RESEARCH PAPER

Method Development and Validation of RP-HPLC Method for the Simultaneous Estimation of Captopril and Hydrochlorothiazide in Bulk Drugs and Tablet Formulation

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Abstract: -
A simple reproducible and efficient reversible high performance liquid chromatography (RP-HPLC) method has been developed for estimation of Captopril (CAP) and Hydrochlorothiazide (HTZ) in its pure and tablet dosage form. The mobile phase consisting of methanol: water (PH 3.0 adjusted with ortho phosphoric acid) in the ratio of (80:20%v/v) was delivered at the flow rate of 1.00mL/min and was carried out at 205nm.The separation was achieved using C8 reverse phase column (250mm x 4.6 mm i.d.and 5 µm particle size. The retention time of Captopril and Hydrochlorothiazide was found to be 3.10 and 2.90 min, respectively. The developed method was validated in terms of accuracy, precision, linearity, and recovery, limit of detection and limit of quantitation and can be used for the estimation of these drugs in combined pharmaceutical dosage forms.

Key words: - Captopril, Hydrochlorothiazide, methanol, water, 0.45µ nylon filter paper, RP-HPLC.
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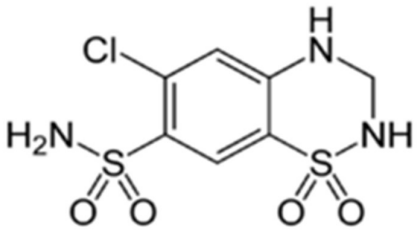
Introduction:-
Captopril is chemically 1-(2 methyl-3-sulphonylpropanoyl) pyrolidine-2-carboxylic acid. With molecular formula $C_9H_{15}NO_3S$ and molecular wt. 217.29 g/mol. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyl dipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss. Hydrochlorothiazide is chemically 6-chloro-1, 1-dioxo-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide.With molecular formula $C_7H_8ClN_3O_4S_2$ and molecular wt. 608.18g/mol.It belongs to Thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electro neutral Na^+-Cl^- co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport. Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.



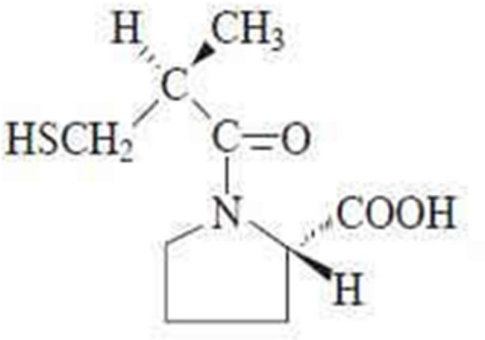


Fig.No1.Captopril

Fig.No.2 Hydrochlorothiazide

Materials and methods:-

Instrumentation:-

Wufeng gradient system UV detector used. In this two samples were injected and it was mixed with the help of mixing vessels. The flow rate was adjusted 1ml/min and the detection wavelength was 205 nm. Gases which was present in the samples were removed by degassing system. Before injecting the sample it was filtered through 0.45µ nylon membrane and then the solution was sonicated for 10min.The column used in this method C_8 grace. The configuration of the column is 4.6 x 250 mm, particle size 5µm.

Chemicals and reagents:-

Captopril and hydrochlorothiazide were obtained as gift samples from Wockhardt Limited Aurangabad (India).Methanol (AR) grade and HPLC grade was purchased and Acetonitrile HPLC grade, Water HPLC grade were purchased and used. The combination of CAP of HTZ are available as tablet dosage forms with trade names CAPOTRIL-H (25 mg captopril and 15 mg hydrochlorothiazide) (TEVA Pharmaceuticals, USA.)

Preparation of stock solution:-

25 mg of Captopril and 15 mg of Hydrochlorothiazide was weighed accurately and transferred to separate 10 ml volumetric flask, dissolved in sufficient quantity of HPLC grade methanol and water (80:20) diluted to 10 ml with the same solvent to give a stock solution of 1000 µg/ml. From that stock solution 1 ml sample was diluted to 10 ml of same solvent that was 100 µg/ml.

