WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 12, Issue 8, 85-96 Review Article ISSN 2278 – 4357

A REVIEW ON: ANALYTICAL METHOD FOR DETERMINATION OF EFONIDIPINE HYDROCHLORIDE ETHANOLATE AND CHLORTHALIDONE

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Article Received on
29 May 2023,

Revised on 19 June 2023,
Accepted on 09 July 2023

DOI: 10.20959/wjpps20238-25216

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ABSTRACT

Efonidipine Hydrochloride Ethanolate is the L- type and T-type calcium channel blocker of Dihydropyridine class of drug. It is chemically 2-(*N*-benzyl anilino) ethyl 5-(5, 5-dimethyl-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-1, 4dihydropyridine- 3 carboxylate; ethanol; hydrochloride. It has negative chronotropic and vasodilator effect. Chlorthalidone is a Thiazide - diuretic class of drug. It is chemically is 2-chloro-5-(1-hydroxy-3-oxo-2*H*-isoindol-1-yl) benzene sulfonamide. Which lowers blood pressure by removing extra water and certain electrolytes from the body. Over time it also relaxes blood vessels and improves blood flow. Combination of both drugs used in the treatment of mild to moderate hypertension in adult patient whose blood pressure is not adequately controlled by monotherapy. Two simple, precise and economical UV spectrophotometric methods have been developed for the simultaneous estimation of Efonidipine Hydrochloride Ethanolate and Chlorthalidone in their synthetic mixture. This review focuses on the recent developments in analytical techniques for estimation of Efonidipine Hydrochloride Ethanolate and Chlorthalidone.

KEYWORD: Efonidipine Hydrochloride Ethanolate, Chlorthalidone, Analytical Techniques.

INTRODUCTION

High blood pressure (HBP), commonly known as hypertension (HTN or HT), is a chronic medical condition in which the blood pressure in the arteries remains consistently high. A chronic medical illness commonly known as the "silent killer" is characterized by a persistent elevation of either the systolic or diastolic pressure above 140/90 mmHg. Numerous illnesses, such as pheochromocytoma, hyperthyroidism, hyperaldosteronism, primary renal failure, and aortic coarctation, raise arterial pressure.

To achieve the therapeutic objectives, the majority of hypertension patients will require a combination of antihypertensive medications. To lower blood pressure below the prescribed level, over 70% of hypertension individuals need to take at least two antihypertensive medications together. Diuretics, ACE inhibitors, angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]), -adrenoceptor antagonists (-blockers), renin inhibitors, calcium channel blockers, and central sympatholytic are some of the main drug classes used to treat hypertension therapeutically.

Efonidipine Hydrochloride Ethanolate is the L- type and T-type calcium channel blocker of Dihydropyridine class of drug. It blocks both L and T-type Calcium channels. It differs from other dihydropyridine in having a phosphonate nucleus at 5th position of the dihydropyridine ring. It has negative chronotropic and vasodilator effect. It has weak inotropic effect. It causes increase in glomerular filtration rate without increasing intra glomerular pressure. It causes relaxation of afferent and efferent arterioles and reduces proteinuria. It has organo-protective effects on heart and kidney. Efonidipine Hydrochloride Ethanolate has a more benefits Compared to the Amlodipine, Nifedipine and Cilnidipine.

Chlorthalidone is a thiazide-like diuretic used for the treatment of hypertension and for management of edema caused by conditions such as heart failure or renal impairment. Chlorthalidone improves blood pressure and swelling by preventing water absorption from the kidneys through inhibition of the Na+/Cl− symporter in the distal convoluted tubule cells in the kidney.

Combination of both drugs used in the treatment of mild to moderate hypertension in adult patient whose blood pressure is not adequately controlled by monotherapy.[1-3]

Physical and Chemical properties

- Efonidipine Hydrochloride Ethanolate is pale yellow to Greenish yellow crystalline powder. IUPAC name of Efonidipine Hydrochloride Ethanolate is 2-(*N*-benzyl anilino) ethyl 5-(5,5- dimethyl-2-oxo-1, 3,2λ^5- dioxaphosphinan-2-yl)-2, 6-dimethyl-4-(3-nitrophenyl)-1, 4dihydropyridine -3carboxylate; ethanol; hydrochloride. The Molecular formula is $C_{36}H_{45}ClN_3O_8P$ and Molecular weight is 714.19 g/mole. Solubility of Efonidipine Hydrochloride Ethanolate is practically insoluble in water, soluble in Dimethylformamide, sparingly soluble in methanol. Chemical structure of Efonidipine Hydrochloride Ethanolate isshow in Fig 1. [4,5]

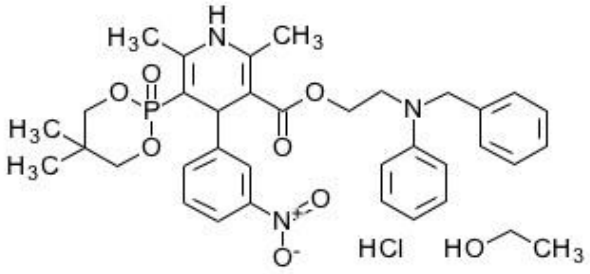

Fig. 1: Chemical Structure of Efonidipine Hydrochloride Ethanolate.

