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Simultaneous Spectroscopic Estimation by Ratio Derivative Method of Metformin Hydrochloride and Gliclazide in Uncoated Bilayered Extended Release Combined Solid Dosage Form and its Application to Dissolution Studies

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Shraddha S. Ghodke

Department of Pharmaceutical Chemistry, Maharashtra Institute of Pharmacy, Faculty of Pharmacy, University of Pune, Maharashtra, India

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ABSTRACT

A simple, rapid, precise & efficient UV Spectroscopic method for simultaneous analysis of metformin hydrochloride and gliclazide in extended release combined tablet solid dosage form has been developed and validated. Practically no interference from tablet excipients was observed in these developed methods. As their λmax does not differ more than 20 nm, (232 nm for Metformin Hydrochloride and 229.5 nm for Gliclazide); hence, absorption corrected method was tried for their simultaneous estimation in extended-release tablet formulation. Quantitative estimation of GLZ was carried out by subtracting interference of MTF using experimentally calculated absorption factor. Both the methods are accurate, simple, rapid, precise, reliable, sensitive, reproducible and economical as per ICH guidelines. The values of % RSD and correlation of coefficient were satisfactory and results of the formulation analysis and result of the recovery study indicate that there is no interference due to excipients present in the formulation. It can be easily and conveniently adopted for routine quality control analysis. The absorption corrected method was successfully applied for the dissolution study. Validation revealed the dissolution method is specific, rapid, accurate, precise, reliable and reproducible.

INTRODUCTION

Literature survey reveals that HPLC and UV Spectroscopic methods are reported for the estimation of MTF and GLZ individually or in combination with other drugs as bulk and in pharmaceutical formulations as described previously in literature survey. The review of the literature revealed that there is no Spectrophotometric ratio derivative method available for determination of this combination. Therefore the aim of the study was to develop simple, rapid, accurate, reproducible and economical spectroscopic methods for both the drugs in combined dosage forms. The proposed methods were optimized and validated as per the International Conference on Harmonization (ICH) analytical method validation guidelines**.**

EXPERIMENTAL

Instrumentation:

A UV-Visible double beam spectrophotometer (Varian Cary 100) with 10 mm matched quartz cells was used. All weighing was done on an electronic balance (Model Shimadzu AUW-220D). Dissolution apparatus (USP II) paddle was used for Dissolution study.

Reagents and chemicals:

Pure drug sample of MTF HCl, % purity 98.80 and GLZ, % purity 99.92 was kindly supplied as a gift sample by Serdia Pharmaceuticals Ltd. Mumbai. These samples were used without further purification. Two tablet formulations Batch no. 191101, 191102, 191103 were supplied by Serdia Pharmaceuticals, Mumbai was used for analysis containing Metformin Hydrochloride IP (extended release) 500 mg and Gliclazide IP (extended release) 60 mg per tablet. Spectroscopy grade methanol was used throughout the study. All the solvents and reagents used were purchased from LOBA Chemie Pvt. Ltd., Thomas Baker Pvt. Ltd. and Rankem Laboratories, Mumbai.

Preparation of Standard Stock Solutions and Calibration Curve:

Standard stock solutions of both the drugs containing 1mg/ml were prepared separately in the methanol and 0.1N HCl for Method A and B, respectively. The

working standard solutions of these drugs were obtained by dilution of the respective stock solution in the methanol for Method A and distilled water for Method B. Ratio Derivative amplitudes of a spectrum, by using the below-mentioned procedures, were used to prepare calibration curves for both the drugs by Ratio derivative method. Absorbance values were measured at selected wavelengths for absorbance corrected method and were used to construct calibration curves. Beer's law obeyed in the concentration range of 50-250 µg/ml for MTF and 6-30 µg/ml for GLC for both the methods.

Preparation of Sample Stock Solution and Formulation analysis:

Twenty tablets were weighed accurately and a quantity of tablet powder equivalent to (500mg of MTF & 60 mg of GLC) was weighed and dissolved in the 80 ml of solvent with the aid of Ultrasonicator for 15 min and the solution was filtered through Whatman paper No. 41 into a 100 ml volumetric flask. The filter paper was washed with the solvent, adding washings to the volumetric flask and volume was made up to mark. The solution was suitably diluted with solvent to get of 500µg/ml of MTF & 60 µg/ml of GLC.