Chromatographic condition:-

The mobile phase was a mixture of Methanol and Water (80:20) pH 3 adjusted with ortho phosphoric acid The contents of the mobile phase were filtered, before it was used, through 0.45 µ membrane filter, and sonicated for 10 min.and pumped from the respective solvent reservoirs to the column at a flow rate of 1ml/min, The column used in this method C_8 grace. The configuration of the column is 4.6 x 250 mm, particle size 5µm. The column temperature was maintained at 30oc and run time 20mins.The injection volume of samples was 20µL. The analyte was monitored at 205nm. The chromatographic conditions were shown in fig.3

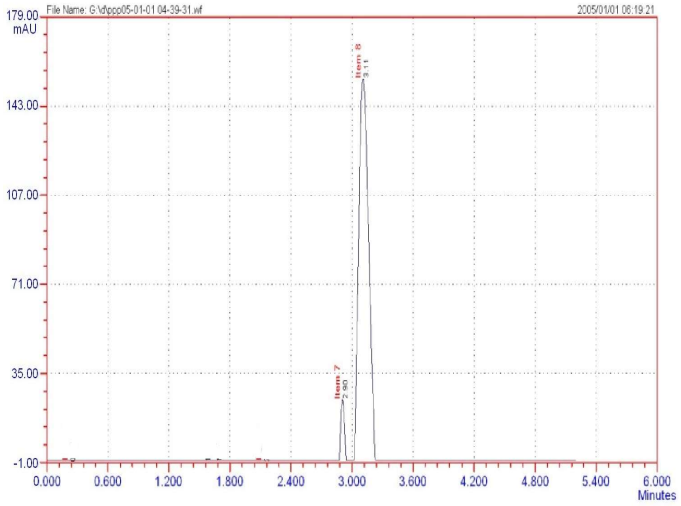


Fig.no.3 Chromatogram of standard mixture of Captopril & Hydrochlorothiazide.

Table No. 1 Details of chromatogram of standard mixture containing Captopril & Hydrochlorothiazide.

Sr.No.	Name of the drug	RT (min)	Area	Therotical plate	Tailing factor
1.	Captopril	3.108	746629	2224	1.90
2.	Hydrochlorothiazide	2.902	227552.6	2402	0.79

Analysis of tablet formulation:

Brand Name: Capotril-H

Each tablet content: Captopril: 25mg

Hydrochlorothiazide: 15mg

Manufacturer: TEVA Pharmaceuticals, USA.
Procedure:-

For analysis of the tablet dosage form, ten tablets were weighed individually and their average weight was determined after that they were crushed to fine powders and powder equivalent to weight 25 mg of Captopril & 15 mg of Hydrochlorothiazide was transferred to 10 ml volumetric flask & dissolved in HPLC grade mix.of methanol and water (80:20). The solution was shaking vigorously for 10 min and filtered through 0.45 µ nylon membrane filters. Then volume was made up to mark with above solution. From the above solution 1 ml of solution was taken and diluted to 10 ml with mobile phase to get a solution containing 100 µg/ml. The solution contains Captopril and Hydrochlorothiazide in the proportions of 1:1. The amounts of Captopril and Hydrochlorothiazide per tablet were calculated by extrapolating the value of area from the calibration curve. Analysis procedure was repeated five times with tablet formulation. Result is shown in (Table No.2.)

Table No. 2 Analysis of marketed formulation.

Sr. No	Amount present in mg		Amount found in mg		% Label claim	
	Captopril	Hydrochlorothiazide	Captopril	Hydrochlorothiazide	Captopril	Hydrochlorothiazide
1	25	15	24.93	14.92	99.75	99.50
2	25	15	24.90	14.99	99.63	99.99
3	25	15	24.78	15.45	99.4	103
4	25	15	24.25	14.96	97	99.79
5	25	15	24.87	15.36	99.48	102.45
Mean	_	_	_	_	99	100.94
SD	_	_	_	_	1.1405	1.6448
%RSD	_	_	_	_	1.1527	1.6294

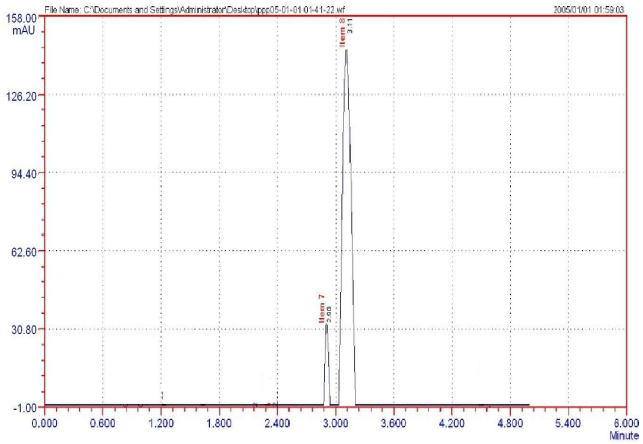


Fig. No.4 Chromatogram of Captopril and Hydrochlorothiazide in tablet formulation.

