



## **Development and Validation of Novel RP-HPLC Method for the Simultaneous Determination of Remogliflozin and Vildagliptin in Bulk and in synthetic Mixture**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Vildagliptin which is DPP-4 inhibitor and Remogliflozin which is SGLT2 inhibitor in single dose regimen lower blood glucose by separate, complementary mechanisms. Both are glucose dependent, accounting for the low risk of hypoglycaemia during treatment. There is no risk factors associated with this combination and moreover it is single dose regimen. The aim of the present study was to develop and validate a simple, rapid and reproducible gradient high performance reverse phase liquid chromatography method for the estimation of Remogliflozin and Vildagliptin in bulk drug sample and in synthetic mixture using Xterra® Waters C18 column (150 mm×4.6 mm, 5 µm) at 25°C with UV detection at 210 nm and for this gradient mode was used. The compounds were eluted gradiently at a flow rate of 1.0ml/min. The average retention times for Remogliflozin and Vildagliptin were 4.881 and 6.334 min, respectively. The calibration curves were linear ( $r^2 = 0.988$ ) over the concentration range 10-200 µg/ml for Remogliflozin and 10-200 µg/ml for Vildagliptin. No spectral or chromatographic interferences from formulation excipients were found

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and hence it was successfully applied for the determination of Remogliflozin and Vildagliptin in bulk and in synthetic mixture. The accuracy of the proposed method was determined by recovery studies and found to be 98-101%. The proposed method was validated and results conformed to ICH parameters.

*Keywords: Accuracy; calibration curve; LOD; LOQ; precision; retention time.*

## 1. INTRODUCTION

In type –II diabetes patient is having insulin resistance. Mainly in this type of diabetes there are two interrelated problems in which one include the irregularity in insulin hormone which is produced by pancreas and other problem include is that the cells very poorly respond to insulin and very less take in sugar.

Remogliflozin inhibits the sodium-glucose transport proteins (SGLT), which are responsible for glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine. Remogliflozin is selective for SGLT2. Inhibitors of sodium-glucose co-transporter type 2 (SGLT2) represent a new class of anti-hyperglycemic agents with a unique mechanism of action. These drugs lower blood glucose by increasing urinary glucose excretion. Remogliflozin etabonate (REM) is a prodrug of remogliflozin, an SGLT2 inhibitor under development [1,2,3].

In patients of type-II diabetes vildagliptin improves glycaemic controls as it is orally active potent and selective DPP-4 inhibitor which enhance pancreatic ( $\alpha$  and  $\beta$ ) islet functions. It improves insulin secretion and suppress the glucagon secretion in diabetic patients. Both are glucose dependent and lowers the risk for hyperglycemia.

The synergistic effect of these two combined drugs lowers the blood glucose by complementary mechanisms of action and in single fixed dose regimen. This combination of this drugs enhance their glucose lowering effects [4,5].

Moreover according to clinical trials of the phase – III of FDC as well as bioequivalence studies of REM +VDG combined fixed dosage form is used to improve the glycaemic control when metformin and one of the mono constituents of fixed dose combination of REM and VDG do not provide adequate glycaemic control [6].

## 2. MATERIALS AND METHODS

Remogliflozin raw material was received as gift sample from Galpha Laboratories; Ankleshwar

Vildagliptin raw material was received as gift sample from Cipla pharmaceutical Pvt. Ltd. Acetonitrile used was HPLC grade, Merck Ltd., ultra - pure water and Membrane filter of 0.22  $\mu$ m nylon membrane filter (RANKEM) were used.

### 2.1 Instrumentation

Chromatographic analysis was carried out on a prominence liquid chromatograph (UFLC Shimadzu Corporation, Tokyo, Japan) with LC-2010AHT series binary pump systems, Auto sampler injection, temperature controller (column oven, HCO-O2, PCI Analytics) system controller and a UV detector (LC-2010). CLASS-VP (version 2.31) software was used to acquire and process the data. A Semi micro analytical balance (Sartorius CD2250, Germany) was used for weighing purpose. HPLC water was obtained using arium®611VF (Sartorius). Magnetic stirrer (1MLH, Remi) was used for mixing purpose. pH tutor (313927, Eutech Instruments) was used for pH measurement. Sonication of solutions was done using Ultrasonic cleaner (D 120/1H, Trans-O-Sonic). All volumetric glasswares were used and were calibrated. In this method reversed phase column Luna C<sub>18</sub> 100A° (250mm×4.6mm i.d.) 5 $\mu$ m (Phenomenex, Luna®) was used. Graduated Pipettes of 1, 2, 5 and 10 ml capacity were used and measuring cylinders of 10, 100 ml and 500 ml capacity were used. All the glassware were class 'B' volumetric glassware. All apparatus and instrument were calibrated before use.

