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Validated Method Development for Simultaneous Estimation of Ramipril and Telmisartan in Tablet Dosage form by UV-spectroscopy

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Abstract
Two simple, accurate, sensitive and specific methods are developed for the simultaneous determination of Ramipril and Telmisartan in binary mixture. The method based on UV-spectrophotometric determination of two drugs, Method A is by using multicomponant method. It involves absorbance measurement at 205.0 nm(λ_{max} of Ramipril) and 291.0 nm (λ_{max} of Telmisartan) in 0.2M H_2SO_4;. Beer's law is obeyed in the concentration range of 5-40 μg mL^{-1} for Ramipril and 2-20 μg mL^{-1} for Telmisartan. Method B is graphical absorbance method which is based on measurement of absorbance of Ramipril and Telmisartan at 222.0nm (iso-absorptive point of Ramipril and Telmisartan) and 291.0 nm (λ_{max} of Telmisartan) Both these methods have been successively applied to pharmaceutical formulation and were validated according to ICH guidelines.

Key words: Ramipril, Telmisartan, Multicomponant Method, Graphical Absorbance Method.

1. Introduction:

Ramipril's chemical name is (2S, 3aS, 6aS) -1[(S)-N-[(S) -1-Carboxy-3-phenylpropyl]alanyl] octahydrocyclopenta[b] pyrrole-2-carboxylic acid, 1-ethyl ester. Ramipril is an angiotensin converting enzyme (ACE) inhibitor. An inactive prodrug, Ramipril is converted to ramiprilat in the liver and is used to treat hypertension and heart failure, to reduce proteinuria and renal disease in patients with nephropathies, and to prevent stroke, myocardial infarction, and cardiac death in high-risk patients. Ramiprilat, the active metabolite, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II [1]. As angiotensin II is a vasoconstrictor and a negative-feedback mediator for renin activity, lower concentrations result in a decrease in blood pressure and an increase in plasma rennin. Ramiprilat may also act on kininase II, an enzyme identical to angiotensin-converting enzyme that degrades the vasodilator bradykinin [2]. The chemical structure of Ramipril is shown in Fig 1. The typical dose of Ramipril is 5 mg per day. Literature survey reveled that various analytical methods for quantitative determination of Ramipril in pharmaceutical formulations have been reported in literature like LC-MS (Liquid chromatography-mass spectrophotometry) [3], Atomic-absorption spectrometry [4], Capillary electrophoresis [5], HPLC (High-performance liquid chromatography) [6,7]. Spectrophotometry and atomic-absorption

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spectrometry [8], Spectrophotometry [9], RP-HPLC (Reverse phase-high performance liquid chromatography) [10].

Telmisartan chemically 4- [[4-methyl-6- (1-methyl-2-benzimidazolyl)-2-propyl- 1-benzimidazolyl] methyl]–2–-biphenyl carboxylic acid, which is Angiotensin II receptor antagonist Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of Telmisartan on blood pressure. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE,) kininase-II. Angiotensin II is the principal presser agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium [11]. The dose of Telmisartan is 40 mg daily]. The structure of Telmisartan is shown in Fig **2.** There are very few methods reported for estimation of Telmisartan in pharmaceutical dosage form, which includes a validated RP –HPLC [12], spectrophotometric method [13].

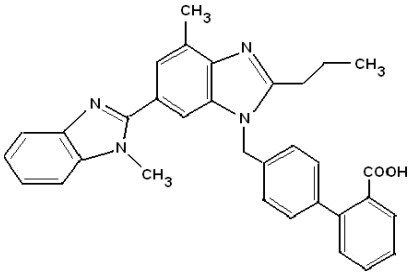

Fig1 Structure of Ramipril

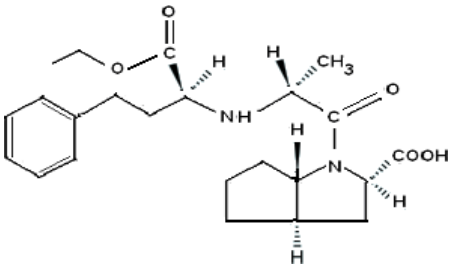

Fig 2 Structure of Telmisartan

Both these drugs are not official in Indian Pharmacopoeia, British Pharmacopoeia, United States and European Pharmacopoeia.

At present no UV spectrophotometric methods are reported for the simultaneous estimation of Ramipril and Telmisartan in combined dosage formulation.

Therefore, it was thought worthwhile to develop simple, precise, accurate UV spectrophotometric methods for simultaneous determination of Ramipril and Telmisartan in tablets.

