RESEARCH ARTICLE

A Validated, Fast and Simple, Simultaneous Determination of Captopril and Telmisartan in Laboratory Prepared Mixture for Use in Haemodialysis Patients Suffering from Inflammation

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ABSTRACT

Captopril and telmisartan are widely used anti-hypertensive drugs, and their fixed dose combination is under phase IV trials. In the present study, spectrophotometry and RP-HPLC methods were successfully developed and validated per standard regulations. In UV spectrophotometry method concentrations of captopril and telmisartan in a synthetic mixture prepared in the laboratory were determined using the simultaneous equation method. The linearity was found 8 to 40 µg/mL for captopril and 5 to 25 µg/mL for telmisartan. The R2 (Coefficient of Correlation) value was found to be 0.999 for both drugs. The %assays of the conc. of captopril and telmisartan in synthetic mixture were found in an acceptable range. In the RP-HPLC method %assay was found to be 100.05 and 100.16% with %RSD value of 0.34 and 0.58 for captopril and telmisartan, respectively. The proposed UV and RP-HPLC method simultaneous estimation of captopril and telmisartan has potential application for qualitative identification as well as quantitative determination.

Keywords: Captopril, Telmisartan, Lab-prepared fixed-dose combination, ACE inhibitor, ARB, BCS Class II, RP-HPLC

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INTRODUCTION

The fixed-dose combination of telmisartan and captopril is under phase IV trials.[1] Enzyme inhibition is more beneficial approach then receptor blocking and many novel molecules are synthesized and screened for treatment of various disorders.[2-10] Captopril is a popular ACE inhibitor which used as an anti-hypertensive drug. Telmisartan is a widely used anti-hypertensive drug which is an angiotensin II receptor blocker (ARB). A study revealed that Enalapril, an ACE inhibitor was effective in reducing the blood pressure in hemodialysis patients although not effective in decreasing the IL-6 and CRP levels which are the markers for inflammation.[11] While another study concluded that telmisartan added to standard drug therapies involving ACE inhibitors significantly lowered mortality, CV death and failure of heart in hemodialysis patients with LVEF ≤ 40% and CHF.[12] Another study suggested that telmisartan effectively reduced inflammation and proteinuria in hemodialysis patients.[13] A combination of both drugs can be very useful to lowering blood pressure in hypertension patients. Various analytical methods are reported for single estimation of captopril and telmisartan using spectrophotometric techniques as well as chromatographic estimation.[14-23] Both the drugs captopril and telmisartan are available as oral formulation and hence a synthetic mixture containing captopril 50 mg and telmisartan 80 mg was prepared in laboratory and analytical method was successfully developed and accurately validated for the simultaneous estimation by RP-HPLC method.

MATERIAL AND METHODS

Telmisartan was gifted by from Zota Healthcare Pvt. Ltd. Surat, Gujarat. Captopril was gifted by Globela Pharma Pvt. Ltd. Surat, Gujarat. IR spectroscopy study was performed by using Bruker Alfa FTIR-ATR. Double beam UV-Visible spectrophotometer (Shimadzu UV-1700) was used for the UV method development. Chromatographic analysis was carried out on a LC 100 (CYBER LAB) using manual sampler injection system, Pump: LC P100 binary pump systems, Column C18 (250 mm x 4.6 mm, 5 µm) with UV detector (LC UV 100).

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RESULTS AND DISCUSSION

Melting Point[24]

MP was determined by popular capillary tube method, captopril was melted at 105 to 108°C (106–108°C) and telmisartan was 261 to 263°C (260–264°C).

Solubility Analysis[25]

The solubility profile of drugs is vital for solvent selection and was confirmed against the literature and both drugs were found to be soluble in 0.1N NaOH.

UV Absorption Study

0.1N NaOH used for stock solutions preparation for both drugs and appropriate dilutions were scanned in UV (200–400 nm). 0.1 N NaOH used as a blank, and maximum absorbance was recorded to determine captopril and telmisartan [λ_{max}]. The wavelength maxima of captopril was 262 nm and telmisartan 240 nm found in 0.1 N NaOH (Figure 1).

Identification by IR Spectra

One mg of drug grounded well with 150mg of KBr and preparing discs. Samples were scanned in FTIR spectrometer to confirm the appropriate functional group presence in substance which indicates purity of the material. IR data of Captopril and Telmisartan sample was displayed in Figure 2 and Figure 3.