### 3. STANDARD SOLUTION PREPARATION [7,8]

#### 3.1 Preparation Standard Solution of Remogliflozin

**Preparation of buffer:** Accurately weighed about 2.86 grams of sodium acetate was taken into 1000ml beaker and dissolved and diluted to 1000ml with HPLC water and degassed in ultrasonic water bath and filtered through 0.45 $\mu$ m filter using vacuum filtration and the pH of 4 was adjusted by using diluted ortho phosphoric acid.

**Preparation of mobile phase:** The optimized mobile phase consists of a mixture of acetate buffer (pH 5.6) and methanol in the ratio of 30:70 v/v.

**The diluents:** The drug was first dissolved in methanol and further dilutions were made using methanol.

**Preparation of standard stock solution:** Accurately weighed 10 mg of Remogliflozin (REM) was taken in a 10 ml standard volumetric flask and dissolved in few ml of methanol. Then the volume was made up to the mark with methanol. From the above solution, 1 ml was diluted to 10 ml with methanol to get a concentration of 100µg/ml of Remogliflozin.

#### 4. PREPARATION STANDARD SOLUTION OF VILDAGLIPTIN

About 100 mg of Vildagliptin (VDG) was weighed accurately into a 100ml volumetric flask and dissolved and diluted to volume with mobile phase acetate buffer and methanol (30:70 v/v) to obtain a concentration of 1000 µg/ml and this solution was used as stock solution. From this stock solution 1ml was taken to dilute 10ml again with mentioned mobile phase to get the concentration 100 µg/ml of Vildagliptin.

##### 4.1 Preparation Standard Solution of Remogliflozin and Vildagliptin in Combination

1ml from working standard stock solutions of REM (100 µg/ml) and 1 ml from working standard stock solutions of VDG (100 µg/ml) were taken in a common volumetric flask diluted up to 10ml with mobile phase acetate buffer and methanol (30:70 v/v) to make final concentration REM (100 µg/ml) and VDG (100 µg/ml)

##### 4.2 Preparation of Test (Formulation) Solution

As per the patent the synthetic mixture is prepared by taking the ratio of 1:1 and talc sufficient to make the quantity. According to this ratio Remogliflozin and Vildagliptin (100 mg+ 100 mg) accurately weighed and mixed in the 100 ml volumetric flask. Talc is added to the sufficient quantity and sonicate for 15 min. Make up the volume with Methanol. The solution was filtered through whatmann filter paper No. 42. This solution had concentration of 1000 µg/ml for REM

and 1000µg/ml for VDG. From this solution pipette out 1ml in 10 ml volumetric flask and volume was made up to mark with mobile phase acetate buffer (pH 5.6) and methanol (30:70 v/v) to make final concentration REM (100µg/ml) and VDG (100µg/ml).Chromatogram of the Test solution containing 100µg/ml of REM and 100 µg/ml of VDG was recorded and peak areas were noted for estimation of REM and VDG.

#### 5. SELECTION OF ELUTION MODE [9,10]

Reverse phase chromatography was chosen because of its recommended use for ionic and moderate to polar compounds. It is not only simple, convenient but also better performs in terms of efficiency, stability and reproducibility. C<sub>18</sub> column (150mm×4.6mm, 5µm) is chosen because of it is least polar compared to C<sub>4</sub> and C<sub>8</sub> columns. C<sub>18</sub> column allows eluting polar compounds more quickly in comparison to non-polar compounds. In addition to this, UV detector is used, which allows easy detection of the compounds in UV transparent organic solvents. Chromatographic separation was achieved on a Xterra® Waters C18 column (150mm×4.6mm, 5µm) with UV detection at 210 nm. Gradient mode was chosen due to simplicity in application and robustness with respect to longer column stability.

#### 6. CHROMATOGRAPHIC CONDITION

Standard and sample solutions were injected in column using ultra-fast auto sampler. The chromatogram was run for appropriate time duration with degassed mobile phase, mixture of acetate buffer (pH 5.6) and methanol (30:70 v/v) . The system was equipped with a UV-visible detector (SPD-20A, Japan) and detection is carried out at wavelength 210 nm. Analyses were performed at 30<sup>0</sup>C The chromatogram was stopped after separation was achieved completely. Data related to peak like area, height, retention time, resolution etc. was recorded using CLASS-VP software (version 2.31).

#### 7. METHOD VALIDATION [11,12,13]

The method of analysis was validated as per the recommendations of ICH for the parameters like system suitability studies, accuracy, linearity, precision, detection limit, quantitation and robustness.

