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REVIEW ON ANALYTICAL METHOD FOR QUANTITATIVE ESTIMATION OF EFONIDIPINE HYDROCHLORIDE ETHANOLATE AND METOPROLOL SUCCINATE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Efonidipine is a dihydropyridine calcium channel blocker, inhibits both L-type and T-type calcium channels, Efonidipine exhibits antihypertensive effect through vasodilatation by blocking L-type and T-type calcium channels. Metoprolol, is a selective β_1 receptor blocker medication. It is used to treat high blood pressure, chest pain due to poor blood flow to the heart, and a number of conditions involving an abnormally fast heart rate. This preferential effect at higher plasma concentrations. It works by blocking the action of certain natural chemicals in your body, such as epinephrine, on the heart and blood vessels. This effect lowers the heart rate, blood pressure, and strain on the heart. This combination use for improve the management of stage II hypertension. This review focuses on the recent development in analytical techniques for estimation of Efonidipine Hydrochloride Ethanolate and Metoprolol Succinate and there was no any methods have been reported for this combination. However, for Efonidipine Hydrochloride Ethanolate HPLC, Stability RP-HPLC methods has been reported. And UV, HPLC, Stability indicating RP-HPLC, HPTLC and UPLC methods have been reported for Metoprolol Succinate individual and along with other.

KEYWORDS: Analytical techniques, Efonidipine Hydrochloride Ethanolate, Metoprolol Succinate, UV, HPLC, Stability indicating RP-HPLC, HPTLC and UPLC.

INTRODUCTION

Hypertension (high blood pressure) is a key risk issue for the future growth of heart disease. It can be referred as a situation where blood pressure is raised to an extent that clinical benefit is obtained from blood pressure lowering. Blood pressure dimension includes systolic and diastolic modules, and both are chief in determining an individual's cardiovascular threat. Now blood pressure measurements are categorized as follows:

- **Normal:** systolic less than 120 mm Hg and diastolic less than 80 mm Hg
- **Elevated:** systolic between 120-129 mm Hg and diastolic less than 80 mm Hg
- **Stage 1:** systolic between 130-139 mm Hg or diastolic between 80-89 mm Hg
- **Stage 2:** systolic at least 140 mm Hg or diastolic at least 90 mm Hg

The fix-dose combination formulation of Efonidipine Hydrochloride Ethanolate and Metoprolol Succinate might increase therapeutic effect to patient who suffering from Hypertension. Efonidipine hydrochloride ethanolate a new generation dihydropyridine (DHP) calcium channel blocker, inhibits both L-type and T-type calcium channels. Efonidipine exhibits antihypertensive effect through vasodilatation by blocking L-type and T-type calcium channels. Metoprolol is a beta 1-selective (cardioselective) adrenergic receptor blocker. This preferential effect at higher plasma concentrations. It works by blocking the action of certain natural chemicals in your body, such as epinephrine, on the heart and blood vessels. This effect lowers the heart rate, blood pressure, and strain on the heart.[15-19]

Physical and Chemical property

Efonidipine Hydrochloride Ethanolate is pale yellow colour 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-carboxylate;ethanol;hydrochloride (Fig.1.). Chemical formula of efonidipine hydrochloride ethanolate is $C_{36}H_{45}ClN_3O_8P$. Molecular weight is 714.2g/mol. It is poorly soluble in water, Soluble in Methanol, Ethanol, Acetonitrile. The chemical structure of efonidipine hydrochloride ethanolate is shown in Fig.1.[16,17]

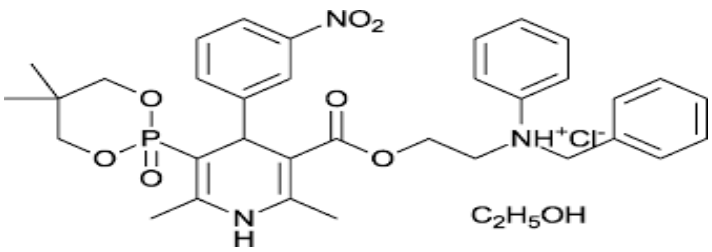

Fig. 1: Chemical structure of efonidipine hydrochloride ethanolate.