Table No 3. Details of chromatogram of Captopril and Hydrochlorothiazide in tablet formulation

Sr. No	Name of drug	RT (min)	Area	Therotical plates	Tailing factor
1	Captopril	3.112	779870.4	2052	1.59

2	Hydrochlorothiazide	2.904	297636	2287	0.82

Validation Parameters:-

1. Linearity:

From Captopril standard stock solution, different working standard solutions (20-100µg/ml) were prepared in mobile phase. Likewise from Hydrochlorothiazide standard stock solution different working standard solution (20-100 µg/ml) were prepared in mobile phase. 100 µl of sample solution was injected into the chromatographic system using fixed volume loop injector. Chromatograms were recorded. The area for each concentration were recorded (Table No. 4, 6). The Calibration curves are shown in Fig. No.5, 6.

Table No. 4 Linearity of Captopril.

Sr.No.	Concentration µg/ml	Area
1	20	52961
2	40	106116
3	60	149889
4	80	206279
5	100	260734

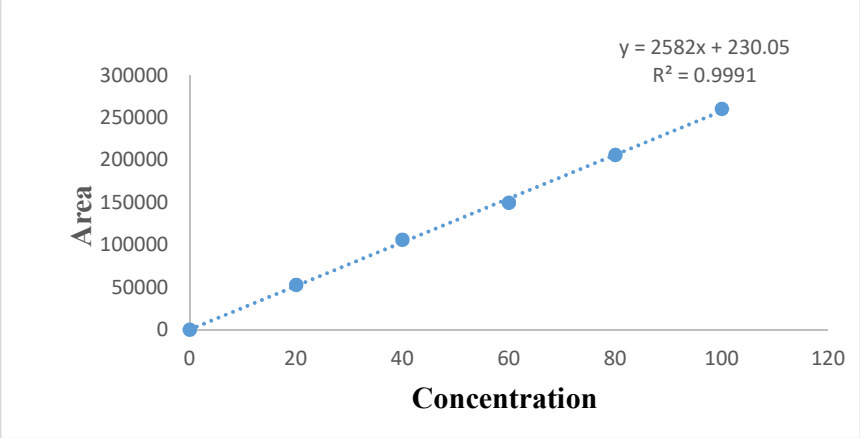


Fig. No. 5 Calibration graph of Captopril.

Table No.5 Regression equation data for Captopril.

Regression Equation Data Y=mx+c	
Slope(m)	2582
Intercept(c)	230.05
Correlation Coefficient	0.9991

Table No.6 Linearity of Hydrochlorothiazide

Sr.No.	Concentration µg/ml	Area
1	20	90083
2	40	198093
3	60	282806
4	80	382300
5	100	478789

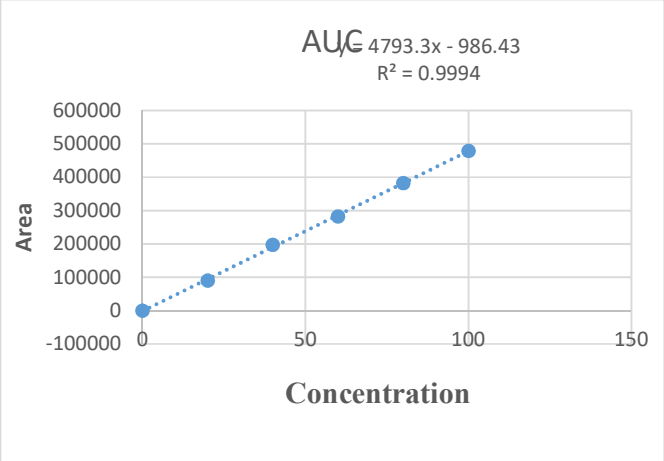


Fig. No.6 Calibration graph of Hydrochlorothiazide.

Table No.7 Regression equation data for Hydrochlorothiazide

Regression Equation Data Y=mx+c	
Slope(m)	4793.3
Intercept(c)	986.43
Correlation Coefficient	0.9994

2. Accuracy:-

Recovery studies were performed to validate the accuracy of developed method. To preanalysed tablet solution, a definite concentration of standard drug (80%, 100%, and 120%) was added and then its recovery was analysed (Table No.8). Statistical validation of recovery studies shown in (Table No.9).

Table No.8 Recovery studies of Captopril and Hydrochlorothiazide.

