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Research Article

RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF TENELIGLIPTIN AND METFORMIN IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

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 Teneligliptin and Metformin in bulk drug sample and pharmaceutical dosage forms using Cosmosil (C18, 250X4.6mm, 5µm) column with mobile phase composition of methanol and water (pH 3.5) 50:50 v/v. Flow rate of 0.7ml/min and uv detection at 242nm was maintain during the entire study. The retention time for Metformin and Teneligliptin was found to be 2.45 min and 6.21 min respectively. Linearity was observed over concentration range of 2-10µg/ml and 50-250 µg/ml for Teneligliptin and Metformin respectively. 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.

Keyword: Teneligliptin, Metformin, Reverse Phase HPLC, Validation

INTRODUCTION

Teneligliptin (TEN) is a novel drug, used for the treatment of type 2 diabetes mellitus. It is an anti diabetic drug that belongs to dipeptidyl peptidase-4 inhibitors or "gliptins" [1]. Teneligliptin is described as {(2S, 4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1, 3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate (figure.1). Its empirical formula is $C_{17}H_{27}NO_4$, with a molecular mass of 309.40 g/mo[2, 3]. It is a highly potent improves postprandial hyperglycemia and dyslipidemia [4]. Teneligliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 inactivates the incretin hormone which is responsible for the secretion of the insulin. Incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released from enteroendocrine cells and enhance insulin secretion[5, 6, 7, 8].

Metformin hydrochloride (MET) is chemically N, N dimethyl imidodicarbonimidic diamide hydrochloride (1, 1 dimethyl biguanide hydrochloride) (figure.2). Its therapeutic effect achieved without raising insulin concentrations, and it appears to reduce insulin resistance[9, 10, 11]. It belongs to the category biguinides. Suppress hepatic gluconeogenesis and glucose output from liver. Enhance insulin-mediated glucose disposal in muscle and fat. Retard intestinal absorption of glucose[12].

MATERIAL AND METHODS

Chemicals and Reagents

TEN reference standard used throughout the experiment was received as gift sample from Pure Chem. India Pvt. Ltd., Ankleshwar, Gujrat, India and MET was obtained from Macleod Pharmaceutical Pvt. Ltd, Mumbai, Maharashtra, India. The pharmaceutical formulation, Olymprix M 500 tablet (Alkem laboratories Pvt. Ltd) containing 20 mg of TEN along with 500 mg of MET was purchased from local market. AR grade methanol and water was used as solvent and procured from Merck India Pvt. Ltd., Mumbai, India.

Instrumentation

The high pressure liquid chromatograpy used was of model Younglin Acme 9000 gradient system equipped with UV Visible detector and C_{18} Cosmosil column (250mm ×406mm, 5µm) was used as stationary phase. The other instruments used are UV-Visible Spectrophotometer of Thermo Electrum Shimadzu having model 07 Bio UV 1601, pH meter, Balance and Ultrasonicator. The output signal was monitored on the Autochro 3000 software.

Methods

The wavelength of maximum absorption for Teneligliptin is 246nm and for Metformin is 232nm. Hence we have selected the single wavelength 242nm for the detection by estimation of Teneligliptin and Metformin in methanol. The overlain spectrum observed is shown in the figure 3.

Chromatographic condition

HPLC: Younglin (S.K) Gradient System
Detector and Pump No.: UV 730 D & SP930 D
Column: C_{18} (YMC) 4.6 ×250
Mobile phase: Methanol: Water (50:50v/v) pH3.5
Detection wavelength: 242nm
Flow rate: 0.7 ml/min
Temperature: Ambient
Injection volume: 20µl
Run time**:** 10 min

Preparation of Teneligliptin and Metformin Standard Solutions

Accurately weighted quantity 2mg and 50mg of Teneligliptin and Metformin was dissolved in Methanol Volume was made up to 10ml mark to get final concentration of about 200µg/ml of Teneligliptin and 5000µg/ml Metformin. A chromatogram was given in figure 4.

Procedure for Calibration Curve

Five standard calibration solutions of Teneligliptin and Metformin in the concentration of 2-10µg/ml and 50-250µg/ml respectively were prepared by diluting the standard solution with the mobile phase (figure 5).

Preparation of Teneligliptin and Metformin Test Solution

Twenty tablets weighted accurately and powdered. Powder equivalent to 20mg of Teneligliptin and 500mg of Metformin was added to the 10ml of methanol separately. Mix both the solution and shake for 15 minutes now it was 20ml solution. Filter this solution through 25µ filter. Now pipette out the 0.2 ml of the solution and add it to the 10ml. We get the final concentration of 2µg/ml and 50µg/ml of Teneligliptin and Metformin respectively.

