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"Development and Validation of RP-HPLC and UV-Spectrophotometric Method for Simultaneous Estimation of Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride in Pharmaceutical dosage form"

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Abstract:

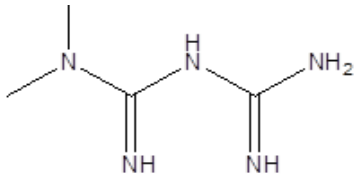
The objective of present research is to develop a simple, sensitive, linear, precise and accurate RP-HPLC and UV-Spectrophotometric method for simultaneous estimation of Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride in bulk and tablet formulation as developed and validated. UV-Spectrophotometric method Calibration plot were linear R^2 =0.9982 over the concentration range 0.8-1.6µg/ml for Teneligliptin Hydrobromide Hydrate, R^2 = 0.997 for the Metformin Hydrochloride 20-40µg/ml. And Chromatographic conditions used are stationary phase Grace C^{18} column (250mm × 4.6mm, 5µ particle size. The mobile phase Methanol: 10mm KH_2PO_4 Buffer (Ph-3) (70:30) and flow rate was maintained 0.8ml/min, detection wavelength was 240nm. The retention times were 4.5 min and 2.8 min for Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride respectively. Calibration plot were linear R^2 =0.9982 over the concentration range 1-5µg/ml for Teneligliptin Hydrobromide Hydrate, R^2 = 0.9981 for the Metformin Hydrochloride 25-125µg/ml. No interference from any component of pharmaceutical dosage form was observed. The proposed method has been validated as per ICH guidelines, validation studies revealed that method id specific, rapid, reliable and reproducible. The developed method successfully employed for routine quality control analysis in the combined pharmaceutical dosage form.

Keywords: Teneligliptin Hydrobromide, Metformin Hydrochloride, UV- Spectrophotometric, RP-HPLC Method, ICH Guideline.

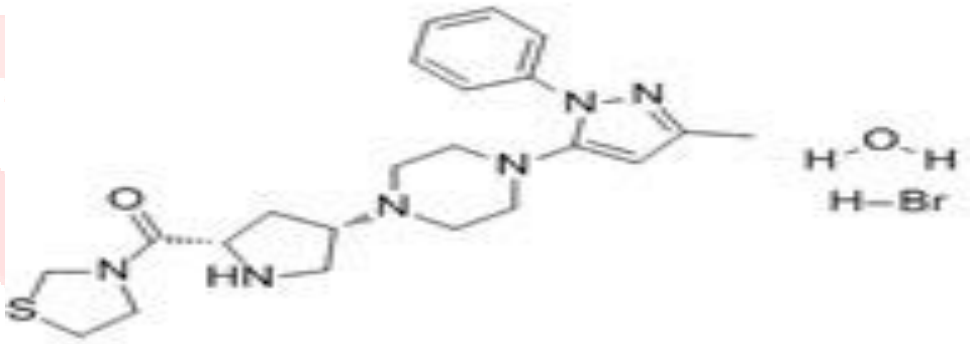
1.0 Introduction:

Metformin is a first line agent for the treatment of type- 2 diabetes that can be used alone or in combination with sulfonylureas, thiazolidinediones or other hypoglycemic agents. The IUPAC name is 1-carbamimidamido-N, N-dimethylmethanimidamide. This medication is used to decrease hepatic glucose production, to decrease GI Glucose absorbtion and to increase target cell insulin sensitivity. This medication is a treatment indicated as an adjunct to diet, exercise, and lifestyle changes such as weight loss to improve glycemic (blood sugar) control in adults with type 2 diabetes. Teneligliptin is a pharmaceutical drug for the treatment of type 2 diabetes mellitus. The IUPAC name is {(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate.It belongs to the class of anti-diabetic drugs known as dipeptidyl peptidase-4 inhibitors or "gliptinshas unique J shaped or anchor locked domain structure because of which it has a potent inhibition of DPP 4 enzyme. Teneligliptin significantly controls glycemic parameters with safety. No dose adjustment is required in renally impaired patients