Level of Recovery (%)	80		100		120	
	CAP	**HTZ**	**CAP**	**HTZ**	**CAP**	**HTZ**
Amount present (mg)	25 25 25	15 15 15	25 25 25	15 15 15	25 25 25	15 15 15
Amount of Std. added (mg)	8 8 8	8 8 8	10 10 10	10 10 10	12 12 12	12 12 12
Amount Recovered (mg)	14.28 14.42 14.40	14.4 14.6 14.8	20.00 20.51 21.05	19.76 20.16 21.62	26.03 27.16 28.62	26.41 26.68 27.78
% Recovery	100.8 99.16 100.01	100 101.6 99.60	100.36 100 99	101.2 101 99	100.3 100.5 99.75	99.74 99.94 100

Table No. 9 Statistical Validation of Recovery Studies.

Level of Recovery (%)	Drug	Mean % Recovery	Standard Deviation*	% RSD
80	**CAP**	99.99	0.82018	0.82026
	HTZ	100.4	1.05800	1.05408
	CAP	101.12	1.18456	1.18314

100				
	HTZ	100.65	0.7858	0.78073
120	**CAP**	100.18	0.3883	0.38766
	HTZ	99.91	0.1473	0.14744

***Denotes average of three determinations.**

3. System suitability parameters:-

To ascertain the resolution and reproducibility of the proposed chromatographic system for estimation of Captopril and Hydrochlorothiazide, system suitability parameters were studied.

The result shown in below Table No. 10

Table No. 10 Result of System Suitability Parameters.

	Proposed Method	
System Suitability Parameters	**CAP**	**HTZ**
Retention time	3.1710	2.902
Area	184937.6	60306.5
Theoretical plate number	2012	2372
Tailing factor	1.42	1.96

4. Precision:-

The method was established by analyzing various replicates standards of Captopril and Hydrochlorothiazide. All the solution were analyzed thrice in order to record any intra-day & inter-day variation in the result. The result obtained for intraday are shown in Table No 11 & 12, the result obtained for interday variation are shown in the Table No 13 & 14 respectively.

Table No. 11 Intra-day precision study of Captopril.

Conc. µg/ml	**Peak area**			**Mean Area**	**SD**	**%RSD**
	Trial 1	**Trial 2**	**Trial 3**			
60	84088	83085	82990	833374	618.66	0.7420
80	193110	193664	189490	192088	2266.92	1.1801
100	214111	214136	219526	215924	3119.15	1.4445

Table No. 12 Intra-day precision study of Hydrochlorothiazide.

Conc. µg/ml	**Peak area**			**Mean Area**	**SD**	**%RSD**
	Trial 1	**Trial 2**	**Trial 3**			
60	195806	192040	191782	193209	2252.47	1.1648
80	272300	263896	268028	268074	4202.19	1.5675
100	428789	423514	419390	423897	4711.23	1.1114

Table No. 13 Inter-day precision study of Captopril.

Conc. µg/ml	**Peak area**			**Mean Area**	**SD**	**%RSD**
	Day 1	**Day 2**	**Day 3**			
60	84075	83078	82987	83380	603.60	0.7239
80	193102	193564	189354	19006	2308.86	1.2024
100	214100	214128	219506	215911	3113.10	1.4418

Table No. 14 Inter-day precision study of Hydrochlorothiazide.

Conc. µg/ml	**Peak area**			**Mean Area**	**SD**	**%RSD**
	Day 1	**Day 2**	**Day 3**			
60	195506	191586	192240	193110	2100.03	1.0874
80	272101	263585	268008	267898	4559.06	1.5898
100	428579	423413	419285	423759	4656.65	1.0988

5.

LOD and LOQ:-

The Limit of Detection (LOD) is the smallest concentration of the analyte that gives the measurable response. LOD was calculated using the following formula and shown in Table No. 15.

LOD = 3.3 (σ / S)
Where, S = slope of calibration curve**,** σ = standard deviation of the response.
The Limit of Quantitation (LOQ) is the smallest concentration of the analyte, which gives a response that can be accurately quantified. LOQ was calculated using the following formula and shown in Table No. 15.
LOQ = 10 (σ / S)
Where, S = slope of calibration curve**,** σ = standard deviation of the response.

Table No. 15 Results of LOD and LOQ

Sample	LOD (µg/ml)	LOQ(µg/ml)
CAP	4.1480	12.569
HTZ	4.4736	13.5563

6. Range:-

The range shown by CAP and HTZ is given as follows.

CAP: 20-100 µg / ml

HTZ: 20-100 µg / ml

7. Robustness:-
The Robustness of a method is its ability to remain unaffected by small deliberate changes in parameters. To evaluate the robustness of the proposed method, small but deliberate variations in the optimized method parameters were done. The effect of changes in mobile phase composition and flow rate on retention time and tailing factor of drug peak was studied.
The mobile phase composition was changed in ± 1 ml proportion and the flow rate was varied by ± 0.1 ml/min of optimized chromatographic condition. The results of robustness studies are shown in Table No. 16. System suitability parameters were also found satisfactory hence the analytical method would be concluded.

