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Development and Validation of Analytical Method for Simultaneous Estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate in Pharmaceutical Dosage Form

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ABSTRACT:

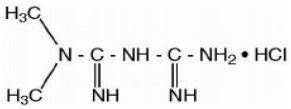
A reversed-phase liquid chromatographic method has been developed and validated for estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate in Pharmaceutical Dosage Form. RP-HPLC method, Column used was 250 x 4.6mm C18, Hypersil BDS with mobile phase containing Water (pH 4.0, adjust with 1% Orthophosphoric acid): Methanol (60:40). The flow rate (1.0 ml/min) and wavelength (236 nm). The retention time was found to Metformin HCl and Teneligliptin HBr Hydrate was found to be 3.317 ± 0.01 min. and 4.783 ± 0.01 min. respectively. Correlation co-efficient for Metformin HCl and Teneligliptin HBr Hydrate was found to be 0.999. Assay result of marketed formulation was found to be in 99.3 % and 98.3 % for Metformin HCl and Teneligliptin HBr Hydrate. The proposed method was validated with respect to linearity, accuracy, precision and robustness. Percentage recovery for Metformin HCl and Teneligliptin Hydrobromide Hydrate was found to be 99.0 – 100.0%. Analysis proves that the developed method was successfully applied for the analysis of pharmaceutical formulations and can be used for routine analysis of drugs in Quality Control laboratories.

KEYWORDS: Metformin HCl, Teneligliptin HBr Hydrate, HPLC, analytical method development, Validation, ICH, USFDA, Chromatography.

INTRODUCTION:

The IUPAC name of the Metformin HCl is 1-carbamimidamido-N,N-dimethylmethanimidamide.With molecular formula and molecular weight $C_4H_{11}N_5$. HCL and 129.16 g/mol respectively.

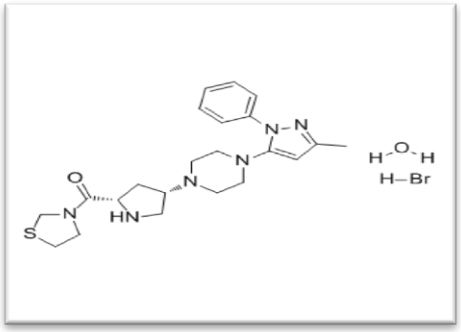
The molecular structure of the drug is given in Fig.1



- Metformin HCl is used as a antidiabetic.

The IUPAC name of the Teneligliptin HBr Hydrate is {(2*S*,4*S*)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate. With molecular formula and molecular weight $C_{22}H_{30}N_6OS.\ 2.5\ HBr.\ H_2O$ and 628.86 g/mol respectively.

The molecular structure of the drug is given in Fig.2



- Teneligliptin HBr Hydrate has antidiabetic properties.
- The anti glycemic effect of DPP-4 inhibitors is mediated by inhibiting the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1) and stimulating insulin release in response to increased blood glucose levels.

However no HPLC method has been reported till date for the estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate using the RP-HPLC method. The present paper describes the analytical method development and validation of estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate in Pharmaceutical dosage form using RP-HPLC. The proposed method are optimized and validated as per ICH guidelines.

Materials and methods

Materials:

a) Instruments

- Analytical Weighing Balance
- Sonicator
- FT-IR spectrophotometer
- HPLC system
- Millipore Filter Unit
- pH Meter
- UV Spectrophotometer

b) Glasswares

- Beaker
- Conical flask
- Measuring cylinder
- Petri dish
- Pipette
- Volumetric flask

c) Chemicals

- Standard Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate Gifted by Montage Laboratories Pvt Limited, Himatnagar.
- The commercial fixed dose combination **Zita Met Plus** 20/500 Tablets 10's manufactured by Glenmark Pharmaceutical was procured from local market. All solvents (HPLC grade) were obtained from S.D. fine chemical.

d) Method

- Chromatographic method

Methods

Working Standard preparation

- **Solution Preparation of metformin HCl: (500 µg/ml)**

  About 50 mg of metformin HCl API was weight and dissolve in 100 ml of methanol.

- **Solution preparation of Teneligliptin HBr hydrate: (20µg/mL)**

  20 mg of Teneligliptin HBr hydrate API was dissolved in 100 ml of diluent, further diluted 1 ml to 10 ml with diluent to get 20µg/ml concentration of Teneligliptin HBr hydrate in solution.

