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REVIEW ON VARIOUS ANALYTICAL METHODS FOR ANALYSIS OF EFONIDIPINE HYDROCHLORIDE ETHANOLATE IN INDIVIDUAL AND COMBINED DOSAGE FORMS.

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ABSTRACT

The present review focus on all the reported analytical methods that have been developed for analysis of Efonidipine Hydrochloride Ethanolate in single and multiple drug Combinations. Efonidipine hydrochloride Ethanolate is a new generation dihydropyridine (DHP). The presented information is useful for future prospective study for researcher in bio analytical research, Quality control, formulation development. The reported analytical methods are UV visible spectroscopy, GC-MS, RP-HPLC, HPTLC and LC-MS/MS for the estimation of Efonidipine Hydrochloride Ethanolate in single and combined dosage forms. Out of all the mentioned techniques Reverse phase High-performance liquid chromatography and LC-MS/MS have been found the most acceptable for the analysis of Efonidipine hydrochloride Ethanolate. The column used in RP-HPLC is Agilent Eclipsed XDB- C18 (250mm x 4.6mm); 5µm, where as in LC-MS/MS CHIRALPAK (®) ID column is used. The solvents used were Acetonitrile, Potassium dihydrogen Phosphate buffer, Ammonium acetate buffer for both RP-HPLC and LC-MS/MS. It was also observed that the optimum flow rate for both the methods was found to be in between 0.8 min/mL to 1.2min/mL.

KEYWORDS: Efonidipine Hydrochloride Ethanolate, RP-HPLC, LC-MS/MS, UV, GC-MS, Stability indicating methods.

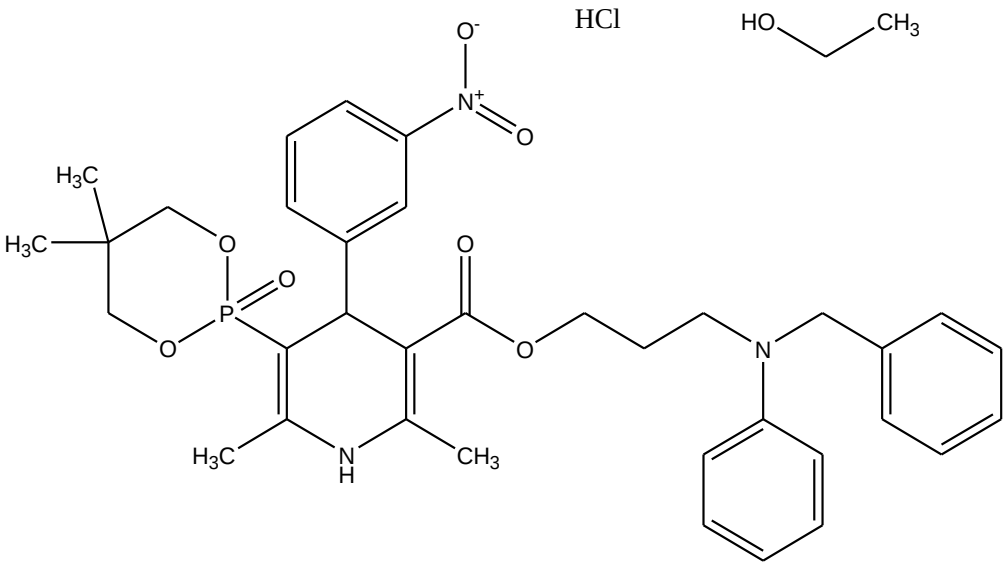
INTRODUCTION

Hypertension is also known as high blood pressure; it is also called as silent killer. It is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. It is a chronic medical condition characterized by constant elevation on systolic or diastolic pressure above 140/90mmHg. There are various conditions such as pheochromocytoma, hyperthyroidism, hyperaldosteronism, primary renal disease and coarctation of aorta elevates the arterial pressure. Therapeutic treatment of hypertension includes several major classes of drugs such as Diuretics, ACE inhibitors, angiotensin II type 1 receptor antagonists angiotensin receptor blockers, β- adrenoreceptor antagonists, rennin inhibitors, calcium channel blockers, and central sympatholytic, alone or in combination.

Efonidipine hydrochloride is a new generation dihydropyridine (DHP). Efonidipine exhibits antihypertensive effect through vasodilation by blocking L- type and T- type calcium channels.[1] Efonidipine has a negative chronotropic effect. These workings on the sino atrial node cells by inhibiting T- type calcium channel. Efonidipine prolongs the late phase – 4 depolarization of the sino atrial node action potential and suppress an elevated HR. The negative chronotroic effect of Efonidipine decreases heart rate, myocardial oxygen demand and increases coronary blood flow [2]

It differs from other dihydropyridine in having a phosphate nucleus at 5th position of the dihydropyridine ring. It has weak inotropic effect. It increases in glomerular filtration rate without change in intra glomerular pressure. It causes relaxation of afferent and efferent arterioles and reduces proteinuria. It has organ protective effects on the heart and kidney.

