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ANALYTICAL METHODOLOGIES FOR ESTIMATION OF EFONIDIPINE HYDROCHLORIDE ETHANOATE AND CHLORTHALIDONE: A DETAILED REVIEW

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ABSTRACT

Hypertension, also known as high blood pressure, is a chronic medical condition in which the force of the blood against the walls of the arteries is consistently too high. Efonidipine hydrochloride ethanoate is a calcium channel blocker, that inhibits both the L and T-type calcium channels, it exhibits an antihypertensive effect. Chlorthalidone is a thiazide-like diuretic. Chlorthalidone improves blood pressure and swelling by preventing water absorption from the kidneys by inhibiting Na^+/Cl^- in the distal convoluted tubule cells in the kidney. This review consolidates the analytical methods, for the estimation of Efonidipine Hydrochloride Ethanoate and Chlorthalidone individually or in combination with other drugs. Various analytical techniques like HPLC, UV, HPTLC, and LC-MS methods have been reported for the estimation of the prescribed drugs.

Keywords: Hypertension, Efonidipine Hydrochloride Ethanoate, Chlorthalidone, Analytical methods

INTRODUCTION:

Hypertension is a chronic medical disorder characterized by consistently raised blood pressure within the arteries over an extended period. High blood pressure typically does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, and chronic kidney disease. To lower blood pressure below the prescribed level, over 70% of hypertension individuals need to take at least two antihypertensive medications together i.e., Diuretics, ACE (Angiotensin-Converting Enzyme) 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 **[1, 2]**.

Hypertension is categorized into various stages based on blood pressure readings: **Normal:** Less than 120/80 mm Hg, **Elevated:** Systolic between 120-129 mm Hg and diastolic less than 80 mm Hg, **Stage 1 Hypertension:** Systolic between 130-139 mm Hg or diastolic between 80-89 mm Hg, **Stage 2 Hypertension:** Systolic at least 140 mm Hg or diastolic at least 90 mm Hg **[3]**.

India's Hypertension Burden: India alone has an estimated 188.3 million adults aged 30–79 years grappling with hypertension. The prevalence of high blood pressure in India is slightly lower than the global average of 31%. To reach a 50% control rate, India needs to ensure that an additional 67 million people with hypertension receive effective treatment. If the progress scenario were achieved, 4.6 million deaths due to high blood pressure would be averted by 2040. Through programs such as India Hypertension Control Initiative Program (IHCI) and the government's push towards **non-communicable disease** screening and treatment at the primary healthcare level, India aims to put 75 million patients with hypertension or diabetes on standard care by 2025 **[4]**.

Efonidipine hydrochloride ethanoate: Pale yellow to greenish yellow Crystalline powder. IUPAC name of Efonidipine hydrochloride ethanoate 2-(N-benzyl aniline) ethyl 5-(5,5- dimethyl-2-oxo-1,3,2λ5-dioxaphosphinan-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4 dihydropyridine -3carboxylate; ethanol; hydrochloride. The Molecular Formula is $C_{36}H_{45}ClN_3O_8P$ and the Molecular Weight is 714.19 g/mol. Solubility of Efonidipine hydrochloride ethanoate Insoluble in water, soluble in dimethyl sulfoxide, methanol **[5, 6]**. Efonidipine hydrochloride ethanoate is a calcium channel blocker that inhibits dihydropyridine class's L and T type calcium channels, causing negative chronotropic and vasodilator effects, relaxation of blood vessels, and reduced proteinuria, facilitating blood circulation **[7]**.

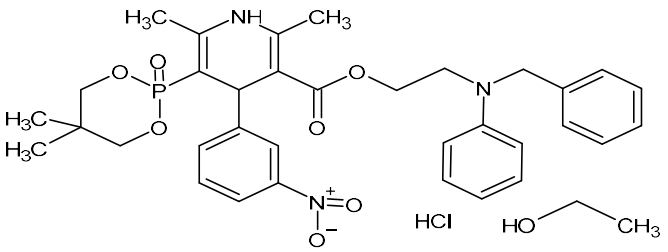

Figure 1: Chemical Structure of Efonidipine hydrochloride ethanoate

Chlorthalidone: It is a White to yellowish-white crystalline powder. IUPAC name of Chlorthalidone is 2-Chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzene sulphonamide. The Molecular Formula is $C_{14}H_{11}ClN_2O_4S$ and the Molecular Weight is 338.8 g/mol. Solubility of Chlorthalidone is Soluble in water, methanol, warm ethanol, slightly soluble in ether and chloroform **[8]**. Chlorthalidone is a diuretic used to treat hypertension and manage edema from heart failure or renal impairment. It improves blood pressure and swelling by inhibiting water absorption from the kidneys, reducing swelling **[1, 9]**.