## 7.1 System Suitability Studies

The system suitability was evaluated by five replicate analyses of REM and VDG mixture at concentration of 100 µg/ml of REM and 100 µg/ml of VDG. The column efficiency, resolution, and peak asymmetry were calculated for the standard solutions. The results of System suitability studies are given in Table 2.

## 7.2 Stability of Analytical Solution

In order to demonstrate the stability of both the standard and sample solutions during analysis, both solutions were analyzed over a period of 24 hours at room temperature. The results indicated that for both the solutions, the retention time and peak area of REM and VDG did not show much variation (% RSD less than 2.0). There was no significant degradation within the indicated period. Hence, it was concluded that both the solutions were stable for 24 hours at room temperature.

## 7.3 Linearity and Range

The linearity response was determined by analyzing 5 independent levels of concentrations in the range of 10-200 µg/ml and 10-200 µg/ml for REM and VDG, respectively with the 25 µl inject volume and chromatograms were recorded. Calibration curve was constructed by plotting average peak areas versus concentrations and regression equation was computed. This is given in Table 3.

### 7.3.1 Preparation of calibration curve for REM and VDG

**Calibration curve for REM:** The calibration curve was constructed with five concentrations ranging from 5-200 µg/ml for Remogliflozin (10, 50, 100, 150, 200 µg/ml of Standard stock solution having concentration 1000 µg/ml). The data of peak area versus concentration were treated by linear least square regression analysis. Calibration curve of ROS is given in Fig. 10.

**Calibration curve for VDG:** The calibration curve was constructed with five concentrations ranging from 10-200 µg/ml for Vildagliptin (10, 50, 100, 150, 200 µg/ml of Standard stock solution having concentration 1000µg/ml). The data of peak area versus concentration were treated by linear least square regression analysis. Calibration curve of TEN is given in Fig. 11.

## 8. PRECISION

### 8.1 Intraday Precision

The precision of the developed method was assessed by analysing samples of the same batch in nine determinations with three Standard solutions containing concentrations 50, 100, 150µg/ml for REM and 50, 100, 150 µg/ml for VDG and three replicate (n=3) each on same day. The % RSD value of the results corresponding to the peak area was expressed for intraday precision. This is given in Table 4.

### 8.2 Inter Day Precision

The precision of the developed method was assessed by analyzing samples of the same batch in nine determinations with three Standard solutions containing concentrations 50, 100, 150 µg/ml for REM and 50, 100, 150 µg/ml for VDG and three replicate (n=3) each on different day.

The % RSD value of the results corresponding to the peak area was expressed for inter-day precision. This is given in Table 4.

## 9. ACCURACY

### 9.1 Preparation of Synthetic Mixture

**Composition of synthetic mixture:** It was determined by calculating the recovery of REM and VDG by standard addition method.

Remogliflozin: 100 mg  
Vildagliptin: 100 mg  
Talc: q. s 1000 mg

All the excipients were mixed in 10ml volumetric flask and sonicate for 15min. Make up the volume with Distilled Water. The solution was filtered through Whatman filter paper No. 42.

Finally the solution had concentration 100µg/ml for REM and 100µg/ml for VDG. From that pipette out 1 ml in 10 ml volumetric flask and make up to the mark with Methanol. Add amount of standard Remogliflozin and Vildagliptin API (80%, 100%, 120%) to amount of formulation equivalent to 10µg/ml of REM and 80µg/ml of VDG in respective flask and volume was made up to the mark with same solvent. Spiking of formulation in the accuracy was as per the Table.

Data from nine determinations over three concentration levels covering the specified range was determined and % recovery was calculated. This is given in Table 5.

## 10. LOD (LIMIT OF DETECTION) AND LOQ (LIMIT OF QUANTIFICATION)

The LOD and LOQ is estimated from the set of 6 calibration curves used to determine method linearity.

The LOD and LOQ may be calculated as

$$LOD = 3.3 \times \frac{SD}{Slope}$$

$$LOQ = 10 \times \frac{SD}{Slope}$$

Where, SD = SD of Six intercept of calibration curve

Slope = the mean slope of the 6 calibration curves

## 11. ROBUSTNESS

Robustness and Ruggedness of the method was determined by subjecting the method to slight change in the method condition, individually, for example, Pump flow rate and change in mobile phase composition etc.

Three replicates were made for the same concentration (25µg/ml of REM and 200µg/ml of VDG). % RSD was calculated. This is given in Table 6.

### 11.1 Analysis of Ten and ROS in Synthetic Mixture

**Composition of synthetic mixture:** It was determined by calculating the recovery of REM and VDG by standard addition method.

- Remogliflozin: 100 mg
- Teneagliptin: 100 mg
- Talc: q. s. 1000 mg

All the excipients were mixed in 10ml volumetric flask and Sonicate for 15min. make up the volume with Distilled Water. The solution was filtered through Whatman filter paper No. 42.

