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RP-HPLC Method for the Simultaneous Estimation of Metformin Hydrochloride and Telmisartan in Bulk and in a Synthetic Mixture

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Abstract: A simple, rapid and precise reverse phase liquid chromatographic (RP-HPLC) method was developed and subsequently validated for simultaneous estimation of Metformin hydrochloride and Telmisartan in bulk drug and in a synthetic mixture. The analysis was carried out using Zodiac ODS C18 (4.6 x 250mm, 5µm, Make: Zodiac Life Sciences), pre-packed column. The separation was carried out using a mobile phase containing a buffer of pH 4.0, Acetonitrile and Methanol (30:30:40 v/v/v), was pumped at a flow rate of 1.4 mL/min with UV-detection at 228 nm. Both the drugs were well resolved on the stationary phase and the retention times were around 2.523 minute for Metformin hydrochloride and 5.437 minute for Telmisartan. The method was validated and shown to be linear for Metformin hydrochloride and Telmisartan. The correlation coefficients for Metformin and Telmisartan are 0.996 and 0.998 respectively.
Keywords: Metformin hydrochloride, Telmisartan, HPLC, Validation.

Introduction

Metformin hydrochloride (MET) is chemically known as 1,1-dimethyl biguanide hydrochloride (Fig. 1) is an anti-diabetic drug from the biguanide class of oral antihyperglycemic agents, and used as the first line agent for the treatment of non insulin-dependent diabetes mellitus (Type II) particularly in obese patients. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by Metformin of AMP-activated protein kinase (AMPK) [1], a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for Metformin inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. It also causes improvements in endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution [2]. Recent clinical trials suggest that Metformin, in addition to its efficacy in treating Type –II diabetes, may also have therapeutic potential in other conditions including diabetic nephropathy, cardiovascular diseases, polycystic ovary disease [3] and the prevention or treatment of cancer [4].

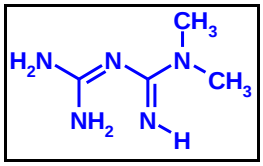

Figure 1: Structure of Metformin

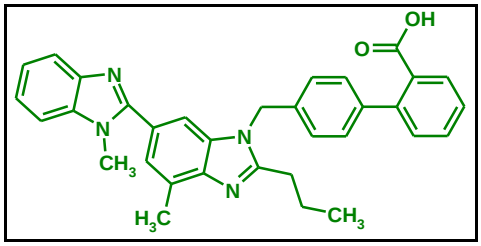

Figure 2: Structure of Telmisartan

Telmisartan (TEL) is chemically known as 4[(1, 4-dimethyl-2-propyl (2, 6-bi-1H-benzimidazol]-1-yl) methyl] [1, 1-biphenyl]-2-carboxylic acid (Fig. 2). Telmisartan is a potent, long lasting, orally acting non-peptide antagonist of angiotensin II Type 1receptor (AT1) used in the management of hypertension. It selectively inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation [5]. The most recent clinical trials demonstrated that Telmisartan also has preventive roles against ischemic heart diseases in diabetic patients with a similar potency to angiotensin converting enzyme inhibitor. Several studies recently [6] suggest that the effects of Telmisartan are mediated via not only blockade of ARB but also activation of peroxisome proliferators-activated- γ receptor (PPAR -γ) a central regulator of insulin and glucose metabolism. It is believed that Telmisartan dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD). Diabetes Mellitus, hypertension and obesity are the most common diseases of this era. The insulin resistance associated with obesity contributes to the development of cardiovascular risk factors such as dyslipidemia, hypertension, and type 2 diabetes. The risk of type 2 diabetes and hypertension are strongly related to obesity and central distribution of fat [7].The coexistence of hypertension and diabetes increases the risk for macrovascular and microvascular complications, thus predisposing patients to cardiac death, congestive heart failure, coronary heart disease, cerebral and peripheral vascular diseases, nephropathy, and retinopathy [8]. Metformin therapy also improves insulin sensitivity and has been associated with decreases in cardiovascular events in obese diabetic patients. However, achieving and maintaining good glycemic control has always been a challenge, implying the need of an adjunct therapy. Antihypertensive treatment in diabetics decreases cardiovascular mortality and slows the decline in glomerular function. The structural similarity of Telmisartan to Pioglitazone is expected to be useful in the treatment of both hemodynamic and biochemical aspects of type 2 diabetes [9, 10].

