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Simultaneous Determination of Ramipril, Hydrochlorothizide and Telmisartan by Spectrophotometry

S. Bankey, G. G Tapadiya*, S. S Saboo, S. Bindaiya, Deepti Jain, S. S. Khadbadi
School of Pharmaceutical Sciences, Rajeev Gandhi Proudyogiki Vishwavidyalaya, Airport By-Pass Road, Gandhi Nagar, Bhopal (M.P.)-462036, India
E-mail : ganeshtapadiya@gmail.com

ABSTRACT: A simple, fast and precise multicomponent mode analysis method has been developed for simultaneous determination of Ramipril (RMP), Hydrochlorothiazide (HCT) and Telmisartan (TEL) in tablet formulation. The wavelengths selected for these drugs were 218nm, 271nm and 296nm respectively using methanol as solvent. The linearity for these drugs at all the selected wavelengths lies between 0.5-3.5 $\mu gml^{-1}$for RP, 1.25-8.75 $\mu gml^{-1}$for HCT and 4-28 $\mu gml^{-1}$for TEL. The concentrations of these drugs were evaluated in laboratory mixture and marketed formulation. Accuracy was determined by recovery studies from tablet dosages forms and ranges from 99.09-99.52%. Precision of method was find out as repeatability, day to day and analyst to analyst variation and shows the values within acceptable limit (R.S.D. $\leq$ 2 percent).

KEYWORD: Ramipril (RP), Hydrochlorothiazide (HCT), Telmisartan (TEL), simultaneous estimation, UV,

INTRODUCTION

Ramipril, (2S, 3aS, 6aS)-1-[(S)-2-[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino] propanoyl]octahydro-cyclopenta[b]pyrrole-2-carboxylic acid and ramiprilate, the active metabolite, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. Angiotensin II contracts the muscles of most arteries in the body, including the heart, thereby narrowing the arteries and elevating the blood pressure.

Hydrochlorothiazide, 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine- 7- Sulphonamide 1, 1-dioxide, is a diuretic, which inhibits active chloride reabsorption at the early distal tubule via the Na-Cl co-transporter, resulting in an increase in the excretion of sodium, chloride, and water.

Telmisartan, 4-((2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) methyl) biphenyl-2- Carboxylic acid, blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.

Literature survey revealed that there are many methods like HPLC, UV-Spectrophotometric and HPTLC for individual determination of RP[1] HCT[3,4,5] and TEL[6,7] but there is no method reported for simultaneous estimation of RP, HCT and TEL in their combined dosage form. An attempt was made to develop accurate, precise and economical multicomponent mode analysis method for estimation of these drugs in combined dosage form.

EXPERIMENTAL

Apparatus

Instrument used in present study was double beam UV/Visible spectrophotometer with resolution of 1nm and 0.5mm slit width (Model UV-1700, Shimadzu, Japan).

Material

Pure samples: Ramipril was kindly supplied by IPCA Laboratory Ltd. Mumbai, India. Hydrochlorothiazide and Telmisartan were supplied by Aristo Pharmaceutical Ltd. Mumbai, India.

Marketed formulation

TERAM-H 5 (Unichem Lab. Ltd. Mumbai, India) was taken for study which contains Ramipril-5mg, Hydrochlorothiazide-12.5mg and Telmisartan- 40mg.

Reagents and chemicals

Methanol (Merck Ltd., Mumbai, India) and other reagents & chemicals used were of analytical grade.

Standard solution

Stock solutions of 1000 μgml^{-1} were prepared for each drug in methanol. From these stock solutions sub stock solution of 25μgml^{-1}, 50μgml^{-1} and 200μgml^{-1} were prepared for RP, HCT and TEL respectively.

Stability

Stability was observed by scanning the drug solutions in selected solvent system in time scan mode of UV-spectrophotometer for 6 hour.

METHOD DEVELOPMENT

Study of overlain spectra and selection of wavelengths

Stock solutions of 1000 μgml^{-1} were prepared for each drug in methanol. From these stock solutions, sub stock solution of 100μgml^{-1} for RP, HCT and TEL were prepared and further diluted to get final concentration of

10μgml^{-1} solution for each drug to study the overlain spectra. [Figure1].