Teneligliptin is marketed in the combination with Metformin under the trade name Zita-Met Plus 20mg/500mg Tablet ER by Glenmark Pharmaceutical Limted.



metformin



The present research invention that there are many methods for the individual determination of Teneligliptin HBr and Metformin HCl; but few methods are cited for determination of combined dosage form so, it was proposed to develop an economical, rapid and simple UV Spectrophotometric and RP-HPLC method for simultaneous estimation of these drugs in combined dosage form.

2.0 Material and Methods:

2.1 Chemicals:

HPLC grade Methanol, HPLC grade Water, Potassium dihydrogen phosphate AR grade, Phosphoric acid. Hydrochloric acid all other chemicals were of analytical grade.

2.2 Methods:

2.2.1.0 UV- Spectrophotometric Method-

2.2.1.1 Selection of Wavelength : - The both drug are soluble in water they prepare different concentration of solution .these solution scan between 200 -400nm using water as blank .the found wavelength of Teneligliptin HBr 243nm and Metformin Hydrochloride 233nm.

The present work was aimed to develop Analytical method Development and validation of RP-HPLC and UV-spectrophotometric method for simultaneous estimation of in Pharmaceutical dosage form.

2.2.1.2 Preparation of Standard Stock Solution - Accurately weighed 10mg of both drug (Teneligliptin HBr and Metformin HCL) was transferred separate to 100 ml volumetric flask and dissolved and diluted to the distilled water. The both solution was scanned between 200 and 400 nm using blank. The UV spectrum Metformin HCL had shown λ_{max} at 233nm and Teneligliptin Hydrobromide Hydrate had shown λ_{max} at 243nm hence, it was selected for the analysis of Metformin Hydrochloride (Fig.No.1) and Teneligliptin Hydrobromide Hydrate (Fig.No.2).

2.2.1.3 Preparation of Calibration Curve - Aliquots of standard stock solution was further diluted with Water to get the solutions of concentration of both drug 10-50 µg/mL. The absorbance was measured at 243 and 233nm against water as blank. All measurements were repeated three times for each concentration. The calibration curve was constructed by plotting mean of absorbance against corresponding concentration.

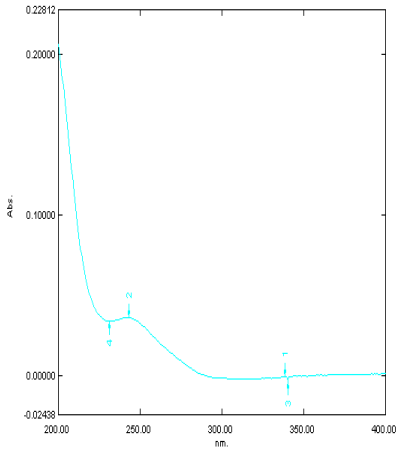


Fig No.1 Teneligliptin HBr

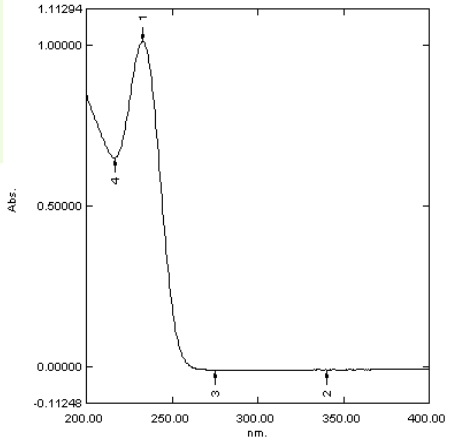
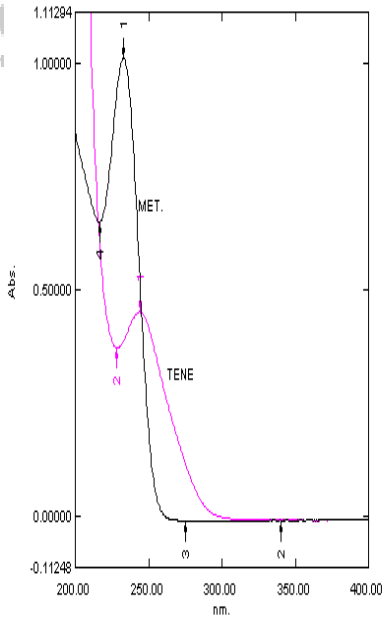


