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A REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CALCIUM CHANNEL BLOCKERS AND ANGIOTENSIN- CONVERTING ENZYME INHIBITORS IN BULK AND PHARMACETICAL FORMULATION

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ABSTRACT

A simple, economical and rapid by UV detector and PDA Detector was used for Estimation of Trandolapril and Verapamil in combination and other drugs in various Pharmaceutical formulation. Calcium channel blockers(CCBs) and angiotensin- converting enzyme (ACE) inhibitors has been developed and fully validated by High performance liquid Chromatographic Methods. Calcium channel blockers (CCBs) or Calcium antagonists are among the most widely used drugs in cardiovascular medicine and hypertension also in angina. CCBs promote vasodilator activity by reducing calcium influx into vascular smooth muscle cells by interfering with calcium channels in the cell membrane. Trandolapril is a potent nonsulfhydryl and dicarboxyl containing Angiotensin converting inhibitor (ACE). Trandolapril used to treatment of hypertension appears to result the inhibition of tissue ACE activity and to improve survival myocardial infarction thereby reduce angiotensin II formation.

It includes drugs like Trandolapril, Norverapamil, Nifedipine, Verapamil. This Review enlists different method Developed, Validated and determination of Calcium channel blockers and angiotensin- converting enzyme inhibitors Like, RP-HPLC, LC-MS/MS and HPLC UV- Spectophotometric method. This method was also validated for various validation terms indicates that precise, accurate, linearly, and limit of Detection and limit of Quantitation as per ICH guidelines.

Keywords: HPLC Chromatography, Calcium Channel blocker, angiotensin- converting enzyme (ACE) inhibitors, Hypertension, Validation etc.

INTRODUCTION

Trandolapril is a colorless and crystalline solid soluble in chloroform, methanol and dichloromethane, odourless powder which melts in the range of 125-130º C. Trandolapril is chemically (2S, 3aR, 7aS)-1- [(S)-2- [[1-Ethoxycarbony l-3-phenylpropyl] amino] propanoyl] octahydro- 1H-indole- 2- carboxylic acid [6,7,8]. Molecular formula and molecular weight of the trandolapril drug are $C_{24}H_{34}N_2O_5$ and 430.537 grams/mol respectively [4,5]. Monoester prodrug of a Trandolapril was hydrolysed by esterases to its active dicarboxylic acid metabolite in syntehsis converted to the Trandolaprilat [9] . Verapamil is solid freely soluble in water, chloroform and methanol which melts range of 138-140 °C. Verapamil hydrochloride (VER) is Chemically, (5- [3,4- dimethoxyphenethyl) methylamino] -2- (3,4- dimethoxyphenyl)- 2-isopropylvaleronitrile hydrochloride), a slow calcium channel antagonist, inhibits the trans membrane influx of calcium ions into the heart and vascular smooth muscle cells [6]. Verapamil is available in oral and intravenous dosage forms. Verapamil appears to be well absorbed orally, is highly protein bound, and is extensively metabolized by the liver to an active demethylated metabolite, norverapamil[7].

Amphoteric compounds like trandolapril is a potent nonsulfhydryl and dicarboxyl containing Angiotensin converting inhibitor(ACE). Trandolapril used to treatment of hypertension appears to result the inhibition of tissue ACE activity and to improve survival myocardial infarction thereby reduce angiotensin II formation, and treatment for congestive heartfailure, decreases the rate of aldosterone secretion, and incease plasma renin. Decreased aldosterone secretion leads to diuresis, natriuresis, and a small rate of change of serum potassium. Some undesirable effects shows commonly used to treatment of trandolapril includes,dizziness, cough, headache. Approximately 10%and 70% oral dose of trandolapril is bioavailable as trandolapril and trandolaprilat

respectively. The t1/2 of trandolapril is maximum 1 hours, and that of Trandolaprilat is, approximately, 75 hours[5, 6]. Calcium channel blockers (CCBs) are a structurally and functionally heterogeneous group of medications that are used widely to control blood pressure and manage symptoms of angina. CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients [8]. calcium channel blocking agents useful in the treatment of vasospastic angina, chronic stable angina, and supraventricular tachyarrhythmias[7].

