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Review Article

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Determination of hydrochlorothiazide and drugs in its combination by HPLC

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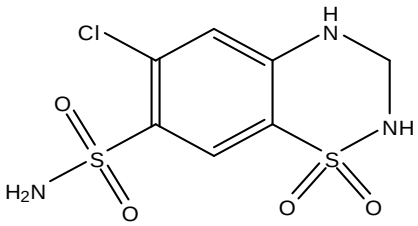
ABSTRACT

In the present time the various diuretic drugs are being used in various combinations and formulations to treat the wide varieties of ailments related to cardiac problems and hypertension. Hydrochlorothiazide is a very important drug which is available in a no. of diuretic combinations. In this review we have represented a few HPLC methods for the determination of Hydrochlorothiazide and other drugs in its combination like amlodipine, telmisartan, candesartan, enalapril, methldopa, bisoprolol, valsartan, lisinopril, losartan etc. in bulk and dosage forms. These drugs are available in various combinations with Hydrochlorothiazide. This review is presenting various newly developed methods and their relevant data for the above mentioned drugs in combination with Hydrochlorothiazide.

Keywords: Hydrochlorothiazide, diuretic, combination.

INTRODUCTION

Hydrochlorothiazide (HCTZ) is a diuretic of the class of benzothiadiazine and widely used in antihypertensive pharmaceutical formulations, alone or combination with other drugs, which decreases active sodium reabsorption and reduced peripheral vascular resistance.[1] It is chemically 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide, and was successfully used as one content in association with other drugs in the treatment of hypertension.[2-3] Hydrochlorothiazide is a diuretic drug of the thiazide class that acts by inhibiting the kidneys ability to retain water.[4]This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance. It is used for the treatment of fluid retention (edema) in people with congestive heart failure, cirrhosis of the liver, or kidney disorders, or edema caused by taking steroids or estrogen.[5] It is frequently given together with other diuretic agents in fixed combination preparations, such as amlodipine, candesartan, losartan, candesartan etc. Hydrochlorothiazide 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 electroneutral Na+-Cl- cotransporter by competing for the chloride site on the transporter.[6-7]



Chemical Structure of Hydrochlorothiazide

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

HPLC (formerly referred to as high pressure liquid chromatography), is a technique in analytical chemistry used to separate the components in a mixture, to identify each component and to quantify each component. It is globally accepted and very popular technique which is nowadays widely used in analytical laboratories and quality control processes.[8] It relies on pumps to pass a pressurized liquid solvent containing the sample mixture through a column filled with a solid adsorbent material. Each component in the sample interacts slightly differently with the adsorbent material, causing different flow rates for the different components and leading to the separation of components as they flow out the column. The principle of HPLC depends on adsorption, partition, exclusion, and ion exchange, depending on the type of chromatography sorbent.[9]

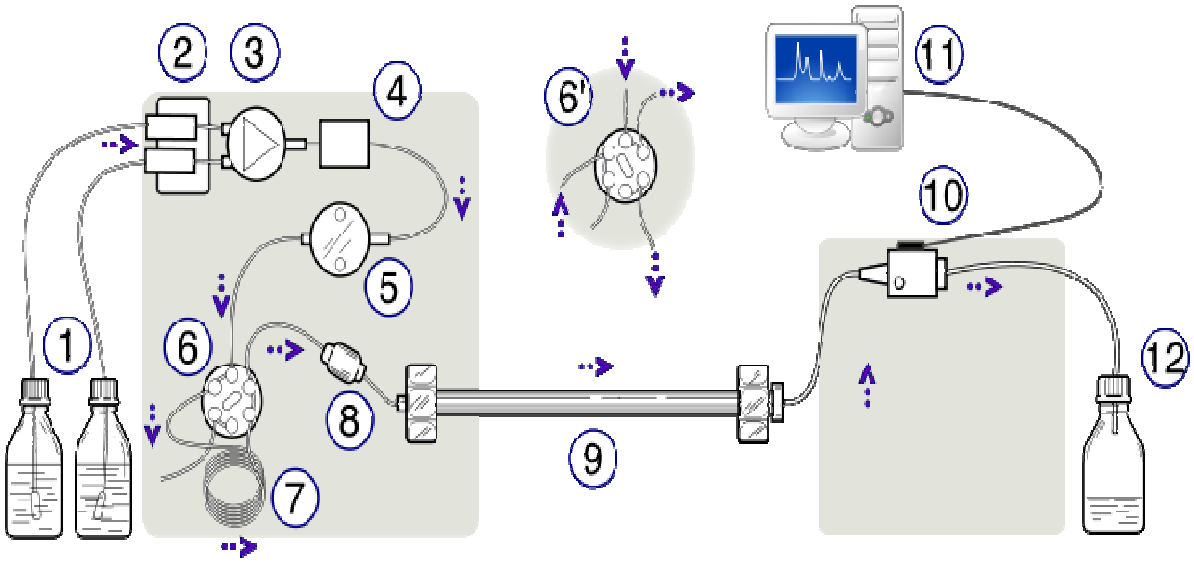


Fig.1: Schematic representation of HPLC unit

(1) Solvent Reservoir (2) Solvent degasser (3) Gradient valve
(4) Mixing vessel for delivery of the mobile phase (5) High-pressure pump
(6) Switching valve in "inject position'' (7) Sample injection loop
(8) Guard column (9) Analytical Column (10) Detector
(11) Data acquisition (12) Waste or fraction collector

