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SIMULTANEOUS ESTIMATION OF METFORMIN AND ROSIGLITAZONE IN PHARMACEUTICAL TABLET FORMULATION

Mrityunjay Banarjee[1]* and Susant Kumar Behera[1]

Institute of Pharmacy & Technology, Salipur, Cuttack, Orissa.

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***Corresponding Author**
Dr. Mrityunjay Banarjee
Institute of Pharmacy & Technology, Salipur, Cuttack, Orissa.

ABSTRACT

Spectrophotometric method was developed for the simultaneous determination of metformin hydrochloride and rosiglitazone maleate using 0.01M hydrochloric acid. Quantitative determination of the drug was performed at the maximum absorption of 228 nm and 241 nm corresponding to metformin and rosiglitazone, respectively. The calibration curves showed good linearity in the range of 4 to 32 µg/ml for metformin and 4 to 32 µg/ml for rosiglitazone. The correlation coefficient (r) of calibration curves of each drug were higher than 0.988. The proposed method showed excellent precision and accuracy. As regards precision, this method showed CV values in the range of 1.12 to 1.30 and 3.13 to 3.52 for metformin hydrochloride and rosiglitazone maleate, respectively. The recoveries of formulations I and II were > 98% over the linear range. All the results of analysis were validated according to the International Conference on Harmonization (ICH) guideline. This method has been successfully used to determine metformin hydrochloride and rosiglitazone maleate content in marketed Formulation.

KEYWORDS: Simultaneous spectrophotometric method, Rosiglitazone, Metformiin.

INTRODUCTION

Combination therapy is effective approach to treat type 2 diabetes. Combination of rosiglitazone, an insulin-sensitizing thiazolidinedione drug, with metformin hydrochloride, a biguanide agent, greatly enhances the management of obese type 2 diabetic patients who are inadequately controlled by metformin hydrochloride alone. This combination improves glycemic control, insulin sensitivity and beta-cell function to a clinically important extent [Jones et al, 2003, Vivian et al, 2000]. Numerous analytical methods, such as spectrophotomery [Ashour et al, 2003, EL-Bardicy et al, 1989, Gomes et al, 2006], High

performance thin layer chromatography (HPTLC) [Ghassempour et al, 2006, Rao et al, 2003, Gaytri et al, 2003], high performance liquid chromatography (HPLC) [Radhakrishnan et al, 2002, Ceren et al, 2007, and capillary zone electrophoresis [Yardimci et al, 2005] has been reported for either metformin hydrochloride or rosiglitazone maleate. In the present investigation an attempt has been made to develop accurate and precise UV spectrophotometric method for the simultaneous estimation of metformin hydrochloride & rosiglitazone maleate formulated in tablets and bulk drugs. The method is suitable for drug monitoring and determination of pharmacokinetic profiles by using the proposed simultaneous equation.

EXPERIMENTAL

Materials

Spectrophotometer analysis was carried out on a Systronics 2201UV/Vis. double beam spectrophotometer with spectral bandwidth of 2 nm and a pair of 1cm quartz cells. Pure drug samples of metformin hydrochloride or rosiglitazone maleate were procured as a gift sample from Macllods Pharmaceuticals Pvt. Ltd., Mumbai and Cipla Limited, Mumbai. Tablets (Risicon-MF, Glenmark Pvt. Ltd.) and (Rosinorm-M, Micro Labs Ltd.) containing metformin hydrochloride (500 mg) and rosiglitazone (2 mg) were procured from local market.

METHODS

Preparation of Standard Stock Solution

Standard stock solution of MET and RZM were prepared separately by dissolving accurately weighed 25mg each of standard MET and RZM in 0.2M HCl to obtain the final concentration of 500 µg/ml of each drug. Working solutions for MET and RZM were prepared separately by further diluting the corresponding stock solutions with 0.01M HCl to obtain the final drug concentrations of 4-28 µg/ml and 4-32 µg/ml, respectively in Table 1. The optical data's are presented in Table 2.