PROCEDURE

METHOD A: RATIO DERIVATIVE SPECTROPHOTOMETRIC METHOD

Theoretical aspects:

The method involves dividing the spectrum of mixture by the standardized spectra of each of the analytic to get ratio spectra and the first derivative of ratio spectrum was obtained which was independent of the concentration of divisor (Fig.1).

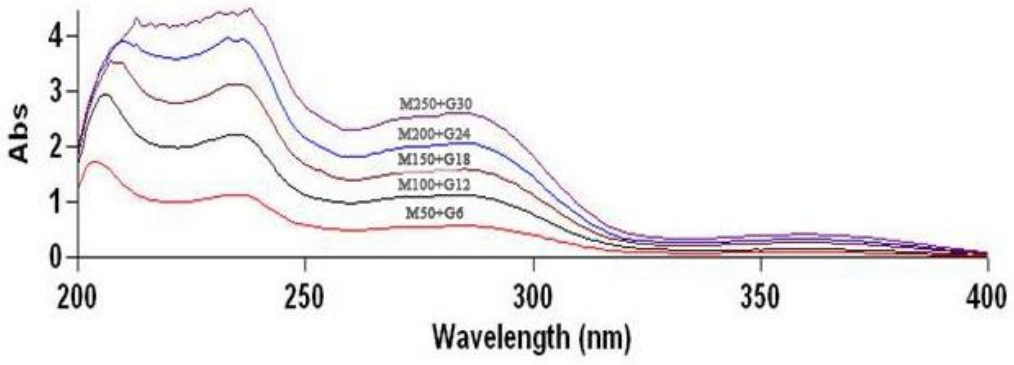

Fig 1: Spectrum of mixture of MTF and GLC for ratio derivative method

The concentration of active compounds is then determined from calibration graph obtained by measuring amplitude at points corresponding to minima or maxima. Using appropriate dilutions of the standard stock solution, the two solutions were scanned separately. The ratio spectra of different MTF standards at increasing concentrations were obtained by dividing MTF+GLC scans with the stored spectrum of the standard solution of the formulation (18µg/ml) (Fig.1A).

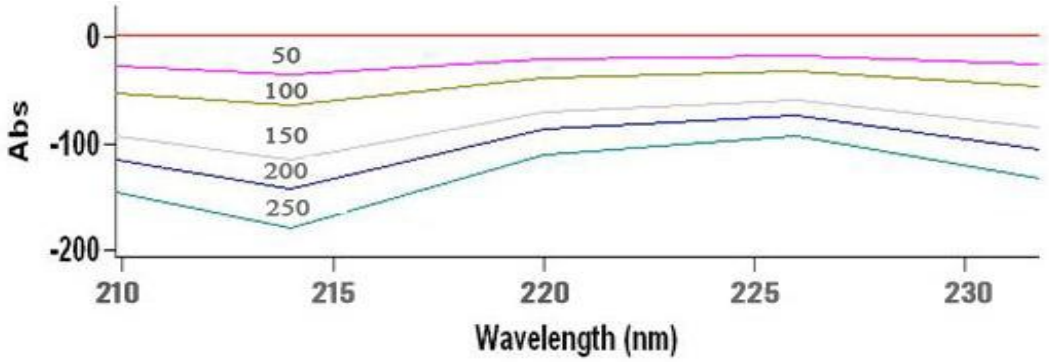

Fig. 1(A) Ratio spectra of MTF using 18µg/ml solution of GLC as divisor

Wavelength 215.71 nm was selected for the quantification of MTF in MTF+GLC mixture (Fig.1B).

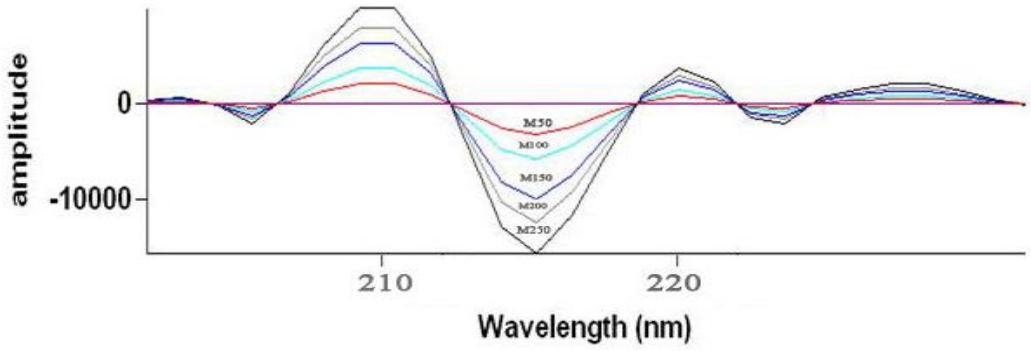

Fig. 1(B) First derivative of the ratio spectra of MTF (50-250µg/ml)

The ratio and ratio derivative spectra of the solutions of GLC at different concentrations were obtained by dividing MTF+GLC scans with the stored standard spectrum of the MTF (150µg/ml) (Fig.1C and 1D, respectively).