MET and TEL is official in IP [11], BP [12], USP [13]. Literature reveals that various UV spectrophotometric [14], FTIR [15], NMR [16], NIR [17], RP-HPLC [18-22], HPTLC [23],GC [24] and LC-MS/MS [25], Capillary electrophoresis [26] methods for the determination of MET either as single or in combination with other drugs in human plasma and in pharmaceutical preparations were reported in literature. Some analytical methods for the quantitative determination of TEL in pharmaceutical formulations are described in literature like Titrimetric [27], voltametry [28], Spectroflourimetric [29], UV spectrophotometric [30], HPLC [31-37], HPTLC [38], LC–MS/MS [39], method in human plasma have been reported.

To the best of our knowledge no HPLC method of analysis has yet been reported for simultaneous analysis of Metformin hydrochloride and Telmisartan. Hence, in the present communication we would like to report a simple, economic, feasible, rapid, sensitive, and validated [40] specific RP-HPLC method for the simultaneous estimation of Metformin hydrochloride and Telmisartan in Bulk and in a synthetic mixture.

Materials and Methods

Equipment and Chromatographic Conditions

A Shimadzu (Software: Synchrome) LC-20 AT equipped with Manual Sampler and SPD 20A Prominence UV-Visible detector was used for HPLC Analysis. All pH measurements were performed on a Digital pH meter (Global, DPH500). Chromatographic separation was carried out at room temperature with Zodiac ODS C18 (Zodiac ODS C18 250×4.6mm, 5µm, Make: Zodiac Life Sciences) column. For the mobile phase, accurately weighed 2.72gm of Potassium dihydrogen orthophosphate (20mM) was dissolved in 900ml of HPLC grade Water and sonicated to remove dissolved gases. The pH of the mobile phase was adjusted to 4.0 ± 0.05 with orthophosphoric acid. The buffer solution was shaked manually to mix finally make up the volume to 1000 mL. A mixture of buffer, Acetonitrile and Methanol in the ratio of 30:30:40 v/v/v was prepared. Finally the mobile phase was filtered through a 0.45 µm membrane filter and degassed for 10 minutes. The injection volumes for samples and standards were 0.02mL and eluted at a flow rate of 1.4 mL/min at 30°C. The eluents

were monitored at 228 nm.

Reagents and Chemicals

Acetonitrile and methanol were of HPLC grade and were purchased from Standard Reagents Pvt Ltd, Hyderabad.Triethyl amine, orthophosphoric acid and other reagents were of analytical-reagent grade and purchased from Standard Reagents, Hyderabad. Water was deionised and double distilled. Metformin hydrochloride and Telmisartan bulk powder received as gift samples from Sohan Health Care Pvt. Ltd. Pune And Ranbaxy Laboratories Limited, Gurgaon, India.

Preparation of Standard solutions

A working standard solution containing Metformin hydrochloride and Telmisartan was prepared by weighing 50 mg of Metformin and 4mg of Telmisartan and dissolved in 10 mL of methanol. The mixture was sonicated for 5minutes and make up to 50 mL with the mobile phase. 2.5 mL from stock solution of MET and TEL were mixed in 25 mL of volumetric flask and made up to volume with mobile phase to get a mixed standard solution containing 100µg/mL of MET and 8µg/mL of TEL. UV spectrum showing isobestic point is shown in Fig 3.