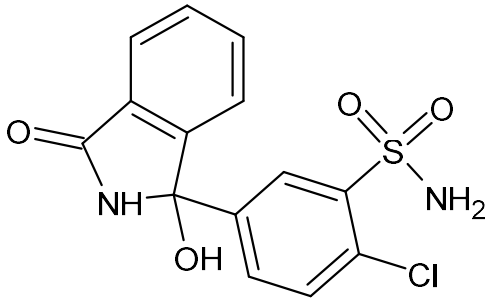

Figure 2: Chemical Structure of Chlorthalidone

The fixed-dose combination formulation of Efonidipine hydrochloride ethanoate and Chlorthalidone is a promising therapeutic approach for managing **hypertension.** This fixed-dose combination (FDC) aims to enhance blood pressure control by leveraging the complementary actions of a calcium channel blocker (CCB) and a thiazide-like diuretic. Efonidipine inhibits the L-type and T-type calcium channels in vascular smooth muscle and cardiac tissue, causing vasodilation and reducing peripheral resistance. Chlorthalidone is a thiazide-like diuretic that helps reduce blood pressure by promoting the excretion of sodium and water, which decreases blood volume and systemic vascular resistance **[1, 10]**.

Table 1: RP-HPLC Method for Estimation of Efonidipine Hydrochloride Ethanoate

Author & Publication	Drug	Column	Mobile Phase	Detector	Flow rate	Results
Rajput A. S, Jha D K, Gurram S, Shah D S and Amin P D (2020) [11]	Efonidipine hydrochloride ethanolate	Agilnt Eclipse d XDB-C18	Acetonitrile and 0.020 mol/L KH_2PO_4 (85:15 v/v)	252 nm	1.2 ml/min	Retention time – 3.4 ± 0.1 Assay –99.74% %Recovery-99.36 ± 0.5 LOD -0.34 µg/ml LOQ- 1.04 µg/ml
Shah P, Gajjar A (2021) [12]	Efonidipine hydrochloride ethanoate	C18	Methanol and water (50:50, % v/v)	270 nm with UV visible detector	0.8 ml/min	Retention time -3.38 min Assay -99.52% %Recovery-99.2-99.5% LOD and LOQ -0.788 µg/ml and 0.2336 µg/ml

Koli P, Dudhrejiya A, Patel A, Chavda J (2021) [13]	**Efonidipine and Telmisartan**	**Waters C18**	**potassium dihydrogen orthophosphate, acetonitrile (30:70 %v/v)**	**254 nm with Dionex sapration modeule with UV detector**	**0.8 ml/min**	**Retention time – 7.933 min and 3.187 min Assay -98.53% and 98.68% %Recovery-98.00-100.10 % and 98.31-100.10% LOD - 0.028 µg/ml and 0.086 µg/ml LOQ -0.032 µg/ml and 0.097 µg/ml**
Patel G H, Adeshra SD, Meshram D B (2021) [14]	**Efonidipine Hydrochloride Ethanolate and Telmisartan**	**Phenomenx Kinetex ® 5µ C18**	**Acetonitrile: Phosphate Buffer (45:55% v/v)**	**253 nm**	**1ml/min**	**Retention time –7.77 and 4.10 mins %Recovery-99.75% - 100.10% LOD -0.15 and 0.07 µg/mL LOQ-0.45 and 0.23 µg/mL**
Patel B, Vekaria H (2022) [15]	**Telmisartan and Efonidipine**	**Inertsil OSD C18**	**0.05M KH2PO4 buffer (pH3.5) and acetonitrile**	**PDA detector at 254 nm**	**1.0 ml/min**	**Retention time - 2.720 and 4.430 min Assay -99.361 and 102.341 % LOD and LOQ - 2.245 µg/ml and 1.35 µg/ml**
Baman V, Ninama H, Gajre R, Dalwadi M, Upadhyay U (2022) [16]	**Efonidipine, Telmisartan, Chlorthalidone**	**Cybersil C18 column**	**KH_2PO_4, methanol, and acetonitrile**	**254 nm**	**1 ml/min**	**Retention time – 6.88, 5.34 and 8.25 min %Recovery-100.10-102.93 %, 97.90-103.37 % and 98.03-101.39% LOD- 0.47 µg/ml, 0.95 µg/ml and 0.34 µg/ml LOQ-1.57 µg/ml, 3.18 µg/ml and 1.15 µg/ml**