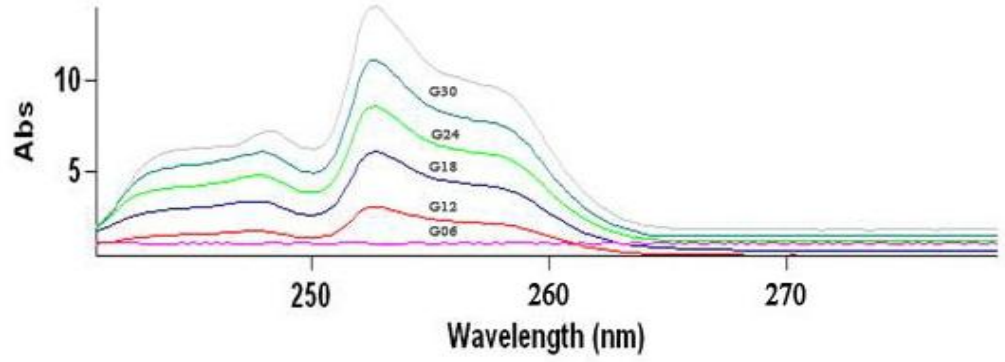

Fig. 1(C). Ratio spectra of GLC using 150µg/ml solution of MTF as divisor

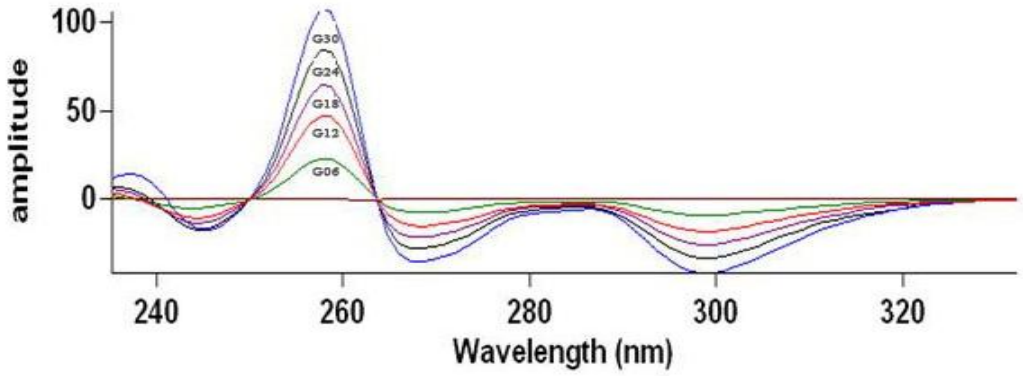

Fig.1 (D) First derivative of the ratio spectra of GLC (6-30µg/ml)

Wavelength 244.17 nm was selected for the quantification of GLC in MTF+GLZ mixture. Measured analytical signals at the selected wavelengths were proportional to the concentrations of the drugs. Calibration curves were prepared from the measured signals at the selected wavelength and concentration of the standard solutions.

The amount of MTF (C_{MTF}) and GLC (C_{GLC}) in tablets was calculated by using following equations-

At 215.71nm: C_{MTF} = (Ratio derivative amplitude for MTF- 0.055)/ 0.641.... (1)

At 244.17nm: C_{GLC} = (Ratio derivative amplitude for GLC - 0.68)/ 0.764.… (2)

METHOD B: ABSORPTION CORRECTED METHOD:

λ_{max} of MTF and GLC was determined by scanning the drug solution in the solvent was found to be at 257.71 nm and 223.19 nm respectively. MTF also showed absorbance at 223.19 nm, while GLC did not show any interference at 257.71 nm. To

construct Beer's plot for MTF and GLC dilutions were made in the solvent using stock solution of100 µg/ml. Also Beer's plot was constructed for MTF and GLC in solution mixture at different concentration (50:6, 100:12, 150:18, 200:24, 250:30µg/ml) levels. Both the drugs followed linearity individually and in the mixture of the concentration range 50-250µg/ml and 6-30µg/ml for MTF and GLC respectively (Fig.2).