2. Experimental:

Materials:

Pharmaceutical grade Ramipril (batch no. AC 1030E03) and Telmisartan (AT120805) were kindly supplied as a gift sample by Blue Cross Laboratories Ltd., Nashik, (M.S.) India,
used without further purification and certified to contain 99.53 % (w/w) and 99.66% (w/w), respectively on dried basis. All chemicals are of AR grade and were purchased from Qualigens fine Chemicals, Mumbai, India

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UV- spectrophotometry:

A. Multicomponant method

UV-Vis spectrophotometer V-630 (Jasco, Japan) with spectral bandwidth of 1 nm and 10 mm matched quartz cells was used. Standard stock solutions of 100 μg.mL^{-1} were prepared by dissolving 10 mg of each in 100mL of 0.2M H_2SO_4. From these stock solutions, working standard solutions having concentration15 μg.mL^{-1} each were prepared by appropriate dilutions. They were scanned in the wavelength range of 400−200 nm and the overlain spectrum was obtained (Fig 3). Two wavelengths 205.0 nm (λ_{max} of Ramipril) and 291.0 nm (λ_{max} of Telmisartan) were selected for the estimation of both drugs by multicomponant mode analysis. The calibration curves were found to be linear in the concentration range of 5−40 μg.mL^{-1}, for Ramipril and 2-20 μg.mL^{-1} for Telmisartan.The absorptivity coefficients of each drug at both wavelengths were determined. The concentration of two drugs in the mixture were calculated [14,15], (Table 1).

B) Graphical Absorbance Method

From the overlain spectra of RAM and TEL shows that both the drugs are having sane absorbance at 218.0 nm. For estimation of tablet content, the two wavelengths 218.0 nm Isobestic point for RAM and TEL and other 291.0nm λmax of TEL , were selected by solving the equation.[14,15].

For RAM

$$\text{For } C1 = \frac{Qm-Qy}{Qx-Qy} \times \frac{A1}{a}$$

$$C1 = \frac{Qm-Qx}{Qx-Qx} \times \frac{A1}{a}$$

Where C1 = Conc. of RAM

C2 = Conc. of TEL

A1 =Absorbance of sample at iso-absorptive wavelength 218.0nm

A = Absorptive of RAM and TEL at iso-absorptive wavelength 218.0nm

Analysis of Pharmaceutical Dosage Forms

To determine the content of Ramipril and Telmisartan simultaneously in tablets(label claim: 5 mg Ramipril and 10 mg Telmisartan, film coated); twenty tablets were weighed; their average weight determined and were finely powdered. The correct amount of powder was dissolved 0.2M H_2SO_4 by stirring for 30 min. The excipients were separated by filtration. After filtration, an appropriate amount of internal standard was added and diluted up to mark with0.2M H_2SO_4. Appropriate aliquots were subjected to above methods and the amount of Ramipril .and Telmisartan were determined. The results are reported in Table 2.

Recovery studies

To check the accuracy of the developed methods and to study the interference of formulation additives, analytical recovery experiments were carried out by standard addition method, at 80, 100 and 120 % level. From the total amount of drug found, the percentage recovery was calculated. The results are reported in Table 3.

3. Results and Discussion

Both, UV spectrophotometric methods were found to be simple, accurate, economic and rapid for routine simultaneous estimation of Ramipril and Telmisartan, in tablet dosage forms. For UV spectrophotometric method, linearity was obtained in concentration range of 5 – 40 μg .mL^{-1}, for Ramipril and 2-20 μg .mL^{-1}, for Telmisartan; with regression 0.9998 and 0.9999, intercept – 0.0677and – 0.0043 and slope 0.0457 and 0.0391 for Ramipril and Telmisartan, respectively.Recovery was in the range of 99 – 101 %; the value of standard deviation and % R.S.D. were found to be < 2 %; shows the high precision of the method.

Acknowledgement:

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Figures

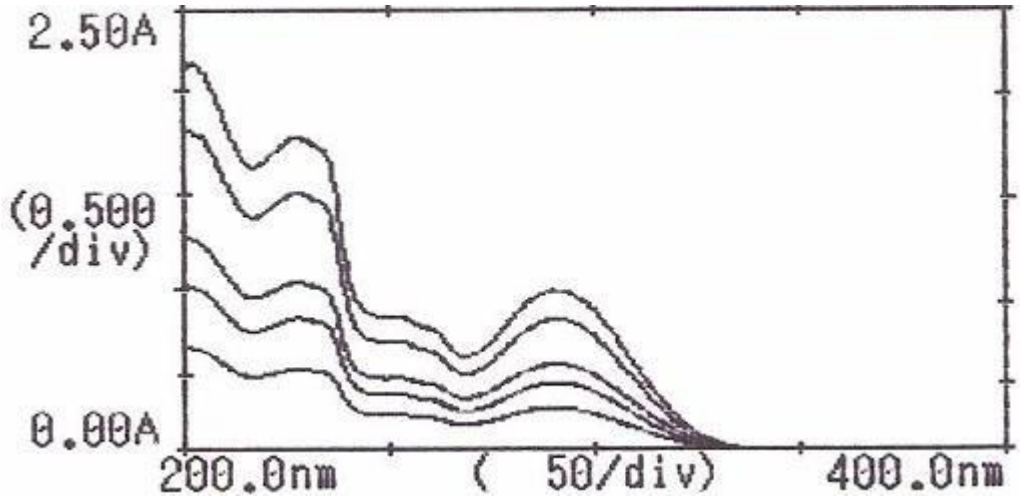

Fig 3. Overlain Spectrum of Ramipril And Telmisartan of different conc. in binary mixtures in 0.2M H_2SO_4. taken on UV – Vis spectrophotometer (Jasco V-630)

