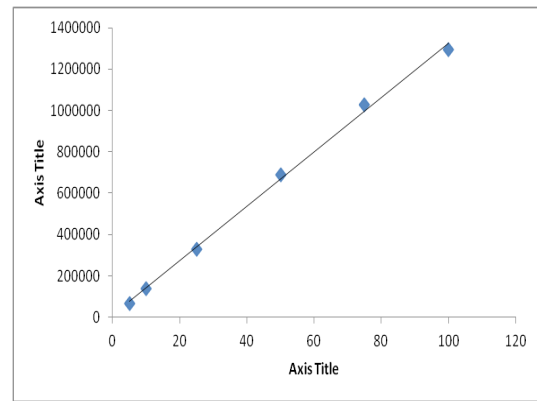**Figure 3c: Zoomed Chromatogram of Tablet Sample for Saxagliptin.**

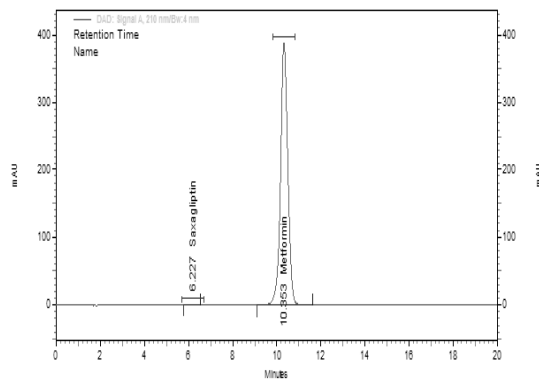**Figure 3h: Calibration curve for Saxagliptin Phosphate.**

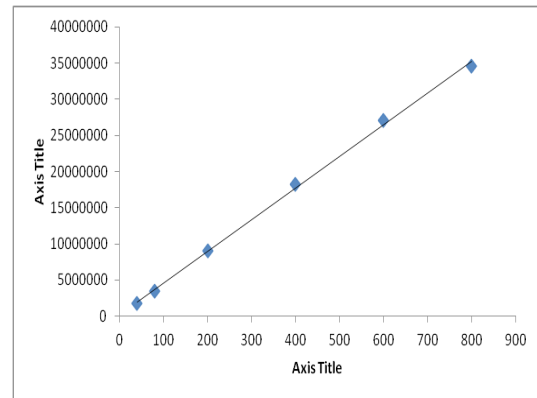**Figure 3d: Chromatogram of Tablet Sample for Metformin.**

Figure 3i: Calibration curve for Metformin HCl.

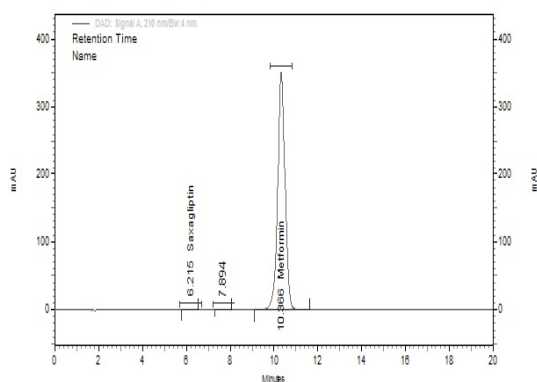| Table 7: Comparison of parameter of developed method with reported method.				
Parameter	**Developed Method**		**Reported method[27]**	
	SAX	**MET**	**SAX**	**MET**
Range	10-200μg/mL	40-800μg/mL	1.5-25 μg/mL	25-1000μg/mL
LOD	0.354	2.546	0.478	8.178
LOQ	1.125	7.243	1.447	24.782

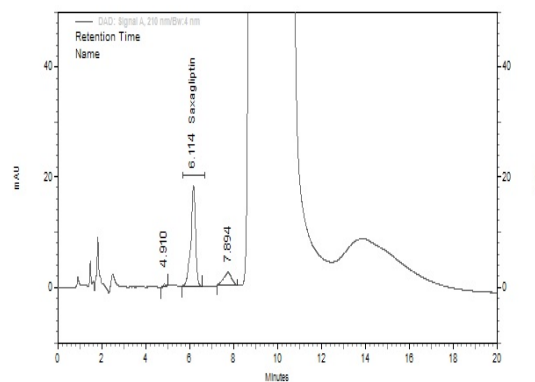**Figure 3j: Chromatogram of Base Degradation for Metformin.**

Figure 3k: Chromatogram of Base Degradation for Saxagliptin.

shown in Table 6. The calculated t and F values show that there is no considerable variation between the two methods with respect to accuracy and precision. The LOD and LOQ values in proposed method for both the drugs are less than that of reported method which indicates method is more sensitive than reported method. Proposed method shows good Linearity than that of reported method. Comparison shown in Table 7.

CONCLUSION

Developed Stability indicating HPLC method is selective, accurate, precise, sensitive, robust and selective and can be used for the simultaneous determination of SAX and MIT in pure form and pharmaceutical tablets formulations. Selective and increased detector detection shows method is more superior. A good recovery of method showed that there is no interference of excipients used in the formulations at analyte. The outcome of the validation study showed that the developed reverse phase HPLC method for SAX and MET can be used for routine analysis in QC departments for the simultaneous determination of the tablets containing SAX and MET.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

**SAX:** Saxaglitin HCl; **MET:** Metformin HCl; **ACN:** Acetonitrile.

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PICTORIAL ABSTRACT

DEVELOPMENT AND VALIDATION OF NOVEL STABILITY-INDICATING LC METHOD FOR THE DETERMINATION OF SAXAGLIPTIN AND METFORMIN
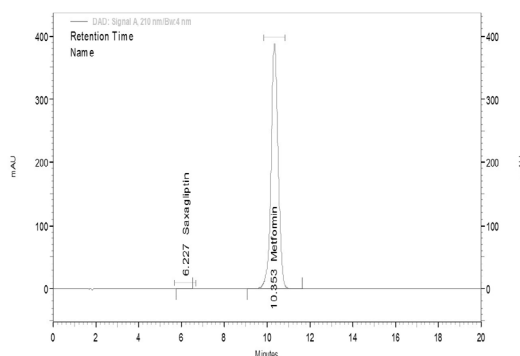
SUMMARY

A new reverse phase stability indicating HPLC method was developed and validated for quantification of Saxagliptin and Metformin from Tablets formulation. Method found specific, accurate precise for intended purpose.