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DEVELOPMENT AND VALIDATION OF STABILITY INDICATING RP-UFLC METHOD FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND METFORMIN HCl

Chaitali Uday Tirodkar, Mahesh Shivabasappa Palled *, Mahendra Kumar Chauhan, Shailendra Sanjay Suryawanshi, Suryamala Majukar and Sunil S. Jalalpure

Department of Pharmaceutical Chemistry, KLE College of Pharmacy, JNMC Campus, Nehru Nagar, Belagavi - 590010, Karnataka, India.

Keywords:

Telmisartan, Metformin HCl, RP-UFLC, Validation, ICH guidelines, Stability indicating

Correspondence to Author:
Palled Mahesh Shivabasappa

Department of Pharmaceutical Chemistry, KLE College of Pharmacy, JNMC Campus, Nehru Nagar, Belagavi - 590010, Karnataka, India.

E-mail: drpalled@gmail.com

ABSTRACT: A Simple, sensitive, precise, and stability-indicating method was developed for the simultaneous estimation of Telmisartan & Metformin HCl in bulk & prepared formulation. The column used for the separation was Phenomenex C18 (150 × 4.6, 5 µ), with a mobile phase containing Phosphate buffer pH 3.6 & acetonitrile (30:70% v/v) at a flow rate of 0.5 ml/min. The retention time of Telmisartan was 6.098 min & Metformin HCl was 2.828 min, respectively. The detection of drugs was carried out at 249 nm. The linearity was carried out at 10-60 µg/ml for Telmisartan & Metformin HCl, in bulk and prepared tablet dosage form. LOD and LOQ were calculated as 0.773 µg/ml and 1.286 µg/ml for Telmisartan, 2.345 µg/ml, and 3.898 µg/ml for Metformin HCl. The drugs were stressed in conditions such as Acidic, Basic, Thermal, Photolytic, and oxidative conditions. All the developed parameters were within the acceptance criteria of ICH guidelines. The developed method was simple, precise, specific, robust and rapid for the quality control analysis for simultaneous determination of Telmisartan & Metformin HCl, respectively.

INTRODUCTION: Telmisartan is an angiotensin receptor blocker drug used in the treatment of hypertension. IUPAC name is [4-[4-methyl-6-(1-methylbenzimidazol-2-yl) -2- propylbenzimidazol-1yl] methyl] phenyl] benzoic acid [1]. Metformin is a biguanide used in the treatment of diabetes mellitus. IUPAC name of drug is 3-(diamino-methylidene)-1,1dimethylguanidine; hydrochloride [2].

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Literature survey stated that there are many analytical methods available for Telmisartan & Metformin HCl alone and in combination with other drugs. Only the RP-HPLC method has been reported for simultaneous estimation of Telmisartan & Metformin HCl & also, there is no combined dosage form is available in the market [5, 6]. Till date, there is no single stability-indicating RP-UFLC method was reported.

Advantage of combined formulation of Telmisartan & Metformin Hydrochloride is, Telmisartan act as an adjunct to the Metformin; it helps to prevent ischemic heart diseases in diabetes patient. It also helps in the activation of the peroxisome proliferator-activated-γ receptor (PPAR- γ), which helps to regulate insulin & glucose metabolism.

Hence to improve the glucose metabolism & vascular blood pressure Telmisartan is given along with Metformin Hydrochloride [6].