Finally the solution had concentration 100µg/ml for REM and 800 µg/ml for VDG. From that pipette out 1ml in 10 ml volumetric flask and volume was made up to mark with mobile phase - acetate buffer (pH 5.6) and methanol (30:70 v/v) to make final concentration REM (10 µg/ml) and VDG (80 µg/ml). Chromatogram of the Test solution containing 10 µg/ml of REM and 80 µg/ml of VDG was recorded and peak areas were noted for estimation of VDG and REM. This is given in Fig. 9.

## 12. RESULTS AND DISCUSSION

### 12.1 Mobile Phase Selection

Various mobile phases with different ratio of different solvents and pH were used are shown in. The mixture of acetate buffer (pH 5.6) and methanol (30:70 v/v) provided optimum polarity for proper migration, separation and resolution of Remogliflozin and Vildagliptin peaks. Under these conditions, the eluted peaks were well defined, resolved and free from tailing.

Due to the non-polar nature of the stationary phase more polar component Remogliflozin will be eluted first because of its more affinity towards the polar mobile phase and less polar component. Vildagliptin will be eluted later due to its more affinity towards non-polar stationary phase. Figure show chromatograms for various mobile phases tried.

### 12.2 Method Development and Validation

After selection of mobile phase of acetate buffer (pH 5.6) and methanol (30:70 v/v) RP-HPLC method was developed and validated for bulk as well as synthetic mixtures. According to ICH guidelines all the validation parameters like System suitability studies, Stability of analytical solution, Linearity and range, Precision, accuracy, LOD, LOQ, robustness are validated and they falls within the acceptance criteria. The data of these parameters and chromatogram are mentioned in respected parameters and covered in the figures and table section. The trials are shown in Figs. 1 to 5.

Tables Selection and Optimization of Mobile Phase

**Table 1. Optimization of mobile phase**

Trial	Column	Mobile phase	Ratio	Remark
1.	C <sub>18</sub>	Acetate buffer (pH 8): water: methanol	25:50:25 v/v	Peak observed but splitting observed in REM and VDG peak
2.	C <sub>18</sub>	acetate buffer (pH 7.4) and methanol	50:50 v/v	Peak observed but no clear separation in ROS and TEN peak
3.	C <sub>18</sub>	acetate buffer (pH 6 ) and methanol	40 : 60 v/v	Peak of ROS observed but broadening of TEN peak
4.	C <sub>18</sub>	acetate buffer (pH 5) and methanol	55:45 v/v	Peak observed but fronting observed in ROS peak
5.	C <sub>18</sub>	acetate buffer (pH 5.6) and methanol	30:70 v/v	Peak sharpness was good, More theoretical plates, Less tailing and good resolution

**System Suitability Test:****Table 2. Observed values for system suitability test \*(n=5)**

Parameters	Observed values		IP Specification
	VDG*	REM*	
Retention Time (min)	6.334	4.881	-
Theoretical plates	6683.25	2067.52	Not less than 2000
Asymmetry (10%)	1.43	0.89	Not greater than 2
Resolution	13.45	-	>2

**Linearity and Range:****Table 3. calibration of REM and VDG**

Sr. No	Conc	REM			VDG		
		Mean Peak area	SD	%RSD	Mean Peak area	SD	%RSD
1	10	24568	8.431	0.032	56986	34.117	0.065
2	50	43765	12.340	0.039	110213	46.628	0.045
3	100	76543	13.436	0.018	129439	62.453	0.056
4	150	95673	15.768	0.016	283438	40.543	0.026
5	200	132419	44.387	0.049	297393	42.687	0.019

**Precision****Table 4. Intraday precision and Inter day precision of REM and VDG**

	Intraday precision			SD	%RSD	Inter day precision			SD	%RSD
	Conc (µg/ml)	Average Peak Area				Conc (µg/ml)	Average Peak Area			
TEN	50	122344		30.551	0.026	TEN	50	116536	51.730	0.045
	100	146740		26.633	0.017		100	125466	35.473	0.023
	150	212647		28.431	0.014		150	137648	19.858	0.010
ROS	50	46483		31.476	0.068	ROS	50	47609	13.786	0.033
	100	67587		35.786	0.053		100	63875	44.896	0.069
	150	98462		12.486	0.029		150	93276	15.786	0.016