- **Sample Preparation for marketed formulation:**

  Weigh and powdered 20 tablets. Take tablet powder equivalent to 50mgMET/2mgTEN in to a 100ml volumetric flask. Add 60 ml methanol. Shake for 15 minutes and sonicate for 10 minutes. Make up volume with methanol. Filter this solution with Whatman filter paper no-1. (TEN-20mcg/ml, MET-500mcg/ml)

METHOD VALIDATION

Chromatographic conditions and System Suitability Parameters:

Mode of chromatography: Reversed Phase Chromatography

Mode of Elution: Isocratic
Flow Rate: 1.0 ml/min
Oven: Oven Temperature: 35° ± 2°C
Detector: Type: UV detector
Wavelength: 236 nm
Column: 250 x 4.6mm C18, Hypersil BDS
Sample Volume: 20 µl
Run time: 10 min
Mobile Phase: Water (pH 4.0, adjust with 1% orthophosphoric acid):Methanol (60:40)

System Suitability Parameters:

Table 1: System Suitability Test Parameters for Metformin HCl and Teneligliptin HBr Hydrate

Sr. No.	System suitability parameter	Metformin HCl	Teneligliptin HBr Hydrate
1	Retention time (min)	3.317	4.783
2	Resolution (R)	-	7.093
3	Theoretical plate number (N)	7512	6025
4	Tailing factor (T)	1.1	1.0

Linearity and Range (n=3):

- The linearity of analytical method is its ability to elicit test results that are directly proportional to the concentration of analytes in sample within a given range.
- The range of analytical method is the interval between the upper and lower levels of analytes that have been demonstrated to be determined within a suitable level of precision, accuracy and linearity.
- The linearity was determined at five levels over the range of 1-3 µg/ml for Metformin HCl and 25-75 µg/ml Teneligliptin HBr Hydrate. Peak area of above linearity solution preparations were taken at each concentration three times. Mean Peak Area at each concentration was calculated and Graph of Mean Peak Area (y axis) versus Concentration (x-axis) was plotted.

Precision

Repeatability

Six replicate of 2 ug/ml concentration of Metformin HCl and 50 ug/ml concentration of Teneligliptin HBr Hydrate were prepared and chromatographic were recorded at the optimized condition . SD and RSD were calculated.

Intraday Precision and Interday Precision

Variations of results within the same day (intra-day), variation of results between days (inter-day) were analyzed. Intra-day precision was determined by analyzing both standard solutions for three times in the same day. Interday precision was determined by analyzing the drugs daily for three days. %RSD was calculated.

Accuracy (% Recovery)

Accuracy is the closeness of the test results obtained by the method to the true value. To study the accuracy 5 tablet powder were weighed and analysis was carried out as per assay. Recovery studies were carried out by addition of standard drug to the sample at 3 different concentration levels (80%, 100% and 120%) taking into consideration percentage purity of added bulk drug samples. These solutions were subjected to re-analysis by the proposed method and Results are calculated.

Limit of detection and Limit of quantification

The limit of detection (LOD) and the limit of quantification (LOQ) were calculated using the standard deviation of y-intercept of calibration curve (σ) and average of slope (S) of the calibration curve.

$LOD = 3.3 \times \sigma / s$

$LOQ = 10 \times \sigma / s$

Robustness

The robustness of the method was established by making deliberate minor variations in the following method parameter

a) Flow rate: ±0.2 ml/min

b) Change in the ratio of component in the mobile phase: ± 2%.

c) pH of mobile phase: ±0.2

RESULT

VALIDATION PARAMETER

Linearity and Range

Linear correlation was obtained between peak area and concentration of Metformin HCl in the range of 25-75 µg/ml and Teneligliptin hydrobromide hydrate in the range of 1-3 µg/ml. The linearity of the calibration curves was validated by the value of correlation coefficients of the regression (r).

Table 2: Linearity data for Metformin HCl

% Linearity Level	Concentration (µg/ml)	Mean area	Correlation Coefficient
50	25	1979.133	
75	37.5	1340.464	
100	50	4054.368	0.999
125	62.5	3332.042	
150	75	2706.050	

Table 3: Linearity data for Teneligliptin hydrobromide hydrate

% Linearity Level	Concentration (µg/ml)	Mean area	Correlation Coefficient
50	1	454.708	
75	1.5	307.931	
100	2	931.652	
125	2.5	774.655	0.999
150	3	621.797	