HPLC is distinguished from traditional (low pressure) liquid chromatography because operational pressures are significantly higher (50-350 bar), while ordinary liquid chromatography typically relies on the force of gravity to pass the mobile phase through the column. Due to the small sample amount separated in analytical HPLC, typical column dimensions are 2.1-4.6 mm in diameter, 30-250 mm in length. Also HPLC columns are made with smaller sorbent particles (2-50 micrometer in average particle size). This gives HPLC superior resolving power when separating mixtures, which is why it is more popular chromatographic technique.[10]

VALIDATION OF ANALYTICAL METHODS

The purpose of any analytical measurement is to obtain reliable, precise, specific, consistent and accurate data. So the validation of a developed analytical method fulfils the above purpose. Validation is very important in Pharma industry apart from final testing and compliance of product with standard that the process adapted to produce itself must assure that the process will consistently produce the expected results. The validation should be required and carried out according to ICH guidelines. The typical validation parameters which must be considered are given below: [11-15]

ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

PRECISION

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. Precision

should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. Precision includes repeatability, intermediate precision and reproducibility.

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision .

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology.

SPECIFICITY

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s). It includes identification, purity testing and assay.

DETECTION LIMIT

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

QUANTITATION LIMIT

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

LINEARITY

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

RANGE

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Following examples show development of analytical methods for Hydrochlorothiazide and its combinations using HPLC :

HYDROCHLOROTHIAZIDE & TELMISARTAN

Parameter	HCTZ	Telmisartan
Column	Zodiac C18,250× 4.5 mm	Zodiac C18,250×4.5 mm
Detector	UV	UV
Mobile phase	methanol:acetonitrile:water (40:20:20% v/v)	methanol:acetonitrile:water (40:20:20% v/v)
Retention Time	6.14 min.	4.13 min.
Api Concen.	12.5µg/ml	40µg/ml
Resolution	6.14	4.63
Area	457173.0	3750445.0
Tailing Factor	0.87	1.63

FORMULATION OF HYDROCHLOROTHIAZIDE AND TELMISARTAN

Brand	Available Form	Label Claim	Concentration µg/ml	Amount found µg/ml	% Assay
TELISTA-H	Tablet	Tel-40mg HCTZ-12.5mg	Tel-120 HCTZ-37.5	Tel-118.59 HCTZ-37.14	Tel-98.82 HCTZ-99.04

VALIDATION PARAMETERS

DRUG	LINEARITY	% RECOVERY	LOD	LOQ
Hydrochlorothiazide	12.5-87.5µg/ml	98.67-100.99%.	2.5µg/ml	8.25µg/ml
Telmisartan	40-280µg/ml	98.19-101.32%	0.75µg/ml	2.5µg/ml

HYDROCHLOROTHIAZIDE AND ENALAPRIL MALEATE

Parameter	HCTZ	Enalapril Maleate
Column	ODS C18, UG 250mm ×4.5 mm	ODS C18, UG 250mm ×4.5 mm
Detector	UV	UV
Mobile phase	Acetate buffer:Methanol:Acetonitrile (60:20:20 v/v)	Acetate buffer:Methanol:Acetonitrile (60:20:20 v/v)
Retention Time	4.1 min.	2.8 min.
Flow rate	1.5 ml/min	1.5 ml/min
Resolution	2.89	2.89
Theoritical Plates	10363	11456
Tailing Factor	1.3	1.1

FORMULATION OF HYDROCHLOROTHIAZIDE AND ENALAPRIL MALEATE

Available Form	Label Claim	Amount Recovered	%Amount found in drug
Tablet	HCTZ-25mg Enal.-5mg	HCTZ-24.95mg Enal.-5.06mg	HCTZ-99.8 Enal.-101.20

VALIDATION PARAMETERS

DRUG	LINEARITY	% RECOVERY	LOD	%RSD	LOQ
Hydrochlorothiazide	10-30 µg/ml	98.8-100.75%.	0.33 µg/ml	0.79	1.01 µg/ml
Enalapril Maleate	10-30 µg/ml	98.2-101.2%	0.16 µg/ml	0.69	0.49 µg/ml