Fig No.2 Metformin HCl



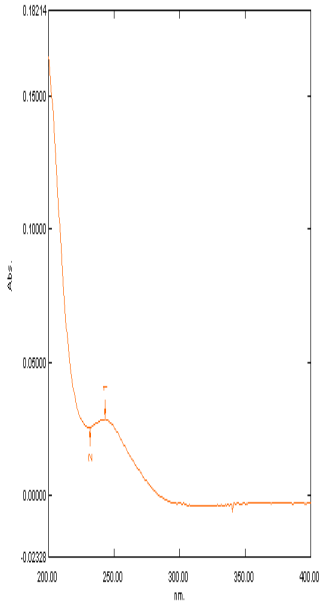


Fig No.3 Overlay of both drug.

Fig No.4 Tablet Solution 25 PPM

2.2.1.4 UV Method validation – The newly developed method was validated according to the ICH guidelines the parameter assessed were with linearity, accuracy, precision, robustness, LOD and LOQ.

2.2.1.4 Linearity –

Table No.1 Linearity of Metformin Hcl

Conc.(µg/ml)	Abs(nm)
20	1.678
25	1.959
30	2.298
35	2.560
40	2.834

Table No.2 Linearity of Teneligliptin HBr

Conc.(µg/ml)	Abs(nm)
0.8	0.038
1.0	0.053
1.2	0.070
1.4	0.091
1.6	0.107

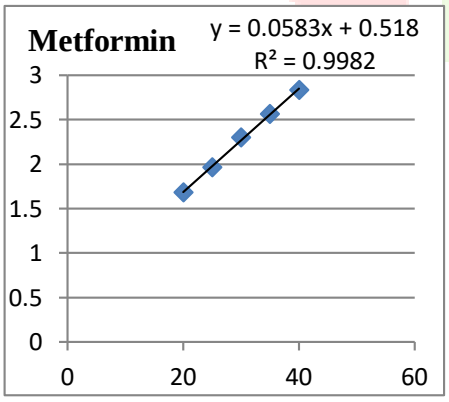


Fig No. 5 Linearity of Metformin Hcl

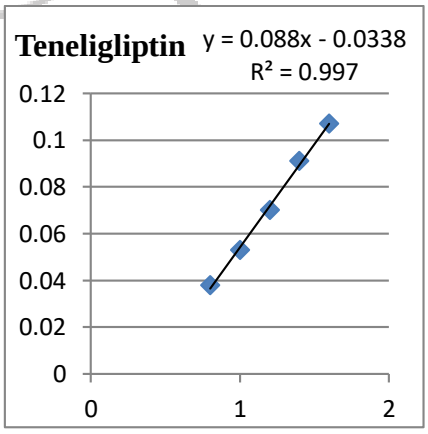


Fig No. 6 Linearity of Teneligliptin HBr

2.2.1.5 Precision -

Table No.3 Analyst to analyst variation - A) Analyst 1:-

Metformin Hydrochloride						
Sr. No.	Conc. (µg/mL)	Abs				% Con.
		R1	R2	R3	Mean	
1	25	1.968	1.992	1.948	1.969	100.04
2	30	2.293	2.318	2.304	2.305	102.70
3	35	2.548	2.593	2.578	2.573	101.23
					% Mean	101.32
					S.D.	0.543
					% R.S.D.	0.535

