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Research Article

DEVELOPMENT AND VALIDATION OF UV SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF METFORMIN HCl, ROSUVASTATIN CALCIUM AND TELMISARTAN IN BULK DRUG

Shreeraj Shah[1]*., Kaushika Patel[2] and Darshil Shah[3]

[1,2]Department of Pharmaceutical Technology, L. J Institute of Pharmacy, Ahmedabad
[3]Department of Quality Assurance, L. J. Institute of Pharmacy, Ahmedabad

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ABSTRACT

The present manuscript describes UV spectrophotometric method for the simultaneous determination of Metformin HCl, Rosuvastatin calcium and Telmisartan in bulk drug. The various parameters, such as linearity, precision, accuracy, specificity, robustness, limit of detection and limit of quantitation were studied according to (ICH) International Conference on Harmonization guidelines. The first derivative UV spectrophotometric method was performed at 208nm, 233nm and 221nm for Metformin HCl, Rosuvastatin Calcium and Telmisartan respectively in 0.1N HCl solution and distilled water (50:50). The linearity was obtained in the concentration range of 2-10 µg/ml for Metformin and Telmisartan, 10-50 µg/ml for Rosuvastatin Calcium with correlation coefficient (R^2) 0.994 for Metformin HCl and Rosuvastatin Calcium & 0.998 for Telmisatan. The mean % recoveries were found to be 99.11±0.15, 99.71±0.47 and 98.88±0.66 for Metformin HCl, Rosuvastatin Calcium and Telmisartan respectively. The proposed method is highly sensitive, precise and accurate and therefore can be used for its intended purpose. The suitability of these methods for the quantitative determination of Metformin HCl, Rosuvastatin Calcium and Telmisartan was proved by validation. The proposed method has been validated as per ICH guidelines and successfully applied to the simultaneous estimation of Metformin HCl, Rosuvastatin Calcium and Telmisartan in bulk drug. The results of analysis have been validated statistically and by recovery studies.

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INTRODUCTION

Diabetes is one of the major health problems in the world. If the glycemic target level is not achieved with Hypertension, combination oral therapy is recommended. Combination oral therapy becomes an obvious choice when glycemic control with Hypertension control needs. The advantages of oral dose combinations as compared to their components which are taken alone are lower cost and better patient compliance. Combination therapy has been shown to achieve greater blood glucose lowering than monotherapy because different classes have different and complimentary mechanisms of action. The rapid introduction of combination therapy with two or three complementary oral anti diabetics with Anti-Hypertensives help to maintain diabetes and hypertension both.

Chemically, Metformin is 1, 1-dimethyl biguanide hydrochloride, Metformin improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis.

Rosuvastatin calcium is calcium;(E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate. It is a Hydroxy Methyl Glutaryl-CoA-Reductase inhibitor, or statin, that reduces the plasma concentrations of LDL-cholesterol; Apolipoprotein B, and Triglycerides while increasing HDL-cholesterol levels in patients with hypercholesterolemia and those at risk for cardiovascular diseases

Telmisartan is Chemically 4'-[(1,4'-Dimethyl-2'-propyl[2,6'-bi-1H benzimidazol]-1'l)methyl][1,1'-biphenyl]-2-carboxylicacid;4'-[[4-methyl-6 (1-methyl-2-biphenylcarboxylic acid. Telmisartan is angiotensin II receptor antagonist. They are more selective blocker of angiotensin effect than ACE inhibitors. They also cause complete potential inhibition of angiotensin action compared with ACE inhibitors because there

Corresponding author:* **Shreeraj Shah
1Department of Pharmaceutical Technology, L. J Institute of Pharmacy, Ahmedabad

are enzymes other than ACE that are capable of generating angiotensin II.

This combination can be achieved by taking each of the drugs separately or alternatively fixed formulations have been developed. A combination tablet formulation is beneficial in terms of its convenience and patient compliance. The review of literature reveals that there were analytical methods of all the three drugs individually in pharmaceutical dosage forms and even in biological samples and a few methods reported for combination of either of the two drugs.

MATERIAL AND METHODS

Apparatus

A double beam UV/Visible spectrophotometer, Shimadzu UV-1800, was employed with a pair of 1 cm quartz cells for all analytical work.

All weighing were done on electronic analytical balance (Wensar Dab 220).