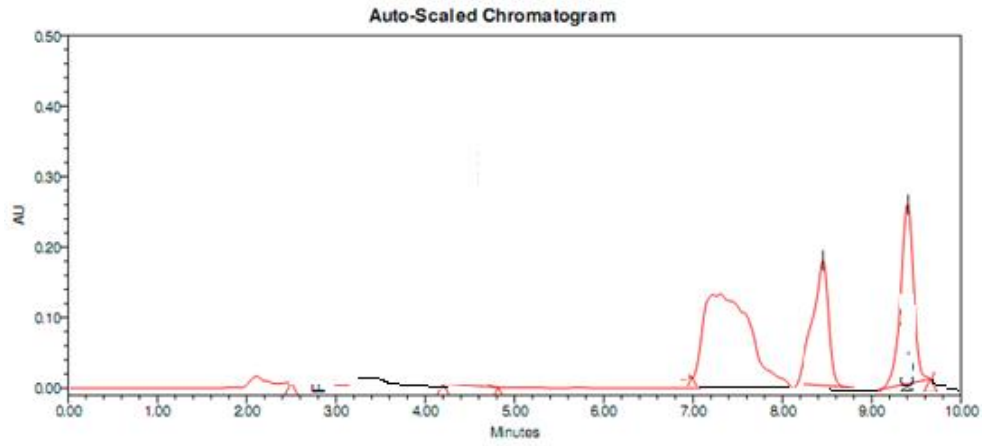


Fig. 1. Chromatogram using mobile phase acetate buffer (ph 8): water: methanol (25:50:25 v/v)

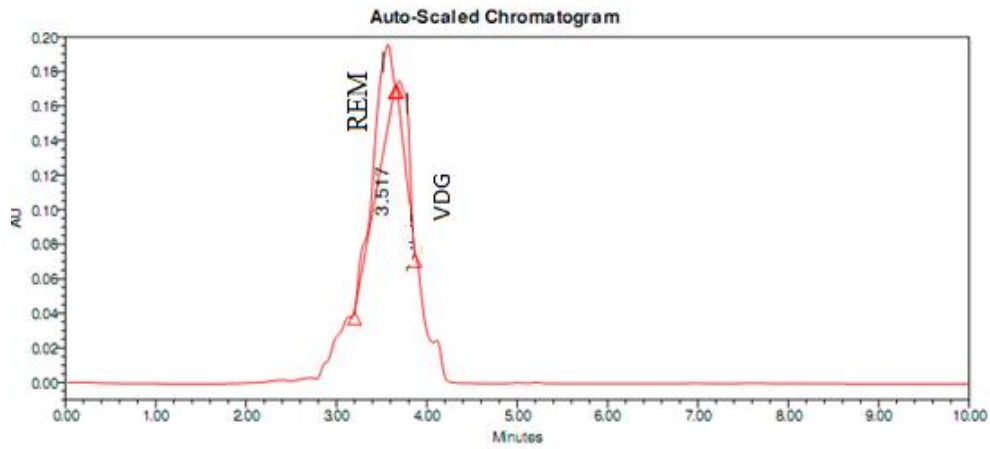


Fig. 2. Chromatogram using mobile phase acetate buffer (pH 7.4) and methanol (50:50v/v)

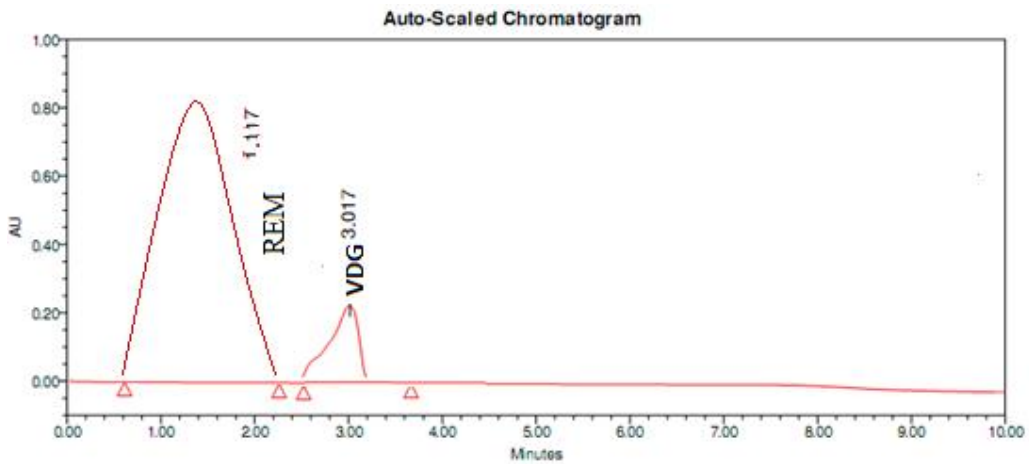


Fig. 3. Chromatogram using mobile phase acetate buffer (pH 6) and methanol (40:60v/v)