Table No.4 B) Analyst 2:-

Metformin Hydrochloride						
Sr. No.	Conc. (µg/mL)	Abs				% Con.
		R1	R2	R3	Mean	
1	25	1.971	1.943	1.989	1.967	99.92
2	30	2.289	2.299	2.321	2.303	102.58
3	35	2.598	2.551	2.583	2.577	101.42
					% Mean	101.30
					S.D.	0.541
					% R.S.D.	0.537

Table No.5 Teneligliptin Hydrobromide Hydrate Analyst -1: -

Teneligliptin Hydrobromide Hydrate						
Sr. No.	Conc. (µg/mL)	Abs				% Con.
		R1	R2	R3	Mean	
1	1	0.055	0.050	0.063	0.056	101.13
2	1.2	0.064	0.080	0.072	0.072	99.41
3	1.4	0.098	0.085	0.093	0.092	101.42
					% Mean	100.65
					S.D	0.443
					% R.S.D.	0.440

Table No. 6 Analyst 2: -

Teneligliptin Hydrobromide Hydrate						
Sr. No.	Conc. (µg/mL)	Abs				% Con.
		R1	R2	R3	Mean	
1	1	0.056	0.060	0.049	0.055	100
2	1.2	0.064	0.073	0.079	0.072	99.41
3	1.4	0.087	0.093	0.096	0.092	101.42
					% Mean	100.27
					S.D	0.421
					% R.S.D.	0.419

2.2.1.6 Accuracy –

Table No.7 Metformin Hydrochloride

Metformin Hydrochloride								
Sr. no.	Level of addition (%)	Conc. of Drug In Sample	Std. drug added	Abs				% Conc
				R1	R2	R3	Mean	
1	80%	15	12	2..129	2.138	2.134	2.133	99.20
2	100%	15	15	2.343	2.338	2.341	2.340	98.84
3	120%	15	18	2.530	2.528	2.521	2.526	100.31
							%Mean	99.45
							S.D	0.496
							%R.S.D.	0.498

Table No. 8 Accuracy for Teneligliptin HBr.

Teneligliptin Hydrobromide Hydrate								
Sr no	Level of addition (%)	Conc. of Drug In Sample	Std. drug added	Abs				% Con.
				R1	R2	R3	Mean	
1	80%	0.6	0.48	0.062	0.057	0.066	0.061	93.54
2	100%	0.6	0.6	0.073	0.071	0.075	0.073	97.26
3	120%	0.6	0.72	0.092	0.087	0.095	0.091	95.60
							%Mean	95.46
							S.D	0.760
							%R.S.D.	0.796

2.2.1.7. Limit of detection (LOD)

It is the smallest quantity of an analyte that can be detected, and not necessarily determined, in quantitative fashion. It was calculated by the following formula;

$$LOD = 3.3 \times S.D / Slope$$

Where; S.D = Standard Deviation

2.2.1.8. Limit of Quantitation (LOQ)

It is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. It was calculated by the following formula;

$$LOQ=10 \times S.D/Slope.$$

2.2.1.9. Assay of Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride in Tablet:-
These were labeled to contain 20mg of Teneligliptin Hydrobromide Hydrate and 500mg of Metformin Hydrochloride as an active substance per tablet. 5 tab. Containing Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride accurately weighed and powdered. The powder equivalent to Metformin Hydrochloride 22.38mg and transferred to a 100 ml volumetric flask.it was dissolved in 100 ml distilled water and sonicate for 15minutes to get homogeneous solution. Then it was first filtered through a 0.45 what man filter paper. A final concentration of 100 mg/ml of solution was prepared. This solution was filtered through filter paper to remove some un-dissolved excipients. After filtration, from this 2 ml was taken and diluted to 10 ml with distilled water which gives 20 µg/ml solution and the absorbance of the solution was measured at 243 nm and 233nm. Show in Fig. No. 4