Metoprolol Succinate is white powder. IUPAC name of Metoprolol Succinate is Butanedioic acid;1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol. Chemical formula of metoprolol succinate is $C_{34}H_{56}N_2O_{10.}$ Molecular weight is 652.8g/mol. It is soluble in water, methanol and sparingly soluble in ethanol. The chemical structure of metoprolol succinate is shown in Fig.2.[18,19]

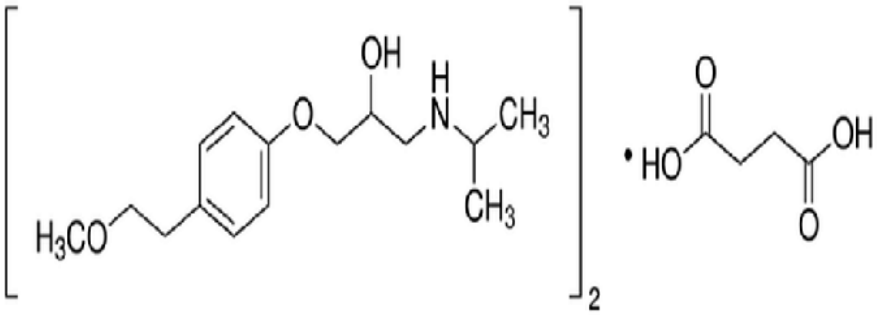

Fig. 1: Chemical structure of metoprolol succinate.

Analytical methods

Analytical method Development and Validation play important role in the Discovery, Development and Manufacture of Pharmaceuticals. Method Development is a process of proving that an analytical method is acceptable for use to measure the concentration of an API in a specific compounded dosage form which will allow simple procedures to be employed to verify that an analysis procedure, consistently accurately and will deliver a reliable measurement of an active ingredient in a mixed preparation. Analytical Method Development helps to understand the critical process parameters and to minimize their influence on accuracy and precision. Method Validation helps to Validate the Analytical Method for a range of concentrations so that the change in Formulation or Concentration do not require additional validation. Analytical Method Development gives important information on the potency of a drug.

Choosing of an analytical method

From the Information obtained from the literature during the literature review, a specific methodology is modified for Accurate output and also because method change with the requirements of the Analyte. The Analytical Method Validation is essential part for Analytical Method Development. Mostly method used are Spectroscopic and Chromatographic Methods.

There is no official method for estimation of Efonidipine Hydrochloride Ethanolate. Here the reported methods for estimation of Efonidipine Hydrochloride Ethanolate.[1-7]

Table no. 1: Reported methods for estimation of efonidipine hydrochloride ethanolate.

<table>
<tr><th>Sr. no</th><th>Reported Method</th><th>Description</th><th>Ref. no</th></tr>
<tr><td>1.</td><td>Development and validation of Liquid Chromatography (RP-HPLC) Methodology for Estimation of Efonidipine HCL Ethanolate (EFD)</td><td>Stationary Phase: C18(150 mm x 4.6 mm,5 µm)
Mobile Phase: Acetonitrile :Water (85:15 %v/v)
Wavelength: 254 nm
Retention time: 6.39 min
Flow Rate: 0.8mL/min
Linearity: 20-140 µg/ml</td><td>[20]</td></tr>
<tr><td>2.</td><td>RP-HPLC method development and validation for Quantification of Efonidipine Hydrochloride In HME Processed solid dispersions</td><td>Stationary Phase: C18(150 mm x 4.6 mm,5 µm)
Mobile Phase: Acetonitrile : Phosphate Buffer pH: 2.5 (85:15%v/v)
Wavelength: 252 nm
Retention time: 15 min
Flow rate: 1.2 mL/min
Linearity: 2.5–100 µg/ml</td><td>[21]</td></tr>
<tr><td>3.</td><td>Forced degradation study of Efonidipine HCL Ethanolate characterization of degradation products by LC-Q-TOF-MS and NMR</td><td>Stationary Phase: C18(150 mm x 4.6 mm,5 µm)
Mobile phase: Acetate Buffer: Ammonium Acetate,:Distilled Water (10:770:1000 %v/v/v)pH -5.8
Wavelength: 254 nm
<table>
<tr><th>Conditions
% Degradation</th><th>Conditions
% Degradation</th></tr>
<tr><td>1 M HCl at 80°C for 5 hours</td><td>28.14 %</td></tr>
<tr><td>10% hydrogen peroxide for 24 hours</td><td>4.01 %</td></tr>
<tr><td>Dry heat at 80°C for 11 days</td><td>8.8 %</td></tr>
<tr><td>0.5 M NaOH at room temperature for 6 hours</td><td>2.17 %</td></tr>
</table></td><td>[22]</td></tr>
</table>