Efonidipine Hydrochloride Ethanolate is pale yellow crystalline powder to Greenish yellow crystalline powder. IUPAC name of Efonidipine Hydrochloride Ethanolate is 2-(N-benzylanilino) ethyl 5- (5,5 – dimethyl – 2- oxo-1,3,2λ5 – dioxaphosphinan-2-yl)-2,6- dimethyl -4-(3-nitrophenyl)-1,4 dihydropyridine – 3 carboxyl ate ;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 Dimethyl formamide, sparingly soluble in methanol. [3, 4]



Efonidipine hydrochloride ethanolate structure

Analytical method development and validation is critical in pharmaceutical discovery, development, and manufacturing. The validation of analytical methods is crucial for the development of analytical methods and involves rigorous testing for robustness, linearity, accuracy, precision, range, detection of limit, and specificity. Every year more medications are being released into 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 develop newer analytical techniques for such medications.

To analyse the analyte there are several methods such as UV,HPLC ,UPLC, Stability indicating High performance liquid chromatography – mass spectroscopy-mass spectroscopy ,spectrofluorimetry, GC/MS etc.

The official test methods that are mentioned in the table are used by quality control laboratories to ensure the identity, purity, potency and performance of drug products.

Table: -Various Analytical Methods for estimation and Forced degradation of efonidipine hydrochloride in single and in combination drugs

S.NO	DRUGS	METHOD	DESCRIPTION	REF NO
1.	Efonidipine hydrochloride in HME processed solid dispersions.	RP-HPLC	**Stationary phase:** Agilent Eclipsed XDB-C18(250mm x 4.6mm); 5µm **Mobile phase:** Acetonitrile: Potassium dihydrogen Phosphate buffer (pH2.5)(85:15%v/v) **Wavelength:** 252nm **Flow rate:** 1.2Ml/min **Retention time:** 3.4min **Linearity:** 2.5-100µg/mL	[5]
2.	Efonidipine HCl Ethanolate	RP-HPLC	**Stationary phase**: C18 (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	[6]
3.	Efonidipine, Telmisartan And Chlorthalidone In Synthetic Mixture	RP- HPLC	**Stationary phase:** Cybersil C18 column (250mm x 4.6mm x 5µm) **Mobile phase:** Potassium dihydrogen phosphate: Methanol: Acetonitrile (30:30:40 v/v/v) (pH :3) **Flow rate**: 1.0 mL/min **Wavelength**: 254 nm **Retention time** Efonidipine: **6.88 min** Telmisartan: **5.34 min** Chlorthalidone :**8.25 min**	[7]

4.	Efonidipine hydrochloride ethanolate and Telmisartan in their synthetic mixture	RP- HPLC	**Stationary phase**: PhenomenexKinetex ® 5µ C18 Size: 150 * 4.6mm column **Mobile Phase**: Acetonitrile: Phosphate Buffer pH 4.9 (45:55). **Wave length:**253 nm **Flow rate:** 1.0 mL/min **Retention time:** Efonidipine Hydrochloride Ethanolate: 7.77 mins Telmisartan: 4.10 mins **Linearity range**: Efonidipine Hydrochloride Ethanolate: 5-30µg/mL Telmisartan: 10-60 µg/mL	[8]
5.	Efonidipine hydrochloride ethanolate and Telmisartan	RP-HPLC	**Column**: C18 (15 cm x 4.6 mm, 5µm) **Mobile Phase**: Potassium Dihydrogen Orthophosphate Buffer pH 3: Acetonitrile (30:70 % v/v) **Flow Rate**: 0.8 ml/min **Wavelength**: 254 nm **Temperature**: 30°C **Retention time**: Efonidipine Hydrochloride Ethanolate - 7.933 min Telmisartan - 3.187 min **Linearity range**: Efonidipine Hydrochloride Ethanolate: 5-30 µg/mL Telmisartan: 10-60 µg/mL	[9]
6.	Efonidipine hydrochloride Ethanolate	RP-HPLC	**Column**: silica gel column 25cm x 4mm **Mobile phase**: Acetonitrile and a buffer solution prepared by dissolving 1.32 g of ammonium phosphate in 900ml of water **Flow rate**: 1.0ml/min **Wavelength**: 250nm	[10]
7.	Efonidipine Hydrochloride ethanolate in solid pharmaceutical dosage form	Stability indicating chromatographic assay method by RP HPLC	**Column:** 250 × 4.6 mm C18 column, 5 µm **Mobile phase**: Methanol and water (50:50v/v) **Flow rate**: 0.8 mL/min. **Detection wave length:** 270 nm. **Forced degradation studies** **Oxidative stress :**10 % **Photo degradation :**8 % **acid degradation:** 4% **base degradation:** 3% **thermal stress conditions:** 6%	[11]
8.	Efonidipine Hydrochloride Ethanolate andTelmisartan in Their Synthetic Mixture	UV Comparison Using ANOVA	**zero-crossing point** **Efonidipine hydrochloride ethanolate** **Wave length** :326 nm **Linearity**: 8-20 µg/mL **Telmisartan** **Wave length**: 272 nm. **Linearity**: 16-40 µg/mL using methanol as a solvent **absorbance correction method** efonidipine Hydrochloride ethanolate-**347 nm** Telmisartan - **296 nm**	[12]