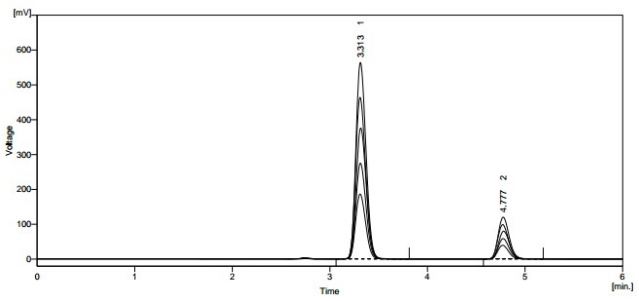


Figure 3: Overlay chromatogram of different concentration of Metformin HCl and Teneligliptin HBr Hydrate

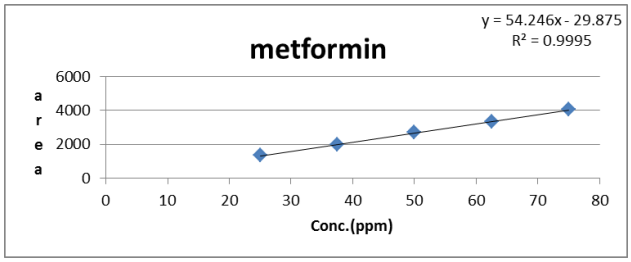


Figure 4: Calibration curve of Metformin HCl

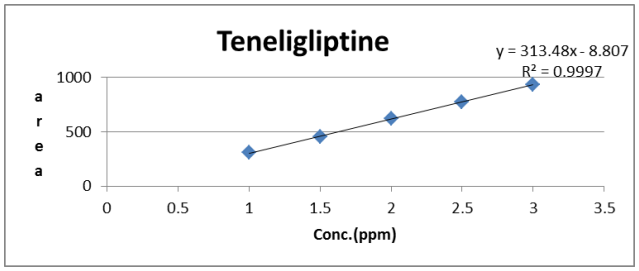


Figure 5: Calibration curve of Teneligliptin HBr hydrate

ACCURACY

Accuracy of the method was confirmed by recovery study from marketed formulation at three level of standard addition. Percentage recovery for Metformin HCl and Teneligliptin Hydrobromide Hydrate was found to be 99.0 – 100.0 %.

Table 4: Recovery Data of Metformin HCl

Accuracy Level %	Set no.	Amount Added (mg)	Amount Recovery (mg)	% Recovery	Mean	% RSD
80	1	20	19.7506885	98.7534428	99.9754592	1.12745047
	2	20	20.1948893	100.974446		
	3	20	20.0396976	100.198488		
100	1	25	24.7633913	99.0535653	99.5141367	0.41205328
	2	25	24.9598852	99.8395409		
	3	25	24.912326	99.649304		
120	1	30	30.0510820	100.170273	99.6869169	0.44940721
	2	30	29.8814581	99.6048605		
	3	30	29.7856851	99.285617		

Table 5: Recovery Data of Teneligliptin Hydrobromide Hydrate

Accuracy Level %	Set no.	Amount Added (mg)	Amount Recovery (mg)	% Recovery	Mean	% RSD
80	1	0.8	0.79037700	98.8971252	99.5591896	0.73124993
	2	0.8	0.79706294	99.6328686		
	3	0.8	0.8019806	100.247575		
100	1	1.0	0.99098797	99.0987917	99.7293847	0.65179894
	2	1.0	1.00397257	100.397257		
	3	1.0	0.99692105	99.6921052		
120	1	1.2	1.19841205	99.8676711	99.6177116	0.26947506
	2	1.2	1.19581783	99.6514858		
	3	1.2	1.19200773	99.3339778		

PRECISION

Repeatability (Method precision, n=6):

Table 6: Repeatability of Metformin HCl

Sr. no	Area	Mean	SD	%RSD
1	2695.278			
2	2681.583	2699.277667	10.41551655	0.385863103
3	2706.074			
4	2711.476			
5	2697.918			
6	2703.337			

Table 7: Repeatability of Teneligliptin HBr Hydrate

Sr. no	Area	Mean	SD	%RSD
1	619.291			
2	620.531			
3	609.293			
4	623.023	618.8698	4.863821	0.78592
5	619.908			
6	621.173			

Repeatability

The data for repeatability of Metformin HCl and Teneligliptin HBr Hydrate is shown in Table 6 & Table 7. The % RSD for Repeatability data was found to be 0.38% and 0.78% respectively.

Intraday precision

The data for intraday precision for Metformin HCl is shown in Table-8. The % RSD For intraday precision was found to be 0.796%. The data for intraday precision for Teneligliptin hydrobromide hydrate is shown in Table-9. The % RSD for intraday precision was found to be 0.938%.