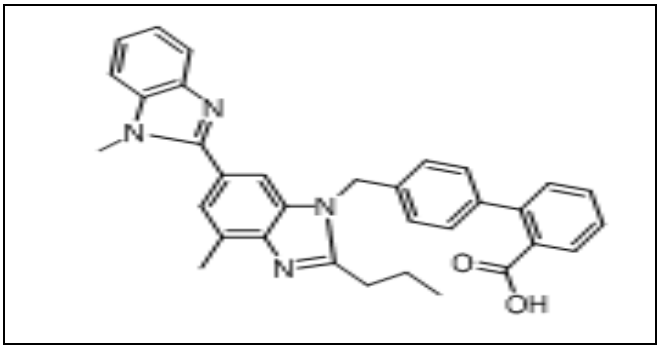

FIG. 1: TELMISARTAN

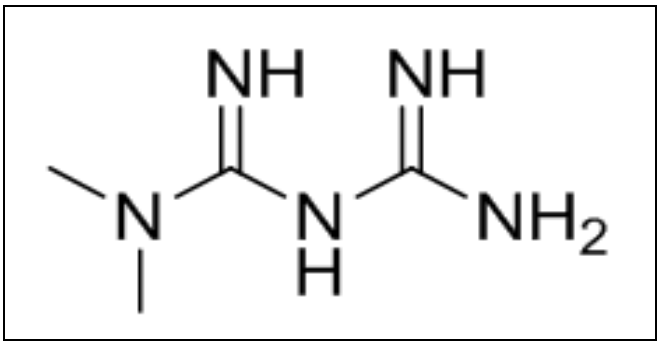

FIG. 2: METFORMIN HCl

Objective of Study: The objectives of present research work are to to develop a simple, fast, robust, specific develop RP-UFLC method for simultaneous estimation of Telmisartan & Metformin HCl in bulk drugs & newly formulated tablet dosage form & to validate the methods according to the ICH guidelines [3].

MATERIALS & METHODS:

Reagent & Chemicals: The pure API with 98.8% purity were supplied from FDC PVT LTD -Verna goa.

The HPLC grade Merck company Methanol and Acetonitrile were supplied from the chemical storeroom of KLE College of Pharmacy, Belagavi.

TABLE 1: DEVELOPED CHROMATOGRAPHIC PARAMETERS

Mobile phase	Phosphate buffer pH 3.62 &Acetonitrile(30:70VV)
Flow rate	0.5 ml/min
Column temperature	30 ℃
Column	(150 × 4.6,5µ)
Pump	Reciprocating pump
Injection volume	10 µl
Detection wavelength	249 nm
Diluent	Methanol

Instrument and Software: A UFLC- Shimadzu Prominent-LC 20AD instrument & Lab solution software was used. The autosampler injector with reciprocating pump. A PDA detector was used. The weighing balance was used was unibloc & the Ultrasonicator was branson-1800. The chromato-graphic conditions of the developed method were specified in **Table 1** and Chromatogram in **Fig. 5**.

METHODS:

Preparation of solutions:

Standard Stock-1 Preparation: Accurately weighed 10 mg of pure API Telmisartan & Metformin HCl & transferred in 10 ml volumetric flask separately to get the concentration of 1000 µg/ml.

Standard Stock-2 Preparation: Working standard solution was prepared in the concentration of 10 µg/ml from stock 1 solution of Telmisartan & Metformin HCl, respectively.

Preparation of Mobile Phase: 3.4 gm of potassium dihydrogen orthophosphate in 500 ml HPLC grade Millipore water to get the solution of 0.02 M phosphate buffer and acetonitrile HPLC grade filtered through PTFE filter. The buffer solution was filtered & degassed for 15 min.

Formulated Tablet Design:

TABLE 2: DESIGN OF FORMULATION

S. no.	Drugs/ Excipients	Amount
1	Metformin HCl	250mg
2	Telmisartan	20mg
3	Crospovidone	30mg
4	MCC (102)	56mg
5	Mannitol	40mg
6	Talc	2mg
7	Magnesium stearate	2mg
8	Total weight	400mg

The fast-dissolving action was formulated using various super disintegrants by the direct compression method. The assay & accuracy were performed from the formulated tablets [10, 11.]

Assay of Formulated Tablet: 10 tablets were weighed & weighed equivalent to 10mg of Telmisartan & Metformin HCl were transferred in a 25 ml volumetric flask. The half quantity methanol was added & sonicated for 20min. The volume was adjusted up to the mark with the solvent & mixed well. The solution was filtered

through a 0.45 µ nylon filter. The final concentration were made 40 µg/ml of Telmisartan & 40 µg/ml of Metformin HCl. Each 10 µl solution was injected in the system (n=3) as the same chromatographic condition as described above. From the peak area of the Telmisartan & Metformin HCl, the % Assay and Accuracy were calculated. The data were presented in **Tables 6** and **9**.

RESULTS AND DISCUSSON:

Method Validation: The developed method was validated in terms of Linearity, System suitability, Precision, Ruggedness, Robustness, Stability, *etc.* as per the ICH guidelines [4].

Linearity: The working stock solution was prepared by aliquots of stock solution in the concentration range from 10-60 µg/ml for Telmisartan & Metformin HCl. The solutions were injected in triplicates & the mean value of peak areas were taken. The calibration curve was plotted and coefficient correlation (r^2) was determined. The regression equation for Telmisartan was Y = 12689x - 16844 & Y = 8787.6x + 57079 for Metformin HCl. The correlation coefficient was 0.999 for both drugs. The result of linearity is mentioned in **Fig. 3** and **4**.

System Suitability: The system suitability parameter was determined by injecting six replicates of working standard. The retention time, theoretical plates, tailing factor were determined in **Table 3**.