- Chlorthalidone is White to yellow- white crystalline powder. IUPAC name of Chlorthalidone 2-chloro-5-(1-hydroxy-3-oxo-2*H*-isoindol-1-yl) benzene sulfonamide. The Molecular formula is $C_{14}H_{11}ClN_2O_4S$ and Molecular weight is 338.8 g/mole. Chlorthalidone is practically insoluble in water in ether and in chloroform; soluble in methanol; slightly soluble in alcohol. Chemical structure of Chlorthalidone is show in Fig 2. [6,7]

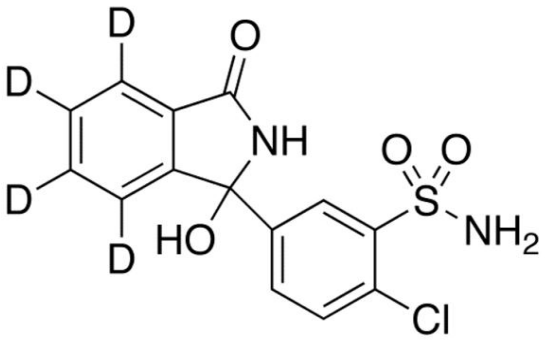

Fig. 2: Chemical Structure of Chlorthalidone.

Analytical method development

The discovery, development, and production of pharmaceuticals depend heavily on the development and validation of analytical methods. An analytical method's suitability for use in determining the concentration of an API in a pharmaceutical dosage form is demonstrated through the process of method development. The validation of analytical methods is crucial for the development of analytical methods and involves rigorous testing for robustness, linearity, accuracy, precision, range, detection limit, and specificity.

Every year, more medications are being released onto the market. These medications could be brand-new substances or structural changes to already-approved medications. Under these circumstances, the pharmacopoeias may not provide analytical processes and standard methods for these medications. Therefore, it is essential to create newer analytical techniques for such medications. Quality control laboratories apply the established test procedures to guarantee the provenance, identity, potency, and effectiveness of pharmaceutical items. To analyze the analyte there are several methods such UV Spectrophotometry, HPLC (High Performance liquid chromatography), HPTLC (High performance thin layer chromatography), UPLC (Ultra performance liquid chromatography), Stability indicating High Performance liquid chromatography, LC- MS/MS (Liquid chromatography-mass spectroscopy-mass spectroscopy), spectrofluorimetric, GC/MS (Gas chromatography-mass spectroscopy etc.[8,9]

LITERATURE REVIEW

Literature review of Efonidipine Hydrochloride Ethanolate

Efonidipine Hydrochloride Ethanolate is not officially available in any pharmacopoeia.

Table no. 1: Reported methods for Efonidipine Hydrochloride Ethanolate in single dosage form.

Sr. No.	Title/Method	Description	Ref. No.
1.	Analytical method development and validation of Efonidipine Hydrochloride Ethanoate in bulk and dosage form by UV-visible spectrophotometry	**Solvent:** Methanol **Wavelength:** 253 nm **Linearity:** 10-30 µg/mL **r^2:** 0.997	[10]
2.	RP-HPLC method development and validation for the quantification of Efonidipine Hydrochloride in HME processed solid dispersions.	**Column:** Agilent Eclipsed XDB-C_{18}(250mm x 4.6mm); 5µm **Mobile phase**: Acetonitrile: Potassium dihydrogen Phosphate buffer (pH2.5), (85:15%v/v)	[11]

		Wavelength: 252nm **Flow rate:** 1.2 ml/min **Retention time:** 6 min **Linearity:** 2.5–100 µg/mL	
3.	Development and Validation of Liquid Chromatography (RP HPLC) Methodology for Estimation of Efonidipine HCl Ethanolate (EFD)	**Column:** C_{18} (250mm ×4.6 mm) ;5 µm **Mobile phase:** Acetonitrile: Water(85:15 %v/v) **Wavelength:** 254nm **Flow rate:** 0.8 ml/min **Retention time:** 6.39 min **Linearity:** 20-140 µg/mL	[12]
4.	Forced degradation studyof Efonidipine HCl Ethanolate, characterization of degradation products by LC-Q-TOF-MS and NMR	**Column:** Thermo Hypersil BDS C_{18}(250mm × 4.6 mm); 5 µm **Mobile phase:** Ammonium acetate buffer (pH 5):Acetonitrile (35:65% v/v) **Wavelength**:254nm**Flow rate:**1 ml/min **Retention time:** 57.66 min **Linearity**: 20–120 µg /mL	[13]

Table no. 2: Reported methods for Efonidipine Hydrochloride Ethanolate in combined dosage form.