Table 8: Intraday precision for Metformin HCl (n=3)

Sr. No.	Concentration (µg/ml)	Mean Area ± SD	% RSD
1	25	1327.719333± 14.1821	1.068160803
2	50	2686.121333± 18.6780781	0.695354966
3	75	4026.226333± 25.15140935	0.624689406
	Mean		0.796

Table 9: Intraday precision for Teneligliptin hydrobromide hydrate (n=3)

Sr. No.	Concentration (µg/ml)	Mean Area ± SD	% RSD
1	1	306.2143333± 0.964596461	0.31500696
2	2	612.9726667± 10.54915174	1.720982404
3	3	923.5223333± 7.210171796	0.780725223
	Mean		0.938

Interday precision

The data for interday precision for Metformin HCl is shown in Table-10. The % RSD For intraday precision was found to be 0.443%. The data for interday precision for Teneligliptin hydrobromide hydrate is shown in Table-11. The % RSD for intraday precision was found to be 0.951%.

Table 10: Interday precision for Metformin HCl (n=3)

Sr. No.	Concentration (µg/ml)	Mean Area ± SD	% RSD
1	25	1330.727± 5.522386	0.41499

2	50	2684.974± 13.48349	0.502183
3	75	4024.98± 16.56048	0.411442
	Mean		0.443

Table 11: Interday precision for Teneligliptin hydrobromide hydrate (n=3)

Sr. No.	Concentration (µg/ml)	Mean Area ± SD	% RSD
1	1	304.81± 2.21183	0.725642
2	2	614.4103± 6.328348	1.029987
3	3	920.2257± 10.1123	1.098894
	Mean		0.951

LIMIT OF DETECTION AND LIMIT OF QUANTIFICATION

The Limit of detection (LOD) and Limit of quantitation (LOQ) Metformin HCl and Teneligliptin Hydrobromide Hydrate as mention below table 12

Table 12: Results of LOD and LOQ

Drug	Metformin HCl	Teneligliptin HBr Hydrate
LOD	1.740314044	0.052093545
LOQ	5.273678922	0.157859228

ROBUSTNESS

Robustness

The method is found to be robust as the results were not significantly affected by slight variation in composition of mobile phase, Mobile phase pH and flow rate of the mobile phase.

Table 13: Change the flow rate

Standard repetitions (n=6)	**0.8ml/min**		**1.2ml/min**	
	MET	TEN	MET	TEN
Mean Area ± SD	2797.685 ± 24.74225	641.2733 ± 6.585731	2635.754 ± 28.89574	604.6393 ± 6.18042
% RSD	0.884383	1.026977	1.096299	1.022166

Table 14: Change the mobile phase composition

Standard repetitions (n=6)	**58:38**		**62:42**	
	MET	TEN	MET	TEN
Mean Area ± SD	2767.797 20.9926	634.9183 5.798525	2634.698 24.5523	602.3517 8.349931
% RSD	0.758459	0.913271	0.931883	1.386222

Table 15: Change the mobile phase pH

Standard repetitions (n=6)	**3.8:6.8**		**4.2:7.2**	
	MET	TEN	MET	TEN
Mean Area ± SD	2773.536 25.26988	635.0817 7.146792	2582.925 15.74927	590.7333 9.713961
% RSD	0.911107	1.125334	0.609746	1.644396

System Suitability tests

Table 16 System Suitability Test Parameters for Metformin HCl and Teneligliptin HBr Hydrate

Sr. No.	System suitability Parameter	Metformin HCl	Teneligliptin HBr Hydrate
1	Retention time (min)	3.317	4.783
2	Resolution (R)	-	7.093
3	Theoretical plate number (N)	7512	6025
4	Tailing factor (T)	1.1	1.0

Assay preparation (Marketed formulation):

Label claim: TEN-20mg and MET-500mg

Sample stock solution:

Weigh and powdered 20 tablets. Take tablet powder equivalent to 50mgMET/2mgTEN in to a 100ml volumetric flask. Add 60 ml methanol. Shake for 15 minutes and sonicate for 10 minutes. Make up volume with methanol.