UV Spectroscopy Method

For the UV spectroscopy method development, 0.1N NaOH was used as a solvent and individual spectra of captopril 8 to 40 µg/mL and telmisartan 5 to 25 µg/mL were found at their λ_{max} (Figure 4 and Figure 5).

Method Validation as Per ICH Regulations

Linearity and range

The correlation coefficient of linear regression analysis is used to express linearity. For the determination of Captopril and Telmisartan linearity 5 different concentration from value

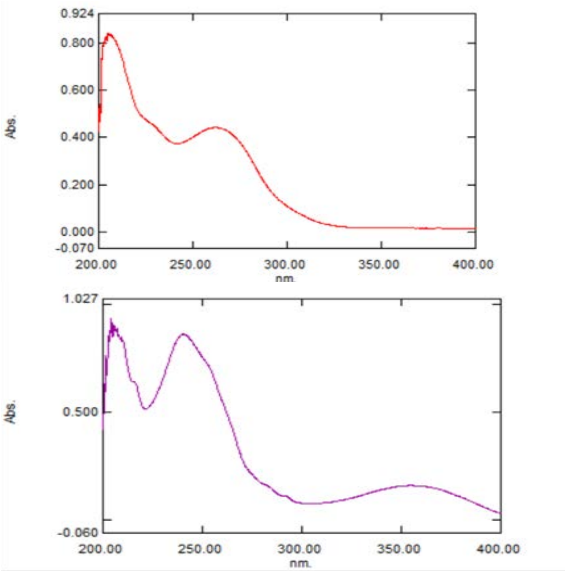

Figure 1: Zero order UV spectra of captopril (10 µg/mL) and telmisartan (10 µg/mL)

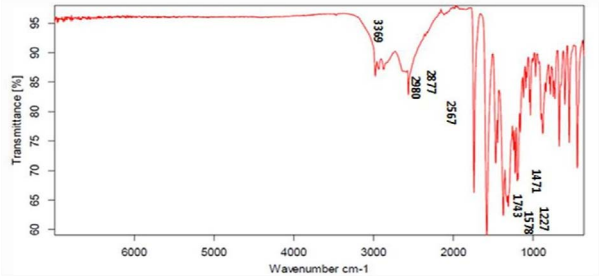

Figure 2: IR spectra of captopril sample

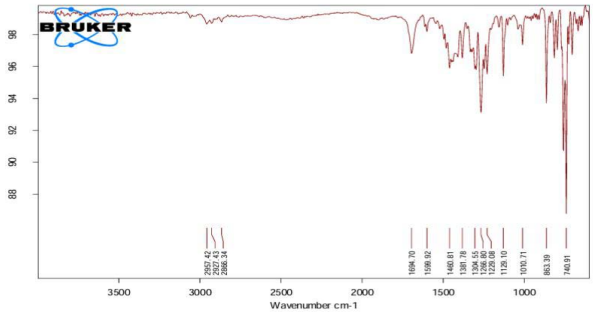

Figure 3: IR spectra of telmisartan sample

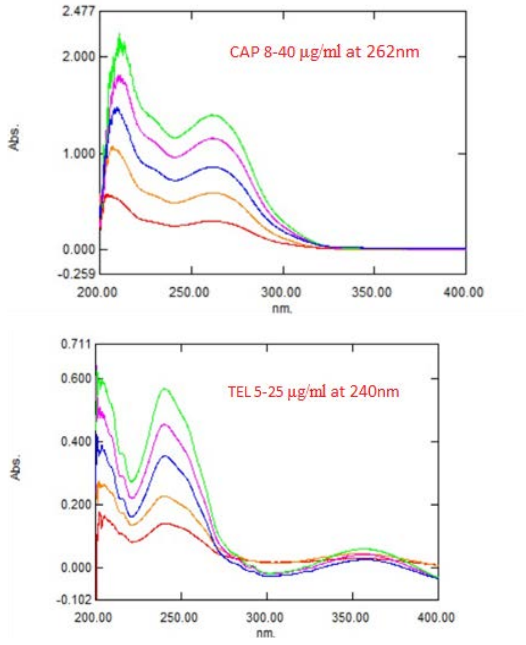

Figure 4: Spectrum of CAP (8–40 µg/mL) and TEL (5–25 µg/mL)