Precision: The precision was determined in terms of Intraday & Interday precision. The precision was carried out in triplicates & results showed good reproducibility with % RSD less than 2%. The results were shown in **Table 4**.

Ruggedness: It was performed by a change in analyst & instrument within the laboratory or in a different laboratory & instrument. The results showed not much deviation with % RSD less than 2% denoted in **Table 5**.

Robustness: Robustness was performed by a small variation in the chromatic conditions.

The conditions are changed in mobile phase composition, change in flow rate, change in wavelength, change in temperature, and change in pH. It was observed that there is no much difference found in the results. **Table 8** can conclude that the proposed method is robust.

Stability: Stability was carried out in Freeze and in bench conditions at 24, 48, and 72 h study in stable condition. **Table 10** shows the better stability condition.

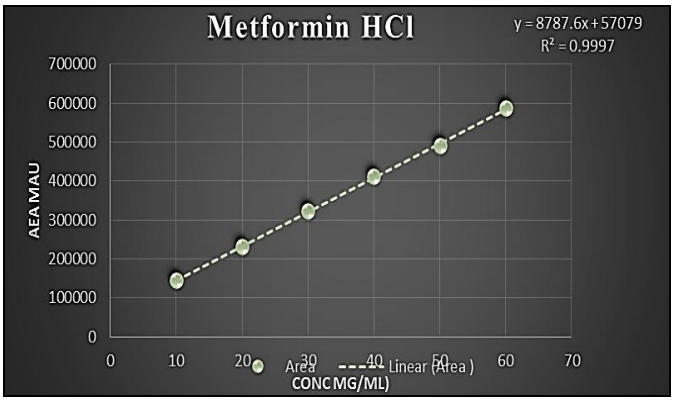

FIG. 3: LINEARITY GRAPH OF METFORMIN HCL

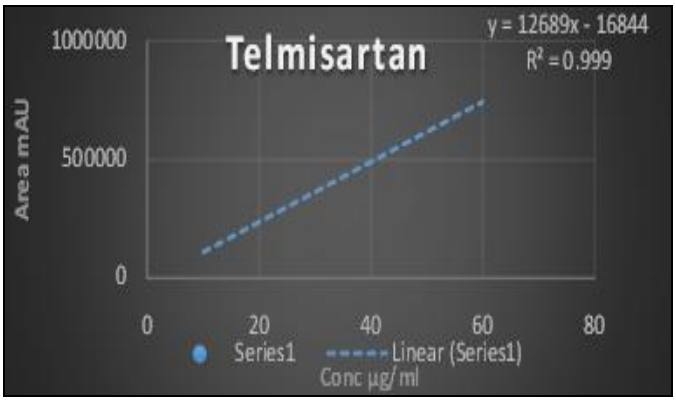

FIG. 4: LINEARITY GRAPH OF TELMISARTAN

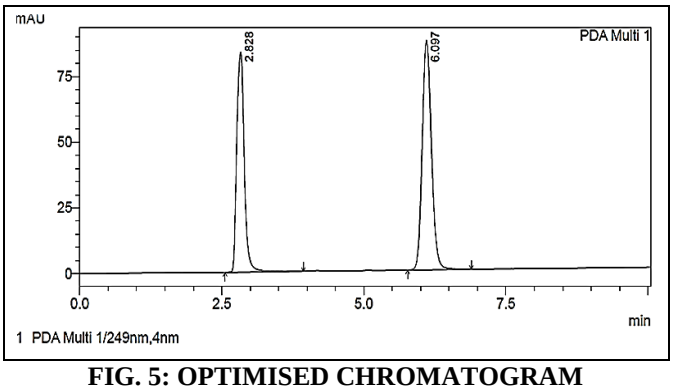

FIG. 5: OPTIMISED CHROMATOGRAM

TABLE 3: SYSTEM SUITABILITY DATA

Parameters	Metformin HCl	Telmisartan
Retention time	2.826	6.098
Theoretical plates	2763	4630
Tailing factor	1.297	1.193
Resolution	-	11.886

n=6

TABLE 4: PRECISION DATA

Precision	Telmisartan (% RSD)			Metformin HCl (% RSD		
	Metformin LOD= 2.345 µg/ml			Metformin LOQ=3.898 µg/ml		
Intraday	1st hr-0.48	2nd hr-0.79	3rd hr-0.41	1st hr-0.8	2nd hr-1.4	3rd hr-0.46
Interday	Day 1-1.39	Day 2- 1.05	Day 0.43	Day 1-0.86	Day 2- 0.61	Day 3-0.58