Reagents and chemicals

Metformin, Rosuvastatin calcium and Telmisartan were obtained from AMNEAL Pharmaceuticals Ltd, India as gift sample and were used as working standards. Hydrochloric acid of analytical grade and double distilled water were used throughout the analysis

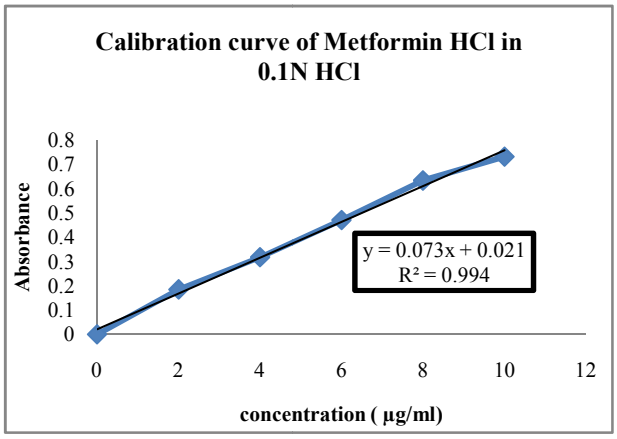
Preparation of standard solution

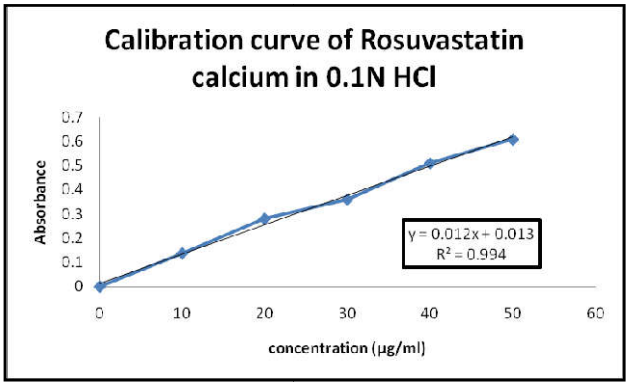
Standard stock solutions of MET, ROSU and TEL were prepared by dissolving 10 mg of each drug separately in 100mL volumetric flask using 0.1N Hydrochloric acid as solvent up to 50 ml and volume made up with distilled water and sonicated upto 20 min. Stock solutions of 100 µg/mL were obtained in this manner. From these stock solutions, working standard solutions of concentration were prepared by appropriate dilutions. Working standard solutions were scanned in the entire UV range to determine the λmax. The λmax of MET, ROSU and TEL were found to be 208 nm, 233 nm and 221 nm respectively.

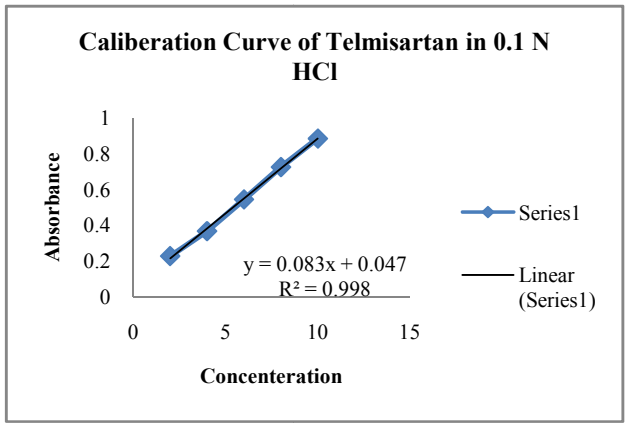
Calibration curve

Calibration curve was taken in 0.1N HCl within concentration range of 2-10 µg/mL for MET and TEL and concentration range of 10-50µg/mL for ROSU. Calibration curve was constructed by plotting absorbance versus concentrations. The readings were recorded in triplicate and the mean values were recorded. The regressed values of absorbance were plotted graphically against the concentration. The absorbances of these standard solutions were measured at 208nm, 233nm and 221nm and calibration curve was plotted. The absorptivity coefficients of the three drugs were determined using calibration curve graph shown below;

Simultaneous equations method and preparation of solutions Method was based on simultaneous equation method of Vierodt's. The method is applicable in the case of sample containing two drugs, each of which absorbs at the λmax of the other (Beckett *et al*, 1997). Three equations were developed using absorptivity coefficient values as an X component.







The content in the mixture was determined by using the following three component equations/ Cramer's rule:

X COMPONENT =A1 (β2γ3 -β3γ2) -A2 (β1γ3-β3γ1) + A3 (β1γ2-β2γ1)/α1 (β2γ3 -β3γ2) -α2 (β1γ3-β3γ1) + α3 (β1γ2 β2γ1) Similarly, y and z components can be estimated. Triple combination equations were constructed based upon the fact that the absorbance of the mixture of MET, ROSU and TEL at 208nm, 233nm and 221nm is the sum of the absorbances at respective wavelengths and the spectra shown in fig no 2. From the absorbance value obtained of all the three λmax, absorptivity were calculated and shown in table no. 3, 4, 5 respectively for MET, ROSU AND TEL.