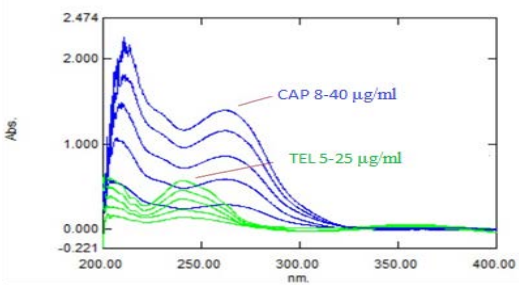

Figure 5: Overlain Spectrum of CAP (8–40 µg/mL) and TEL (5–25 µg/mL)

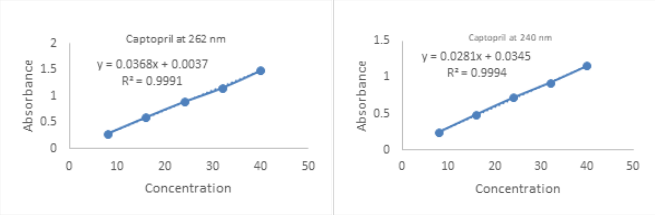

Figure 6: Calibration curve of CAP at 262 and 240 nm

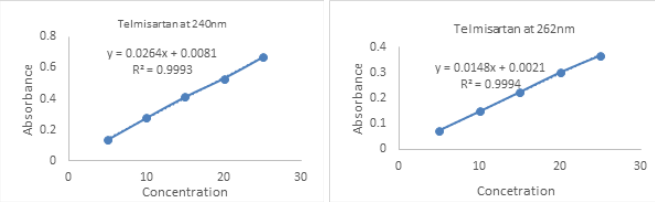

Figure 7: Calibration curve of TEL at 240 and 262 nm

of 8-40 µg/ml and 5-25 µg/ml (n=3) used (Figure 6&7). The absorbance vs. concentration (g/ml) calibration curve was plotted. For Captopril and Telmisartan, the correlation coefficient and regression line equations were determined and tabulated in Table 1.

Precision

Repeatability

24 µg/ml Captopril and 15 µg/ml Telmisartan solutions were scanned six times and %RSD was calculated and tabulated in Table 2.

Intraday precision

Three times (n=3) on the same day, within a brief interval of time, a series of solutions containing 8, 24, and 40 µg/ml of Captopril and 5, 15, and 25 µg/ml of Telmisartan were evaluated, and %RSD was computed and shown in Table 3.

Interday precision

On three consecutive days, a series of solutions containing 8, 24, and 40 µg/ml of CAP and 5, 15, and 25 µg/ml of TEL were evaluated three times (n=3) and percent RSD was computed and shown in Table 4.

LoD and LoQ

The LOD and LOQ for Captopril were found to be 0.5641 and 1.6923 g/ml, respectively. For Telmisartan values of LOD and LOQ were 0.2996 and 0.8988 g/ml respectively. (Table 5)

Table 1: Linear regression parameters for CAP and TEL by simultaneous equation method

Linear regression parameters	*CAP*	*TEL*
Detection wavelength (λmax)	262 nm	240 nm
Range of calibration (µg/mL)	8–40	5–25
Regression equation	Y = 0.0368x + 0.0037	Y = 0.0264x + 0.0081
Regression coefficient	0.9991	0.9993

Table 2: Repeatability study of CAP and TEL

Conc. (µg/mL)		*Mean Abs. ± SD (n=6)*		*% RSD*	
CAP	TEL	CAP	TEL	CAP	TEL
24	15	0.865 ± 0.059	0.395 ± 0.015	0.5986	0.7876

Table 3: Intraday precision study of CAP and TEL

Conc. (µg/mL)		*Mean Abs. ± SD (n=3)*		*%RSD*	
CAP	TEL	CAP	TEL	CAP	TEL
8	5	0.288 ± 0.021	0.134 ± 0.021	0.9562	1.3745
24	15	0.879 ± 0.035	0.396 ± 0.023	1.1426	1.1526
40	25	1.479 ± 0.019	0.651 ± 0.024	0.6843	0.9124