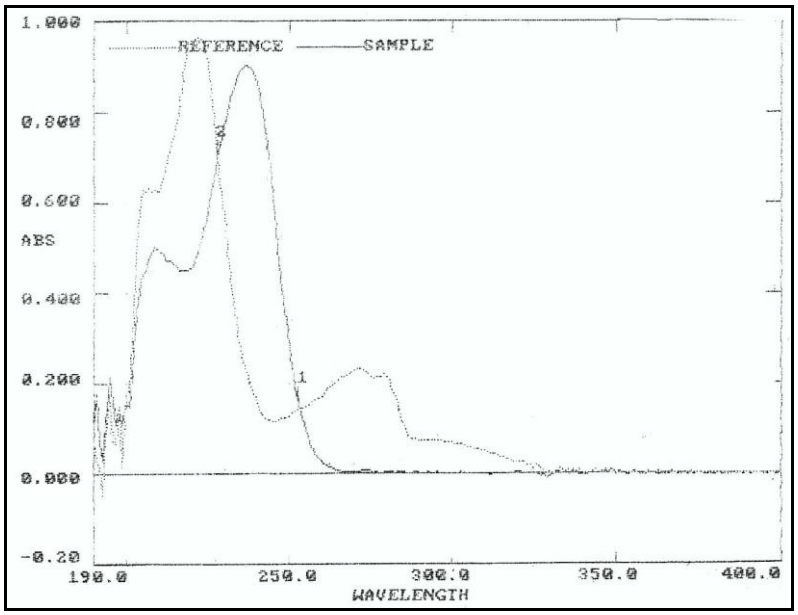

Figure 3: UV spectra of MET & TEL with blank (methanol) (10 µg/mL)

Method Validation

Linearity

In order to check the linearity for the developed method, solutions of five different concentrations ranging from 60-140 µg/mL was prepared for MET and 4.8-11.2 µg/mL for TEL, respectively. The chromatograms peak areas were recorded and calibration curve was plotted of peak area against concentration of drug. The chromatograms were recorded and the peak areas are given in Table 1**.** A linear relationship between areas versus concentrations was observed in the above-mentioned linearity range. This range was selected as the linear range for the development of the analytical method, for the estimation of MET and TEL. The calibration curves for both drugs given in Fig 4 and Fig 5.

Table 1: Linearity data for Metformin hydrochloride and Telmisartan.

MET Conc. (µg/mL)	Mean Peak area of MET	TEL Conc. (µg/mL)	Mean Peak area of TEL
60	4108.596	60	499.993
80	4955.777	80	620.251
100	6667.558	100	805.233
120	7546.732	120	973.442
140	8987.436	140	1151.800

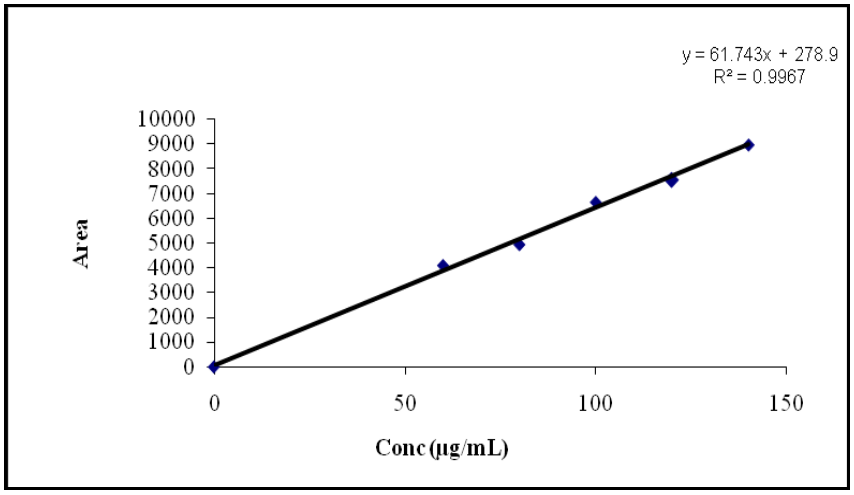

Figure 4: Calibration curve for Metformin hydrochloride at 228 nm.

