Oriental Journal of Chemistry Vol. **25**(1), 137-141 (2009)

Spectrophotometric simultaneous determination of *Ramipril* and *Telmisartan* in combined tablet dosage form

POPAT B. MOHITE[1]*, RAMDAS B. PANDHARE[1] and BHASKAR H. VAUDHUN[2]

[1]Department of Pharmaceutical Analysis, MES College of Pharmacy, Sonai, Ahmednagar (India).
[2]MP Patel College of Pharmacy, Kapadwanj (India).

(Received: December 02, 2008; Accepted: January 11, 2009)

ABSTRACT

Two methods are described 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 simultaneous equation method. It involves absorbance measurement at 205.0 nm(»max of Ramipril) and 291.0 nm (λmax of Telmisartan) in 0.2M H_2SO_4;. Beer's law is obeyed in the concentration range of 5-40 µg mL^{-1} for *Ramipri*l and 2-20 µg mL^{-1} for *Telmisartan*. Method B is Absorbance ratio 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 (»max of Telmisartan) Both these methods have been successively applied to pharmaceutical formulation and were validated according to ICH guidelines.

Key words: *Ramipril, Telmisartan,* simultaneous equation method, absorbance ratio method.

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 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]].

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.

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

UV- spectrophotometry

Simultaneous Equation 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 (λmax of Ramipril) and 291.0 nm (λmax of Telmisartan) were selected for the formation of simultaneous equation. 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 using equations[14,15],

$$CRAM = A2\,ay1 - A1\,ay2 / ax2\,ay1 - ax1ay2 \quad ...(1)$$

$$CTEL = A1\,ax2 - A2\,ax2 / ax2\,ay1 - ax1ay2 \quad ...(2)$$

Where, A1 and A2 are absorbance of mixture at 205.0nm and 291.0 nm; ax1 and ax2, absorptivities of Ramipril at 205.0 nm and 2916.0 nm, respectively; ay1 and ay2 absorptivities of Telmisartan at 205.0 nm and 291.0 nm, respectively. CRAM and CTEL are concentration of Ramipril and Telmisartan in mixture. The absorptivities reported are the mean of six independent determinations (Table 1).

Absorbance Ratio 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 ëmax of TEL , were selected by solving the equation.[14,15].

For RAM

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

for

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

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.

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.

Table 1: Absorptivity Values at 205.0 nm (λmax of Ramipril) and 291.0 nm (λmax 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

	Simultaneous equation method		Absorbance Ratio 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

Simultaneous equation method			absorbance ratio 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.