Sr. No.	Title/Method	Description	Ref. No.
1.	Spectrophotometric simultaneous determination of Efonidipine Hydrochloride Ethanolate and Telmisartan in synthetic mixture by first order derivative method	**Solvent:** Methanol **Wavelength:** Efonidipine HCl Ethanolate: 231 nm Telmisartan: 238 **Linearity:** Efonidipine HCl Ethanolate: 2-18 µg/mL Telmisartan: 4-36 µg/mL **r^2:** Efonidipine HCl Ethanolate: 0.999 Telmisartan:0.999	[14]
2.	Development and validation of UV Spectrophotometric method for simultaneous estimation of Efonidipine Hydrochloride Ethanolate and Chlorthalidone in their synthetic mixture	**Solvent:** Methanol **Wavelength:** Efonidipine HCl Ethanolate: 283.2 nm Chlorthalidone: 250.8 nm **Linearity:** Efonidipine HCl Ethanolate: 6.4-38.4 µg/mL Ch Chlorthalidone:2- 12µg/mL **r^2:** Efonidipine HCl Ethanolate: 0.997 Chlorthalidone:0.997	[15]

3.	RP-HPLC method development and validation for simultaneous estimation of Efonidipine Hydrochloride Ethanolate and Telmisartan in their synthetic mixture	**Column:** Phenomenex Kinetex ® 5µ C18 Size: 150 * 4.6mm **Mobile phase:** Acetonitrile:25mM Phosphate Buffer pH 4.9 (45:55V/V) **Detected Wavelength:** Efonidipine HCl Ethanolate: 253 nm Telmisartan: 238 nm **Flow rate:** 0.8 mL/min **Retention Time:** Efonidipine HCl Ethanolate: 7.77 min Telmisartan: 4.10min **Linearity:** Efonidipine HCl Ethanolate: 5 - 30 µg/mL Telmisartan: 10-60 µg/mL **r^2:** Efonidipine HCl Ethanolate: 0.997 Telmisartan: 0.999	[16]

Literature Review of Chlorthalidone

Table no. 3: Official Methods for Chlorthalidone.

Sr. No.	Official In	Method	Description	Ref. No.
1.	IP	Related substances, determine by thin layer chromatography	**Column:** Coating plate with silica gel GF_{254} **Solvent:** A mixture of 75 volumes of butanol and 15 volumes of 1 M ammonia **Detected Wavelength:** 254 nm **Injection volume:** 10 µl	[17]
2.	USP	Related substances, determine by liquid chromatography	**Column:** 4.6 mm ×25 cm column that contains packing L7 **Mobile phase:** 0.01 M dibasic ammonium phosphate and methanol (3:2) pH 5.5 adjusted with phosphoric acid. **Detected Wavelength:** 254 nm **Injection volume:** 25 µl	[18]
3.	EP	Related substances, determine by thin layer chromatography	**Column: S**ilica gel GF_{254} R **Mobile phase:** Water: Acetone **Detected Wavelength:** 254 nm **Injection volume:** 5 µl	[19]

Table 4: Reported methods for Chlorthalidone in single dosage form.

Sr. No.	Title/Method	Description	Ref. No.
1.	Development and Validation for Estimation of Chlorthalidone in Bulk and Tablet Dosage Form by UV Spectrophotometry	**Solvent:** 0.1 N NAOH **Wavelength:** 229 nm **Linearity:** 4-9 µg/mL **r^2:** 0.996	[20]
2.	Method Development and Validation for Estimation of Chlorthalidone in Bulk and Tablet Dosage Form by UV Spectrophotometry	**Solvent:** Methanol **Wavelength:** 227 nm **Linearity:** 2-10 µg/mL **$r^{2:}$** 0.999	[21]
3.	A Validated RP-HPLC Stability Method for the Estimation of Chlorthalidone and Its Process-Related Impurities in an API and Tablet Formulation	**Column:** C8(250 × 4.6 mm; ‘5 µm particle size) **Mobile phase**: buffer solution (diammonium hydrogen orthophosphate (10 mM, pH 5.5) and Methanol (65: 35v/v) **Wavelength**: 220 nm **Flow rate: 1.4ml/min** **Retention time:** 7.4 ml/min **Linearity:** 10-50 µg/mL **r^2:** 0.999	[22]

Table 5: Reported methods for Chlorthalidone in combined dosage form.