UV multicomponent mode analysis method:

Multicomponent analysis was successfully attempted by using an on-line computer with an UV detection system to collect and compare spectral data. The absorbance values at several wavelengths[1] are processed by means of matrix equations to obtain concentration of two or more drugs known in the sample solution. With the development, sophisticated spectrophotometers like Shimadzu model 160 A, 260 A, 1601 and 1700 have an inbuilt microprocessor for spectral data processing. The instrument computes accurate results within minimal time. The concentration of each of the components in the mixture is printed through inbuilt system[9].

Working Linearity and Range

Stock solutions of 1000 μgml^{-1} were prepared for each drug in methanol. From these stock solutions sub stock solution of 25μgml^{-1}, 50μgml^{-1} and 200μgml^{-1} were prepared for RP, HCT and TEL respectively. These sub stock solutions were further diluted to get the solutions range of 0.5-3.5 μgml^{-1} for RP, 1.25-8.75 μgml^{-1} for HCT and 4-28 μgml^{-1} for TEL for linearity study. Table [T1-T3].Calibration curves were plotted concentration vs. absorbance. Fig. [F2-F4].

Preparation of mixed standard

Stock solutions of 1000 μgml^{-1} were prepared for each drug in methanol. From these stock solutions sub stock solution of 25μgml^{-1}, 50μgml^{-1} and 200μgml^{-1} were prepared for RP, HCT and TEL respectively. From these sub stocks seven mixed standards were prepared having RP, HCT and TEL in the ratio of 1:2.5:8 respectively as shown in table T4.

Analysis of Mixed standard

All mixed standards were scanned at selected wavelengths to study the range of Beer Lambert's range. Analysis and results of mixed standards are reported in table T5- T6.

Analysis of laboratory sample

The method was checked by analyzing a solution containing known concentration of the drugs. Laboratory sample solutions were prepared from standard stock solution. Analysis and results of laboratory sample were reported in table T7-T8.

Analysis of Marketed formulation

Twenty tablets were weighed, crushed and mixed thoroughly. Weighed tablet powder equivalent to 40 mg of TEL was taken in 100 ml volumetric flask and dissolved in 75ml methanol and volume was adjusted with the same. The above prepared solution was further diluted to get concentration in the range of Beer Lambert's range. These solutions were scanned over the range of 200-400 nm in multicomponent mode of instrument. Analysis and results are reported in table T9-T10.

VALIDATION OF THE METHOD

Linearity and Range

Linearity of each drug was observed and response ratio of each drug was found out linearity of each drug is reported in table T11.

Accuracy

Accuracy was evaluated by fortifying tablet samples with known concentrations of the drug. The recovery of the added drug was determined. Results of recovery study are reported in table T11.

Precision

Standard stock solutions of Ramipril, Hydrochlorothiazide and Telmisartan were prepared in same manner as in section 1.2.5. The repeatability was performed for three times for all concentration. The intermediate precision was performed by doing day-to-day variation and analyst- to-analyst variation. Results of repeatability and intermediate precision are reported in table T11.

RESULTS AND DISCUSSION

The multicomponent mode method was developed and validated according to ICH guidelines for determination of RP, HCT and TEL in their combined tablet dosage form. RP, HCT and TEL in mixture have shown linearity response over the range of 0.5-3.5 μgml^{-1} for RP, 1.25-8.75 μgml^{-1} for HCT and 4-28 μgml^{-1} for TEL at the selected wavelengths. The percent of drug in laboratory mixture with ±S.D. was found to be 99.97±0.76, 99.87±0.76 and 101±0.76 for RP, HCT and TEL respectively. The percent drug in marketed formulation ±S.D. was found to be 98.55±1.14, 99.50±1.14and 99.58±1.13.

The accuracy of the proposed method was evaluated by percentage recovery (by standard addition method) of all three drugs. The average recovery was found to be 99.31±0.64, 99.52±0.87 and 99.09±0.94 for RP, HCT and TEL respectively. The results of the method lie within the prescribed limit, showing that method is free from interference from excipients.

CONCLUSION

The obtained results from the multicomponent mode analysis method for simultaneous estimation of Ramipril, Hydrochlorothiazide and Telmisartan indicate that the method is simple, accurate and precise hence can be used for routine analysis of commercially available drugs.