Advantages of CCBs are:

- Do not compromise haemodynamic: No impairment of physical work capacity
- No sedation or other CNS effect, cerebral perfusion is maintained: compatible with intense mental activity
- Do not affect male sexual function, deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.

Advantages of ACE Inhibitors are:

- The therapy of hypertension and heart failure.
- Trandolapril is associated with a low rate of transient serum amino transferase elevations, but has yet to be linked to instances of acute liver injury.
- This prevents the potent vasocontrictive action of angiotensin II and result in vasodilation

Reported methods are categorized depending on the following considerations:

Analyzed by Single component with other class drugs for combination with Calcium channel blocker with angiotensin- converting enzyme (ACE) inhibitors by UV-Spectroscopy methods and Chromatographic method.

Table 1: Analysis of Trandolapril and Verapamil combination with other drugs by RP-HPLC Method and UV-Spectrophotometric Mthods

Sr. No.	Drug	Method	Description	ef
1.	Development and Validation of Trandolapril in Tablets	RP-HPLC Method with UV- Detector	**Detection wavelength:** **Trandolapril:** 210nm **Stationary phase:** ODS INERTSIL C18, (250×4.6mm, 5µm) **Linearity range:** **Trandolapril:** 6 -14 µg/ml **Mobile Phase:** phosphate buffer (pH3.0) and acetonitrile (1: 1) **Flow rate:** 1.0 ml/min **Retention time:** 5.8 min **Co-relation co-efficient:** 0.9995 **% Recovery range:** 100.38% to 99.18% **LOD:** 0.36 µg/mL**, LOQ:** 1.21 µg/mL	
2.	Quantification of Trandolapril	UV- Spectrometric Detection	**Detection wavelength:** **Trandolapril:** 220nm **Stationary phase:** LiChroCART -RP C18 column (250x4.0, 5 µm) **Linearity range:** **Trandolapril:** 2.5- 17.5 µg/mL **Mobile Phase:** acetonitrile: methanol: phosphate buffer (0.025mM) pH3.0 (40:35:25) **Flow rate:** 1.0 ml/min **Retention time:** 2.750 ±0.008 min **Co-relation co-efficient:** 0.999 **% Recovery range:** 100.38% to 99.18% **LOD:** 0.099 µg/mL **, LOQ:** 0.300834 µg/ml	**0**

3.	Estimation of Verapamil and Trandolapril in Pharmacetical formulations tablets	Liquid Chromatographic (RP-LC) Method	**Detection wavelength:** **Verapamil:** 202 nm **Trandolapril:** 206nm **Stationary phase:** X-Terra RP-18 column (250 × 4.60 mm × 5 µm) **Linearity range:** **Verapamil:** 0.50-18.00 µg/mL **Trandolapril:** 0.05-1.00 µg/mL **Mobile Phase:** MeOH and water (50-65) (v/v) **Flow rate:** 1.2 ml/min **Injected volume**: 20 µL **Retention time:** **Verapamil:** 2.964 min **Trandolapril:** 5.497 min **Co-relation co-efficient:** **Verapamil:** 0.9999 **Trandolapril:** 0.9999 **% Recovery range:** **Verapamil:** 99.99 %, **Trandolapril:** 101.60 % **Verapamil :** **LOD:** 0.008 µg/mL **,LOQ:** 0.025 µg/ml **Trandolapril:** **LOD:** 0.018 µg/mL **,LOQ:** 0.050 µg/ml	
4.	Determination of Trandolapril in bulk and formulations	RP-HPLC Method	**Detection wavelength: Trandolapril:** 215nm **Stationary phase:** Hypersil gold C18(100mm, 4.6mm-ID, 5µm) **Linearity range:** **Trandolapril:** 25.0-150 µg/mL **Mobile Phase:** buffer and acetonitrile (50:50) v/v **Flow rate:** 1.0 ml/min **Retention time:** 6 min **Co-relation co-efficient:** 0.9999 **% Recovery range**: 99.78% to 100.23 **LOD:** 1.149 µg/ml.**, LOQ:** 3.832 µg/ml.	**1**
5.	Validation and Determination of Trandolapril in bulk and formulations	RP-HPLC Method (PDA)	**Detection wavelength:** **Trandolapril:** 210 nm **Stationary phase:** Hypersil-Gold C18 column (250 mm × 4.6 mm, 5 μm) **Linearity range:** **Trandolapril:** 1-24 µg/mL **Mobile Phase:** acetonitrile and Buffer (Triethylamine, pH 3.0 ± 0.1) (50:50) v/v **Flow rate:** 1.0 ml/min **Retention time:** 4.6 min **Co-relation co-efficient:** 0.9999 **% Recovery range**: 99 % **LOD:** 0.0566 µg/ml.**, LOQ** 0.1715 µg/ml.	**2**