Table 1 System Suitability Parameters for Teneligliptin and Metformin

Parameters	Teneligliptin	Metformin
Retention Time	6.27	2.38
Tailing factor	1.1583	1.1385
Theoretical plate	9699.5	3451.4

Table 2 Recovery Studies of Teneligliptin and Metformin

Level of Recovery (%)	80		100		120	
	TEN	MET	TEN	MET	TEN	MET
Amount present (mg)	3.60 3.63	90.45 90.72	3.95 3.99	101.46 101.16	4.44 4.48	109.47 109.68
Amount of Std. Added (mg)	1.6 1.6	40 40	2.0 2.0	50 50	2.4 2.4	60 60
Amount Recovered (mg)	1.60 1.63	40.45 40.72	1.95 1.99	51.46 51.16	2.44 2.48	58.70 58.91
% Recovery	100.12 102.4	100.12 101.80	97.81 99.71	102.93 102.32	101.86 103.54	90.11 90.46

Table 3 Statistical Validation of Recovery Study

Level of Recovery (%)	**Drug**	**Mean % Recovery**	**Standard Deviation**	**% RSD**
80	Teneligliptin	101.08	1.36	1.34
	Metformin	100.96	1.19	1.18
100	Teneligliptin	98.76	1.34	1.36
	Metformin	101.05	0.43	0.42
120	Teneligliptin	101.58	1.19	1.17
	Metformin	98.00	0.25	0.25

Table 4 Precision data of Teneligliptin and Metformin

Compounds(n=6)	**Intra-day Precision**		**Inter-day Precision**	
	% Amt. found	**% RSD**	**% Amt. found**	**% RSD**
Teneligliptin	**100.84**	**1.16**	**98.79**	**1.28**
Metformin	**99.83**	**0.12**	**101.03**	**0.32**

Table 5 Robustness Study of Teneligliptin and Metformin

Parameters	**Amount detected (mean ±SD)**		**%RSD**	
	TEN	**MET**	**TEN**	**MET**
Mobile phase (51+49)	304.13±1.37	5746.3±45.24	0.45	0.79
Mobile phase (49+51)	345.1±1.17	5779.24±91.49	0.34	1.58
Wavelength 241nm	386.15±4.86	5497.9±101.26	1.26	1.54
Wavelength 243 nm	321.4 ± 0.72	5693.50±6.07	0.22	0.11
Flow rate (0.6ml)	396.69±2.06	5566.40±20.53	0.52	0.37
Flow rate (0.8ml)	307.27±1.17	5520.72±96.62	0.38	1.75