TABLE 5: RUGGEDNESS DATA

Parameter	Telmisartan (% RSD)	Metformin HCl (%RSD)
Analyst 1	0.56	0.80

TABLE 6: ASSAY DATA

Name	% Assay
Telmisartan	102.99%
Metformin HCl	103.55%
Average weight	399.41 mg
Metformin HCl	250 mg
Telmisartan	20 mg

Forced Degradation Study: Forced degradation study was performed to determine the chemical stability of the compound in various conditions. The study was carried out at 80 ˚C because at 60˚C forced degradation does not occur. The study was performed in acidic, basic, thermal, photolytic & oxidation condition using 0.1NHCl, 0.1N NaOH, Hot air oven, UV chamber & 30% H_2O_2 [8, 9]. The data of forced degradation were presented in **Table 11**.

TABLE 7: LOD &LOQ

Analytes	LOD	LOQ
Telmisartan	0.773	1.286

TABLE 8: ROBUSTNESS DATA

Parameters	Telmisartan			Metformin		
	RT	Peak area	% RSD	RT	Peak area	% RSD
Change in composition (35:65)	6.469	656676	0.46	2.754	470032	0.7
Change in wavelength at 251 nm (±)	6.078	679393	0.49	2.789	606286	0.74
Change in pH 3.62 ± 0.02	6.085	644715	0.19	2.791	456545	0.05
Change in Temperature 35℃ (±5)	5.84	645637	0.38	2.792	477593	0.46
Change in flow rate ± 2 (0.52 ml/min)	5.84	620448	0.32	2.68	457353	0.35

TABLE 9: ACCURACY DATA

Metformin HCl Accuracy						
Level	Std. Conc.	Sample conc	Total conc.	Sample Area	Obtained conc.	%Recovery
50	40	20	60	453361	56.50	94.21
100	40	40	80	478299	79.50	99.39
150	40	60	100	502922	104.50	104.50
Telmisartan Accuracy						
50	40	20	60	510851	57.09	95.00
100	40	40	80	541904	80.75	100.93
150	40	60	100	573483	106.81	106.81

TABLE 10: STABILITY DATA

Bench Study	Metformin HCl		Telmisartan	
	Average	% RSD	Average	% RSD
24	396810	1.126	412354.7	0.590
48	374957.3	1.037	403897.3	0.839
72	341580	0.143	375561.7	0.314
FreezeStudy	Average	% RSD	Average	% RSD
24	40421.7	0.333	467366.3	0.348
48	361562	0.650	436375.7	0.112
72	356589.7	1.480	426452.7	0.501

TABLE 11: FORCED DEGRADATION STUDY

Conditions	Telmisartan			Metformin		
	Initial	Final	%degradation	Initial	Final	%degradation
Acid	1196027	1059623	11.40	776503	656302	15.47
Base	707868	613946	13.26	486201	405901	16.51
Thermal	1289201	1146359	11.07	1059241	929951	12.20
Oxidation	991635	921985	7.02	994182	856149	13.88
Photolytic	891659	881731	1.11- No degradation occurred	854956	842923	1.4% - No degradation occurred