Quantitative equations method

Method was based on Quantitative equation method. Primary stock solution was prepared by using 0.1N HCl. From this different dilutions were prepared to determine λmax and beer's law range. Calibration curve was prepared by using different

concentrations of standard solution. MET, ROSU and TEL in dosage form were estimated by calibration curve. Developed method was validated as per ICH guidelines with the help of several parameters like accuracy, precision, LOD and LOQ.

Estimation in the mixture

An accurately weighed powder sample mixture equivalent to 10mg of MET, ROSU and TEL was transferred to a 10mL volumetric flask, dissolved in 5mL 0.1N HCl, shaken for 10 min and the volume was made up to the mark with 0.1N HCl. The solution was then filtered through Whatmann filter paper no. 41. The solution was further diluted to get concentrations in the range for all the drugs. The analysis procedure was repeated three times with the formulation. The result of analysis of the formulation is shown in Table.

Method validation

The method validation parameters like linearity, precision, accuracy, repeatability, limit of detection and limit of quantitation were checked as per ICH guidelines.

Linearity and range

The linearity for MET, ROSU and TEL were determined at some concentration levels for MET and TEL from 2-10 µg/ml and for ROSU ranging from 10-50µg/ml using working standards.

Precision and Accuracy

The precision of the method was evaluated by performing interday and intraday variation studies. In intraday studies, working solutions of standard and sample were analysed thrice in a day and percentage relative standard deviation (% RSD) was calculated. In the interday variation studies, working solution of standard and sample were analysed on three consecutive days and percentage relative standard deviation (% RSD) was calculated. The data is shown in table 1-6.

The accuracy of the method was determined by recovery studies. The recovery studies were performed by the standard addition method at 50%, 100% and 150% level and the percentage recoveries were calculated and are shown in Table.

Limit of detection and Limit of quantitation

The Limit of Detection (LOD) is the smallest concentration of the analyte that give the measurable response. LOD was calculated using the following formula and shown in Table.
LOD = 3.3 (σ/ S)
Where, S = slope of calibration curve,
σ= standard deviation of the response.

The Limit of Quantification (LOQ) is the smallest concentration of the analyte, which gives a response that can be accurately quantified. LOQ was calculated using the following formula and shown in Table.
LOQ = 10 (σ/ S)

Where, S = slope of calibration curve,
σ= standard deviation of the response

RESULTS AND DISCUSSION

In the present work, new method, namely, simultaneous equation method (Vierordt's method) was used for the simultaneous spectroscopic estimation of MET, ROSU and TEL in bulk drug. The concentrations in the range of 2-10 µg/ml for MET, TEL and 10-50 µg/ml for ROSU were analysed and three sampling wavelengths of 208nm (λmax of MET), 233nm (λmax of ROSU) and 221nm (λmax of TEL) gave optimum accuracy, precision, time, economy and sensitivity for this method.

Table 1 The absorptivity values of MET, ROSU and TEL in the proposed method (n=6)

Absorptivity Value	208 nm	233 nm	221 nm
Ax1	0.050	-	-
Ax2	-	0.009	-
Ax3	-	-	0.037
Ay1	0.0129	-	-
Ay2	-	0.0103	-
Ay3	-	-	0.0111
Az1	0.0974	-	-
Az2	-Specific	0.1754	-
Az3	-	-	0.0934

The proposed procedure was successfully applied to the determination of MET, ROSU and TEL in the mixture of bulk drug commercially. The recovery studies were carried out at different concentrations by spiking a known concentration of standard drug to the reanalysed sample and contents were reanalyzed by proposed methods. The results of analysis and Recovery studies are depicted in Table No.2.

Table 2 Determination of Accuracy by percentage recovery method for MET, ROSU and TEL

Ingredients	Conc. of Solution (µg/ml)	Level of Addition	Std. Added	Amt. recovered (µg/ml)	% Recovery	Avg. % Recovery Mean ± SD (n=3)
MET	4	50	2	5.96	99.25	99.11±0.15
		100	4	7.92	98.95	
		150	6	9.91	99.15	
ROSU	20	50	10	29.81	99.35	99.71±0.47
		100	20	39.82	99.54	
		150	30	50.10	100.244	
TEL	4	50	2	3.94	98.56	98.88±0.66
		100	4	7.97	99.65	
		150	6	9.84	98.45	

The method was validated statistically for range, linearity, precision, accuracy, repeatability, LOD, and LOQ (Table No. 3,4,5).

