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Stability Indicating HPLC Method For Efonidipine and Telmisartan In Combination

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ABSTRACT:This New, simple stability indicating RP-HPLC method for the simultaneous estimation of efonidipine and telmisartan in its pharmaceutical dosage form has been developed and validated as per ICH. Column used was Agilent Eclipse XDB-C8 (4.6×150mm, 5µm) with mobile phase Acetonitrile:Phosphate Buffer pH 2.4 (70:30 V/V) in isocratic mode. Efonidipine and telmisartan were detected at a wavelength 250 nm. The retention times for telmisartan and efonidipine were found to be 1.7±0.02 min and 4±0.02 min, respectively. Validation of the method was done according to ICH guidelines. The method was found accurate, precise, robust and specific. Linearity for both drugs over range of 5-25 µgmL-1 Was observed .Both drugs were exposed to hydroltytic stress conditions under different pH, Oxidative, Thermal, and Photolytic . Both drugs were found to be susceptible to all stress conditions.

KEYWORDS: Stability indicating method, efonidipine, telmisartan, HPLC.

I. INTRODUCTION

Efonidipine Hydrochloride Ethanolate is a novel dihydropyridine derivative calcium channel blocker. It is chemically 2-(N-benzylanilino)ethyl 5-(5,5- dimethyl-2-oxo-1,3,2λ5-dioxaphosphinan-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro pyridine-3-carboxylate;ethanol;hydrochloride and its chemical structure is shown in Fig 1. Telmisartan is chemically 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid and its chemical structure1 shown in Fig 2. Efonidipine is used to treat the hypertension and angina pectoris. It inhibits both L- and T- type calcium channels, leading to vasodilation and decrease the automaticity of heart. Telmisartan is an angiotensisn-II subtype AT1 receptor antagonist which lowers the high blood pressure and prevents the heart strokes, heart attacks and kidney problems. It also improves the carbohydrate and lipid metabolism. Therefore, this combination of efonidipine and telmisartan is mainly used to treat hypertension as it provides effective control of blood pressure through synergistic mechanism, efonidipine cause vasodilation of arterioles and telmisartan counteracts the stimulation of RAS and is used to reduce the incidence of peripheral oedema2,3.

As per literature search methods like LC-MS/MS4,5, RP-HPLC6-8, UV9 and HPTLC10were reported for estimation of efonidipine. Many analytical methods are reported to estimate telmisartan individually or in combination with other drugs and some of them are RP-HPLC11-17, RP-UPLC18, HPTLC19,20and UV spectrometric21,22. However, until now there is no any study found on stability indicating method disclosed for simultaneous estimation of efonidipine and telmisartan in their combination.

II. MATERIALS AND METHODS

Chemicals and Reagents

Efonidipine was received as giveaway from Zuventus Healthcare Limited, Pune and telmisartan from Glenmark Generics Limited, Mumbai. Methanol (HPLC and AR Grade),hydrochloride acid (HCl), potassium dihydrogen phosphate, 30 % V/V hydrogen peroxide (H_2O_2) and sodium hydroxide were acquired from

Loba Chemie Pvt. Ltd., Mumbai, India. HPLC grade water was collected with the conductivity below 0.05 µS cm-1 using Extrapure Lab Link water purifier system .

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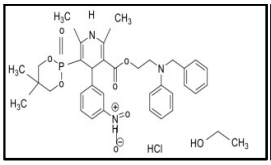

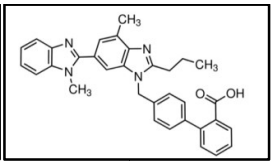

Fig. 1:Structure of efonidipine Fig. 2:Structure of telmisartan

III. Instrumentation and chromatographic condition

The samples were analysed on JASCO HPLC system, with PU 2080 Plus model pump with Rheodyne sample injector port (20 µL). The study was performed using Agilent Eclipse XDB-C8 (4.6 × 150 mm, 5 µm) column and detection was carried with PDA detector (MD 2010) with Borwin chromatography software (version 1.5) at wavelength of 250 nm. Mobile phase was optimized to contain Acetonitrile: Phosphate Buffer pH 2.4 (70: 30 V/V) at the flow rate of 1 mL min-1, employed in isocratic mode. The study involved other instruments like UV-Visible spectrophotometer (Jasco V-730), Photo stability chamber (Newtronic), Vacuum pump (JET-VAC-J1) and hot air oven (Kumar Laboratory Oven).