6.	Simultaneous estimation of Calcium channel blockers in API and dosage formulations and Human serum	RP-HPLC Method (UV-Detector)	**Detection wavelength:** **Trandolapril:** 238 nm **Stationary phase:** Nucleosil® C18 (10 µm, 25 × 0.46 cm) column **Linearity range:** **Verapamil:** 10-600 µg/mL **Other Drugs:** 5-100 µg/mL **Mobile Phase:** methanol: water: acetonitrile (55:35:10 v/v/v; pH 2.65 with OPA **Flow rate:** 1.0 ml/min **Injected volume**: 20 µL **Run time:** 10 min **Co-relation co-efficient:** 0.9998	**3**
7.	Determination and Comparison Between Cyano and C-18 Columns for Separation of Trandolapril and Verapamil	HPLC-UV Method /LC-MS/MS	**Detection wavelength:** **Verapamil:** 215nm **Trandolapril:** 215nm **Stationary phase:** **a)** Inertsil C-18, (250×4.6 mm, 5 µ) **b)** Inertsil C-18, (150×4.6 mm, 5 µ) **c)** Cyano (150×4.6 mm, 5 µ) **Linearity range:** **Verapamil:** 30–140 µg/mL−1 **Trandolapril:** 0.5–10 µg/mL−1 **Mobile Phase:** **For C 18 Column:** acetonitrile: potassium di-hydrogen ortho-phosphate buffer pH 6 (50:50)v/v **For Cyano Column:** acetonitrile: potassium di-hydrogen ortho-phosphate buffer pH 4.5 (25:75)v/v. **Flow rate:** 1.0 ml/min **Retention time:** **Column C18 150 mm**: TRP-3.1, VRP-4.2 **Column C18 250 mm:** TRP -3.3, VRP- 8.8 **Cyano Column 150 mm**: TRP - 3.4, VRP- 5.2 **Co-relation co-efficient:** **Column C18 150 mm**: TRP-0.9999, VRP-0.9999 **Column C18 250 mm:** TRP - 0.9999, VRP-0.9999 **Cyano 150 mm**: TRP - 0.9998, VRP- 0.9998 **% Recovery range**: **C18 150 mm**: TRP-100.29%, VRP-100.08% **C18 C18 250 mm:** TRP- 100.23%, VRP-100.33% **Cyano 150 mm**: TRP- 100.066%, VRP-100.089% **LOD: C18 150mm/C18 250mm/ Cyano 150 mm** TRP -0.16 µg/ml, VRP- 10 µg/ml. **LOQ: C18 150mm/C18 250mm/ Cyano**	**4**

			150 mm TRP -0.5 µg/ml, VRP- 30µg/ml.	
8.	Verapamil and Norverapamil in Human Plasma	RP-HPLC Method	**Detection wavelength:** **Verapamil:** 201 nm **Stationary phase:** Cyanopropylsilane column (Dupont, Wilmington, DE), 15 cm × 4.6 mm **Linearity range:** **Verapamil:** 20-100 µg/mL **Mobile Phase:** acetonitrile and buffer (65:35%)v/v **Flow rate:** 3.0 ml/min **Injected volume**: 20 µL **Retention time:** **Verapamil:** 3.92 min **Co-relation co-efficient:** **Verapamil:** 0.9935 **% Recovery range:** **Verapamil:** 99.99 % **Verapamil :** **LOD:** 2 ng/ml	**5**
9.	Estimation of Trandolapril Impurity in API	RP-UPLC-MS Method	**Detection wavelength:** **Trandolapril:** 210 nm **Stationary phase:** Acquity BEH C18, (100mm x 2.1mm) ,1.7µm **Linearity range:** **Trandolapril:** 0.05 to 1.0 % **Mobile Phase:** **Solution A** : 0.1% TFA in water, **Solution B** : 0.1% TFA in Acetonitrile. Solution **A** : Solution **B** (20:80 %) **Flow rate:** 0.4 ml/min **Retention time:** 5.56 min **Co-relation co-efficient:** 0.9997 **% Recovery range:** 100 to 101.0%	**6**
10.	Estimation of Combination of Trandolapril and Verapamil in Bulk and Pharmaceutical formulation	RP-HPLC Method (UV-Detector)	**Detection wavelength:** **Verapamil:** 240 nm, **Trandolapril:** 240 nm **Stationary phase:** Hypersil BDS C18 (100 mm x 4.6 mm, 5µ) **Linearity range:** **Verapamil:** 60-360 µg/Ml**,** **Trandolapril:** 1-6 µg/mL **Mobile Phase:** phosphate buffer and acetonitrile (60:40 v/v) **Flow rate:** 0.8ml/ min **Retention time:** **Verapamil:** 3.481 min **Trandolapril:** 2.905 min **Co-relation co-efficient:** **Verapamil:** 0.9998, **Trandolapril:** 0.9999	**7**