Preparation of Mixture of MET and RZM Standard Solutions

Mixture of solutions, containing MET and RZM in the ratio 1:1, 3: 2, 2:1, 3: 4 in µg/mL concentration of MET : RZM, respectively were prepared by diluting a suitable aliquots of the standard stock solutions with 0.01M HCl. Data's are presented in Table 3.

Preparation and Analysis of Tablet Sample

Two formulations were selected, Risicon-MF (Formulation I) and Rosinorm-M (Formulation II). Twenty tablets were weighed, and crushed to a fine powder. Powder equivalent to 500 mg of MET and 2 mg of RZM was weighed and transferred in a 100 ml volumetric flask and dissolved in 0.01M HCl. The content was kept in ultrasonicator for 20 min. Finally the volume was made up to the mark with 0.01M HCl and filtered through Whatmann's filter paper No. 41. The filtered solution was suitably diluted with 0.01M HCl so that the concentration can be read directly from the calibration curve, and the absorbances were measured at 228 nm and 241 nm. Using the equation 1, 2, 3 and 4 concentrations were determined. The percent amount and standard deviation of both the formulations I and II were calculated. Results are presented in Table 4.

Simultaneous Equation Method [Davidson etal, 2001, Sahu et al, 2006. Dahivelkar et al, 2006]

Working standard solutions of MET and RZM were scanned in the range of 200 to 400 nm. The maximum absorbance of MET and RZM was observed at 228 nm and 241 nm, respectively. MET and RZM show linearity in absorbances in the concentration range of 4-28 µg/ml and 4-32 µg/ml at their respective maxima against 0.01M HCl as a reagent blank. Calibration curves for both the drugs were plotted separately at both the wavelengths i.e., 228 nm and 241 nm. Fig.1 and 2.

The absorptivities/specific absorbances were determined for both the drugs at both the wavelengths and the average value was taken.

Absorbances of mixture solutions and tablet solutions were measured at 228 nm and 241 nm. Two simultaneous equations were developed using absorptivity coefficient values. Data's are presented in Table 5.

$A_1 = 471.89\ C_M + 267.11\ C_R$ ---------- (1)

$A_2 = 248.21\ C_M + 399.18\ C_4$ ---------- (2)

Where C_M and C_R are the concentrations of MET and RZM, respectively in g/100ml, in the sample solutions, A_1 and A_2 are the absorbances of mixture at selected wavelengths of 228 nm and 241 nm, respectively. 471.89 and 248.21 are the absorptivity values of MET and 267.11 and 399.18 are the absorptivity values of RZM at 228 and 241 nm, respectively.

By applying vierodt's method [16-18] to equation 1 and 2, the connotation C_M and C_R can be obtained as follows:

$C_{MET} = A_2 (267.11) - A_1 (399.18) / -1214.97$ --------- (3)

$C_{RZM} = A_1 (248.21) - A_2 (471.89) / -1214.97$ --------- (4)

Validation of Method

The method was validated in terms of linearity, accuracy, precision, specificity and reproducibility of the sample applications. The linearity of the method was investigated by serially diluting the stock solution of MET and RZM and measuring the absorbance values at 228 nm and 241 nm. Calibration curves were constructed by plotting absorbances against concentrations of drug in μg/ml.

For validity and reproducibility of the proposed method, recovery studies were carried out. A known amount of the standard drug was added to pre-analyzed tablet solution sample, at three levels (80%, 100%, 120%) and the resulting solutions were analyzed by the proposed method. Percentage recoveries were calculated.

Repeatability is established by inter-day and intra-day precision. Intra-day precision was determined by analyzing, the three different concentration of drug for three times on the same day. Inter-day precision was determined by analyzing the three different concentration of the drug for three days in the same week.

Ruggedness of the proposed method is determined by analyzing the aliquots from homogenous slot in different laboratories of different analyst using similar operational and environmental conditions.