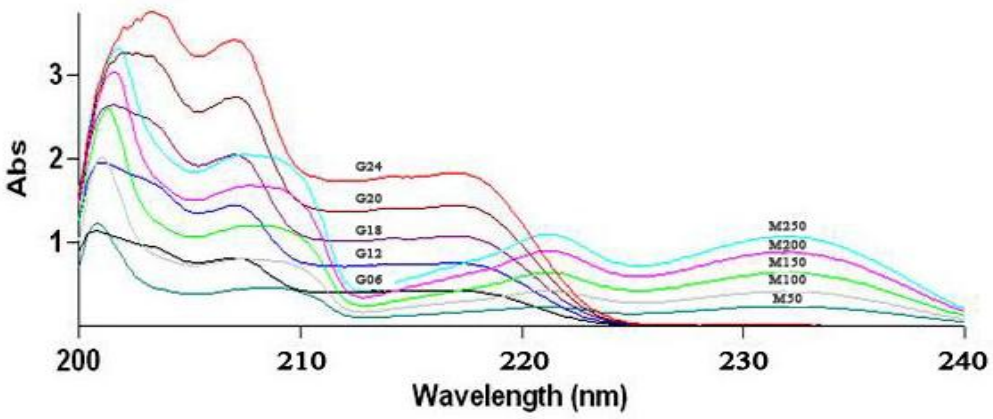

Fig. 2 Overlay spectrum of MTF and GLC. MTF (50-250µg/ml) and GLC (6-30µg/ml)

Determination of Absorption Factor at Selected Wavelengths:

MTF and GLC solution in the solvent of known concentrations were scanned against blank on a spectrophotometer. The value of absorption factor was found to be 1.266.

Quantitative estimation of MTF and GLC was carried out using following equation:

Corrected Absorbance of GLC at 213.19nm = $Abs_{223.19}$ (MTF+GLC) – [($abs_{213.19}$ (MTF)/ $abs_{257.71}$ (MTF)] × $abs_{257.71}$ (MTF)

or

Corrected Absorbance of GLC at 213.19nm = $abs_{213.19}$ (MTF+GLC) – 1.266 × $abs_{257.71}$ (MTF)

Where; abs: Absorption value at given wavelengths.

Dissolution Studies:

The dissolution study was carried out for the above combination and was validated. A calibrated dissolution apparatus (USP II) paddle 60 rpm & bath temp at 37±1^{o}C. Nine hundred ml freshly prepared and degassed 0.1N HCl solution was used as the dissolution medium. Six tablets were evaluated and dissolution sample was collected at 5, 10, 15, 20, 25, 30, 35, 40 min interval. At each time point, a 5mL sample was removed from each vessel sample, filtered through a nylon filter (0.45µm, 25 mm), 1.8 mL of filtrate was diluted to10 mL with distilled water and analyzed by absorption corrected method (Fig. 8.3), percentage release of MTF and GLC was calculated by using equations 3 and 4, respectively.

MTF % release = (C_{MTF}× 900×10×100)/ (1000×500) … (3)

GLC % release = (C_{GLC}× 900×10×100)/ (1000×60) … (4)

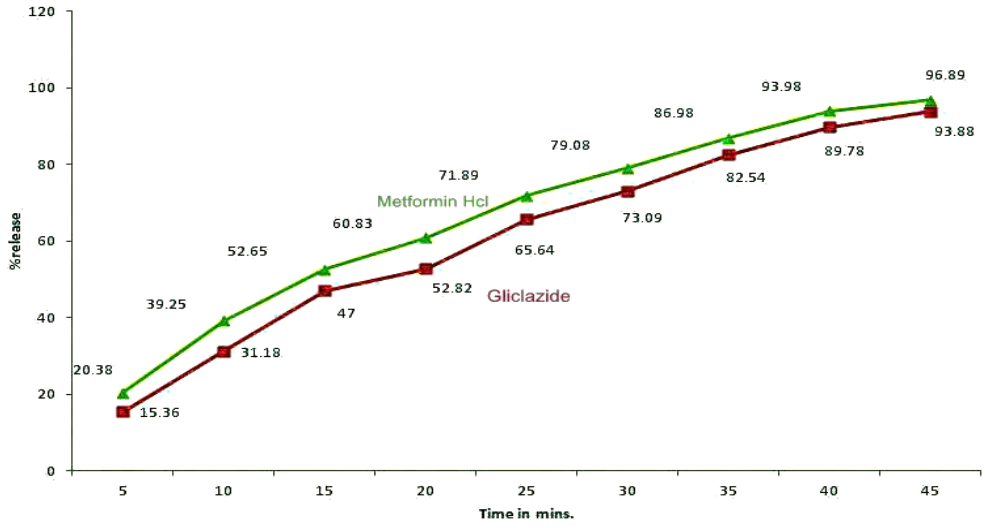

Fig.3 Dissolution study of MTF and GLC by Absorption corrected method.