Table 4: Interday precision study of CAP and TEL

Conc. (µg/mL)		*Mean Abs. ± SD (n=3)*		*% RSD*	
CAP	TEL	CAP	TEL	CAP	TEL
8	5	0.292 ± 0.011	0.138 ± 0.0121	0.7698	1.1563
24	15	0.886 ± 0.015	0.402 ± 0.016	1.1256	1.1256
40	25	1.482 ± 0.021	0.662 ± 0.019	0.9586	0.8658

A %RSD value less than 2 indicates the method is highly précised

Table 5: LoD and LoQ values of CAP and TEL

Drug	LoD(g/mL)	LoQ(g/mL)
Captopril	0.5641	0.2996
Telmisartan	1.6923	0.8988

Accuracy

The recovery investigations were conducted in triplicate by adding known amounts of standard to pre-quantified samples

Table 6: Accuracy data of CAP and TEL

Drug	*%Level of spike*	*Amt of drug in sample (µg/mL)*	*Amtof std. added (µg/mL)*	*Total amount of drug (µg/mL)*	*Total amount of std. found (µg) Mean ± SD (n=3)*	*%Recovery*
CAP	0	16	0	16	-	-
	50	16	8	24	8.11 ± 0.0875	101.38
	100	16	16	32	15.86 ± 0.0125	99.06
	150	16	24	40	24.26 ± 0.0458	101.08
TEL	0	10	0	10	-	-
	50	10	5	15	5.11 ± 0.0215	102.2
	100	10	10	20	9.95 ± 0.0264	99.50
	150	10	15	25	15.51 ± 0.0152	103.40

Table 7: Composition of CAP and TEL synthetic mixture

Composition	*Quantity (mg)*
Captopril	80
Telmisartan	50
Lactose Monohydrate	110
Microcrystalline cellulose	10
Croscarmellose sodium	11
Mg. stearate	3
(HPMC) K100	9

Table 8: Analysis data of synthetic mixture

Drug	*Conc (µg/mL)*	*Detected conc. (µg/mL)*	*%Assay Mean ± SD (n=3)*	*%RSD*
CAP	24	24.2	100.8472 ± 0.1879	0.1863
		24.16		
		24.25		
TEL	15	15.37	100.7556 ± 1.7010	1.6873
		14.86		
		15.11		

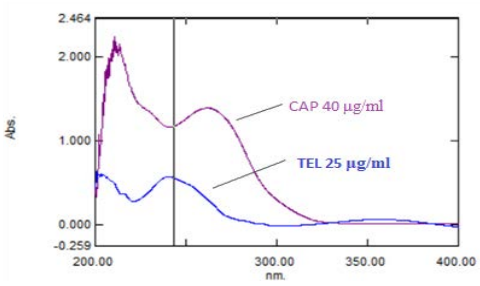

Figure 8: Overlay spectrum of CAP (40 µg/mL) and TEL (25 µg/mL)

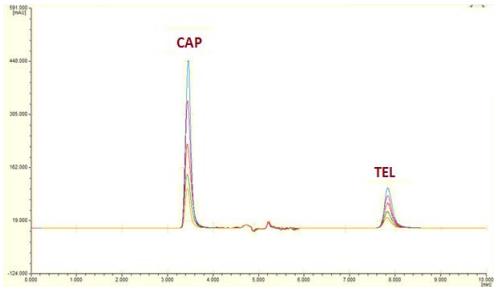

Figure 9: Overlay chromatogram of cAP (8-40 µg/mL) + TEL (5-25 µg/mL) at Rt = 3.53 and 7.83, respectively

Table 9: System suitability test for CAP + TEL = 40 + 25 µg/mL

Parameters	*CAP*	*%RSD*	*TEL*	*%RSD*
Retention time (Rt)	3.52 ± 0.008125	0.22	7.81 ± 0.015725	0.21
Tailing Factor	1.52 ± 0.007124	0.47	1.24 ± 0.012045	0.91
Number of theoretical plates	385896.8 ± 2358.12	0.65	137496.1 ± 1298.24	0.93
Resolution (Rs)	----	----	13.54 ± 0.01642	0.13

(n = 5 determinations)