Table T1: Linearity of Ramipril (RP)

Conc. (µg/ml) / Rep.	Absorbance at 218 nm						
	0.5	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**	**3.5**
Replicate-1	0.024	0.058	0.074	0.108	0.126	0.153	0.179
Replicate-2	0.025	0.054	0.075	0.106	0.131	0.148	0.172
Replicate-3	0.026	0.053	0.077	0.104	0.124	0.154	0.174
Replicate-4	0.024	0.055	0.074	0.107	0.122	0.149	0.176
Replicate-5	0.025	0.054	0.073	0.109	0.125	0.152	0.178
Mean	0.025	0.055	0.075	0.107	0.126	0.151	0.176
S.D.	0.0008	0.0019	0.0015	0.0019	0.0033	0.0025	0.0028
% R.S.D.	3.2	3.4	2.0	2.8	3.0	1.6	1.5

Table T2: Linearity and range of Hydrochlorothiazide (HCT)

Conc. (µg/ml) / Rep.	Absorbance at 271 nm						
	1.25	**2.50**	**3.75**	**5.0**	**6.25**	**7.5**	**8.75**
Replicate-1	0.321	0.648	0.959	1.306	1.611	1.926	2.247
Replicate-2	0.328	0.641	0.964	1.311	1.598	1.921	2.252
Replicate-3	0.326	0.649	0.961	1.299	1.604	1.932	2.243
Replicate-4	0.329	0.653	0.965	1.304	1.607	1.934	2.246
Replicate-5	0.321	0.649	0.957	1.308	1.602	1.924	2.251
Mean	0.325	0.648	0.961	1.305	1.604	1.927	2.247
S.D.	0.0034	0.0038	0.0030	0.0040	0.0044	0.0048	0.0033
% R.S.D.	1.04	0.58	0.31	0.30	0.27	0.24	0.14

Table T3: Linearity and range of Telmisartan (TEL)

Conc. (µg/ml) / Rep.	Absorbance at 296 nm						
	4	8	12	16	20	24	28
Replicate-1	0.347	0.695	1.045	1.386	1.738	2.084	2.431
Replicate-2	0.351	0.692	1.048	1.379	1.736	2.079	2.426
Replicate-3	0.354	0.706	1.039	1.384	1.741	2.082	2.429
Replicate-4	0.343	0.702	1.035	1.381	1.738	2.075	2.434
Replicate-5	0.346	0.705	1.041	1.387	1.744	2.078	2.432
Mean	0.348	0.699	1.041	1.383	1.739	2.079	2.431
S.D.	0.004	0.006	0.005	0.003	0.003	0.004	0.003
% R.S.D.	1.23	0.88	0.48	0.24	0.17	0.16	0.12

Table T4: Mixed standard for method development

S.No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Ramipril	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Hydrochlorothiazide	1.25	2.5	3.75	5.0	6.25	7.5	8.75
Telmisartan	4	8	12	16	20	24	28

Table T5: Analysis of Mixed standard

S. No	Concentration Present (µg/ml)			Concentration Found (µg/ml)			Percentage Concentration Found		
	RP	HCT	TEL	RP	HCT	TEL	RP	HCT	TEL
1	0.5	1.25	4	0.498	1.247	3.992	99.6	99.8	99.8
2	1.0	2.5	8	0.989	2.473	7.915	98.9	98.9	98.9
3	1.5	3.75	12	1.496	3.742	11.99	99.7	99.8	99.9
4	2.0	5.0	16	2.012	5.021	16.09	100.6	100.4	100.5
5	2.5	6.25	20	2.489	6.211	19.93	99.6	98.7	99.6
6	3.0	7.5	24	3.035	7.589	24.29	101.2	101.2	101.2
7	3.5	8.75	28	3.508	8.779	28.10	100.2	100.3	100.2

Table T6: Results of Analysis of Mixed standard

S. No.	Drug	%Mean	S.D.	% RSD	Standard Error
1	RP	99.97	0.759	0.759	0.286
2	HCT	99.87	0.759	0.760	0.286
3	TEL	101.0	0.759	0.751	0.286

Table T7: Analysis of laboratory sample

S. No.	Concentration Present (µg/ml)			Concentration Found (µg/ml)			Percentage Of Concentration Found		
	RP	HCT	TEL	RP	HCT	TEL	RP	HCT	TEL
1	1.25	3.125	10	1.232	3.072	9.85	98.4	98.4	98.5
2	2.5	6.5	20	2.471	6.422	19.76	98.8	98.8	98.8
3	3.75	9.625	30	3.723	9.556	29.79	99.28	99.29	99.28

Table T8: Results of Analysis of laboratory sample

S. No	Drug	%Mean	S.D.	% RSD	Standard Error
1	RP	98.83	0.44	0.45	0.259
2	HCT	98.83	0.45	0.46	0.254
3	TEL	98.86	0.39	0.40	0.225