HYDROCHLOROTHIAZIDE AND LISINOPRIL

1.Parameter	**2.HCTZ**	**3.Lisinopril**
4.Column	**5.**Li Chrosorb C18,10µ,250mm×4.6mm	**6.**Li Chrosorb C18,10µ,250mm×4.6mm
7.Detector	**8.**UV/Vis. SPD-20A	**9.**UV/ Vis. SPD-20A
10. Mobile phase	**11.** potassium dihydrogen phosphate buffer solution : acetonitrile (30:70 v/v)	**12.** potassium dihydrogen phosphate buffer solution : acetonitrile (30:70 v/v)
13. Retention Time	**14.** 6.9 min.	**15.** 3.4 min.
16. Flow rate	**17.** 0.8 ml/min	**18.** 0.8 ml/min

FORMULATION OF HYDROCHLOROTHIAZIDE AND LISINOPRIL MALEATE

Available Form	Label Claim	Amount Recovered	%Amount found in drug
Tablet	HCTZ-12.5mg Lisinopri-20mg	HCTZ-12.3mg Lisinopril.-19.8mg	HCTZ-99.6 Lisinopril.-100.80

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	% RECOVERY	LOD	%RSD	LOQ
Hydrochlorothiazide	25-250µg/ml	0.995	99.84±0.434	100 ng	0.852	50 ng
Lisinopril	50-400µg/ml	0.999	100.1±0.683	20 ng	0.831	10g

HYDROCHLOROTHIAZIDE AND AMLODIPINE

Parameter	HCTZ	Amlodipine
Column	Phenomenex C18,5µ,250mm x 4.6mm	Phenomenex C18,5µ,250mmx 4.6mm
Detector	UV	UV
Mobile phase	Triethylamine:Acetonitrile:Methanol (50:25:25 v/v)	Triethylamine:Acetonitrile:Methanol (50:25:25 v/v)
Retention Time	2.3 min.	6.63 min.
Flow rate	2.0 ml/min	2.0 ml/min
Resolution	9.5	
Theoritical Plates	2919.54	4328.04
Tailing Factor	1.36	1.49

FORMULATION OF HYDROCHLOROTHIAZIDE & AMLODIPINE BESYLATE

Available Form	Label Claim	Amount Estimated	% Recovery
Tablet	HCTZ-12.5mg Amlodipine-5mg	HCTZ-12.41mg Amlodipine-4.9dmg	HCTZ-99.48 Amlodipine-99.37

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	% RECOVERY	LOD	LOQ
Hydrochlorothiazide	200-300µg/ml	0.9998	100.16	3.4 µg/ml	10.31µg/ml
Amlodipine	80-120 µg /ml	0.9999	98.80	0.80 µg/ml	2.43µg/ml

HYDROCHLOROTHIAZIDE AND BISOPROLOL FUMARATE

Parameter	HCTZ	Bisoprolol Fumarate
Column	Inertsil ODS 3V (25cm×4.6mm)	Inertsil ODS 3V (25cm×4.6mm)
Detector	PDA	PDA
Mobile phase	Potassium dihydrogen phosphate buffer : acetonitrile (70:30, v/v)	Potassium dihydrogen phosphate buffer : acetonitrile (70:30, v/v)
Retention Time	5.628 min.	6.916 min.
Flow rate	1.0 ml/min	1.0 ml/min
Resolution	2.87	4.84
Theoritical Plates	38085	43585
Tailing Factor	1.1	0.67

FORMULATION OF HYDROCHLOROTHIAZIDE & BISOPROLOL FUMARATE

Available Form	Label Claim	% Assay
Tablet	HCTZ-6.25 mg Bisoprolol Fumarate-5mg	HCTZ- 100.6 Bisoprolol Fumarate- 100.2

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	% RECOVERY	LOD	LOQ
Hydrochlorothiazide	6.25-125µg/ml	0.9998	100.6	0.01 µg/ml	0.05µg/ml
Bisoprolol Fumarate	2.5-50 µg/ml	0.9996	99.8	0.01 µg/ml	0.03µg/ml

HYDROCHLOROTHIAZIDE AND LOSARTAN POTASSIUM

Parameter	HCTZ	Losartan Potassium
Column	Neosphere C18,10µ, 250mm×4.6mm	Neosphere C18,10µ, 250mm×4.6mm
Detector	UV	UV
Mobile phase	Potassium dihydrogen phosphate buffer solution: acetonitrile (55:45)	Potassium dihydrogen phosphate buffer solution: acetonitrile (55:45)
Retention Time	4.63 min.	7.43 min.
Flow rate	1.0 ml/min	1.0 ml/min
Resolution	11.45	
Theoritical Plates	6792.9	11129.4
Tailing Factor	1.6000	1.2500