Table 2: UV Method for Estimation of Efonidipine Hydrochloride Ethanoate

Author	Drug	Solvent	Wavelength selected	Assay	Recovery	LOD	LOQ
Jalkote NR, Kaulage MS, Kshirsagar PN, Khan BW, Mane PS, Kuber GV (2022) [17]	**Efonidipine**	**Methanol**	**253 nm**	**98%**	**96.8-99.1%**	**2.82 µg/ml**	**8.57µg/ml**
Dudhrejiya A, Patel A, Chavda J, GolD, Koli P (2022) [18]	**Efonidipine Hydrochloride Ethanoate and Telmisartan**	**Methanol**	**231nm and 238nm**	**100 % and 99.95 %**	**98-101 % and 98.46-99.77%**	**0.40 µg/ml and 0.11 µg/ml**	**1.21 µg/ml and 0.34 µg/ml**

Pandya CP, Rajput SJ (2019) had proposed aof ammonium acetate buffer and acetonitrile in degradation pathway for Efonidipinegradient mode. Detection of degradation products hydrochloride ethanoate where 6 degradationwas carried out at a wavelength of 254 nm with a products were identified in alkaline conditions,flow rate of 1ml/min. The method was found and four products were identified in photolyticlinear over the concentration range of 20-120 conditions using LC-Q-TOF-MS (Liquidµg/ml, with co-relation coefficient (R^2) 0.999. The Chromatography Quadrupole Time-of -Flightresults % recovery was found in the range of 99.7-Mass Spectrometry). To identify the degradation100.25% and % RSD for precision study was less products, HPLC was used with a ThermoHypersilthan 2 % **[19]**.