Table no. 2: Official methods for metoprolol succinate.

Sr. no	Official in	Method	Description	Ref. no
1.	Indian Pharmacopoeia 2018	Liquid Chromatography	**Stationary Phase**: A stainless steel column 12.5 cm x 4 mm, packed with octylsilane bonded to porous silica(3 to 10 µm) **Mobile Phase**: A mixture of 60 volume of buffer prepared by dissolving 1.3 g of sodium dodecyl sulphate in 1000 ml of 0.1 % w/v phosphoric acid and 40 volume of Acetonitrile **Flow rate**: 0.9 mL/min **Wavelength**: 223 nm **Injection volume**: 10 µL	[12]
2	United States Pharmacopeia 2007	Liquid chromatography	**Stationary Phase**: A 4 mm x 12.5 cm column that contains 4 µm packing L7. **Mobile Phase**: Sodium Dodecyl sulphate solution : Acetonitrile (60:40 %v/v) **Flow rate**: 0.9 mL/min **Wavelength**: 223 nm **Injection volume**: 10 µL	[13]
3	British Pharmacopoeia 2016	Liquid chromatography	**Stationary Phase**: End capped octadecylsilyl silica gel **Mobile Phase**: Dissolve 3.9 g Ammonium Acetate in 810 ml of water add 2 ml of triethylamine ,3 ml of phosphoric acid,10 ml of glacial acetic acid and 146 ml of acetonitrile and mix **Flow Rate**: 1 mL/min **Wavelength**: 223 nm **Injection Volume**: 20 µL	[14]

Table no. 3: Reported methods for estimation of metoprolol succinate.

Sr. no	Reported Method	Discription	Ref
1.	**Absorption Correction Method** for Simultaneous Estimation of Metoprolol Succinate and Olmesartan Medoxomil in Combined Tablate Dosage Form	**Model**: Shimadzu (1700) **Solvent**: Methanol **Absorption Correction Method** **Wavelength:-** Metoprolol succinate:233 nm Olmesartan medoxomil : 244 nm	[23]
2.	Development And Validation of **Spectrophotometric Method** for Simultaneous Estimation Of Metoprolol Succinate	**Model**: Shimadzu (1700) **Solvent**: Methanol **Absorption ratio method** **Isoabsorptive point:** 231.8 nm λ max of Metoprolol Succinate : 230.2 nm λ max of Telmisartan : 237 nm **Linearity:**	[24]