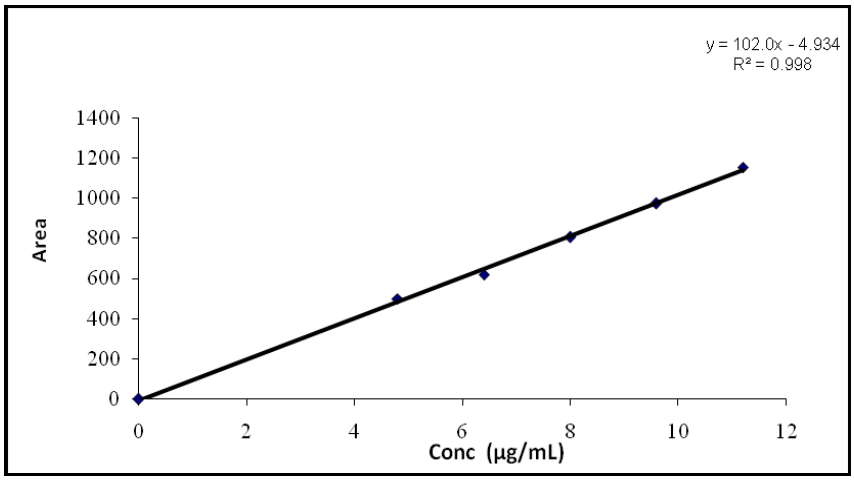

Figure 5: Calibration curve for Telmisartan at 225 nm.

Sensitivity

The sensitivity of the measurement of Metformin hydrochloride and Telmisartan using the proposed method was estimated as the limit of quantification (LOQ) and the lowest concentration detected under these chromatographic conditions as the limit of detection (LOD). The LOD and LOQ were calculated by using the equations LOD =3.3 × σ / S and LOQ = 10 × σ / S, where σ was the standard deviation of the peak areas of the drug (n = 5), and S was the slope of the corresponding calibration plot. The limits of detection and quantification for MET were 1.69µg / mL and 5.12µg/ mL, respectively, and those for TEL were 0.08 µg / mL and 0.24 µg /mL, respectively.

System Suitability

The system suitability test is an integral part of chromatographic analysis. It is used to verify that the resolution and reproducibility of the system are adequate for the analysis. A system suitability test according to the United States Pharmacopeia Convention was performed on chromatograms obtained for standard and test solutions to check differences in the above mentioned parameters. The results obtained with six replicate injections of the standard solution are summarized in Table 2.

Table 2: System suitability parameters for Metformin hydrochloride and Telmisartan.

Parameter (*n=6)	MET	TEL
Retention time	2.523	5.437
Plate count	3174	2551
USP Tailing	1.778	1.300

***n=Six replicate.**

Precision

Precision of the method was assessed by Repeatability, determined by analysing 100µg/mL of MET and 8µg/mL of TEL for six times, The relative standard deviation was calculated from the ratio of the standard deviation to the mean and expressed as a percentage, the results are reported in Tables 3 and 4.

Table 3: Results of Repeatability for MET

Concentration(µg/ml)	Area	Avg Area	S.D	%RSD
100	6139.128			
100	6214.295			
100	6134.093	6145.868	45.851	0.75
100	6098.820			
100	6103.039			
100	6185.833			

% RSD = SD/mean × 100.

Table 4: Results of Repeatability for TEL

Concentration(µg/ml)	Area	Avg Area	S.D	%RSD
8	768.291			
8	769.058			
8	761.519	768.755	11.589	1.51
8	775.057			
8	752.294			
8	786.309			

% RSD = SD/mean × 100.

Accuracy

The accuracy of the method was determined by calculating the recoveries of MET and TEL by the standard addition method. Known amounts of standard solutions of MET and TEL were added at 20% concentration to pre quantified sample solutions of MET (80,100 and120 µg/mL) and TEL (6.4, 8.0 and 9.6 µg/mL). Results from the recovery studies are given in Tables 5 and 6**.**

Table 5: Results of the recovery study of Metformin hydrochloride.

%Added	Constant amount added[a] (µg/ml)	Amount added[b] (µg/ml)	Total amount found[c] (µg/ml)	Amount found[d] (µg/ml)	% Recovery[e]	%RSD
80	20	80	99.43	79.43	99.28	0.321
	20	80				
	20	80				
100	20	100	117.97	97.97	97.97	0.147
	20	100				
	20	100				
120	20	120	142.39	122.39	101.99	0.202
	20	120				
	20	120				

a. Pure drug added; b. Preanalyzed sample found; c.Total concentration found i.e. c=Spiked average area / actual area (standard) X amount added in µg; d. Amount found i.e. d=c-a;

e. % Recovery of MET = MET recovery (_µg/ml)/MET input (_µg/ml) × 100 or d/b×100

Table 6: Results of the recovery study of Telmisartan.