Mobile phase optimisation

In order to achieve optimal system suitability parameters, various columns were tried out such as Thermo CN and Agilent Eclipse XDB-C8 columns. Initially, Acetonitrile: PhosphateBufferpH 2.4 (60: 40 V/V) was tried gave broad peak of efonidipine andtheoretical plates were not sufficient of telmisartan. Significant resolution and desired system suitability parameters were obtained by using Acetonitrile: Phosphate Buffer (pH 2.4)as mobile phase in the ratio 70: 30 V/V.

Preparation of mobile phase

Acetonitrile and Phosphate Buffer were taken in the ratio 70: 30 (V/V) and filtered through 0.45 µm membrane filter. Then it was sonicated for 15 min on ultrasonication bath.

Preparation of standard stock solution

Anprecisely weighed 10 mg of efonidipine was transferred to a10mL volumetric flask, and 1 mL DMSO was added. It was shaken well till it gets dissolved. After that volume built up with methanol, to get separate standard stock solutions of efonidipine1000 µgmL-1. Pipetted1mL of efonidipine standard stock solution (1000 µgmL-1)and transferred to a 10mL volumetric flask and volume was built up with methanol to 10 mL to obtain solution of efonidipine (100 µgmL-1).

An precisely weighed 10 mg of telmisartan was transferred to a10mL volumetric flask, and the volume built up with 1 N NaOH, to get separate standard stock solutions of telmisartan1000 µgmL-1.Pipetted1mL of telmisartan standard stock solution (1000 µgmL-1)and transferred to a 10 mL volumetric flask and volume was built up with water to 10 mL to obtain solution of telmisartan(100 µgmL-1).

Now 1 mL from each stock solution taken and diluted to 10 mL to get efonidipine (10 µgmL-1)and telmisartan (10 µgmL-1). Representative chromatograms are shown in Fig. 3 and data is summarized in Table I.

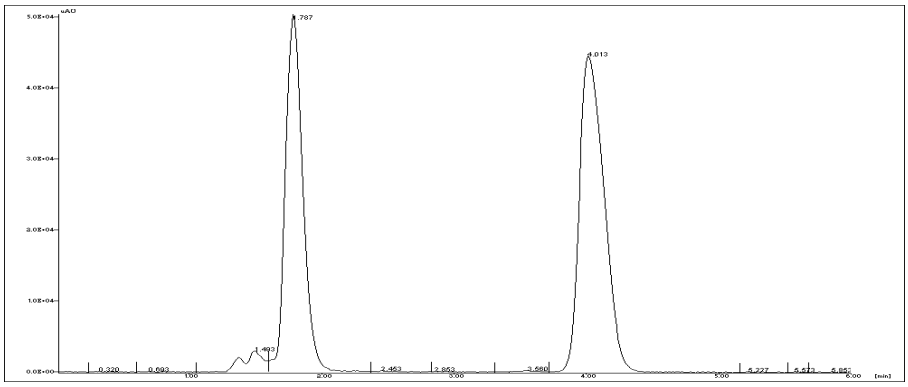

Fig. 3:Representative chromatogram of telmisartan(10 µg mL-1, RT 1.7±0.02) And efonidipine(10 µg mL-1, RT 4±0.02)

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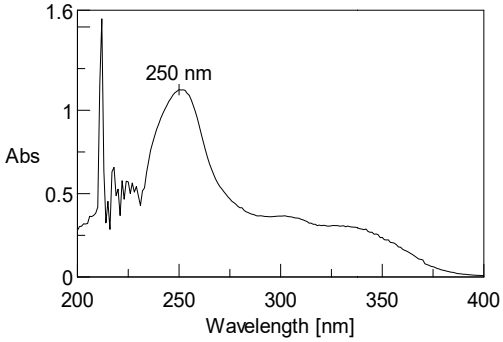