	and Telmisartan In Combined Pharmaceutical Formulation	Metoprolol Succinate : 3-20 µg/ml Telmisartan : 4-16 µg/ml	
3.	Development and Validation of **First Order Derivative Spectrophotometric method** for simultaneous estimation of Metoprolol Succinate and Olmesartan Medoxomil in tablets	**Model**: Shimadzu (1700) **Solvent**: Methanol **First Order Derivative** **ZCP** of Olmesartan Medoxomil:- 204.6 nm **ZCP** of Metoprolol Succinate :-275.6 nm **Linearity :-** Olmesartan Medoxomil :-5-30 µg/ml Metoprolol Succinate :-5-30 µg/ml	[25]
4.	Development and Validation of **Spectrophotometric Method** for Simultaneous Estimation of Trimetazidine Hydrochloride and Metoprolol Succinate in Pharmaceutical Dosage Form	**Model**: Shimadzu (1800) **Solvent**: Distilled Water **Absorbance Ratio Method:** **Isoabsorptive point:** 249.5 nm **λ max:** 274 nm **Linearity:** Trimetazidine Hydrochloride : 40-200 µg/ml Metoprolol Succinate : 54-270 µg/ml	[26]
5.	Bioanalytical Method Development And Validation for Metoprolol Succinate And Telmisartan **Using Uv Spectrophotometry And RP-HPLC**.	**Model**: Shimadzu (1700) **Solvent**: Methanol **Simultaneous Equation Method** **Wavelength**:- Metoprolol succinate : 240.5 nm Telmisartan : 237.5 nm **Stationary Phase**: C-18 (4.6 x 250 mm, 5 µm) **Mobile phase**: Methanol:Acetonitrile:Phosphate Buffer (pH-5)(35:35:30 %v/v/v) **Wavelength**: 225 nm **Retention Time:** Metoprolol succinate: 6 min Telmisartan: 8 min **Flow rate:** 1.0 mL/min **Linearity:** Metoprolol succinate: 5-25 µg/ml Telmisartan: 8-40 µg/ml	[27]
6.	Development and Validation Of **Spectrophotometric Method for Determination of** Metoprolol Succinate	**Solvent**: Dil.Water, 0.1N HCL, Phosphate Buffer pH 6.8 **Wavelength**: 224 nm **Linearity :-** In Phosphate Buffer ,Distilled Water: 5-30 µg/ml In 0.1N HCL: 10-50 µg/ml	[28]
7.	Development and Validation of	**Model**: Shimadzu (1700) **Solvent**: Methanol	[29]

	Spectrophotometric Method for **Simultaneous Determination of** Metoprolol Succinate and Olmesartan Medoxomil in Tablet Dosage Form	**Simultaneous Equation Method** **Wavelength**: Metoprolol Succinate: 223 nm Olmesartan Medoxomil: 255 nm **Linearity:-** Metoprolol Succinate: 5-30 µg/ml Olmesartan Medoxomil: 5-30 µg/ml	
8.	**Simultaneous Estimation** of Metoprolol Succinate and Olmesartan Medoxomil in Pharmaceutical Dosage Form by UV Spectroscopy	**Model**: Shimadzu (1800) **Solvent**: Methanol **Simultaneous Equation method and Absorbance Ratio method.** **Wavelength**: - Metoprolol succinate : 223 nm Olmesartan : 256 nm **Isoabsorptive point**:- 230 nm **λ max:** Metoprolol succinate: 230nm Olmesartan: 256 nm **Linearity**: Metoprolol succinate: 5-30 µg/ml Olmesartan: 2-12 µg/ml	[30]
9.	Development and Validation of **First Order Derivative Spectrophotometric** Method for Simultaneous Estimation of Metoprolol Succinate and Clopidogrel Bisulphate in Tablet Dosage from.	**Model**: Shimadzu(1800) **Solvent**: 0.1 N HCl **First order derivative method** **λ max**: Metoprolol succinate: 223 nm Clopidogrel: 222.2 nm **ZCP** of Metoprolol succinate: 245.7 nm **ZCP** of Clopidogrel: 276.13 nm **Linearity**: Metoprolol Succinate: 5-25 µg/ml Clopidogrel: 5-25 µg/ml	[31]
10.	Development and Validation of **Spectrophotometric Method for Determination of** Metoprolol Succinate	**Model**: Jasco(V630) **Solvent**: Dil.Water , Phosphate buffer pH 6.8 **Wavelength**: In distilled water 221 nm In phosphate buffer 223 nm **Linearity:** 5-25 µg/ml	[32]
11.	New analytical methods and their validation for the estimation of Metoprolol Succinate in bulk and marketed formulation	**Model:** JascoV-630 **Solvent**: Dil.Water **Wavelength**: 516 nm and 688 nm **Linearity:** Metoprolol Succinate : 5-25 µg/ml	[33]
12.	**Absorbance Correction Method** for Simultaneous Estimation of	**Model**: Shimadzu (2450) **Solvent**: Methanol **Absorbance Correction Method** **Wavelength**:-	[34]