9.	Efonidipine hydrochloride ethanolate and Chlorthalidone	UV Spectrophotometric method	**Wave length** Efonidipine Hydrochloride Ethanolate - 283.2 nm Chlorthalidone - 250.8 nm. **Linearity concentration range** Efonidipine hydrochloride ethanolate: 6.4-38.4 µg/mL Chlorthalidone: 2-12 µg/ mL^{-1} **Solvent**–methanol	[13]
10.	Efonidipine hydrochloride ethanolate and Telmisartan	simultaneous estimation by UV spectroscopic method in synthetic mixture by first order derivative method	**Wave length:** **Telmisartan**:231.00 nm **Efonidipine hydrochloride ethanolate:**238.60 nm **Linearity**: **Efonidipine Hydrochloride Ethanolate :**(2-18 µg/ml) **Telmisartan:** 4-36 µg/ml **Recovery:** Efonidipine Hydrochloride Ethanolate **98-101%** Telmisartan: **98.46-99.77%**	[14]
11.	Efonidipine Hydrochloride Ethanolate	UV-Visible Spectrophotometric	**Wave length**: 253nm **Concentration range**: 10-30 µg /mL **Correlation coefficient**: R2 =0.997 **Recovery**: 96-99% **Limit of detection**: 2.82 µg/ml **Limit of quantification**: 8.57µg/ml **Solvent**: Methanol	[15]
12.	Efonidipine hydrochloride ethanolate	Stability and physicochemical characterization by (GC - MS)	**Detector**: A mass spectrometer Efonidipine hydrochloride ethanolate was placed in a thermolysis furnace and heated at 5 °C min−1 from 80 °C to 180 °C. **Column**: A DB-1 LTM inert column (0.18 mm × 20 m × 0.40 µm, **Flow rate**: 0.5 mL min^{-1} **Split ratio**: 1/5 **Column oven temperature** : 50 °C **Injection port temperature**: 300 °C.	[16]
13.	Efonidipine HCL Ethanolate	A chiral method for the stereo specific by LC-MS/MS in human plasma	**Stationary phase:** CHIRALPAK(®) ID column **Mobile phase**: Acetonitrile :water (60:40, v/v) **Flow rate:**1 mL/min **isocratic transitions** of m/z 632.3-91.1 **Linear range** - 0.100-20.0 ng/mL for each enantiomer. **LLOQ**: 0.100 ng/mL	[17]
14.	Efonidipine HCl Ethanolate.	Forced degradation study by LC-Q-TOF-MS	**Stationary phase:** Thermo Cybersil BDS C18 (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 **Force degradation study** **Condition** | **%degradation** 1 M HCl at 80°C for 5 hours | No degradation	[18]

			Dry heat at 80°C for 11 days	No degradation		
			0.5 M NaOH at room temperature for 6 hours	44.18%		
			photolytic condition	11.6%		
15	Efonidipine hydrochloride Ethanolate	HPTLC	**Stationary phase**: TLC silica gel 60F 254 aluminium plates **Mobilephase**:ethylacetate:dichloromethane:triethylamine(3:2:0.5v/v) **R f value**: 0.35 ± 0.25 **Wave length** :251 nm **Detection limit**: 10.41ng **Qualification limit**: 31.57ng **Chamber saturation**: 17 min **Development distance**: 8.50cm			[19]

CONCLUSION

The present review is on analytical method development, validation and stability studies for estimation of efonidipine hydrochloride ethanolate in single and in combination with other pharmaceutical drugs. The analytical methods discussed include UV, RP-HPLC, LC-MS/MS, GC-MS, and HPTLC. From the above mentioned techniques it was found that RP-HPLC, LC-MS/MS is acceptable technique. The column used in RP- HPLC is Agilent Eclipsed XDB- C18 (250mm x 4.6mm); 5µm, where as in LC-MS/MS CHIRALPAK (®) ID column is used. The solvents used were Acetonitrile, Potassium dihydrogen Phosphate buffer, Ammonium acetate buffer when compared to other solvents buffers are low in cost and shows better resolution for both RP-HPLC and LC-MS/MS. It was also observed that the optimum flow rate for both the methods was found to be in between 0.8 min/mL to 1.2min/mL gives the better compounds detection .Hence this approach offers reliable in compared with advanced technology.

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