			% Recovery range: **Verapamil:** 99.65 %, **Trandolapril:** 99.64 % **Verapamil :** **LOD:** 4.923 µg/mL **, LOQ:** 14.918 µg/ml **Trandolapril:** **LOD:** 0.166 µg/mL **, LOQ:** 0.503 µg/ml	
11.	Estimation of Trandolapril in Tablets dosage form	RP-HPLC Method (PDA detector)	**Detection wavelength:** **Trandolapril:** 220 nm **Stationary phase:** Altima, C18 column (4.6 x150mm, 5µ) **Linearity range:** **Trandolapril:** 6-36 µg/mL **Mobile Phase:** phosphate buffer and acetonitrile (35:65)v/v **Column temperature**: 30^{0}C **Injection volume**: 10ul **Flow rate:** 1.0 ml/min **Retention time:** 2.9 min **Run time:** 5 min **Co-relation co-**efficient**:** 0.9999 **% Recovery range**: 100.13 % **LOD:** 0.28 µg/ml.**, LOQ:** 0.85 µg/ml.	**8**
12.	Verapamil Hydrochloride and Trandolapril in bulk and Their Pharmaceutical formulation	RP-HPLC Method (UV detection)	**Detection wavelength:** **Verapamil:** 230 nm, **Trandolapril:** 230 nm **Stationary phase:** symmetrical C18 column (4.6 x 150mm, 3.5µ) **Linearity range:** **Verapamil:** 10-65 µg/Ml**,** **Trandolapril:** 2-15 µg/mL **Mobile Phase:** Phosphate buffer (pH2.2):acetonitrile (35:65) v/v **Flow rate:** 0.6ml/ min **Retention time:** **Verapamil:** 2.5 min **Trandolapril:** 3.8 min **Co-relation co-efficient:** **Verapamil:** 0.999, **Trandolapril:** 0.998 **% Recovery range:** **Verapamil:** 98.44 %, **Trandolapril:** 98.01 % **Verapamil :** **LOD:** 0.018µg/mL **, LOQ:** 0.06µg/ml **Trandolapril:** **LOD:** 0.05 µg/mL **, LOQ:** 0.19 µg/ml	**9**
13.	Nifedipine and Verapamil in Rat Plasma	HPLC Method	**Detection wavelength:** **Verapamil:** 235 nm **Nifedipine:** 235 nm **Stationary phase:** Microsorb-MV C18, (25 cm x 4.6 mm) i.d., 5 µm **Linearity range:**	**0**