Sr. No.	Title/Method	Description	Ref. No.
1.	Simultaneous UV Spectrophotometric Estimation of Amlodipine and Chlorthalidone in Bulk and Combined Tablet Dosage Form	**Solvent:** Methanol **Wavelength:** Chlorthalidone: 284 nm Amlodipine: 225 nm **Linearity:** Chlorthalidone: 2.5-12.5 µg/mL Amlodipine: 6.25-31.5 µg/mL **r^2:** Chlorthalidone: 0.999 Amlodipine: 0.999	[23]
2.	Development and validation of an UV spectrophotometric method for simultaneous determination of Cilnidipine and Chlorthalidone	**Solvent:** Methanol **Wavelength** Chlorthalidone: 278 nm Cilnidipine:271nm **Linearity** Chlorthalidone: 2.5-12.5 µg/mL Cilnidipine: 2-10 µg/mL **r^2**: Chlorthalidone: 0.998 Cilnidipine: 0.999	[24]
3.	Development and validation of an UV spectrophotometric method for	**Solvent:** Methanol **Wavelength**	[25]

	simultaneous determination of Chlorthalidone and Losartan potassium	Chlorthalidone: 280 nm Losartan: 235 nm **Linearity** Chlorthalidone: 2-10 µg/mL Losartan: 4-20 µg/mL **r^2** Chlorthalidone: 0.997 Losartan: 0.999	
4.	RP-HPLC Method For Simultaneous Determination of Losartan and Chlorthalidone in Pharmaceutical Dosage Form `	**Column:** Phenomenex C18 **Mobile phase:** Acetonitrile: Water (80:20) **Detected Wavelength:** Chlorthalidone:284 nm Losartan: 238 nm **Flow rate:** 1.0 mL/min **Retention Time:** Chlorthalidone: 1.72 min Losartan: 2.84 min **Linearity:** Chlorthalidone: 20 - 100 µg/mL Losartan:10-60 µg/mL **r^2:** Chlorthalidone: 0.999 Losartan: 0.996	[26]
5.	Stability Indicating RP – HPLC Method Development and Validation for Simultaneous Estimation of Amlodipine and Chlorthalidone in Bulk and Tablet Dosage Form	**Column:** Octadecylsilane C18 (5 µm, 25cm × 4.6 mm) **Mobile phase:** 0.1 formic acid: methanol: acetonitrile (50:5:45v/v) **Detected Wavelength:** Chlorthalidone: 266 nm Amlodipine:266 nm **Flow rate:** 1.0 mL/min **Retention Time:** Chlorthalidone: 6.32 min Amlodipine: 5.32 min **Linearity:** Chlorthalidone: 2.5-7.5 µg/mL Amlodipine: 6-18 µg/mL **$r^{2:}$** Chlorthalidone: 0.9940 Amlodipine:0.9990	[27]

6.	Validated HPTLC Method For the Simultaneous Estimation of Losartan Potassium and Chlorthalidone in Combined Tablet Dosage Form	**Mobile phase:** Chloroform: Methanol: Ammonia (9: 2: 0.2, v/v) **Detected Wavelength:** 254 nm **Flow rate:** 1.0 mL/min **Linearity** Chlorthalidone: 0.5-1.1ng/spot Losartan: 1.4 – 2ng/spot **$r^{2:}$** Chlorthalidone:0.999 Losartan: 0.996 **Rf Value:** Chlorthalidone: 0.458(±0.03) Losartan:0.115 (±0.03)	[28]
7.	Development and validation of HPTLC method for simultaneous determination of Telmisartan and Chlorthalidone in bulk and pharmaceutical dosage form	**Mobile phase:** Acetonitrile: Toluene: Glacial Acetic acid (7.5: 2.5: 0.05 v/v/v **Detected Wavelength:** 242 nm **Flow rate:** 1.0 mL/min **Linearity** Chlorthalidone: 125-750 ng/spot Telmisartan: 400 – 2400 ng/spot **r^{2}:** Chlorthalidone: 0.999 Telmisartan: 0.997 **Rf Value:** Chlorthalidone: 0.67(±0.02) Telmisartan: 0.26 (±0.02)	[29]

CONCLUSION

The presented review conducting Literature on Analytical method development for Efonidipine Hydrochloride Ethanolate and Chlorthalidone. However, for estimation of Chlorthalidone, UV, HPLC, HPTLC and methods were reported for individual drug and along with other drugs and for Efonidipine Hydrochloride Ethanolate only UV, HPLC, and LC/MS methods were reported on individual drugs. Only UV method available on this combination. Thus, there is a scope to develop chromatographic methods for combination of Efonidipine Hydrochloride Ethanolate and Chlorthalidone and Validation of the same. This review carried out an overview of the current Updating analytical method for analysis of Efonidipine Hydrochloride Ethanolate and Chlorthalidone. Presented information is useful for future prospective study for researcher in bio analytical research and Quality Control.

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