<table>
<tr><td></td><td>Nifedipine and Metoprolol Succinate in Their Synthetic mixture using from Spectrophotometry</td><td>Nifedipine: 313 nm
Metoprolol succinate: 275 nm
Linearity:
Nifedipine: 5-25 µg/ml
Metoprolol succinate: 25-125 µg/ml</td><td></td></tr>
<tr><td>13.</td><td>Development and Validation of UV Spectrophotometric Methods for Simultaneous Estimation of Trimetazidine Hydrochloride and Metoprolol Succinate in Tablet Dosage Form</td><td>Model: Shimadzu (1800)
Solvent: Water
First Order Derivative method
Wavelength:-
Trimetazidine hydrochloride: 270 nm
Metoprolol succinate: 254 nm
ZCP of Trimetazidine Hydrocholoride : 268.92 nm
ZCP of Metoprolol Succinate: 243.90 nm
Linearity:
Trimetazidine hydrochloride :
40-200 µg/mL
Metoprolol succinate :
54- 270 µg/mL</td><td>[35]</td></tr>
<tr><td>14.</td><td>Validated and Stability Indicating of RP-HPLC Method for Simultaneous Estimation of S(-)Metoprolol Succinate & Clopidogrel Bisulfate In Bulk and Tablet Dosage Form</td><td>Stationary Phase: C8 (250mm x4.6mm, 5µm)
Mobil Phase: Methanol: Acetonitrile: Phosphate Buffer (15:40:45 % v/v/v) pH: 3
Wavelength:- 220 nm
Retention Time:
Metoprolol succinate: 7 min
Clopidogrel bisulfate: 20 min
Flow Rate: 1.5 ml/min
Linearity: 50-150 µg/mL
<table>
<tr><th>Agent</th><th colspan="2">Degradant peak</th><th colspan="2">RT (min)</th><th colspan="2">% Degradation</th></tr>
<tr><td>0.5 N HCL</td><td>MS</td><td>CB</td><td>MS</td><td>CB</td><td>MS</td><td>CB</td></tr>
<tr><td>1 N NaOH</td><td>1</td><td>1</td><td>4.4</td><td>17.9</td><td>13</td><td>6</td></tr>
<tr><td>3% H_2O_2</td><td>2</td><td>1</td><td>3.8</td><td>-</td><td>25</td><td>3.2</td></tr>
<tr><td>U.V. Light</td><td>1</td><td>-</td><td>5.6</td><td>-</td><td>16</td><td>-</td></tr>
<tr><td>0.5 N HCL</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table></td><td>[36]</td></tr>
<tr><td>15.</td><td>Quantification of Metoprolol Succinate in bulk and tablet formulation by HPLC Method development and validation</td><td>Stationary Phase: C8 (150 mm x 4.6 mm, 5 µm)
Mobile Phase: Ammonium Acetate Buffer: Acetonitrile : Acetic Acid (84:15:1 % v/v/v) pH : 2.7
Wavelength: 280 nm
Retention time:-
Metoprolol succinate: 3.4 min
Flow rate: 1.0 mL/min
Linearity:
Metoprolol succinate: 10-50 µg/ml</td><td>[37]</td></tr>
</table>