Table 3 Validation parameters for MET

Sr. No.	Parameters	Results
1	Wavelength(nm)	208
2	Linearity range(µg/ml)	2-10
3	Standard regression Equation	Y=0.073x+ 0.021
4	Correlation coefficient(r^2)	0.994
5	A(1%,1 cm)	0.050
6	Accuracy (% recovery ± SD)	99.71±0.47
7	Precision (%CV) Specific	0.38
8	LOD(µg/ml)	0.24
9	LOQ(µg/ml)	0.79

Accuracy was ascertained on the basis of recovery studies. Precision was calculated as inter and intraday Variation for all the drugs shown in table 6, 7 and 8. The percentage recoveries for MET, ROSU and TEL were found to be 99.11±0.15, 99.71±0.47 and 98.88±0.66 for this method respectively. The relative standard deviation was found to be within the limit, indicating good accuracy, precision, and repeatability of the proposed method.

Table 5 Validation parameters for TEL

Sr. No.	Parameters	Results
1	Wavelength(nm)	221
2	Linearity range(µg/ml)	2-10
3	Standard regression Equation	Y=0.088x+ 0.029
4	Correlation coefficient(r^2)	0.998
5	A(1%,1 cm)	0.097
6	Accuracy (% recovery ± SD)	98.88±0.66
7	Precision (%CV) Specific	0.31
8	LOD(µg/ml)	0.18
9	LOQ(µg/ml)	0.59

Table 6 Precision data for METFORMIN (% Assay) (n=6)

Sample Number	Analyst - I (Intra-day precision)	Analyst – II (Inter-day precision)
1	98.4	98.5
2	98.5	98.6
3	99.2	99.4
4	98.6	98.6
5	98.6	99.3
6	99.3	98.7
Mean	98.77	98.85
SD	0.3830	0.3937
%RSD	0.3878	0.3983

Table 7 Precision data for ROSUVASTATIN (% Assay) (n=6)

Sample Number	Analyst - I (Intra-day precision)	Analyst – II (Inter-day precision)
1	99.32	99.8
2	98.25	100.32
3	99.63	99.85
4	99.34	98.61
5	98.56	99.25
6	98.33	99.36
Mean	98.91	99.53
SD	0.5943	0.5921
%RSD	0.6008	0.5949

Table 8 Precision data for TELMISARTAN (% Assay) (n=6)

Sample Number	Analyst - I (Intra-day precision)	Analyst – II (Inter-day precision)
1	98.36	100.25
2	98.54	99.36
3	98.31	99.34
4	98.47	99.61
5	98.33	99.44
6	99.05	99.57
Mean	98.51	99.60
SD	0.2789	0.3389
%RSD	0.2831	0.3402

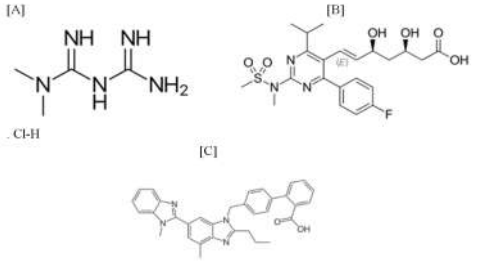


Fig 1 shows the structure of [A] Metformin, [B] Rosuvastatin calcium and [C] Telmisartan

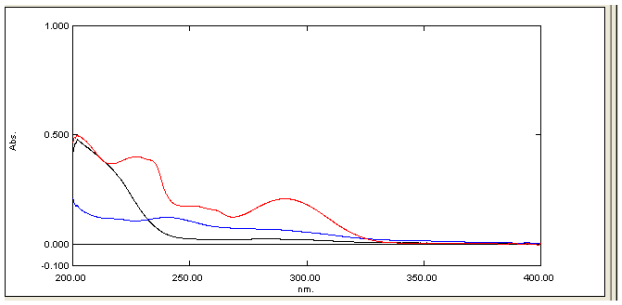


Fig 2 Overlain Spectra of Metformin, Telmisartan and Rosuvastatin

CONCLUSION

The results of present study indicate that the proposed UV spectrophotometric method is simple, rapid, precise and accurate. The developed UV spectrophotometric method was found suitable for determination of Metformin HCl, Rosuvastatin calcium and Telmisartan in mixture of bulk drug without any interference from the excipients. Statistical analysis proves that the method is repeatable and selective for the analysis of Metformin HCl, Rosuvastatin calcium and Telmisartan in combination. The spectrophotometric method requires only wavelength scan and automatic calculation of the first derivative value. It can therefore be concluded that the developed analytical method was precise & accurate and can be used for routine Analysis of these drugs in combination

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