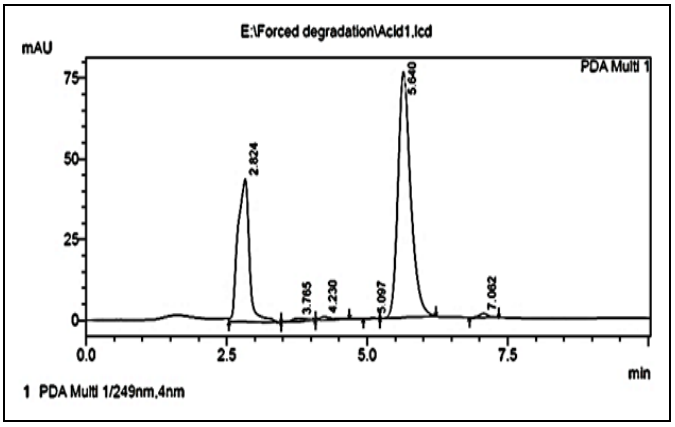

FIG. 6: ACID HYDROLYSIS

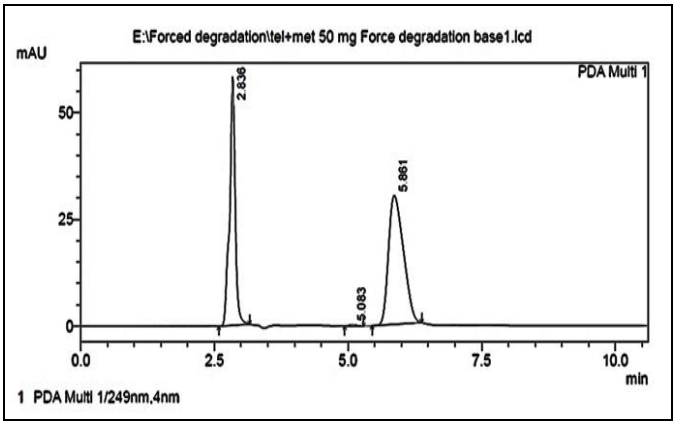

FIG. 7: BASE HYDROLYSIS

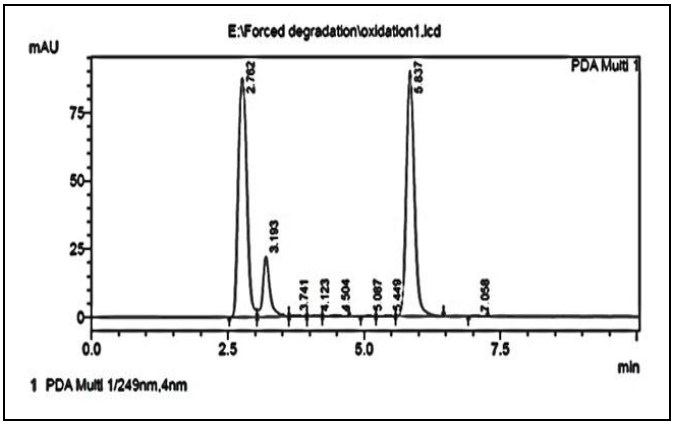

FIG. 8: OXIDATION HYDROLYSIS

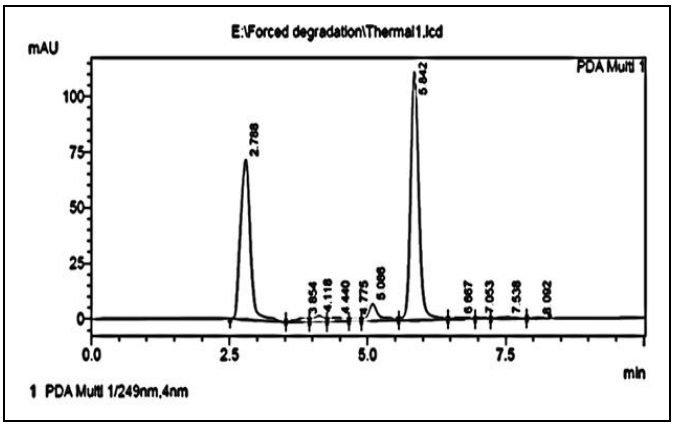

FIG. 9: THERMAL HYDROLYSIS

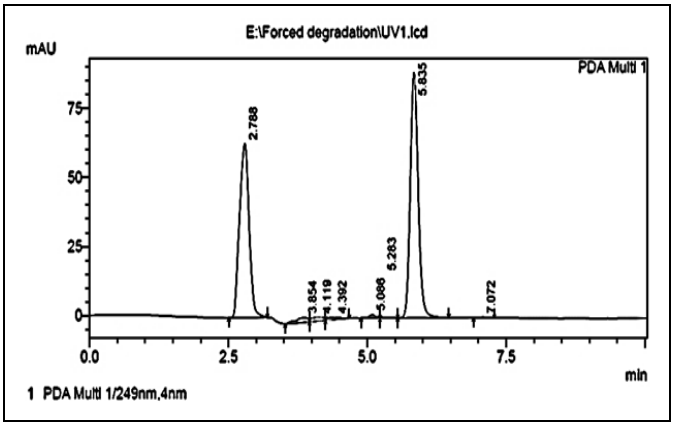

FIG. 10: PHOTOLYTIC HYDROLYSIS

CONCLUSION: The stability-indicating RP-UFLC method was developed & validated for the simultaneous estimation of Telmisartan & Metformin HCl in bulk drugs & in the prepared formulation. The developed method has given good resolution with a retention time less 10 min & the flow rate was 0.5ml/min. The prepared formulation gave assay & accuracy value within 90-110%. The method was validated according to the ICH guidelines. Any change in parameters does not give any change in result so, it can be concluded method is robust, simple, precise, fast & specific & can be utilized for the daily quality control analysis.

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CONFLICTS OF INTEREST: The authors have declared no conflicts of interest.

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