RESULTS AND DISCUSSION

The spectrophotometric analysis was performed at the wavelength of 228 nm for MET and 241 nm for RZM. The calibration curves showed good linearity in the range of 4 to 28 μg/ml for MET and 4 to 32 μg/ml for RZM. The correlation coefficients of calibration curves of each drug were higher than 0.988 as determined by least square method. The recovery was studied at concentration of 80%, 100% and 120% of the target level in tablets. It is evident from Table 4 that the percentage recoveries from the analyzed formulations were in the range of 98.11 to 99.56 and 98.01 to 99.48 for MET and RZM, respectively. This indicates that the

method is accurate, reproducible and the commonly used excipients and additives, which are present in the formulation, did not interfere at their regularly added levels.

Tablet analysis results are in good agreement with the label claim for both the commercial formulations I and II. It is evident from Table 4 that the amount of MET and RZM present in both the formulations I and II is not less than 99.51% and 97.52%, respectively. Percentage RSD results of mixture analysis are presented in Table 3. RSD data values are not more than 0.23% and 0.31% for MET and RZM, respectively.

Inter-day and intra-day variation study demonstrated precision of the method. Drug samples were analyzed at three different concentrations. The inter-day and intra-day % RSD value was calculated and found to be lying within the range 0.382-0.419 for MET and 0.374-0.561 for RZM.

The system suitability studies were carried out. The values obtained are well within the specified limits. Ruggedness of the proposed method was determined with the help of two analysts. The RSD values ranged from 0.240 to 0.314% for MET and 0.250 to 0.282% for RZM.

Table 1: Range of Calibration Curves of MET and RZM.

Metformin(MET) (µg/mL)	Metformin Absorbances	Rosiglitazone (RZM) (µg/mL)	Rosiglitazone Absorbances
4	0.186	4	0.158
8	0.376	8	0.319
12	0.564	12	0.481
16	0.758	16	0.636
20	0.942	20	0.796
24	1.134	24	0.955
28	1.320	28	1.118
32	1.498	32	1.259

Table 2: Optical Characteristics and Precision.

Parameters	MET	RZM
Absorption maximum (nm)	228	2401
Beer's law limit (µg/ml)	4-32	4-32
Absorptivity	471.89	399.18
Sand ell's sensitivity (µg/cm^2/0.001)	0.0211	0.022
Molar absorptivity (1$mole^{-1}$,cms^{-1})	$7.799*10^3$	$1.4253*10^4$
Correlation coefficient (r^2)	0.988	0.988
Regression equations (Y^*)	Y= 0.047X+0.0014	Y= 0.0396X +0.0031
Slope (a)	0.048	0.037
Intercept (b)	0.001	0.003