Table No.9 % Assay for Teneligliptin and Metformin

Tablet formulation	Label Claim	Amount Taken	Amount found [mg/cap]	% Assay
Metformin Hcl	500mg	25mg	25.27	101.08%
Teneligliptin Hbr	20mg	1mg	0.984	98.4%

2.3.0 High Performance Liquid Chromatography:-

2.2.3.1 Instrumentation-

HPLC 3000 series instrument, P-3000-M Reciprocating pump 40M pal. Separation and quantitation were made on RP-HPLC Binary gradient system with Grace C_{18} column (250mm × 4.6 mm, particle size 5µ) UV -3000 detector used, Wenser high precision balance used for weighing standard and sample.

2.2.3.2 Selection of Mobile Phase- in Selection of chromatograph the Mobile phase consist of Methanol: Phosphate Buffer (70:30v/v) PH 3.0 adjusted with phosphoric acid gives good resolution of peaks with acceptable peak symmetry, as compared to other

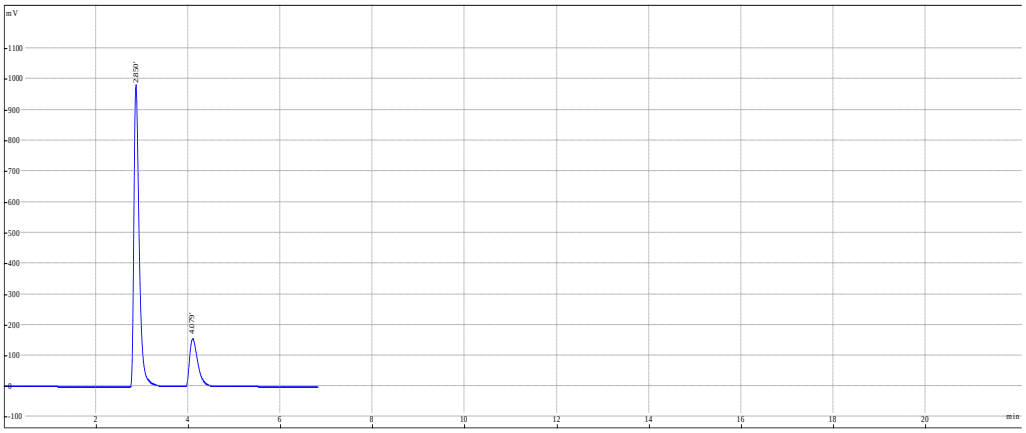


Fig No.7 Chromatogram for lab mixture of pure drug

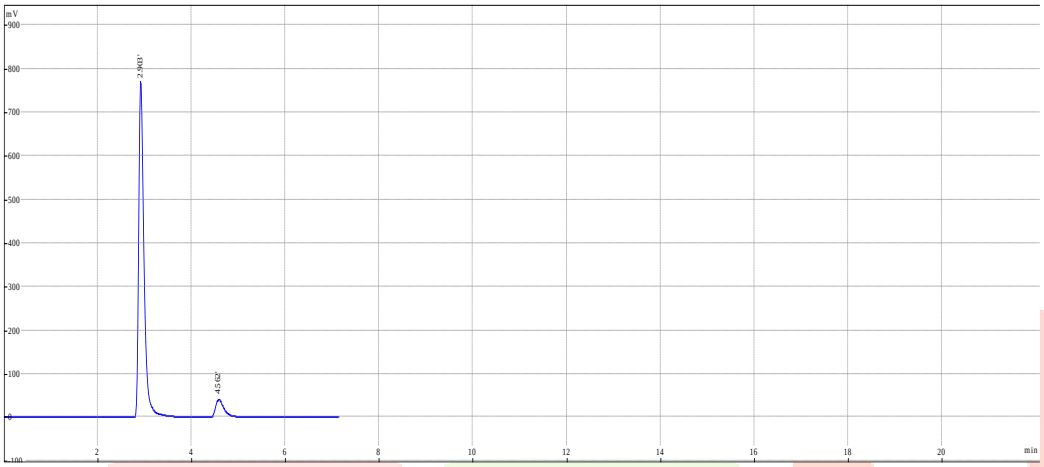


Fig No.8 Chromatogram for Combination of Tablet mixture

2.2.3.3. Preparation of Mobile Phase: Methanol and Phosphate Buffer in ratio [70:30], filter through 0.45 µ nylon membrane filter and degassed.