BDS C18 column, and mobile phase was consisted

Table 3: RP-HPLC Method for Estimation of Chlorthalidone

Author & Publication	Drug	Column	Mobile Phase	Detector	Flow rate	Results
Mhaske R. A, Sahasrabudhe S and Mhaske A A (2012) [20]	Irbesartan, Losartan, Hydrochlorothiazide and Chlorthalidone	Hypersil BDS	Sodium dihydrogen phosphate buffer and ACN	UV detection at 220 nm	1.0 ml/min	Assay-99.59 %, 99.49%, 99.57% and 99.59% %Recovery- 99.79%, 100.11%, 100.42% and 98.41%
Kasimala M B , Babu B K. (2012) [21]	Azilsartan Medoxomil and Chlortalidone	Symmetry C18 column	Methanol: Water: ACN: 0.1% OPA 30:35:15:5 (%v/v/v/v)	UV detected at 251nm	0.9 ml/min	Retention time-7.208 min and 3.923min %Recovery –99.735% and 99.80% LOD-0.07ppm and 0.009ppm LOQ-0.02ppm and 0.03ppm
Raval K, Srinivasa U (2013) [22]	Chlorthalidone and Metoprolol Succinate	Hypersil BDS C18	Methanol: acetonitrile (50:25:25)	UV detection at 223 nm	1 ml/min	Retention time-4.390 min and 6.127 min %Recovery –100.90% and 100.38% LOD-0.22 µg/ml and 0.39 µg/ml LOQ-0.67 µg/ml and 1.20 µg/ml
Jyothi A. N, Ali S S, Nalluri B N ,Unnisa A(2014) [23]	Metoprolol succinate and Chlorthalidone	Inertsil ODS column	10mM ammonium acetate: acetonitrile (70:30%v/v)	PDA detection at 220 nm	1 ml/min	Retention time-5.6min and 7.5min Assay-99.86% and 100.8% %Recovery –99.17 and 99.75% LOD-0.339 µg/ml and 1.029 µg/ml LOQ-0.217 µg/ml and 0.659 µg/ml
Naazneen S, Sridevi A (2014) [24]	Azilsartan Medoxomil and Chlorthalidone	BDS C18 column	Phosphate Buffer and Acetonitrile (90:10 %v/v)	PDA detected at 260 nm	0.9 ml/ min	Retention time-2.36±0.1 mins and 5.54±0.5 min Assay-100.24% and 99.75% %Recovery –100.16% and 99.88% LOD-0.027 µg/ml and 0.033µg/ml LOQ-0.080 µg/ml and 0.100 µg/ml
Sravani P, Kumar S, Duganath N, and Devanna (2014) [25]	Azilsartan and Chlorthalidone	ODS (250 mm: 4.6 mm, 5µm)	0.1% Ortho phosphoric acid buffer and acetonitrile (30:70 % v/v)	230 nm	1 ml/min	Retention time- 3.923 min and 7.208 min Assay-100.08 % and 100.15 % %Recovery – 99.92% and 99.845 LOD-0.39 µg/ml 0.34 µg/ml LOQ- 1.17 µg/ml, 1.02 µg/ml
Aneesh T P, Renju R, Aravind P M , Sasidharan A, Choyal M (2015) [26]	Losartan and Chlorthalidone	Phenomenex C18 column	Acetonitrile and water (80:20 % v/v)	284 nm	1.0 ml/ min	Retention time-2.14 and 3.80 min Assay-99.56% and 99.36% %Recovery –99.86-100.41 and 99.47-100.22% LOD-1.97 µg/ml and 5.63 µg/ml LOQ-1.67 µg/ml and 5.12 µg/ml
Dangre P, Sawale V, Meshram S, Gunde M (2015) [27]	Eprosartan mesylate and Chlorthalidone	Gemini C18 (250×4.6 mm, 5 µm)	water: acetonitrile (pH 3.4) 55:45 %v/v	UV detector	1.0 ml/ min	Retention time-2.14 and 3.80 min LOD-30 ng/ml and 80 ng/ml LOQ-15 ng/ml and 60 ng/ml
Panchal R S, Thakkar D, Patel M B(2015) [28]	Clonidine HCl and Chlorthalidone	LC- 20 AT C18	Buffer (pH 4.0)-Methanol (70:30)	220 nm	1.0 ml/min	Retention time-5.980 min and 4.150 min %Recovery –99.56-101.02% and 99.11-100.88% LOD-0.293 µg/ml, 3.916 µg/ml LOQ-0.888 µg/ml, 11.866 µg/ml
Patel R D, Luhar S V, Narkhede S B (2016) [29]	Cilnidipine, Olmesartan and Chlorthalidone	Shiseido C18 column	acetonitrile, methanol and water (40:20:20 %v/v/v)	226 nm	1.0 ml/min	Retention time-5.366 min, 2.693 min and 3.760 min Assay-99.9-100.15%,100.1-100.12%, and 99.62-100.16% %Recovery –98.9-101.52%,99.21-100.88% and 99.03-100.81% LOD-15.06 ,31.57, 18.33 µg/ml LOQ-45.63, 95.69, 55.55 µg/ml
Sonawane S, Jadhav S, Rahade P, Chajed S, Kshirsagar S (2016) [30]	Chlorthalidone	C18 column	Methanol: acetonitrile: phosphate buffer	241 nm	1.0 ml/min	Retention time-6.72 min LOD-0.678 µg/ml LOQ-0.678 µg/ml