**Accuracy:****Table 5. Recovery data of rem and vdg**

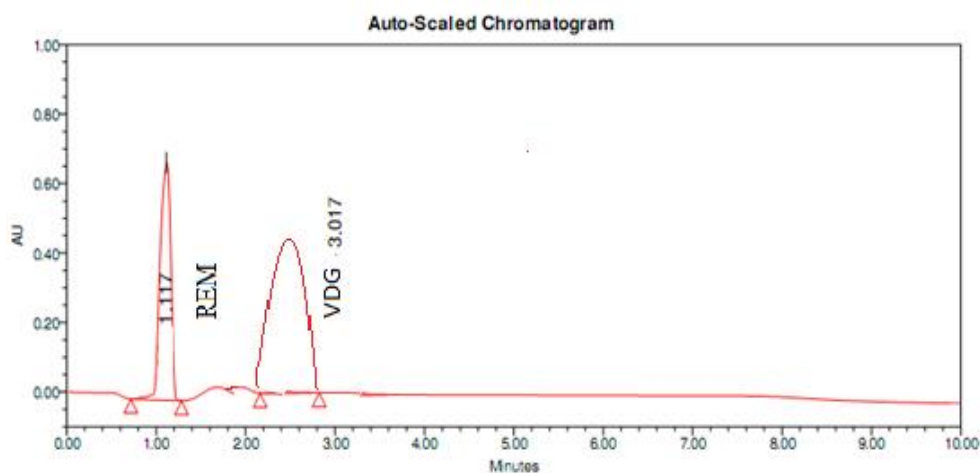
Sr. No	Std added	REM ( $\mu\text{g/ml}$ )	VDG ( $\mu\text{g/ml}$ )	STD Spiking ( $\mu\text{g/ml}$ )		Total Amount Taken		Total amount found		% Recovery	
				REM	VDG	REM	VDG	REM	VDG	REM	VDG
1	-	50	50	-	-						
2	80%	50	50	40	40	90	90	88.89	90.5	98.99	100.54
3	100%	50	50	50	50	100	100	100.04	99.5	100.04	99.50
4	120%	50	50	60	60	110	110	120.92	110.5	100.84	99.55

**Robustness:****Table 6. Robustness of REM and VDG**

Change in Parameter	REM			Change in Parameter	VDG		
	Mean Peak area	SD	%RSD		Mean Peak area	SD	%RSD
Change in pH	48543	30.765	0.068	Change in pH	113478	54.654	0.054
Change in flow rate	48395	30.874	0.067	Change in flow rate	116547	54.873	0.065
Change in Wavelength (241 nm)	48654	30.699	0.054	Change in Wavelength (244nm)	119844	54.332	0.056

**LOD and LOQ**

Name of the Compound	LOD ( $\mu\text{g/ml}$ )	LOQ ( $\mu\text{g/ml}$ )
Rosuvastatin	0.0138-0.0860 $\mu\text{g/ml}$	0.0419-0.2615 $\mu\text{g/ml}$ ,
Vildagliptin	0.0267-0.0435 $\mu\text{g/ml}$	0.0567-0.376 $\mu\text{g/ml}$

**Fig. 4. Chromatogram using mobile phase acetate buffer (pH 5) and methanol (55:45v/v)**



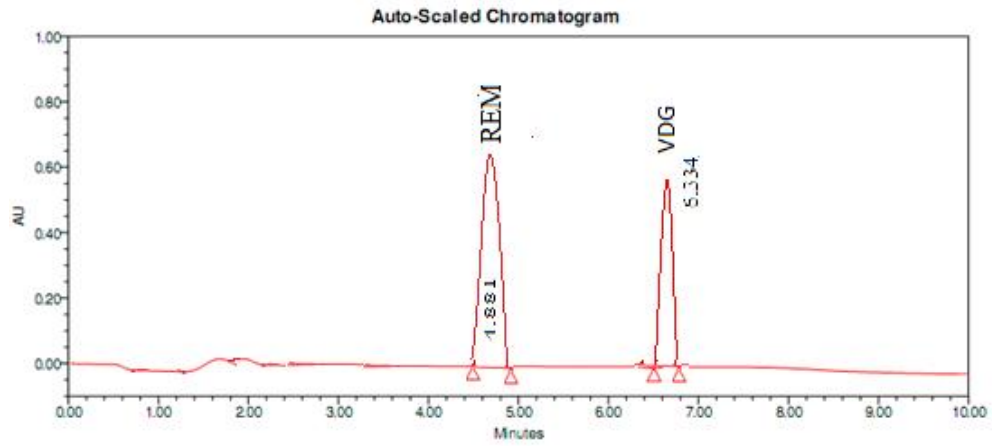


Fig. 5. Chromatogram using mobile phase acetate buffer (pH 5.6) and methanol (30:70v/v)