Table 10: Calibration curve data of CAP

Conc (µg/mL)	*Area Mean ± SD (n=6)*	*% RSD*
8	86001.33 ± 475.76	0.55
16	174392.17 ± 1727.79	0.99
24	258133.50 ± 1174.06	0.45
32	356620.33 ± 3308.90	0.93
40	441252.67 ± 3313.99	0.75

Table 11: Calibration curve data of TEL

Conc (µg/mL)	*Area Mean ± SD (n=6)*	*%RSD*
5	30650.17 ± 227.22	0.74
10	61451.00 ± 353.14	0.57
15	94515.33 ± 306.21	0.32
20	124796.33 ± 1192.93	0.96
25	158547.83 ± 829.95	0.52

Table 12: Regression Analysis of calibration curve

Parameter	*CAP*	*TEL*
Drug amount (µg/mL)	8–40 µg/mL	5–25 µg/mL
Regression equation	y = 11159x - 4539.3	y = 6382.8x - 2350.1
Regression coefficient (r^2)	0.9994	0.9997
mean of slope	11159.5	6382.8
Standard deviation of Intercept	1669.9	485.19
LoD (µg/mL)	0.4935	0.2508
LoQ (µg/mL)	1.4806	0.7522

Table 13: Repeatability data of CAP + TEL (24 + 15 µg/mL)

TRIAL	*CAP (24 µg/mL) Area of Peak*	*TEL (15 µg/mL) Area of peak*
1	257654	94248
2	254789	91879
3	256745	94865
4	256248	94264
5	259754	94785
6	258456	94647
Mean	257274.33	94114.66
SD	1743.54	1125.52
%RSD	0.68	1.19

of synthetic mixture at 50, 100, and 150 percent levels and analysing them using the suggested approach. At 262 nm and 240 nm, the absorbance was measured. As shown in Table 6, The percentage recovery for Captopril was determined to be 99.06-101.38 percent, while for Telmisartan it was 99.5-103.4 percent which reveals that method is highly accurate.

Preparation of Synthetic Mixture

Captopril and telmisartan were mixed in a ratio of 80:50 mg and suitably with excipients. Amount of excipients tabulated in Table 7.

24 µg/mL captopril and 15 µg/mL telmisartan were collected from the synthetic mixture and scanned at 262 nm

Table 14: Precision data of CAP and TEL

Drug	*Conc. (µg/mL)*	*Intraday Precision*		*Interday Precision*	
		Area (Mean ± SD) (n=3)	*%RSD*	*Area (Mean ± SD) (n=3)*	*%RSD*
CAP	8	85925.67 ± 432.99	0.50	86165.00 ± 334.26	0.39
	24	257293.00 ± 2595.10	1.01	257539.67 ± 2668.03	1.04
	40	445516.67 ± 3182.77	0.71	446691.00 ± 4731.44	1.06
TEL	5	60595.00 ± 407.71	0.67	60738.33 ± 745.6	1.23
	15	180948.33 ± 1045.04	0.58	180939.33 ± 918.16	0.51
	25	365650.67 ± 3805.25	1.04	366603.33 ± 5336.51	1.46

Table 15: Accuracy data of CAP and TEL

Drug	*%Levelof spike*	*Amount of drug in sample (µg/mL)*	*Amountof std. added (µg/mL)*	*Total amount of drug (µg/mL)*	*Total amount of std. found (µg) Mean ± SD (n=3)*	*%Recovery*
CAP	0	16	0	16	-	-
	50	16	8	24	8.11 ± 0.91	101.375 %
	100	16	16	32	16.18 ± 1.02	101.125 %
	150	16	24	40	23.89 ± 0.83	99.54 %
TEL	0	10	0	10	-	-
	50	10	5	15	5.08 ± 0.21	101.6 %
	100	10	10	20	9.98 ± 0.39	99.80 %
	150	10	15	25	15.09 ± 0.87	100.6 %

(λ_2) and 240 nm (λ_1) for estimation. In Table 8 shown that the percent assay of the conc. of CAP and TEL in synthetic combination was found to be within acceptable limits.

Analysis of CAP and TEL

Exactly about 80 mg captopril and 50 mg telmisartan were taken and diluted in series with 0.1 N NaOH to make 24 µg/mL. Captopril and 15 µg/mL telmisartan for degassing sonication was used. Solutions were scanned between 200–400 nm in triplicate and a simultaneous equation was used to calculate the concentrations of captopril and telmisartan.