16.	Method Development and **Validation for Simultaneous Estimation** of Benidipine Hydrochloride and Metoprolol Succinate in Tablet dosage form	**Stationary Phase**: C18(250 mm x 4.6 mm, 5µm) **Mobile Phase**: Potassium Dihydrogen Phosphate Buffer (pH 4.0): Methanol (65: 35% v/v) **Wavelength**: 269 nm **Retention time**:- Metoprolol succinate: 3.4 min Benidipine hydrochloride: 5.9 min **Flow rate**: 1.0 mL/min **Linearity :** Metoprolol succinate: 25-75 µg/ml Benidipine hydrochloride: 4-12 µg/ml	[38]
17.	**Development of Reverse-Phase HPLC Method** for Simultaneous Analysis of Metoprolol Succinate and Hydrochlorothiazide in a Tablet Formulation	**Stationary Phase**: C-18 using 50mM **Mobile Phase**: Hydrogen Phosphate: Methanol: Acetonitrile (525:225:250 %v/v/v) **Wavelength**: 222 nm **Retention time** :- Metoprolol succinate: 5.38 min Hydrochlorothiazide: 3.04 min **Flow rate**: 1.0 mL/min **Linearity**: Hydrochlorothiazide: 2-10 µg/ml Metoprolol Succinate: 5-30 µg/ml	[39]
18.	A Rapid And Sensitive **Validated High Performance Liquid-chromatography Method** for Determination Of Related Substances in Metoprolol Succinate(API)	**Stationary Phase**: C18, (250 mm x 4.6 mm,5µm) **Mobile Phase:** Acetonitrile: Methanol: Water (5:4:1 %v/v/v) **Wavelength**: 223 nm **Retention time**: 10.5 min **Flow rate**: 1.0 mL/min **Linearity**: 5-30 µg/ml	[40]
19.	**RP-HPLC method development and validation** for Simultaneous Estimation of Atorvastatin, Aspirin, Ramipril and Metoprolol Succinate in tablet dosage form	**Stationary Phase**: C18, (250 mm x 4.6 mm, 5µm) **Mobile phase**: Phosphate buffer :Acetonitrile (90:10 %v/v) pH : 3.4 **Wavelength**: 210 nm **Retention time** :- Atorvastatin: 8 .01 min Aspirin: 4.4 min Ramipril: 7.2 min Metoprolol succinate: 3.4 min **Flow rate**: 1.0 mL/min **Linearity:** Atorvastatin: 3-9 µg/ml Aspirin: 20-60 µg/ml Ramipril: 1.5-5 µg/ml Metoprolol succinate: 15-45 µg/ml	[41]
20.	**Development and Validation of RP-HPLC** Method for The Simultaneous Estimation	**Stationary Phase:** C18, (250 mm x 4.6 mm, 5µm) **Mobile phase:** Acetonitrile : Methanol (70:30 % v/v)	[42]

<table>
<tr><td></td><td>of Amlodipine and Metoprolol in bulk and Pharmaceutical Dosage Form</td><td>Wavelength: 222 nm
Retention Time :-
Amlodipine: 1.6 min
Metoprolol: 2.8 min
Flow rate: 1.0 mL/min
Linearity:-
Amlodipine: 2-24µg/ml
Metoprolol: 5-60 µg/ml</td><td></td></tr>
<tr><td>21.</td><td>An Improved Rapid HPLC Method for the Separation of Five Anti-Hypertensive Agents Using C18 Stationary Phase: Application to Hydrochlorothiazide Determination in Bulk and Tablet Dosage Form</td><td>Stationary Phase: C18,(250mm x 4.6 mm,5 µm)
Mobile phase: Phosphate buffer : Acetonitrile (50:50 % v/v)
Wavelength: 235 nm
Retention Time:
Atenolol hydrochloride: 2.3 min
Metoprolol succinate: 2.8 min
Hydrochlorothiazide: 3.5 min
Amlodipine besylate: 4.2 min
Nebivolol hydrochloride: 4.9 min
Flow rate: 1.0 mL/min
Linearity:
Hydrochlorothiazide: 2-10 µg/ml</td><td>[43]</td></tr>
<tr><td>22.</td><td>Validated stability indicating RP-HPLC method for simultaneous determination of Metoprolol Succinate and Olmesartan Medoxomil in tablet dosage form.</td><td>Stationary Phase: C18, (250 mm x 4.6 mm, 5 µm)
Mobile Phase: Ophosphoricacid :water (50:50 % v/v)
Wavelength: 228 nm
Retention time :-
Metoprolol Succinate: 3.485 min
Olmesartan Medoxomil: 7.085 min
Flow rate: 1.0 mL/min
Linearity:
Metoprolol Succinate: 5-80 µg/ml
Olmesartan Medoxomil: 5-70 µg/ml
Stability Results:
<table>
<tr><td>Acidic</td><td>0.1 N HCl</td><td>Stable</td></tr>
<tr><td>Alkali</td><td>1 N NaOH</td><td>Stable</td></tr>
<tr><td>Neutral</td><td>Reflux with dil water</td><td>Stable</td></tr>
<tr><td>Oxidative</td><td>With H_2O_2 for 2 hrs</td><td>Stable</td></tr>
<tr><td>photolytic stress</td><td>Exposing fluroscence light</td><td>Stable</td></tr>
</table></td><td>[44]</td></tr>
<tr><td>23.</td><td>Development of Reverse-Phase HPLC Method for Simultaneous Analysis of Metoprolol Succinate and Hydrochlorothiazide in a</td><td>Stationary Phase: C18, (250 mm x 4.6 mm, 5 µm)
Mobile phase: Phosphate: Methanol: Acetonitrile (525:225:250 %v/v/v/v)
Wavelength: 222 nm
Retention Time:-Metoprolol succinate: 5.3 min</td><td>[45]</td></tr>
</table>