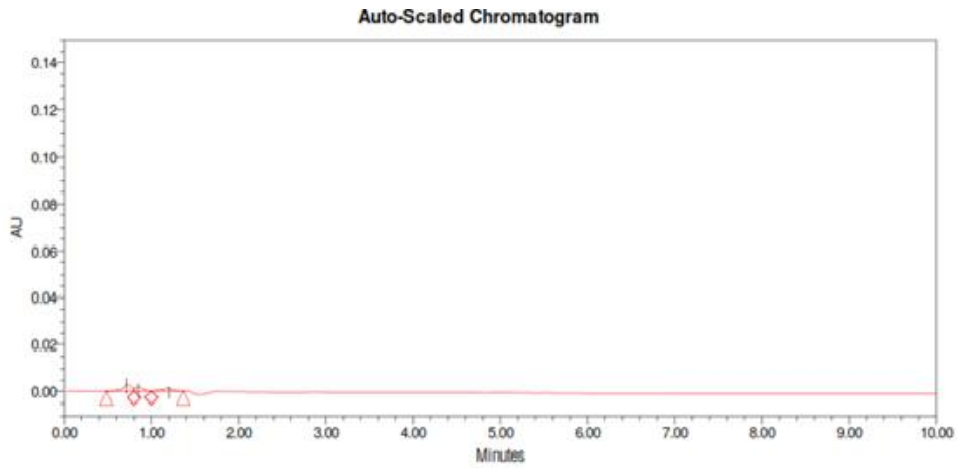


Fig. 6. Chromatogram of Blank solution (Mobile Phase)

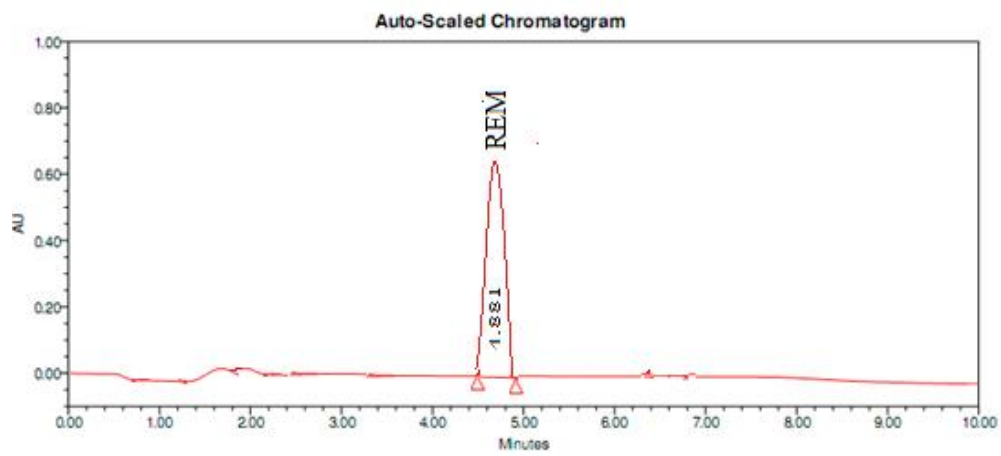


Fig. 7. Chromatogram of Standard REM solution (10µg/ml)

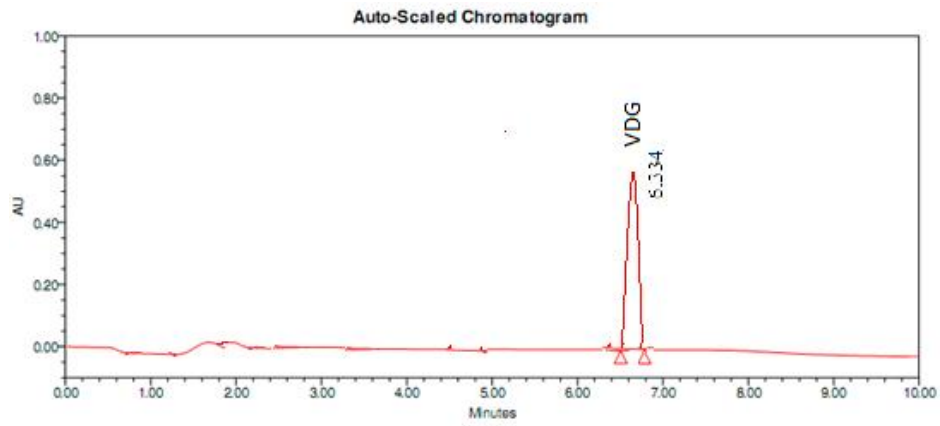


Fig. 8. Chromatogram of Standard VDG solution (10µg/ml)