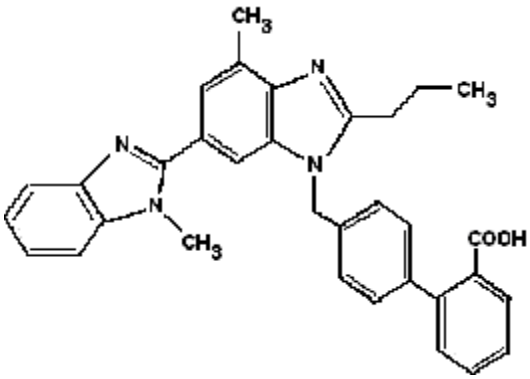

Fig. 1: Structure of Ramipril

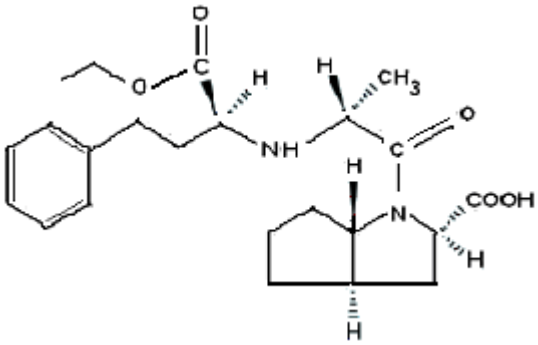

Fig. 2: Structure of Telmisartan

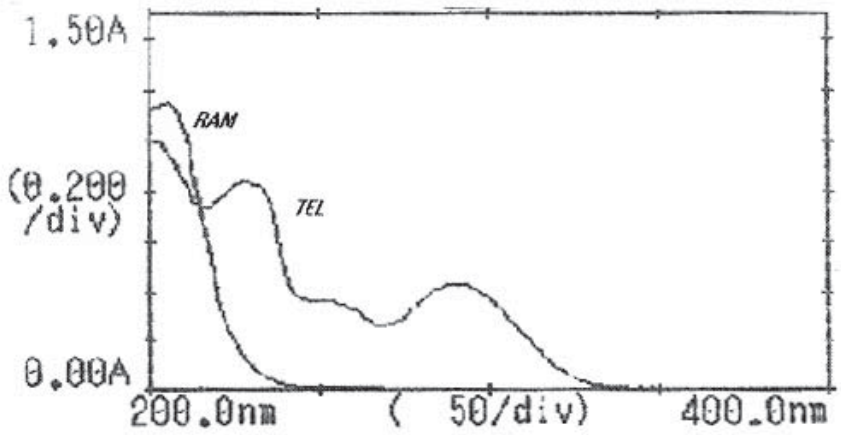

Fig. 3: Overlain Spectrum of Ramipril And Telmisartan in 0.2M H_2SO_4. RAM is Ramipril, TEL is Telmisartan (each 15 ¼g.mL-1) taken on UV – Vis spectrophotometer (Jasco V-630)

Table 4: Summary of repeatability, precision and ruggedness Parameter UV-spectrophotometry

Parameter	Simultaneous Equation method		Absorbance Ratio 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

ACKNOWLEDGEMENTS

The authors are thankful to Blue Cross Labs. Ltd. (Nashik), for providing drug samples and V.K.Deshmukh, Principal MES College of Pharmacy, Sonai for providing facilities to carry out this work.

REFERENCES

1. Kukushkin S K, Lebedev A V, Manoshkina E M, Shamarin V M,. *J Pharm Biomed Anal* **70**(9): 69-71 (1998).
2. Reinhard H A., Becker M D, Bernard M D, Schlkens M D. *J Clin Pharmacol* **59**(10): 3-11 (1987).
3. Zhimeng Z, Andre V, Len. J Chromatogr B 779(2): 297-306,(2002).
4. Magda M, Ayad A, Shalaby E, Abdellate. F. J, *PharmBiomed Anal* **28**(2): 311 (2002).
5. Hillaert S, Grauwe K, Bossche W *J Chromatogr A* **924**(1): 439 (2001).
6. Belal F, Al-Zaagi A, Gadkariem E, *Abounassif M J Pharm Biomed Anal* **24**(3): 335 (2001).
7. Barry L, Mark Williams, H, Anna I, Veysoglu T, Parente E ,*J Pharm Biomed Anal* **23**(4): 637-651 (2000).
8. Hisham E, Magda M, Elham A ,*J Pharm Biomed Anal* **18**(6):1027, (1999).
9. Bonazzi D, Gotti R, Andrisano V, Cavrini V ,*J Pharm Biomed Anal* **16**(3): 431- 438: (1997).
10. Zarapkar S S, Rane S H,. *J Pharma Sci* **37**(12): 589-593. (2000).
11. Strawn W B, Chappell M C, Dean R H, *J.Pharm.Biomed Anal.*, **101**(7): 1586 (2000).
12. Wankhede S.B; Tajne M.R; GuptaK.R, Wadodkar S.G., *Indian. J Pharma Sci* **69**(2): 298-300 (2007) .
13. Palled M.S.; Chatter M.; Rajesh P.M.N.; Bhat A.R vol. **68**(5): 685-686 (2006).
14. Daharwal S J, Garg G, Saudagar R B, Saraf S, *Indian J Pharma Sci* **19**(8):102 (2006).
15. Stenlake J B, Backett A H *Practical pharmaceutical Chemistry,* 4th Edition, Part 2, C. B. S. Publishers, 281, (1997).