<table>
<tr><td></td><td>Tablet Formulation</td><td>Hydrochlorothiazide: 3.4 min
Flow rate: 1.0 mL/min</td><td></td></tr>
<tr><td>24.</td><td>**Development and validation of RP-HPLC method** for Simultaneous Determination of Metoprolol and Amlodipine in Tablet Dosage Form</td><td>**Stationary Phase**: C18, (250 mm x 4.6 mm, 5µm)
Mobile Phase: Phosphate buffer (pH 3.0): Acetonitrile (50:50 %v/v)
Wavelength: 235 nm
Retention time:-
Metoprolol: 2.6 min
Amlodipine: 3.7 min
Flow rate: 1.0 mL/min
Linearity:
Metoprolol: 5-25 µg/ml
Amlodipine: 1-5 µg/ml</td><td>[46]</td></tr>
<tr><td>25.</td><td>**RP-HPLC Method for Estimation** of Metoprolol Succinate and Olmesartan Medoxomil in Pharmaceutical Formulation with forced degradation studies</td><td>**Stationary Phase**: C18, (250 mm x 4.6 mm, 5 µm)
Mobile phase: methanol :water (80: 20 % v/v)
Wavelength: 240 nm
Retention time: -
Metoprolol succinate: 3.986 min
Olmesartan: 6.09 min
Flow rate: 1.0 mL/min
Linearity:
Metoprolol succinate: 4-40 µg/ml
Olmesartan: 5-60 µg/ml
<table>
<tr><th>Stress Conditions</th><th colspan="2">% Drug decomposed</th><th colspan="2">Retention Time (min)</th></tr>
<tr><th></th><th>OM</th><th>MS</th><th>OM</th><th>MS</th></tr>
<tr><td>Acid Degradation</td><td>0.21</td><td>1.55</td><td>6.016</td><td>4.012</td></tr>
<tr><td>Alkaline Degradation</td><td>20.19</td><td>9.63</td><td>6.092</td><td>3.986</td></tr>
<tr><td>Oxidative Degradation</td><td>9.01</td><td>15.17</td><td>5.606</td><td>3.786</td></tr>
<tr><td>Thermal Degradation</td><td>5.18</td><td>12.8</td><td>6.092</td><td>3.986</td></tr>
<tr><td>Photolytic Degradation</td><td>4.28</td><td>6.55</td><td>6.052</td><td>3.98</td></tr>
</table></td><td>[47]</td></tr>
<tr><td>26.</td><td>**Ultra Performance Liquid Chromatographic** Method Development and Validation for the Quantification of Impurities and Degradation Products in the Metoprolol Succinate Tablets</td><td>**Stationary Phase**: C18 (100mm x 2.1 mm, 1.7µm)
Mobile phase: phosphoric acid : Acetonitrile (60:40 %v/v) pH : 3.4
Wavelength: 223 nm
Retention time: -
Metoprolol succinate: 28 min
Flow rate: 0.28 mL/minute</td><td>[48]</td></tr>
</table>