% Added	Constant amount added[a](µg/ml)	Amount Added[b] (µg/ml)	Total Amount found[c] (µg/ml)	Amount found[d] (µg/ml)	% Recovery[e]	%RSD
80	1.6	6.4	7.90	6.3	98.43	1.073
	1.6	6.4				
	1.6	6.4				
100	1.6	8.0	9.74	8.14	101.75	0.496
	1.6	8.0				
	1.6	8.0				
120	1.6	9.6	11.39	9.79	101.97	0.457
	1.6	9.6				
	1.6	9.6				

a. Pure drug added; b. Preanalyzed sample found; c.Total concentration found i.e. c = Spiked average area / actual area (standard) X amount added in µg; d. Amount found i.e. d = c – a;

e. % Recovery of TEL = TEL recovery (_µg/ml)/TEL input (_µg/ml) × 100 or d/b×100

Solution Stability

The stability of MET and TEL standard and sample solutions was determined by storing the solutions at an ambient temperature (30 ± 5°C). The solutions were checked in triplicate after three successive days of storage and the data were compared with the freshly prepared samples. In each case, it could be noticed that the solutions were stable for 48 hours, as during this time the Results did not decrease below 98%. This showed that MET and TEL were stable in standard and sample solutions for at least two days, at ambient temperature.

Robustness

The robustness of the method was determined by making slight changes in the chromatographic conditions like flow rate (±0.2), wavelength (±2nm). It was observed that there were no marked changes in the chromatograms, which demonstrated that the RP-HPLC method developed was robust.

Assay

The proposed method was successfully applied for the estimation of Metformin hydrochloride and Telmisartan in bulk drug and in a synthetic mixtue.Ten tables powered equivalent were mixed in the ratio of 50mg of MET and 4mg of TEL.A quantity of this Synthetic Mixture powder equivalent to 83mg taken and dissolved in 10 mL of methanol and made upto 50 mL with mobile phase. The solution was sonicated for 5 min. This solution was further diluted to obtain a concentration of 100 µg/mL MET and 8 µg/mL TEL. The assay results were compiled, found satisfactory and show that there is a no interference of tablet matrix with the drug and the results are summarized in Table 7, and the standard and test chromatograms are given in Fig. 6 and 7. Low % RSD shows that this method can be easily applied for the estimation of MET and TEL in bulk drug and in the synthetic mixture.

Table 7: Determination of % assay for MET and TEL.

Synthetic mixture	Drug	Label claim mg/tab	Amount taken (mg)	Conc. estimated (mg)	Mean conc. Estimated (mg)	% Assay (w/w)	% RSD
MET+TEL	MET	500	50	48.753	47.97	95.94	1.05
				46.731			
				48.885			
				46.731			
				48.753			
	TEL	40	4	4.0172	3.96	99.17	1.018
				3.8499			
				4.1028			
				3.8499			
				4.0172			

% Assay of MET or TEL =MET or TEL Mean Conc. estimated (mg)/TEL or MET input (mg) X 100; % RSD = SD/mean X 100.