			(30:10:60 %v/v/v)			
Sreelatha P, Reddy D. V, Palavai S R and Devi B.R (2016) [31]	**Olmesartan and Chlorthalidone**	**BDS C18**	**10 mM orthophosphoric acid buffer and ACN (45:55 %v/v)**	**PDA detector**	**1.0 ml/min**	**Retention time-3.216 and 2.113 min Assay-99.9% to 102.6% and 97.8% to 99.6%**
Solanki V S, Bishnoi R S, Baghel R, and Jain D (2018) [32]	**Cilnidipine, Atenolol, and Chlorthalidone**	**Hypersil-keystone C18**	**Methanol and triple distilled water 80: 20 %v/v**	**UV detected at 225nm**	**1.0 ml/min**	**Retention time-3.25 min, 5.366 min and 9.025 min %Recovery –99.31%, 98.26% and 98.00%**
Muthyala N, Naresh B (2019) [33]	**Chlorthalidone**	**Develosil ODS HG-5 RP C18**	**0.1% Orthophosphoric acid:ACN: Methanol (12:18:70 %v/v/v)**	**UV detection at 245 nm**	**1ml/min**	**%Recovery –98% -102% LOD-0.08 µg/ml LOQ-0.24 µg/ml**
Patel BD, Chaudhary A, Gami S. (2019) [34]	**Chlorthalidone, Benidipine HCl and Telmisartan**	**C18 HyPersil BDS**	**Buffer (pH 3.0): methanol in a ratio of (50:50 %v/v)**	**230 nm with UV detector**	**1ml/ min**	**Retention time - 4.887 min, 6.690 min and 8.813 min Assay-98.89%,96.80%and 97.01 %Recovery-100.56,101.12 and 100.37% LOD-0.281,0.122 and 1.587 µg/ml LOQ-0.850,0.369 and 4.810 µg/ml**
Subudhi S K, Gayathri, Khanam M F, Akshitha M, Ali, M F (2019) [35]	**Chlorthalidone**	**Phenomenex Luna C18**	**Phosphate dihydrogen phosphate buffer: Methanol 55:45 %v/v (pH-3.4)**	**244 nm**	**1.0 ml/ min**	**Retention time- 7.0 min Assay-99.06% %Recovery –98.95% -100.40% LOD-0.09 µg/ml LOQ-0.27 µg/ml**
Muthyala N, Naresh B. (2019) [36]	**Chlorthalidone**	**Phenomenex Luna C18**	**0.1% Orthophosphoric acid: Acetonitrile: Methanol (12:18:70 v/v/v)**	**UV detection at 245 nm**	**1.0 ml/ min**	**Retention time- 3.444 min Assay-99.86% %Recovery –100.725 LOD-0.08 µg/ml LOQ-0.24 µg/ml**
Jagadeesh K, Annapurna N (2020) [37]	**Benidipine and Chlorthalidone**	**…**	**methanol-0.1M dipotassium hydrogen phosphate buffer (40:60, v/v)**	**photodiode array (PDA) 260nm**	**1.0 ml/ min**	**Retention time- 4.573 min and 6.422 min %Recovery –99.95 - 100.25% and 99.60 - 99.63% LOD-0.004 µg/ml,0.005 µg/ml LOQ-0.013 µg/ml, 0.016 µg/ml**
Mahaparale SP, Chopade JR, Kudale MR (2020) [38]	**Chlorthalidone, Telmisartan, and Amlodipine**	**C18 Column**	**0.1 % v/v of orthophosphoric acid: acetonitrile in a ratio of 60: 40% v/v**	**221nm**	**0.8 ml/min**	**Retention time -0.8 ml/min %Recovery-99.10-100.63 %, 99.36-100.93% and 99.43-101.84 % LOD-0.59 µg/ml , 0.71 µg/ml and 0.45 µg/ml LOQ-0.71 µg/ml, 1.69 µg/ml and 1.37 µg/ml.**
Kharat C, Shirsat VA,Kodgule YM, and Kodgule M. (2020) [39]	**Chlorthalidone**	**C_8**	**Buffer solution and methanol**	**220nm with PDA detector**	**1.4 ml/min**	**Retention time- 6.729min %Recovery-97.74- 100.99 LOD-0.12 µg/ml LOQ-0.10 µg/ml**
Paliwal A, Tiwari N, Patani P J Emerg Tech Inno Res (2021) [40]	**Chlorthalidone, Metoprolol succinate and Telmisartan**	**HyPersil BDS C18**	**buffer solution mixed with methanol in a ratio of 50:50 %v/v**	**215nm with SPD 20 A UV Detector.**	**1.0 ml/ min**	**Retention time- 6.690, 8.813 and 4.887min Assay-96.80%,97.0%and 96.89% %Recovery -100.39-101.12 %, 99.0-101.4 %, and 100.56- 101.37 % LOD-0.2819 µg/ml, 7.2120 µg/ml and 1.0264 µg/ml LOQ-0.8543 µg/ml, 21.8547 µg/ml and 3.1105 µg/ml**

Shaikhmulani HI, Tamboli AM, Tamboli NA, Kshirsagar RT, Suryawanshi HT, Khandare O (2022) [41]	Benidipine hydrochloride and Chlorthalidone	C18 Aglient Zorbax Bonus-RP (250× 4.6mm, 5 µm)	Methanol and 0.1 % v/v orthophosphoric acid (45:55 %v/v)	Photodiode Array Detector	1.0 ml/ min	Retention time-3.52 min and 1.09 min Assay-100.99 % and 100.15 % LOD-2.05 µg/ml and 7.71 µg/ml LOQ-6.22 µg/ml and 23.38 µg/ml