2.2.3.4. Preparation of Buffer: Preparation 10mM Phosphate Buffer - Weigh accurately 0.136gm of KH_2PO_4 dissolved in distilled water, filter through 0.45 µ nylon membrane filter.

2.2.3.5. Preparation of Standard Solution:

a) Accurately weigh 10mg of Teneligliptin Hydro bromide Hydrate was transferred into a 10ml volumetric flask it was dissolved with from this solution 1ml was diluted to 10ml to give the stock solution containing 100µg/ml of Teneligliptin Hydrobromide Hydrate.

b) Accurately weigh 10mg of Metformin Hydrochloride was transferred into a 10ml volumetric flask it was dissolved with from this solution 1ml was diluted to 10ml to give the stock solution containing 100µg/ml of Metformin Hydrochloride.

2.2.3.6. Preparation of Sample Solution: - These were labeled to contain 20mg of Teneligliptin Hydrobromide Hydrate and 500mg of Metformin Hydrochloride as an active substance per tablet. 5 tab. Containing Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride accurately weighed and powdered. The powder equivalent to Metformin Hydrochloride 21.76mg and transferred to a 50ml volumetric flask. The volume was adjusted to 50ml with solution, and filtered through what man filter paper. From this filtrate 1ml was transferred to a 10ml volumetric flask and diluted in order to obtain the final concentration.

2.2.3.7. Method Validation

2.2.3.7.1 Working Linearity - A calibration curve is the relationship between instrument response and known concentration of the analyte. Linearity was established by analysing five concentrations of ranging between 1-5 and 25-125 µg/ml respectively, by plotting the peak area ratio against corresponding concentration. Teneligliptin 2 ppm + Metformin 50ppm. The stock solution was prepared by taking the Methanol: 10mM KH_2PO_4 Buffer in the ratio of (70:30) and pH: The Flow rate was taken 0.8 ml/min and Wavelength 240nm. The pressure noted was 9-10MPa and Run time: 7.37min