Recovery Studies:

The accuracy of the proposed methods was checked by recovery study, by addition of standard drug solution to pre-analyzed sample solution at three different concentration levels (50 %, 100 %, and 150 %) within the range of linearity for both the drugs. The basic concentration level of sample solution selected for spiking of the

drugs standard solution was 70 µg/ml of MTF and 82.5 µg/ml of GLC for both the methods.

The precision of the Method:

To study intraday precision, the method was repeated 5 times in a day and the average % RSD was calculated by method A and B, respectively. Similarly, the method was repeated on five different days and average % RSD was calculated. These values confirm the intra and inter-day precision.

RESULTS AND DISCUSSION:

Practically no interference from tablet excipients was observed in these methods. As their λmax doesn't differ more than 20 nm, absorption corrected method was tried for their simultaneous estimation in formulation. Quantitative estimation of GLC was carried out by subtracting interference of MTF using experimentally calculated absorption factor. Both the methods are accurate, simple, rapid, precise, reliable, sensitive, reproducible and economical as per ICH guidelines. The values of % RSD and correlation of coefficient were satisfactory and results of the formulation analysis (Table no.1) and result of the recovery study (Table no.2) indicates that there is no interference due to excipients present in the formulation. It can be easily and conveniently adopted for routine quality control analysis. The absorption corrected method was successfully applied for the dissolution studies.

Table 1: Optical characteristics of the proposed methods and the results of Formulation analysis and Precision (% RSD)

PARAMETER		METFORMIN HCL		GLICLAZIDE	
		METHOD A	METHOD B	METHOD A	METHOD B
(NM)		230.91	260.90	228.19	249.10
BEER'S LAW LIMIT (MG ML^{-1})		50-250	50-250	6-30	6-30
REGRESSION EQUATION (Y = MX + C)	SLOPE (M)	0.641	0.026	0.764	0.0005
	INTERCEPT (C)	0.055	0.006	0.680	-0.005
CORRELATION COEFFICIENT		0.999	0.999	0.999	0.998
PRECISION (% R.S.D.)	REPEATABILITY (N=5)	0.76	0.96	1.09	0.92
	INTRA-DAY(3×3 TIMES)	0.58	0.98	1.19	0.95
	INTER-DAY(3×5 DAYS)	0.65	0.82	1.02	0.93
FORMULATION ANALYSIS (% ASSAY, % RSD) N=6	FORMULATION (A)	99.01, 0.89	99.12, 1.12	99.55, 1.06	99.54, 1.04
	FORMULATION (B)	99.86, 0.63	99.74, 0.93	99.64, 0.55	99.69, 0.65

Table 2: Result of recovery analysis.

Formulation	Recovery Level (%)	Weight spiked		Weight recovered		Recovery (%)		R.S.D. (%) n = 3	
		MTF	GLC	MTF	GLC	MTF	GLC	MTF	GLC
Formulation (A)	50	6	6.25	5.96	6.23	99.96	99.68	0.52	0.58
	100	12.0	13.5	12.01	13.54	99.76	99.12	0.57	0.86
	150	18.0	19.75	17.82	19.71	99.56	99.98	0.69	0.88
Formulation (B)	50	6.0	6.25	5.99	6.24	99.93	99.96	0.59	0.68
	100	12.0	13.5	11.98	13.46	99.83	99.70	0.58	0.78
	150	18.0	19.75	18.02	19.72	100.01	99.84	0.73	0.86

CONCLUSION

The proposed methods are simple, precise, accurate, economical and rapid for the determination of MTF and GLC in combined tablet dosage forms. Analysis of authentic samples containing MTF and GLC showed no interference from the

common additives and excipients. Hence, the recommended procedure is well suited for the assay and evaluation of drugs in pharmaceutical preparations. It can be easily and conveniently adopted for routine quality control analysis and Absorption corrected method was successfully applied for dissolution study.

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