			Verapamil: 0.4-2 µg/mL **Nifedipine:** 0.2-1 µg/mL **Mobile Phase:** Acetonitrile: methanol: phosphate buffer (pH 5.2, 0.01 M) (55:15:30) **Flow rate:** 1.0 ml/min **Retention time:** **Verapamil:** 6.4 min **Nifedipine:** 3.4 min **Co-relation co-efficient:** **Verapamil:** 0.998 **Nifedipine:** 0.998 **% Recovery range:** **Verapamil:** **Nifedipine:** >97%, (range = 97.9-98.3%) **Verapamil :** >95%, (range = 95.7-97.1%)	
14.	Trandolapril and Verapamil in Human Plasma	Liquid Chromatography Tandem mass Spectrometry	**Stationary phase:** waters symmetry-RP18 (150 mm×4.0 mm), 5µ **Linearity range:** **Verapamil:** 1-2000 µg/Ml**,** **Trandolapril:** 5-1500 µg/mL **Mobile Phase:** Ammonium formate (10 mmol) and acetonitrile (70:30 %) V/V **Flow rate:** 0.9 ml/ min **Co-relation co-efficient:** **Verapamil:** 0.999, **Trandolapril:** 0.998 **% Recovery range:** **Verapamil:** 98.37%, **Trandolapril:** 97.60%	**1**
15.	Trandolaprl and Verapamil Hydrochloride in Capsule Formulation	Liquid Chromatographic Method	**Detection wavelength:** **Verapamil HCl:** 220 nm, **Trandolapril:** 220 nm **Stationary phase:** LiChrosorb RP-18 column (250 × 4 mm, 10 µm) **Linearity range:** **Verapamil HCl:** 4–20 µg/mL **Trandolapril:** 4–20 µg/mL **Mobile Phase:** Acetonitrile: methanol: buffer (pH2.7) (40:40:20) v/v/v **Flow rate:** 1.0 ml/ min **Co-relation co-efficient:** **Verapamil HCl:** 0.9996, **Trandolapril:** 0.9995 **% Recovery range:** **Verapamil HCl:** 98.13%, **Trandolapril:** 99.94%	

16.	Determination of Verapamil in Pharmaceutical formulation	HPLC Method	**Detection wavelength:** **Verapamil:** 280 nm **Stationary phase:** C18 column (30 cm x 4 mm), 10 µm **Linearity range:** **Verapamil:** 0- 274 µg/mL **Mobile Phase:** Methanol: water: acetic acid: triethylamine (55:44:1:0.1) **Flow rate:** 1.2 ml/min **Injected volume**: 20 µL **Co-relation co-efficient:** **Verapamil:** 0.9999 **% Recovery range:** **Verapamil :** 100.0% (80 mg Tablets), 101.0% (120 mg Tablets)	**2**
17.	Determination of Verapamil Hydrochloride and its Related compounds in raw material	HPLC Method	**Detection wavelength:** **Verapamil:** 278 nm **Stationary phase:** Spherisorb ODS-2 column, (150 x 4.6 mm), 3 µm **Linearity range:** **Verapamil:** 50% - 150% **Mobile Phase:** Buffer-Acetonitrile: 2-aminoheptane (55:45:0.5) v/v/v **Flow rate:** 0.9 ml/min **Retention time:** **Verapamil:** 5.78 min **Co-relation co-efficient:** **Verapamil:** 0.994 **% Recovery range:** **Verapamil :** 99.0-100.5%.,	**3**
18.	Comparative pharmacokinetics of trandolapril and its active metabolite, and verapamil in human plasma	HPLC Method	**Detection wavelength:** **Verapamil:** nm, **Trandolapril:** nm **Stationary phase:** Phenomenex C18 (3 µm, 110 A°, 100 × 1 mm) **Linearity range:** **Verapamil:** 1.50–500 ng.mL −1 **Trandolapril:** 1.00–500 ng.mL−1 **Retention time:** **Verapamil:** 5.51 min **Nifedipine:** 6.61 min **Mobile Phase:** **phase A**: 2% acetic acid (v/v) **phase B**: 90% methanol and 2% acetic acid (v/v) **Run Time:** 10 min **Flow rate:** 50 µL/min, gradient (30% B from 0 to 1 min, 100% B from 1 to 3 min, 100% B from 3 to 8 min, 30% B from 8 to 9 min and maintained at 30% B till 10 min.	**4**

			Co-relation co-efficient: **Verapamil:** 0.9819, **Trandolapril:** 0.993	

CONCLUSION:

This Review represents the Reported Spectrophotometric and Chromatographic Methods Developed and Validated for determination of Calcium channel blocker and angiotensin-converting enzyme (ACE) inhibitors in different Pharmaceuticals formulations. Here Calcium channel blocker and angiotensin- converting enzyme (ACE) inhibitors shows the simple, accurate, precise method development and validate of the different drug formulations. The RP-HPLC, and LC-MS/MS, UV- Spectrophotometric method etc.

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