Table No.10 Linearity of Metformin Hcl

Conc.(µg/ml)	Area
25	1756690
50	3669608
75	6075586
100	8005486
125	9883881

Table No.11 Linearity of Teneligliptin HBr

Conc(µg/ml)	Area
1	134296
2	315823
3	520016
4	744534
5	964960

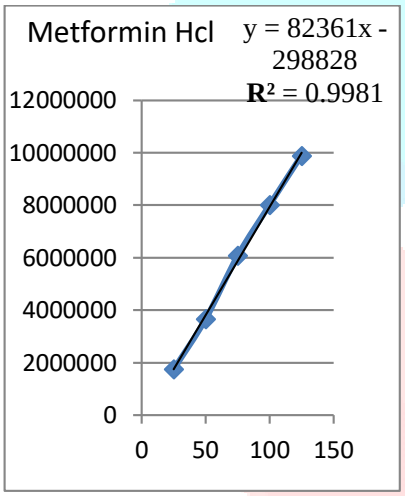


Fig. No. 10 Linearity of Metformin HCl

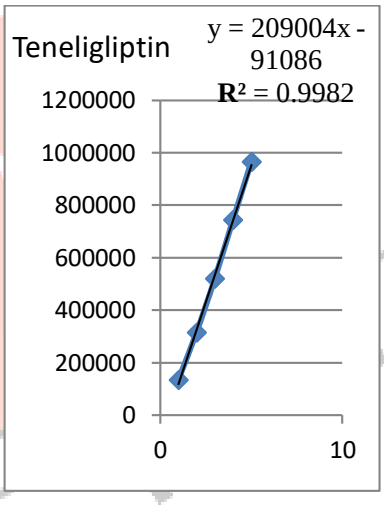


Fig. No.11 Linearity of Teneligliptin HBr

2.2.3.7.2 Precision: -

Table No.12 Intra-day Precision of Metformin Hydrochloride

Sr. No.	Conc. (µg/ml)	Area (m/V)			Intra-day (Morning)		
		R_1	R_2	R_3	Mean	S.D.	%R.S.D.
1.	75 µg/ml	60765	607735	60786	60775	0.017	0.0174
Intra-day (Evening)							
2.	75 µg/ml	60745	60756	60760	60754	0.013	0.0133

Table No.13 Intra-day Precision of Teneligliptin HBr.

Sr. No.	Conc. (µg/ml)	Area (m/V)			Intra-day (Morning)		
		R_1	R_2	R_3	Mean	S.D.	%R.S.D.
1.	3µg/ml	520016	520006	520588	520203.33	0.0640	0.0640
Intra-day (Evening)							
2.	3µg/ml	520800	520848	520631	520759.66	0.0218	0.0218

2.2.3.7.3 Assay: -

Teneligliptin 3ppm+Metformin 75ppm of Tablet. The stock solution was prepared by taking the Methanol : 10mM KH_2PO_4 Buffer in the ratio of (70:30) and pH:3. The Sample volume was taken 20µ, the Flow rate was 1 ml/min and Pressure noted was 9-10MPa, run time: 7.04min and Wavelength: 240nm.

Table No.14 Assay of Metformin and Teneligliptin:-

Sr. No.	% Composition	Area of Standard	Area of Sample	% Assay
1	% Assay Metformin HCl	6076586	6074932	99.9728
2	% Assay Teneligliptin HBr	520016	520281	100.051

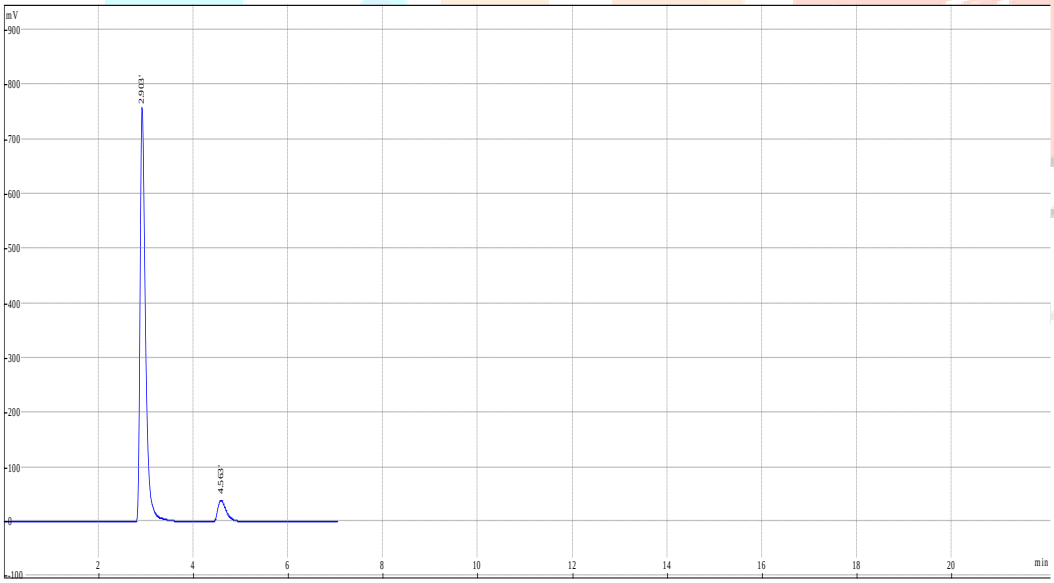


Fig. No.12 Assay of Drug

2.2.3.7.4 Limit of detection (LOD):-

It is the smallest quantity of an analyte that can be detected, and not necessarily determined, in quantitative fashion. It was calculated by the following formula;

$$LOD = 3.3 \times S.D / Slope$$

Where; S.D = Standard Deviation

2.2.3.7.5 Limit of Quantitation (LOQ):-

It is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. It was calculated by the following formula;