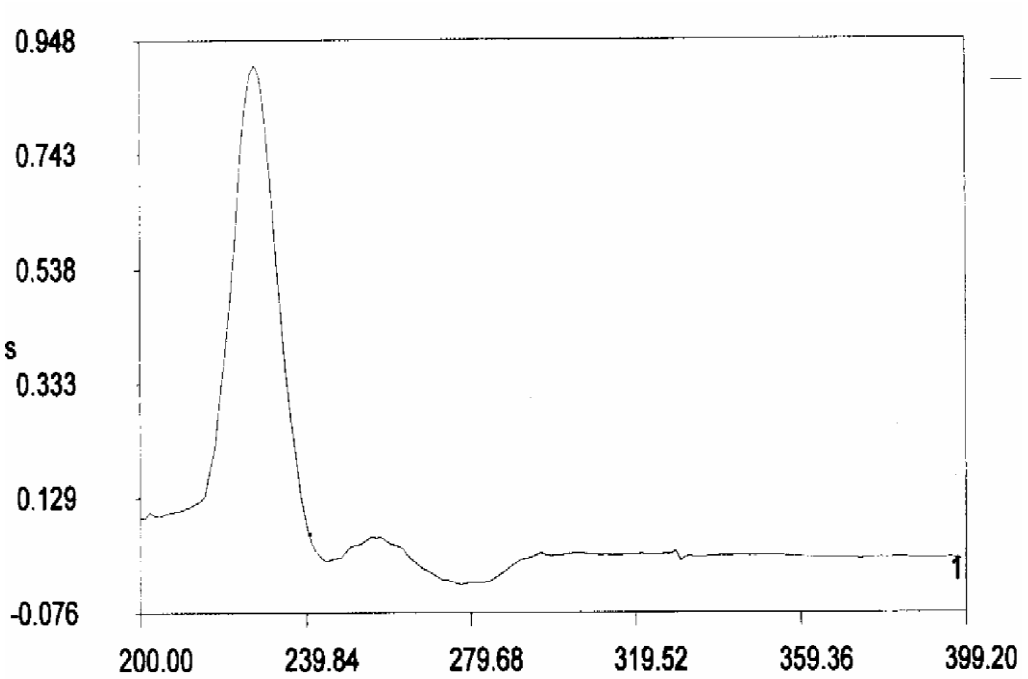

Figure 1: Spectra of Metformin Hydrochloride in 0.01M Hydrochloric acid.

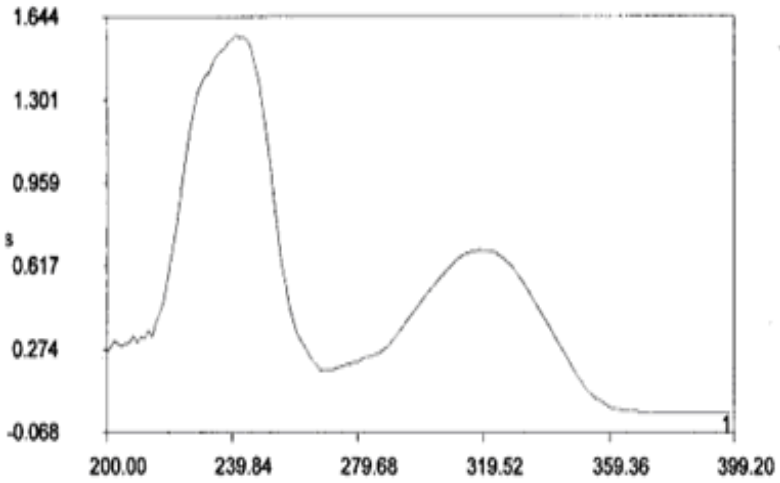

Figure 2: Spectra of Rosiglitazone Maleate in 0.01M Hydrochloric acid.

Table 3: Analysis of Mixtures with Different Strengths of MET and RZM.

Sl.No.	Mixture (µg/mL)		Conc. found (µg/mL) Mean		*% Amount found (µg/mL) Mean ± S.D.		% RSD	
	MET	RZM	MET	RZM	MET	RZM	MET	RZM
1	8	8	7.97	7.98	99.62±0.21	99.75±0.324	0.212	0.325
2	12	8	11.99	8.00	99.91±0.15	100.09±0.27	0.151	0.270
3	16	8	15.96	8.00	99.75±0.16	100.05±0.19	0.162	0.195
4	12	16	11.98	15.98	99.83±0.09	99.87±0.247	0.098	0.246
5	8	12	7.99	12.01	99.87±0.13	100.08±0.15	0.130	0.158

*Each value is average of three determinations ± standard deviation

Table 4: Results of Analysis of Tablet in Commercial Formulations Rosicon-MF and Rosinorm-M.

Formulation	Labeled Amount (mg/tab)		Amount obtained* (mg/tab)		% Drug present		% RSD	
	MET	RZM	MET	RZM	MET	RZM	MET	RZM
Rosicon-MT	500	2	496.20±0.273	1.95±0.12	98.11	98.01	0.272	0.127
Rosinorm-M	500	2	496.60±0.294	1.98±0.14	98.56	99.48	0.294	0.152

*Each value is average of three determinations ± standard deviation

CONCLUSIONS

Simultaneous equation method is a suitable technique for the reliable analysis of commercial formulations containing combination of metformin hydrochloride and rosiglitazone maleate. The proposed simultaneous equation method is simple, sensitive and reliable with good precision and accuracy. This method is specific while estimating the commercial formulations without interference of excipients and other additives as evident from the high percentage recovery. Hence this method can be used for the simultaneous determination of metformin hydrochloride and rosiglitazone maleate. in combined pharmaceutical formulations.

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