Table No. 16 Result of Robustness Studies.

Chromatographic Changes					
Factor	**Level**	**Retention time**		**Tailing factor**	
Flow rate(ml/min)		**CAP**	**HTZ**	**CAP**	**HTZ**
0.9	-0.1	3.14	2.90	1.42	1.96
1.0	0	3.12	2.91	1.40	1.94
1.1	+0.1	3.13	2.92	1.41	1.95
	Mean	3.13	2.91	1.41	1.95
	SD	0.01	0.01	0.01	0.01
	%RSD	0.3194	0.3436	0.7092	0.5128
Mobile Phase (v/v)		**CAP**	**HTZ**	**CAP**	**HTZ**
79:21	-1.0	3.10	2.90	1.42	1.95
80:20	0	3.11	2.92	1.42	1.93
81:29	-1.0	3.14	2.94	1.40	1.96
	Mean	3.116	2.92	1.413	1.946
	SD	0.020817	0.02	0.1154	0.01527
	%RSD	0.6680	0.6849	0.8167	0.7846

Result:-
RP-HPLC method was developed for simultaneous estimation Captopril and Hydrochlorothiazide in bulk and tablet dosage form. The separation was achieved by C_8 Grace column of 4.6×250 mm with particle size packing 5 µm and Methanol: Water (80:20v/v) pH 3 with OPA (orthophosphoric acid) as mobile phase at a flow rate of 1.0 ml/min. The detection was carried out at 205 nm. The retention time of Captopril and Hydrochlorothiazide was found to be 3.10 ± 0.5 min and 2.90 ± 0.5 min respectively. After establishing the chromatographic conditions, analysis of tablet formulation was done. The results are given in **(Table No.2)**
Method validation:

1. Linearity:
Captopril and Hydrochlorothiazide was found to be linear in the range of 20-100 µg/ml and 20-100 µg/ml. Detection wavelength

used was205 nm. **(Table No. 4, 6)** The calibration curve yielded correlation coefficient (r^2) 0.9991 & 0.9994 for Captopril and Hydrochlorothiazide respectively. **(Fig. No. 5, 6)**

2. Precision:

Precision studies were carried out using parameter like intra-day and inter-day precision, the study showed that the results were within acceptance limit. i.e. % RSD below 2.0 indicating reproducibility of the method. **(Table No.11, 12, 13, 14)**

3. Recovery Studies:

Accuracy of method is ascertained by recovery studies performed at different levels of concentrations (80%, 100% and 120%). The % recovery was found to be within 99-101% (**Table No. 8, 9)**

4. System suitability test:

System suitability was performed to verify, whether the resolution and reproducibility of the chromatographic system are adequate. **(Table No. 10)**

5. LOD and LOQ:

The LOD and LOQ were determined by HPLC for Captopril 4.1480µg/ml, 12.569 µg/ml and for Hydrochlorothiazide 4. 4736 µg/ml, 13.5563 µg/ml, respectively. **(Table No. 15)**

6. Robustness:

To evaluate the robustness of the method, the parameters selected were varied at three levels. The results indicate that less variability in retention time and tailing factor were observed. **(Table No. 16)**

Discussion:

The analysis of tablet formulation was done and results obtained within the limits. The results obtained for validation study were also within the limit specified by the ICH guidelines and hence the method was found to be accurate, linear, and precise. The method developed can be used for the routine analysis of Captopril and Hydrochlorothiazide in bulk and tablet dosage form.

Conclusion:-

Attempts were made to develop RP-HPLC method for simultaneous estimation Captopril and Hydrochlorothiazide from Capotril-H tablet. For the RP - HPLC method, Wufeng gradient System UV Detector and C_8 column with 250mm x4.6 mm i.d and 5µm particle size. Methanol: Water (80:20) pH 3 with OPA was used as the mobile phase for the method. The detection wavelength was 205 nm and flow rate was 1 ml/min. In the developed method, the retention time of Captopril and Hydrochlorothiazide were found to be 2.90 min and 3.10 min. The developed method was validated according to the ICH guidelines. The linearity, precision, LOD, LOQ, range, robustness were within the limits as specified by the ICH guidelines. Hence the method was found to be simple, accurate, precise, economic and reproducible.

So the proposed methods can be used for the routine quality control analysis of Captopril and Hydrochlorothiazide in bulk drug as well as in formulations.

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