RP-HPLC Method

Preparation of mobile phase

The solution was prepared by combining 0.1 M KH_2PO_4 buffer (pH 3.5 adjusted with OPA): methanol: ACN in the proportion of 20:20:60 v/v/v). The solution was pass out through 0.45 µm membrane filter and degassed by sonication.

Selection of analytical wavelength

Solutions of Captopril (40 µg/ml) and Telmisartan (25 µg/ml) in methanol was scanned properly at 200-400 nm, and it was determined that the drugs show optimum absorbance (Figure 8) without any interferences at 243 nm, and so 243 nm was chosen as the analytical wavelength.

Chromatographic conditions

Column: C18, Cyber - Sil (250 mm x 4.6 mm, 5 µm)
Mobile Phase: 0.1 M KH_2PO_4buffer: methanol: ACN (20:20:60 v/v), pH 3.5
Detector: UV detector (LC UV 100)
Flow rate: 1.0 mL/min
Volume of each injection: 20 µL
Detection wavelength: 240 nm
Mode: Isocratic
Run Timing: 10 minutes

Table 16: LoD and LoQ data of CAP and TEL

Drug	*LoD(g/mL)*	*LoQ(g/mL)*
Captopril	0.4935	0.2508
Telmisartan	1.4806	0.7522

Table 17: Robustness data of CAP and TEL

Parameters	*Normal condition*	*Drug (*µg/mL*)*	*Change in condition*	*Area (Mean ± SD) (n=3)*	*%RSD*
Detection wavelength	240 nm	CAP (24)	238 nm	252208 ± 1264.63	0.5014
			242 nm	259346.33 ± 1273.88	0.4908
		TEL (15)	238 nm	94543 ± 404.08	0.4274
			242 nm	94939 ± 437.34	0.3553
Flow rate	1.0 mL/min.	CAP (24)	0.9 mL/min.	252115 ± 2433.03	0.9650
			1.1 mL/min.	249506 ± 2564.12	1.0276
		TEL (15)	0.9 mL/min.	94844 ± 577.21	0.6085
			1.1 mL/min.	95304 ± 464.51	0.4874

Table 18: Data of determination of CAP and TEL in synthetic mixture

Drug	*Conc. (µg/mL)*	*Amount found (µg/mL)*	*%Assay Mean ± SD (n=3)*	*%RSD*
CAP	24	23.92	100.07 ± 0.63	0.64
		24.19		
		23.93		
TEL	15	15.28	100.85 ± 1.22	1.21
		14.92		
		15.18		

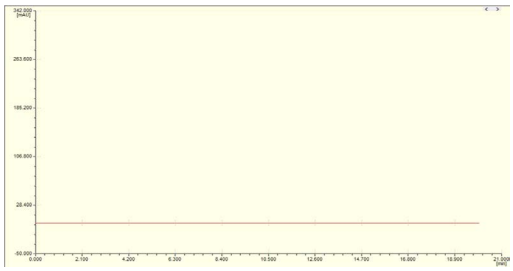

Figure 10: Chromatogram of mobile phase using KH_2PO_4:methanol:ACN (20:20:60 v/v)

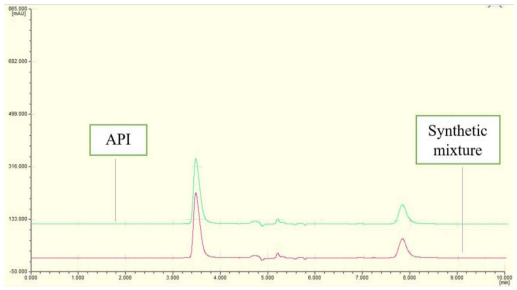

Figure 11: Overlay Chromatogram of CAP (24 µg/mL) + TEL (15 µg/mL)ofAPI and Synthetic mixture at RT = 3.52 and 8.83 minutes, respectively.

Validation of RP-HPLC method

System Suitability Parameters

Results of system suitability parameters are tabulated in Table 9.