Table T9: Analysis of tablet Sample

S. N.	Concentration Present (µg/ml)			Concentration Found (µg/ml)			Percentage Of Concentration Found		
	RP	HCT	TEL	RP	HCT	TEL	RP	HCT	TEL
1	0.5	1.25	4	0.486	1.214	3.885	97.09	97.12	97.13
2	1.0	2.5	8	0.988	2.465	7.914	98.80	98.60	98.92
3	1.5	3.75	12	1.488	3.722	11.91	99.26	99.25	99.27
4	2.0	5.0	16	2.003	5.008	16.03	100.2	100.2	100.2
5	2.5	6.25	20	2.440	6.102	19.52	97.61	97.64	97.67
6	3.0	7.5	24	2.938	7.345	23.51	97.93	97.74	97.93
7	3.5	8.75	28	3.456	8.663	27.73	99.01	99.02	99.02

Table T10: Results of analysis of tablet Sample

S. No	Drug	%Mean	S.D.	% RSD	Standard Error
1	RP	98.55	1.142	1.159	0.431
2	HCT	98.50	1.141	1.158	0.431
3	TEL	98.58	1.130	1.146	0.427

Table T11: Validation parameters for UV multicomponent mode analysis method:

Validation parameters	RP			HCT			TEL		
	Mean	SD	RSD	Mean	SD	RSD	Mean	SD	RSD
Linearity	0.5-3.5µg/ml			1.25-8.75µg/ml			4-28µg/ml		
Accuracy	99.52	0.64	0.64	99.52	0.87	0.87	99.09	0.94	0.95
Precision:									
Repeatability	98.96	1.042	0.105	99.40	0.512	0.514	99.08	0.760	0.767
Intermediate Precision:									
Day to Day	99.40	0.945	0.950	99.42	0.696	0.700	99.12	0.941	0.941
Analyst to Analyst	98.66	0.749	0.759	98.82	1.011	1.023	98.68	0.830	0.841

Fig.F1 Overlay spectra of Ramipril, Hydrochlorothiazide and Telmisartan

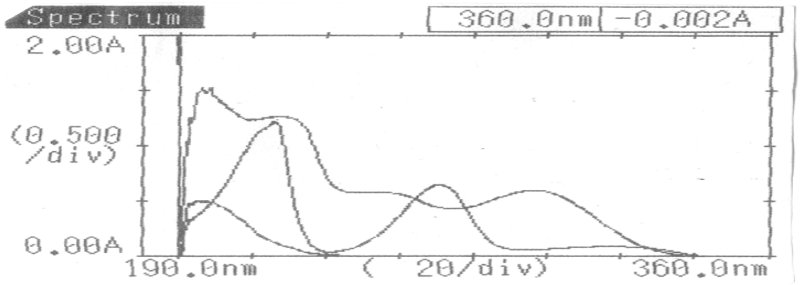
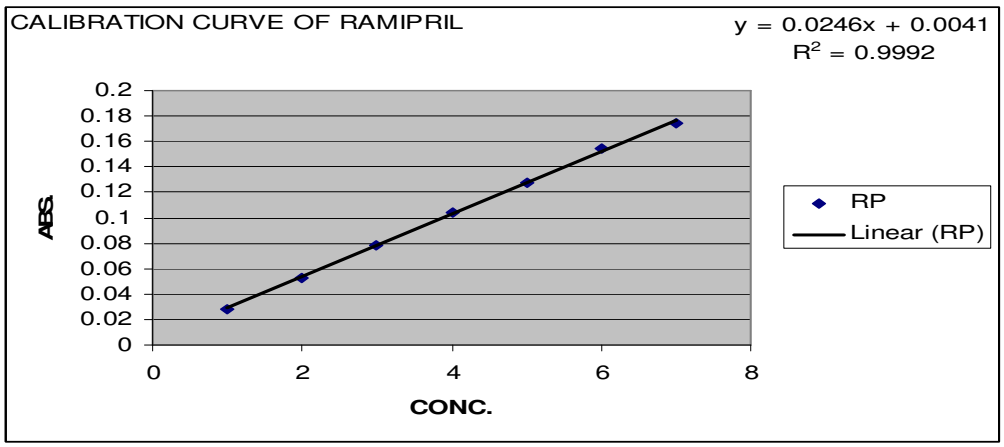


Fig.F2 Calibration curve of Ramipril



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