FORMULATION OF HYDROCHLOROTHIAZIDE & LOSARTAN POTASSIUM

Available Form	Label Claim	Estimation	% Recovery
Tablet	HCTZ-12.5mg Los. Pot.-50mg	HCTZ-12.41mg Los. Pot.- 49.98 mg	HCTZ-99.99 Los. Pot.-99.85

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	LOD	LOQ
Hydrochlorothiazide	200-300 µg/ml	0.9995	0.91mg/ml	0.31mg/ml
Los. Pot.	80-120 µg/ml	0.9994	0.10 mg/ml	2.77mg/ml

HYDROCHLOROTHIAZIDE & METOPROLOL SUCCINATE

Parameter	HCTZ	Metoprolol Succinate
Column	C-18 column (Lichrospher Merck) 250×4 mm	C-18 column (Lichrospher Merck) 250×4 mm
Detector	UV	UV
Mobile phase	Disodium hydrogen phosphate : methanol: acetonitrile (525:225:250)	Disodium hydrogen phosphate : methanol: acetonitrile (525:225:250)
Retention Time	3.04 min.	5.38 min.
Flow rate	1.0 ml/min	1.0 ml/min

FORMULATION OF HYDROCHLOROTHIAZIDE & METOPROLOL SUCCINATE

Available Form	Label Claim	Estimation	% Recovery
Tablet	HCTZ-12.5mg Met. Suc.-95mg	HCTZ-12.2mg Met. Suc.-93.1mg	HCTZ-99.6 Los. Pot.-100.7

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	% Recovery
Hydrochlorothiazide	2-32 µg/ml	0.9929	97.6 ± 0.5
Met. Suc.	2-32 µg/ml	0.9971	96.1 ± 0.49

HYDROCHLOROTHIAZIDE AND CANDESARTAN CILEXITIL

Parameter	HCTZ	Candesartan cilexitil
Column	Hypersil BDS C18(150×4.6mm, 5µ)	Hypersil BDS C18(150×4.6mm, 5µ)
Detector	SPD 20-A UV/VIS	SPD 20-A UV/VIS
Mobile phase	Phosphate: acetonitrile (55:45 v/v)	Phosphate: acetonitrile (55:45 v/v)
Retention Time	3.6 min.	2.6 min.
Flow rate	1.0 ml/min	1.0 ml/min
Resolution	2.87	4.84
Theoritical Plates	3048	3940

FORMULATION OF HYDROCHLOROTHIAZIDE AND CANDESARTAN CILEXITIL

Brand	Available Form	Label Claim	% Assay
Atacand HCT	Tablet	CAND-32mg HCTZ-25mg	CAND-100.41 HCTZ-99.85

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	LOD	LOQ	ACCURACY	PRECISION
Hydrochlorothiazide	30-70 µg/ml	0.9999	2.59mg/ml	7.85mg/ml	99.86%	0.62
Candesartan cilexitil	38.4-86.6 µg/ml	0.9999	2.04 mg/ml	6.20mg/ml	101.37%	0.34

HYDROCHLOROTHIAZIDE AND METHYLDOPA

Parameter	HCTZ	Methyldopa
Column	Hypersil BDS C8(250×4.6mm, 5µ)	Hypersil BDS C8(250×4.6mm, 5µ)
Detector	UV/VIS	UV/VIS
Mobile phase	Phosphate buffer: acetonitrile (50:50 v/v)	Phosphate buffer:acetonitrile (50:50 v/v)
Retention Time	3.56 min.	2.17 min.
Flow rate	1.0 ml/min	1.0 ml/min
Resolution	5.47	--------
Theoritical Plates	2962.34	2019.92
Tailing Factor	1.32	1.14

FORMULATION OF HYDROCHLOROTHIAZIDE AND METHYLDOPA

Available Form	Label Claim	Amount found	% Assay
Tablet	Methyldopa-250mg HCTZ-25mg	Methyldopa-248.7mg HCTZ-24.94mg	Methyldopa-99.48 HCTZ-99.77

VALIDATION PARAMETERS

DRUG	LINEARITY	r^2	LOD	LOQ	ACCURACY	PRECISION (RT)
Hydrochlorothiazide	6.25-37.5	1.0	0.37mg/ml	1.13µg/ml	99.66%	0.06
Methyldopa	62.5-375 µg/ml	1.0	5.75 mg/ml	17.44µg/ml	99.78%	0.05

CONCLUSION

This review represents determination of Hydrochlorothiazide and other drugs in its combination by HPLC. It can be seen here that there is wide variety of methods in which various parameters differs which affect the relevant data. Analysts can use different types of columns, solvent systems, detectors and validation methods to develop a suitable method. Hence this article will help analysts in their analytical works.

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