Filter this solution with Whatman filter paper no-1. (TEN-20mcg/ml, MET-500mcg/ml)

Working sample preparation:

Take 1ml from sample stock solution into a 10ml and make up with mobile phase. (TEN-2mcg/ml, MET-50mcg/ml)

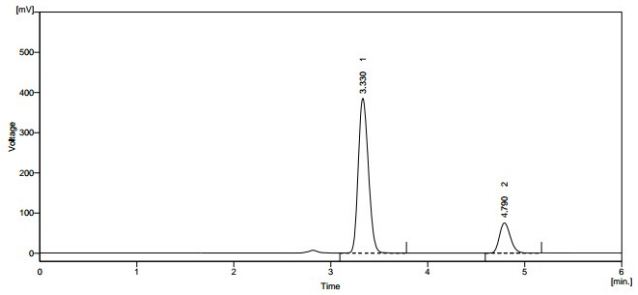


Figure 6: Injection of marketed formulation

Peak Table:

Table 17: Injection of marketed formulation

Sr. No	Peak name	Retention time	Area	Tailing factor	Theoretical Plates	Resolution time
1	Metformin HCl	3.390	2784.689	1.1	7512	-
2	Teneligliptin HBr Hydrate	4.790	584.538	1.0	6025	7.159

Observations:

In formulation sample preparation, both peaks are found well separated with good peak shape.

% Assay Results from Formulation:

Table 18

Sr. No.	Sample name	% Assay of MET	% Assay of TEN
1	Formulation	102.37 %	93.09 %

SUMMARY OF REGRESSION PARAMETERS

Table 19 Summary of Regression Parameters for Metformin HCl and Teneligliptin HBr Hydrate

Sr. No.	Parameters	Metformin HCl	Teneligliptin HBr Hydrate	REMARK
1	Linearity (µg/ml)	25-75 µg/ml	1-3 µg/ml	Linear
2	%Recovery	99.5-99.9	99.5-99.7	Accurate (98.0%-102%)
3	Precision (%RSD) Repeatability (n=6)	0.38%.	0.78%.	Precise (%RSD < 2)
	Intra-day (n=3)	0.79%	0.93%	
	Inter-day (n=3)	0.44%	0.95%	
4	LOD (µg/ml)	1.740314044	0.052093545	Sensitive
5	LOQ (µg/ml)	5.273678922	0.157859228	Sensitive
6	Specificity	Specific	Specific	Specific (No interference)
7	Robustness	Robust	Robust	(No difference in result)

DISCUSSION

A simple, accurate and precise RP-HPLC method for the simultaneous estimation of Metformin HCl and Teneligliptin HBr Hydrate in Pharmaceutical Dosage form has been developed and validated. Water (pH 4.0, adjust with 1% Orthophosphoric acid):Methanol (60:40 % v/v) Separation of drugs was carried out using mobile phase at 10 min. run time and 236 nm. The Rt value for Metformin HCl and Teneligliptin HBr Hydrate were found to be 3.317 ± 0.01 min. and 4.783 ± 0.01 min. respectively.

The drug response with respect to peak area was linear over the concentration range 25-75µg/ml Metformin HCl and 1-3 µg/ml for Teneligliptin HBr Hydrate. The percentage recovery of Metformin HCl and Teneligliptin HBr Hydrate was found to be 99.5-99.9% and 99.5-99.7% respectively.

The %RSD values for intra-day precision study and inter-day study were ≤ 2.0%, confirming that the method was sufficiently precise. The limit of detection and limit of quantitation were found to be 1.7403µg/ml and 5.2736µg/ml for Metformin HCl and 0.0520µg/ml and 0.1578µg/ml for Teneligliptin HBr Hydrate.

The %RSD values of Robustness study were ≤ 2.0%, confirming that the proposed method was found to be robust enough to withstand such deliberate changes and allow routine analysis of the sample. Interference studies reveals that the common excipients and other additives usually present in the dosage form did not interfere in the proposed method.

So it is concluded that the developed method is specific. The system test parameters were also performed and were found to be within acceptable criteria. The method can be successfully employed for the simultaneous determination of Metformin HCl and Teneligliptin HBr Hydrate in pharmaceutical dosage form.

CONCLUSION

A simple, economic, specific and robust RP-HPLC method has been developed and validated for the simultaneous estimation of Metformin HCl and Teneligliptin Hydrobromide Hydrate in pharmaceutical dosage form. There was no interference from any excipients in the determination of drugs in tablets which indicates the method is specific. All method validation parameters lie within its acceptance criteria as per ICH Q2(R1) guideline so we can conclude that method is Specific, Linear, Accurate and Precise. Hence it can be successfully used for the routine analysis of Metformin HCl and Teneligliptin Hydrobromide Hydrate in pharmaceutical dosage form.

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