LOQ=10 × S.D/Slope.

Table No.15 LOD & LOQ of Teneligliptin HBr & Metformin Hcl:-

Sr.No.	Parameter	Teneligliptin HBr	Metformin Hcl
1	LOD	0.01210	0.05905
2	LOQ	0.03667	0.17894

3.0 Result and Dicussion:-

3.1.0 Result:-

3.1.1 UV Method-

Table No.16 Result Summary of UV Method

Parameter			Teneligliptin HBr	Metformin HCl
Absorption maxima (nm)			243 nm	233 nm
Beers range (µg/ml)			0.1-80(µg/ml)	1-50(µg/ml
Standard Regression Equation			y = 0.088x - 0.0338	y = 0.0583x + 0.518
Correlation Coefficient (r2)			R^2 = 0.997	R^2 = 0.9982
Tab mixture (25ppm)			0.96 (µg/ml)	25.27 (µg/ml)
Accuracy	S.D		0.760	0.496
	% R.S.D.		0.796	0.498
Precision	Analyst -1	0.543	0.443	0.543
		0.535	0.440	0.535
	Analyst -2	0.554	0.421	0.554
		0.537	0.419	0.537
LOD			28.5	28.22
LOQ			86.36	85.51

3.1.2. High Performance Liquid Chromatography:-

Table No.17 Result Summary of RP-HPLC Method:-

Validation Parameters	Parameters	Results			
		Teneligliptin HBr		Metformin HCl	
Linearity	λmax (nm)	240nm		240nm	
	Berr's law limit µg/ml	1-5µg/ml		1-125 µg/ml	
	Correlation coefficient (r^2)	0.9982		0.9981	
	Regression equation	Y=209004x-91086		Y=82361x-298828	
	Slope (m)	209004		82361	
	Intercept (c)	91086		298828	
Precision	Statistical Parameter	Morning	Evening	Morning	Evening
	SD	0.0640	0.0218	0.0173	0.0132
	%RSD	0.0640	0.0218	0.0174	0.0133
% Recovery	50% Recovery	100.034		99.869	
	100% Recovery	99.179		99.934	
	150% Recovery	99.987		99.932	
LOD		0.01210		0.05905	
LOQ		0.03667		0.17894	
% Assay		100.05		99.97	

3.2.0 Discussion:-

A new, accurate and selective gradient RP-HPLC and UV-Spectrophotometric method was proposed for the determination Teneligliptin Hydrobromide Hydrate and Metformin Hydrochloride was validated as per the ICH guidelines. The method has higher sensitivity towards the determination of related substances. The method was found to be simple, selective, precise, accurate, isolated and characterized using spectral data. The method is low time consuming due to simply mobile phase composition and relatively short analysis time. by considering different system suitability parameters like retention time ,tailing no, HETP .The mobile phase found to be most suitable chromatographic condition take placed on Grace C-18,.In programme mobile phase consisting of Methanol : 10mM KH_2PO_4 Buffer in the ratio of (70:30) and pH : 3.

All statistical results S.D, % R.S.D., percentage difference and recovery, % Assay) were within the acceptance criteria. Validation experiments provided proof that the UV and HPLC analytical method is linear in the proposed working range as well as accurate, precise (repeatability and intermediate precision levels). The method is very sensitive to pH 3 of mobile phase.

4.0 References:-

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