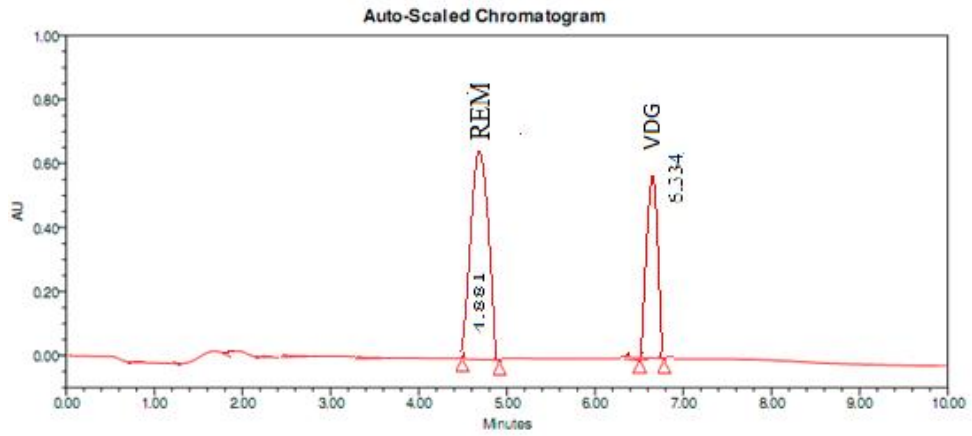


Fig. 9 Chromatogram of REM and VDG in the ratio of 10:10

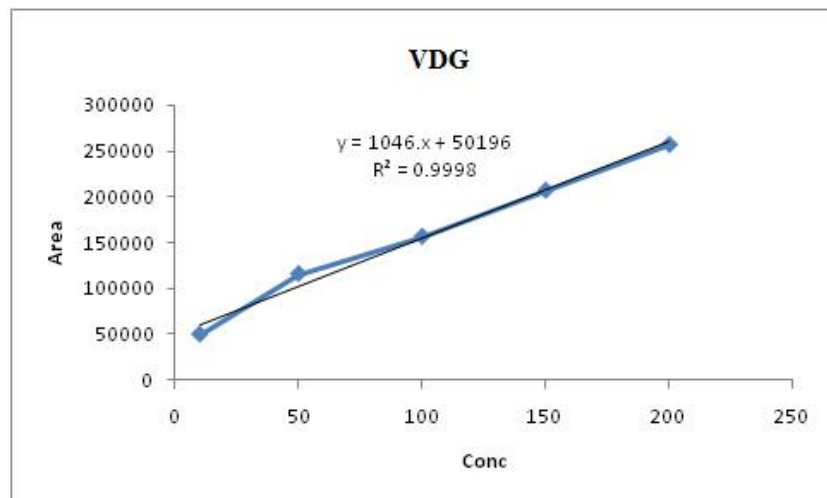
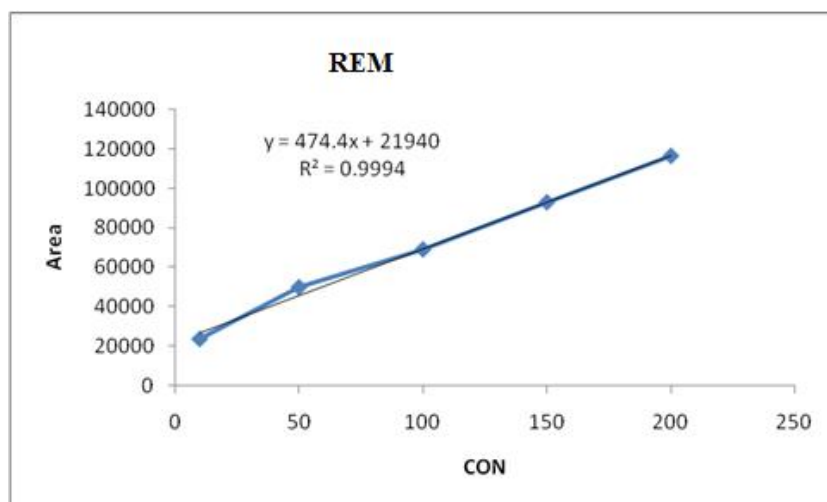


Fig. 10. Calibration curve of VILDAGLIPTIN



**Fig. 11 Calibration curve of REMOGLIFLOZIN**

### 13. CONCLUSION

The combination of these two drugs Remogliflozin and Vildagliptin is maintain the blood sugar level by complementary mechanism without any side effects of hypoglycaemia and lowering of HbAc level in single dose regimen. The RP-HPLC method is developed and validated for the same combination. This method is effective, accurate and precise.

### CONSENT

It is not applicable.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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