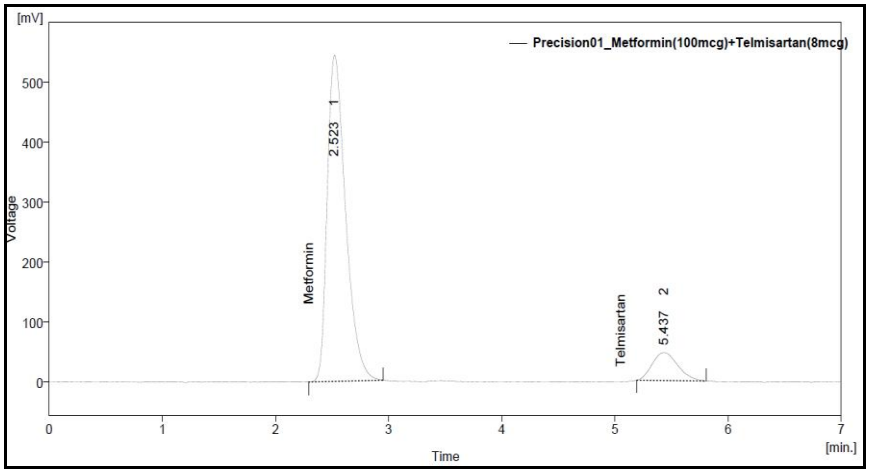

Figure 6: Chromatogram of the standard preparation of MET and TEL.

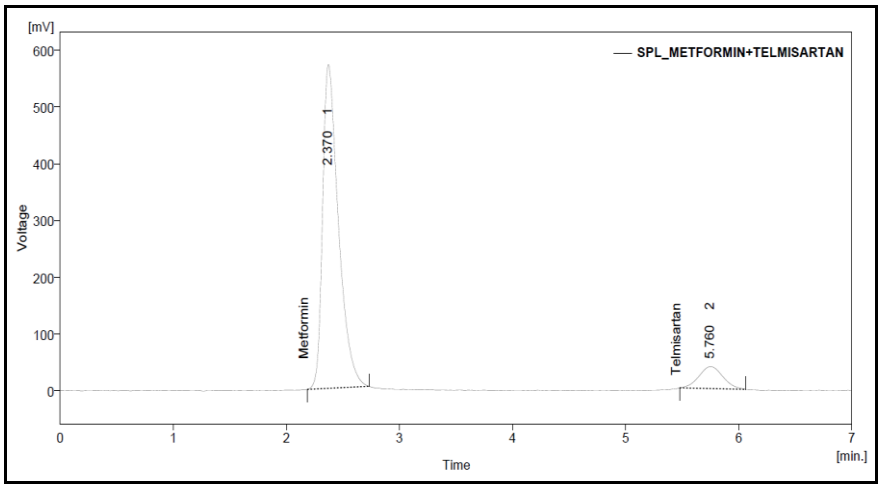

Figure 7: Chromatogram of the Sample preparation of MET and TEL.

Results and Discussion

The RP-HPLC procedure was optimized with a view to develop an accurate and stable assay method with the pure drugs MET and TEL, in a Bulk drugs and in a synthetic mixture using Zodiac C18 (4.6×250mm, 5µm,Make:Zodiac life sciences) column in isocratic mode using a mobile phase containing buffer, Acetonitrile and Methanol (30:30:40 v/v/v). The flow rate was 1.4 mL/min at 30 °C with UV detection at 228 nm. Linearity was assessed by plotting concentration versus area, which is shown in Table 1, and it is linear in the range of 60–140 µg/mL for MET and 4.8-11.2 µg/mL for TEL with correlation coefficients of 0.996 and 0.998 respectively. The % recovery was found to be within limits of the acceptance criteria with a recovery range of 99.28% –101.99% for Metformin and 98.43% –101.97% for Telmisartan. The %RSD for precision was less than 2% for MET and TEL. The detection limit of the proposed method was 1.69 µg/mL and 0.08 µg/mL, and the quantification limit was 5.12 µg/mL and 0.24 µg/mL for MET and TEL respectively. A typical chromatogram of the standard solution of MET and TEL at the test level is shown in Fig 6. The assay procedures were repeated five times and the results were found to give 95.94 % of MET and 99.17% of TEL as shown in Table 6.

Conclusion

The proposed study describes a new and simple RP-HPLC method for the estimation of MET and TEL in Bulk drug and in a synthetic mixture. The method has been validated and found to be simple, rapid, sensitive, accurate, and precise. Moreover, the lower solvent consumption along with the short analytical run time of 7.0 minutes leads to an environmentally friendly chromatographic procedure that allows the analysis of a large number of samples in a short period of time. Therefore, the proposed method can be used for routine analysis of both drugs in the process control of bulk drugs and formulation products without any interference from excipients in Laboratories and in the pharmaceutical industries.

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