Table 4: UV Method for Estimation of Chlorthalidone

Author	Drug	Solvent	Wavelength selected	Assay	Recovery	LOD	LOQ
Haque A M, Nivedita G, Kumar PK, Kumar PT, Hasan A S and Diwan PV (2012) [42]	Atenolol and Chlorthalidone	Methanol	225nm & 284nm	98.3% and 100.16%	_	4 µg /ml and 10 µg/ml	10 µg/ml and 30 µg/ml
Abdullah NS, Hassan MA, Hassan R((2014) [43]	Chlorthalidone	Methanol	Zero order 276nm First order-278&288 Second order-286&292	Zero-101.77% First-100.46% &101.37% Second-101.42&102.28%	_	_	_
Ingle SU, Patil PA, Kulkarni VC, Patil SV, Salunke PA, Wagh RS (2014) [44]	Chlorthalidone	0.2M NaOH	274.5 nm	100.04%	97.87-107.39 %	_	_
Patel SN, Hinge M A, Bhanushali V M. (2015) [45]	Cilnidipine and Chlorthalidone	Methanol	271-278 nm and 233-250 nm	100.98-102.45% and 100.06-101.46%	100-104.16% and 99.62-100.2%	0.4174 and 0.068 µg/ml	1.264 and 0.206 µg/ml
Bhanushali VM, Hinge MA, Patel SN. (2015). [46]		Methanol	280-290.5nm 235-245nm	98.99-102.32% & 99.74-101.02%		0.01 µg/ml & 0.02 µg/ml	0.03µg/ml & 0.07 µg/ml
Chaudhari SR and Shirkhedkar AA (2021) [47]	Chlorthalidone and 1, 2-naphthoquinone-4-sulfonate		440.50nm	99.17±0.40	_	0.58 µg/ml	1.72 µg/ml

Table 5: HPTLC Method for Estimation of Chlorthalidone

Author	Drug	Description & Results
Sangle S, P Deshpande, N Shinde and V Tayade (2017) [48]	Olmesartan medoxomil and Chlorthalidone	Stationary Phase: Silica gel 60F254 (10 × 10 cm) Mobile Phase: Toluene: Ethyl acetate: Methanol (5: 3: 2, v/v/v) Wavelength: 229 nm Rf valve:0.48±0.02 and 0.72±0.02 %RSD for Precision: >2 %Recovery: 98-102% LOD: 53.73 ng/ band and 7.43 ng/ band LOQ: 162.83 ng/ band and 22.52 ng/ band % Assay:99.71 and 100.45%
Chaudhary BR, Dave JB (2020) [49]	Telmisartan, Amlodipine and Chlorthalidone	Stationary Phase: Silica gel 60 F254 Mobile Phase: chloroform: toluene: methanol: glacial acetic acid (6:2:2:0.1 % v/v/v/v) Wavelength: 254nm Rf valve: 0.64±0.008, 0.25±0.008 and 0.48±0.01 %RSD for Precision: >2 %Recovery: 98-101% LOD: 19.98, 5.32, and 11.28 ng/band LOQ: 60.55, 16.12, and 34.18 ng band % Assay: 99.71 and 100.45%
Prajapati P, Patel M, Shah S (2021) [50]	Chlorthalidone and Metoprolol succinate.	Stationary Phase: Silica gel GF254 Mobile Phase: toluene-methanol-triethylamine (8:2:0.5 v/v/v) %RSD for Precision: >2 %Recovery: 98-102% LOD: 29.13ng/spot and 151.36 ng/spot LOQ: 58.87 ng/spot and 88.29 ng/spot % Assay: 99.62 % ± 0.71% and 100.25 % ± 0.65 %.

CONCLUSION

From this review, the literature survey revealed that no analytical method was reported for Efonidipine Hydrochloride Ethanoate and Chlorthalidone. However, for estimation of Efonidipine Hydrochloride Ethanoate UV, HPLC and LC-Q-TOF-MS methods were reported for individual and along with other combinations. Similarly, for Chlorthalidone UV, HPLC and HPTLC methods were reported for individual and along with other drug combinations. Thus, there is a scope to develop spectroscopic and chromatographic methods for the combination of Efonidipine Hydrochloride Ethanoate and Chlorthalidone and validate the same. This review carried out an overview of the current analytical methods for the estimation of Efonidipine Hydrochloride Ethanoate and Chlorthalidone which will be useful for further research on this combination.

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