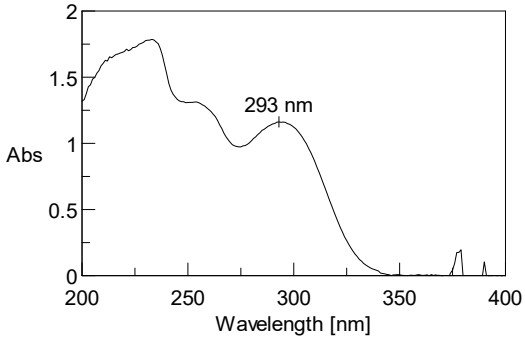

Fig. 4:UV spectrum of efonidipine (25 µg mL^{-1}) Fig. 5:UV spectrum of telmisartan (25 µg mL^{-1})

Preparation of sample solution

Precisely weighed Andpowdered marketed preparation (EFNOCAR 40/40 mg) which is equivalent to 10 mg of drug content and transferred to a10 mL volumetric flask, add 1 mL DMSO and made up the volume with NaOH, to get 1000 µgmL-1sample stock solution. The solution was sonicated, filtered and further dilution was prepared in methanol.

Stress degradation studies

The degradation conditions were as per International Council for Harmonisation guidelines Q1A (R2)23. The strength of reagent and the time of exposure were optimized to obtain10-30 %degradation. We have reported the optimized conditions which are asfollows:

Acid catalyzed hydrolysis

For sample preparation, 5 mL of efonidipine working solution of 1000 µgmL-1 was mixed with 5 mL 1 M HCl and the volume was built up with methanol upto 50 mL. The solution was refluxed for 30 min at 80°C, cooled to room temperature. 1 mL of telmisartan working solution of 1000 µgmL-1was mixed with 1 mL 1 N HCl and made up the volume to 10 mL. The solution was kept for 48 h at room temperature. After that take 1 mL of each drug for hydrolysis the solution was neutralized and the volume was built up with mobile phase upto10 mL and injected into system .

Parameter	Obtained values	
	Telmisartan	Efonidipine
Concentration(µg mL^{-1})	5-25	5-25
RT(min)	1.7±0.02	4±0.02
Asymmetry	1.05	0.98
Plates(N)	2175	2379

Table I: Sytem suitability parameters

Base catalyzed hydrolysis

For sample preparation, 1 mL of efonidipine working solution of 1000µgmL-1was mixed with 1 mL of 0.5 M NaOH and made up the volume to 10 mL. The solution was kept for 2 h at room temperature.1 mL of telmisartan working solution of 1000 µgmL-1was mixed with 1 mL 1 N NaOH and made up the volume to 10 mL. The solution was kept for 48 h at room temperature. After that take 1 mL of each drug for hydrolysis the solution was neutralized and the volume was built up with mobile phase upto 10 mL and injected into system.

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Oxidation degradation

For sample preparation, 1 mL of efonidipine working solution of 1000 µgmL-1mixed with 1 mL of 30% H_2O_2V/V and made up the volume of 10 mL. The solution was kept for 24 h at room temperature. 1 mL of telmisartan working solution of 1000 µgmL-1mixed with 1 mL of 30% H_2O_2V/V and made up the volume of 10 mL. The solution was kept for 48 h at room temperature. After that take 1 mL of each drug and the volume was made up with mobile phase up to 10 mL and injected into system.

Thermal degradation

The thermal degradation was carried out by placing efonidipine in solid state in an oven at 80°C for 4 h and telmisartan at 80°C for 3 h. A sample was taken from oven, cooled to room temperature, weighed and diluted separately. After that take 1 mL of each drug and the volume was built up with mobile phase upto 10 mL and injected into system.