27.	**Rapid Separation of Five Anti Hypertensive** Agents-Atenolol, Metoprolol, Hydrochlorothiazide, Amlodipine and Nebivolol**:** Application to Estimation of Metoprolol Succinate in Tablet Dosage Form.	**Stationary Phase**: C18 (100mm x 4.6 mm, 1.7 µm) **Mobile Phase**: Phosphate buffer : Acetonitrile (50:50 %v/v)pH : 3 **Wavelength**: 235 nm **Retention time: -** Atenolol: 2.3 min Metoprolol: 2.8 min Hydrochlorothiazide: 3.5 min Amlodipine: 4.2 min Nebivolol: 4.9 min **Flow rate**: 1.0 mL/min	[49]
28.	Green micellar **HPLC-fluorescence method** for simultaneous determination of Metoprolol and Amlodipine in their combined dosage form: Application on metoprolol in spiked human plasma	**Stationary Phase**: C18 (150×4.6 mm, 5 µm) **Mobile phase**: Sodium Dodecyl Sulfate: Sodium Dihydrogen Phosphate buffer pH 3.0 (90:10% v/v) Wavelength : 275 nm **Retention Time**:- Metoprolol: 5 min Amlodipine: 15 min Linearity:- Metoprolol: 0.1–10 µg/ml Amlodipine: 0.2–2 µg/ml	[50]
29.	Development and Validation of **RP-HPLC** Method for Simultaneous Determination of Metoprolol Succinate and Olmesartan Medoxomil in Bulk and Pharmaceutical Dosage Form	**Stationary Phase**: C18(150mm x 4.6mm, 5 µm) **Mobile phase**: Acetonitrile:Pottasium Phospahte buffer(70:30 % v/v) pH -2.75 **Wavelength**: 225 nm **Retention time**: Metoprolol succinate: 2.2 min Olmesartan: 3.0 min **Flow rate**: 1.0 mL/min	[51]
30.	**RP-HPLC** Method for Simultaneous Estimation of Metoprolol Succinate and Clopidogrel Bisulphate	**Stationary Phase**: C18(150 mm x 4.6 mm,5 µm) **Mobile phase**: Methanol: Water: Acetonitrile (70:20:10 % v/v/v), Ortho Phosphoric Acid with pH-3.4 **Wavelength**: 280 nm **Retention time**: Metoprolol Succinate: 3.7 min Clopidogrel Bisulphate: 7 min **Flow rate**: 1.0 mL/min **Linearity:** Metoprolol succinate: 5-40 µg/ml Clopidogrel Bisulphate: 7.5-60 µg/ml	[52]
31.	**HPTLC** Method Development and Validation of Cilnidipine and Metoprolol Succinate in Combined Dosage Form	**Stationary Phase**: Silica Gel G60 F254 **Mobile phase**: Toluene: Chloroform: Methanol: Glacial acetic acid (45: 25: 25: 5 %v/v/v/v) **Wavelength**: 231 nm **R_f Value** : Cilnidipine: 0.70 ± 0.01 Metoprolol succinate: 0.34 ± 0.005 **Flow rate**: 1.0 mL/min	[53]

32.	Normal and Reversed-Phase **HPTLC** Methods for Simultaneous Estimation of Telmisartan and Metoprolol Succinate in Pharmaceutical Formulation	**Stationary Phase:** Aluminium Coated With RP-18 Silica Gel 60 F254S **Mobile Phase:** Toluene: Propanol: Methanol**:** Triethylamine (8 : 1 : 1 : 0.5 %v/v/v/v) **Wavelength**: 242 nm **R_f values**: Telmisartan: 0.45 ± 0.02 Metoprolol: 0.70 ± 0.02 **Flow rate**: 1.0 mL/min	[54]

CONCLUSION

From this review literature revealed that, there was no method reported for Efonidipine Hydrochloride Ethanolate and Metoprolol Succinate fixed dose combination. However, for estimation of Efonidipine Hydrochloride Ethanolate HPLC and Stability indicating HPLC methods were reported for individual drug and for Metoprolol Succinate UV, HPLC, Stability indicating HPLC, HPTLC and UPLC methods were reported for individual drug and along with other drugs. Thus, there is a scope to develop spectophotometric and chromatographic methods for combination of Efonidipine Hydrochloride Ethanolate and Metoprolol Succinate and validation of the same. This review carried out an overview of the current statee-of-art analytical methods for determination of Efonidipine Hydrochloride Ethanolate and Metoprolol Succinate which will supportive for further research on this combination. The review would also help to select the solvents and mobile phase in practical work.

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