Linearity and range

On a linear regression analysis, linearity is measured by the correlation coefficient. Analysis of five distinct levels in the range of 8-40 µg/ml and 5-25 µg/ml for Captopril and Telmisartan, respectively (n=6) was used to assess the linearity of response (Figure 9). Peak area vs. concentration was used to create the calibration curve. For Captopril and Telmisartan, the correlation coefficient and regression line equations were calculated. (Tables 10, 11 and 12)

Precision

Repeatability

Injection repeatability was used to test consistency. Injection repeatability was determined by injecting six times with a standard solution of captopril and telmisartan with amounts of 24 and 15 µg/mL, respectively, and calculating peak area of all with %RSD. Injection repeatability was used to determine repeatability in the RP-HPLC process. Injection repeatability was determined by analyzing the sample solution of captopril + Telmisartan (18 + 3 µg/mL) six times and measuring peak area and %RSD (Table 13).

Intraday and interday precision

It was determined by analyzing standard captopril and telmisartan solutions at three separate levels on the same day for captopril 8, 24, and 40 µg/mL and telmisartan 5, 15, and 25 µg/mL, respectively (Table 14).

Accuracy

The method's accuracy is directly proposal to percentage recovery. In nine different 10 mL volumetric flasks, a pre-quantified sample solution of the synthetic combination was taken. In this pre-quantified sample, a standard CAP and TEL API solution was spiked at three levels (50, 100, and 150%). Data from nine determinations across three concentration levels covering a specific range were determined for each solution, and percent recoveries were calculated.

Recovery studies from synthetic mixtures at 3 levels of standard addition (50, 100, and 150%) validated the method's accuracy. CAP and TEL percent recovery ranged from 99.54 to 101.375% and 99.80 to 101.60%, respectively (Table 15).

Detection Limit (LoD) and Quantitation limit (LoQ)

LOD and LOQ value for Captopril was 0.4935 g/ml and 0.2508 g/ml respectively. For telmisartan values are 1.4806 g/ml and 0.7522 g/mL (Table 16).

Robustness

Small purposeful variations in instrumental settings like mobile phase composition, flow rate, and wavelength of detection were used to test the method's robustness by injecting triplicate injections of standard solutions of 24 and 15 µg/mL of captopril and telmisartan. The effect was investigated by measuring the peak area of solutions and calculating the %RSD. Table 17 shows the results expressed as a %RSD. Less than 2% RSD indicates that the developed method is highly robust.

Specificity

A working standard solution of the captopril and telmisartan bulk drugs and a synthetic mixing solution of captopril and telmisartan and a placebo were injected to verify for the interference of any excipients. There was no interfering peak from the excipient added in the preparation of the synthetic mixture at RT of captopril and telmisartan, validating the method's specificity. Overlay chromatogram of API and Synthetic mixture of Captopril + Telmisartan (24 + 15 µg/mL), respectively, and the chromatogram of mobile phase utilizing buffer:methanol:acetonitrile (20:20:60 v/v), pH 3.5.

The developed HPLC technique for determining captopril and telmisartan has been validated and shown to be specific, linear, precise, and accurate.

Analysis of synthetic mixture

For the determination of captopril and telmisartan in a synthetic combination, the developed and validated HPLC technique was used. Three times the sample was examined. Figure 12 shows an overlay chromatogram of API and a synthetic mixture of

captopril + telmisartan (25 + 15 µg/ml), and Table 21 shows the results of the Captopril and Telmisartan assay in the synthetic mixture. For Captopril and Telmisartan, the percent assay was found to be 100.05 and 100.16%, respectively, with percent RSD values of 0.34 and 0.58. The method's usefulness for determining Captopril and Telmisartan in synthetic mixtures is ensured by a less RSD value (Table 18, Figure 10 and 11).

Selection of analytical wavelength

At 243 nm both drugs showed optimum absorbance without any interference so, 243 nm was chosen as the analytical wavelength.

CONCLUSION

The %assays of the concentraton of CAP and TEL in the synthetic mixture were found in an acceptable range. The % RSD values of 0.34 and 0.58 are well within the prescribed limits. And ensure the applicability of the method. The sample preparation is not tedious and easy without any requirement of costly and toxic chemicals and reagents. The chromatographic separation takes less than 10 minutes, saving the analysts' time and is a preferred timeline ensuring quick separation and quantification of the drugs. For future work, the proposed method can be extended for stability indicating and can also be experimented to prove effective in biological fluids.

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