Sr.No.	Stresscondition	Efonidipine		Telmisartan	
		Temperature And time	%recovery	Temperature And time	%recovery
1	Acid hydrolysis	1 M HCl for 30 min at 80°C	84.85	1 N HCl for 48h at RT	71.73
2	Alkaline hydrolysis	0.5 M NaOH for 2 h at RT	85.54	1 N NaOH for 48h at RT	86.86
3	Oxidative degradation	30 % V/V H_2O_2 for 24 h at RT	79.23	30 % V/V H_2O_2 for 48h at RT	84.42
5	UVdegradation	UV Cabinet 254 nm 2h	94.60	UV Cabinet 254 nm 2h	92.08
6	Thermal degradation	80°C for 4h	86.32	80 0C for 3h	84.21
7	Sunlight degradation	Sunlight 4h	90.65	Sunlight 4h	90.52

Table II :Summary stressed degradation

Photolytic degradation

For sample preparation, both drugs were exposed to UV light for 254 nm at 2 h and sunlight at 4 h. After exposure powder was weighed and diluted separately. After that take 1 mL of each drug and the volume was built up with mobile phase up to 10 mL and injected into system.

Method validation

The method development and validation of proposed analytical method includes specificity, linearity, precision, accuracy, limit of detection (LOD), limit of quantitation (LOQ) and robustness. It was validated according to ICH Q2(R1)24.

Drug	Sr.No	Parameter	Peak purity (purity front)	Peak purity (purity tailing)
Efonidipine	1	Standard	998.56	999.45
	2	Sample	999.30	998.70
Telmisartan	1	Standard	999.16	998.85
	2	Sample	998.47	999.05

Table III: Specificity studies

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Sr. No	Efonidipine		Telmisartan	
	Intraday precision	Interday precision	Intraday precision	Interday precision
1	230521.8	230521.8	253684.3	252823.4
2	230521.8	235893.2	254332	253975
3	226518.3	234480.8	252823.4	254332
4	226518.3	231595.6	250010.4	250342
5	233141.7	226518.3	257665.6	258998.2
6	234480.8	230933.6	258998.2	248910.7
Mean	230031	231657.2	254585.6	253230.2
SD	3250.115	3290.625	3282.43	3527.153
%RSD	1.41	1.42	1.28	1.39

TableIV: Precision studies
(n=3, for interday precision 6 replicates for consecutive 3 days

IV. RESULTS

Stress degradation results are summarized in Table II. Standard stock solution was scanned over 200-400 nm, whereby maximum absorbance was observed at 250 nm (efonidipine) and 293 nm (telmisartan). Spectra are shown in Fig. 4 and Fig. 5.

Further, by following ICH guidelines method was validated.

Drug	Amount Recovered (µg mL^{-1})	% Drug content	Mean ± % RSD
Efonidipine	10.605	106.05	105.98 ± 0.08
	10.592	105.92	
Telmisartan	9.628	96.28	96.56 ± 0.41
	9.685	96.85	

Table V: Assay

Specificity

The specificity studies were done by monitoring peak purity for both sample and standard. It was identified to be acceptable as shown inTable III.

Linearity and range

The mixtures for linearity were prepared from standard stock solution (1000µgmL-1 and 1000µgmL-1 of efonidipine and telmisartan,respectively). Both drugs were found to be linear over range of 5-25 µg mL-1.The procedure was repeated for 5 times to get the linear regression equation. Overlain chromatograms are shown in Fig.5.Then values were plotted as concentration against peak area and calibration curve is shown in Fig.6 .andFig. 7

Drug	Sr. No	Amount from marketed formulation (µg mL^{-1})	Amount of standard added	Total amount of the drug (µg mL^{-1})	Amount recovered	% recovery
Efonidipine	1	10	8	18	17.7851	98.8
	2	10	10	20	20.1186	100.59
	3	10	12	22	22.2975	101.35
Telmisartan	1	10	8	18	17.7193	98.44
	2	10	10	20	19.941	99.7
	3	10	12	22	22.3346	101.52

Table VI: Recoverystudies

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Drug	LOD (µg mL^{-1})	LOQ (µg mL^{-1})
Efonidipine	1.64	4.98
Telmisartan	1.10	3.35

Table VII: LOD and LOQ

Precision

The precision was checked, both for intraday and inter day study. The precision was assessed by injecting 6 replicates of 5 µg mL-1 concentration for efonidipine and telmisartan within the same day and consecutive days (% RSD was determined) respectively. The results obtained are summarized in Table IV.