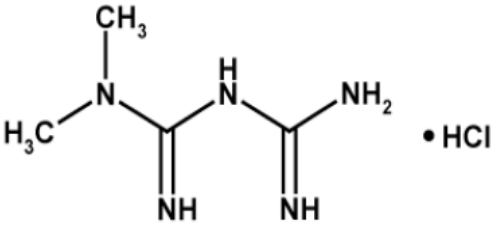

Figure 1. Structure of Teneligliptin

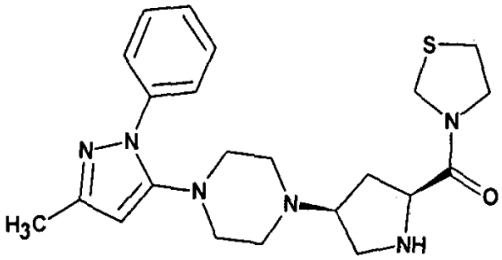

Figure 2. Structure of Metformin

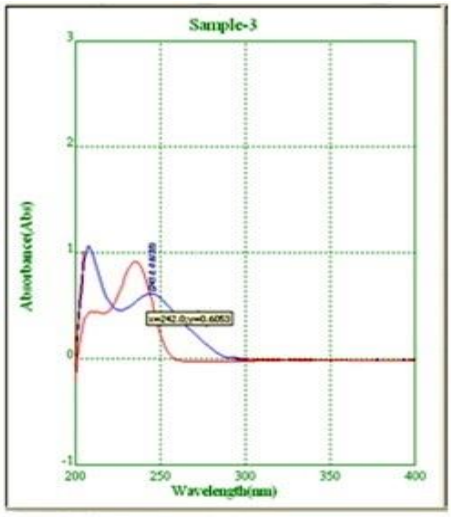

Figure 3. Overlain Spectra of Teneligliptin and Metformin

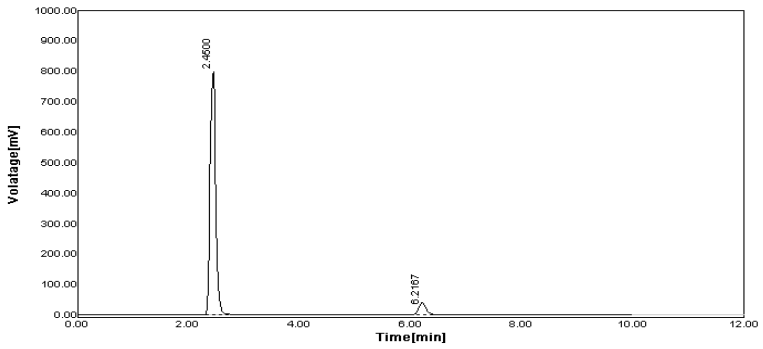

Figure 4. Chromatogram of Teneligliptin and Metformin

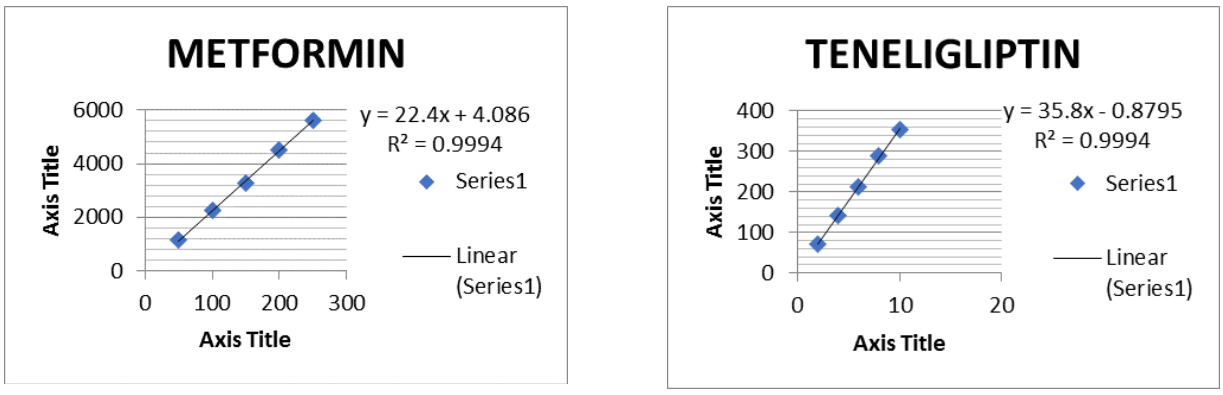

Figure.5 Linearity curve for Teneligliptin and Metformin

RESULT AND DISCUSSION

The purpose of the present study was to develop rapid, sensitive and reliable method for the estimation of the Teneligliptin and Metformin in the combined pharmaceutical dosage forms. After establishing the chromatographic condition for the Teneligliptin and Metformin the results obtained are given as below:

System Suitability

System suitability parameters such as theoretical plate, retention time and tailing factor were carried out and the results are given in the table 1.

Accuracy

This parameter is performed to determine the closeness of test results to that of the true value obtained expressed in the % recovery. This study was performed at three different levels (80%, 100% and 120%) and the percentage recovery of Teneligliptin and Metformin was calculated. The % recovery was found to be within 98-101%. (Table 2 and 3)

Precision

The method was established by analyzing six replicates standards of Teneligliptin and Metformin. All the solution was analyzed thrice in order to record any intra-day & inter-day variation in the result. The results obtained for intraday and inter-day variation are shown in Table 4.

Robustness

The Robustness of a method is its ability to remain unaffected by small deliberate changes in parameters. To evaluate the robustness of the proposed method, small but deliberate variations in the optimized method parameters were done. The effect of changes in mobile phase composition and flow rate on retention time and tailing factor of drug peak was studied.
The mobile phase composition was changed in ± 1 ml proportion and the flow rate was varied by ± 0.1 ml min^{-1}, of optimized chromatographic condition. The results of robustness studies are shown in Table 5.

CONCLUSION

A simple rapid, precise and reliable method was developed for the estimation of the Teneligliptin and Metformin in combined dosage forms. The results obtained are within the specified limit by the ICH guidelines. Analytical column used and the mobile phase provide good separation and gives the sharp results. The retention time observed for both the drugs was good hence the method can be used for routine analysis in quality control laboratories.

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