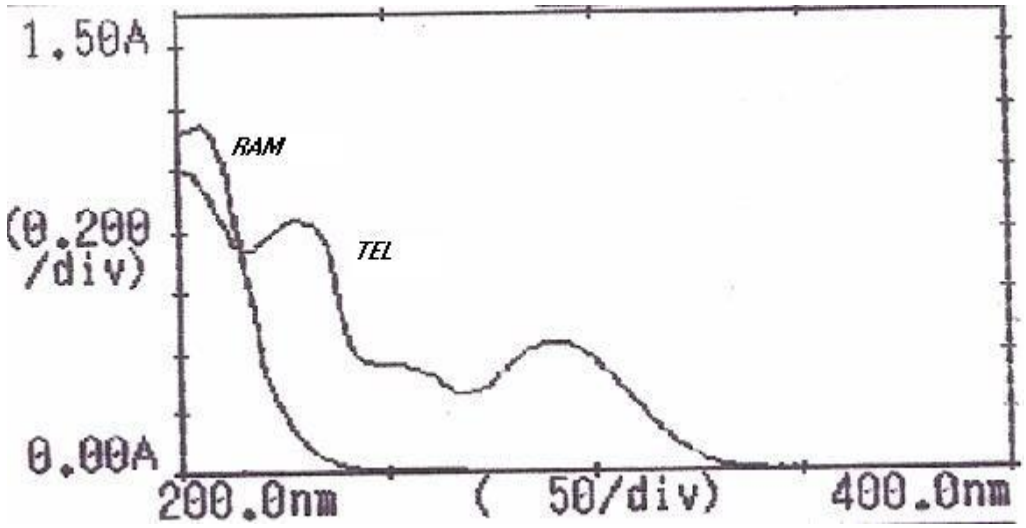

Fig 4. Overlain Spectrum of Ramipril And Telmisartan in 0.2M H_2SO_4. RAM is Ramipril, TEL is Telmisartan (each 15 μg.mL^{-1}) taken on UV – Vis spectrophotometer (Jasco V-630)

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Table 1: Absorptivity Values at 205.0 nm (λ_{max} of Ramipril) and 291.0 nm (λ_{max} of Telmisartan)

	Absorptivity at 205.0 nm		Absorptivity at 291.0 nm	
	Ramipril	Telmisartan	Ramipril	Telmisartan
*Mean	ax1= 327.12	ay1= 394.97	ax2= 352.08	ay2= 288.96
± S.D.	1.05	0.38	0.61	0.54

* Absorptivity values are the mean of six determinations. S.D. is standard deviation. ax1 and ax2 absorptivities of Telmisartan at 205. nm and 205.0 nm, respectively; ay1 and ay2 absorptivities of Ramipril at 205.0 nm and 291.0 nm, respectively.

Table 2. Analysis Data of Tablet Formulation

	Multicomponant method		Graphical Absorbance method	
Parameter	Ramipril	Telmisartan	Ramipril	Telmisartan
~~Label Claim~~	~~5~~	~~40~~	~~5~~	~~40~~
*Drug content	100.06	99.89	101.11	101.43
± S. D.	0.2621	0.2080	0.6368	0.5321
% R.S.D.	0.3614	0.4083	0.5285	0.4268

* Value for Drug content (%) are the mean of five estimations; S.D. is standard deviation and R.S.D. is relative standard deviation

Table 3. Recovery studies

Multicomponant method			Graphical Absorbance Method		
Excess drug	*Recovery	%RSD	Excess drug	*Recovery	%RSD
Ramipril					
80	99.83	0.2753	80	99.37	0.7405
100	99.72	0.1026	100	100.11	0.0119
120	99.07	0.0254	120	100.58	0.8547
Telmisartan					
80	100.69	0.2953	80	100.32	0.1238
100	100.43	0.1236	100	99.33	0.0357
120	99.52	0.1265	120	98.80	1.0540

* Recovery is mean of three estimations.

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Table 4. Summary of repeatability, precision and ruggedness

Parameter UV – spectrophotometry

Parameter	Multicomponant Method		Graphical Absorbance Method	
	Ramipril	Telmisartan	Ramipril	Telmisartan
Repeatability	1.62	0.09	0.72	0.37
Precision				
Intra-day	1.17	0.13	0.29	0.43
Inter-day	0.67	0.24	0.56	1.55
Ruggedness				
Analyst 1	0.58	0.54	0.36	0.77
Analyst 2	0.22	0.59	0.30	1.54