Accuracy

Accuracy of the method was determined by standard addition method. Known amount of API to be analyzed was added to the marketed formulation. In the assay solution pure drug was spiked at 80%, 100% and 120% level. The 2 replicates of 3 concentrations were evaluated to calculate % recovery. The results obtained are summarized in TableVI.

Assay

The2 replicates of the sample solution (10 µg mL-1) were prepared from 100 µg mL-1 sample stock solution and injected to system. The results obtained are summarized in Table V.

Limit of detection (LOD) and Limit of quantitation (LOQ)

The limits were calculated from values of regression equation. Both LOD and LOQ were determined using formula 3.3 SD/S and 10 SD/S, respectively. Here, S is slope of calibration curve and SD is standard deviation of area at lowest concentration. The results obtained are summarized in Table VII.

Parameter	Condition	% RSD	
		Efonidipine	Telmisartan
Mobile phase ratio (Acetonitrile: Phosphate buffer pH 2.4)	68:32 V/V	1.44	0.83
	72:28 V/V	0.40	0.89
Flow rate	0.95mL min^{-1}	1.52	1.04
	1.05mL min^{-1}	1.87	1.41
Wavelength	248 nm	0.37	1.02
	252 nm	1.41	1.28
Buffer pH	2.2	1.13	1.29
	2.6	0.61	1.03

Table VIII: Robustness studies

Robustness

Robustness was performed by carrying out small and deliberate changes to developed system. Peak area was checked after doing the changes to mobile phase ratio, pH of mobile phase, flow rate, wavelength. The results obtained are summarized in Table VIII. The results of the validation proved that the established method complied with the validation parameters and data is summarized in Table IX.

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Sr. No	Validation Parameter	Result	
		Efonidipine	Telmisartan
1	Specificity	Specific	Specific
2	Linearity Range	y = 47238x+13646 R^2 = 0.9995 5-25 µg mL^{-1}	y = 49501x-1431.8 R^2= 0.9976 5-25 µg mL^{-1}
3	Intraday Precision% Interday Precision%	1.41 1.42	1.28 1.39
4	Assay%	105.98	96.56
5	Accuracy Level 80% Level 100% Level 120%	 98.8 100.59 101.35	 98.44 99.7 101.52
6	LOD LOQ	1.64 µg mL^{-1} 4.98 µg mL^{-1}	1.10µg mL^{-1} 3.35µg mL^{-1}
7	Robustness	Robust	Robust

Table IX: Summary of validation parameters

V. DISCUSSION

The developed stability indicating HPLC method for efonidipine and telmisartan was validated as per ICH guidelines .ICH guidelines. The developed method was indentified to be linear within the range of 5-25µg mL-1and the correlation coefficient was discovered to be R^2 = 0.9995 and R^2= 0.9976 for efonidipine and telmisartan, respectively.

As per the previously reported methods for efonidipine was stable in acidic, oxidative, and photolytic conditions and no degradation was shown in acidic condition.

We have observed degradation under hydrolytic, oxidative and thermal conditions. As per the previously reported methods for telmisartan, there are four methods[11,12,18,21] which follow a refluxing approach for hydrolytic and oxidative degradation conditions. But in the proposed method, extended time of exposure to the stress condition without refluxing was implemented to study the effect of hydrolytic stress without thermal component. Degradation was observed for efonidipine and telmisartan under different stress condition, but no degradation product was found in any stress condition. Non-interference by any degradant was confirmed by peak purity profile study.

The method was found to consent to all validation parameters as per ICH guideline. The developed method is accurate, precise, specific and robust. The validated method could be applied to the quality control and routine stability monitoring of efonidipine and telmisartan .

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