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Analytical methodologies for determination of Lercanidipine and valsartan: An overview

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Abstract
Lercanidipine is a calcium channel blocker of the dihydropyridine class. It is commonly used for the treatment of hypertension. It lowers the blood pressure and allows the heart to work more efficiently. Valsartan is angiotensin II receptor antagonist, a selective for the type I angiotensin receptor. Combination therapy of Lercanidipine and Valsartan had been proven to be more effective than monotherapy in terms of reduction of blood pressure. This paper provides a crtitical review on the methodologies available for determination of Lercanidipine and Valsartan in different pharmaceutical dosage forms. The review highlights a variety of analytical techniques such as UV- Spectroscopy, HPLC (High Performance Liquid Chromatography), HPTLC (High Performance Thin Layer Chromatography), LC (Liquid Chromatography) for the analysis of Lercanidipine and Valsartan.

Keywords: lercanidipine, valsartan, UV- spectroscopy, HPLC (high performance liquid chromatography), HPTLC (high performance thin layer chromatography), LC (liquid chromatography)

Introduction [1-4]

Lercanidipine: 3-{1-[(3, 3 diphenylpropyl) (methyl) amino]-2-methylpropan-2-yl} 5-methyl 2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate with molecular formula $C_{36}H_{41}N_3O_6$. Chemical structure is shown in figure.

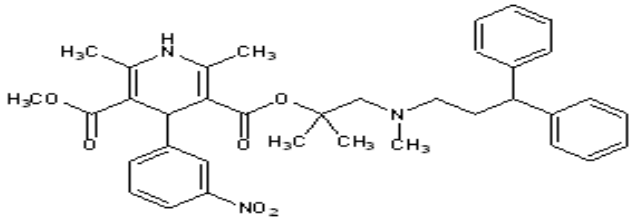

Fig 1

Lercanidipine is a calcium channel blocker of the dihydropyridine class. It is commonly used for the treatment of hypertension. Lercanidipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

Valsartan is a tetrazole derivative; (2S)-3-methyl-2-pentanoyl-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] amino] butanoic acid with molecular formula C24H29N5O3...chemical structure is shown in figure.

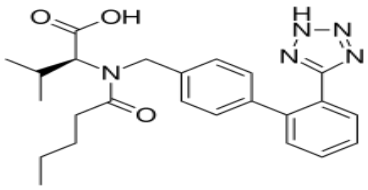

Fig 2

Valsartan is an antihypertensive agent known as angiotensin II receptor antagonist (ARB), which is selective for the type I (AT1) angiotensin receptors. Valsartan is used for the treatment of high blood pressure and congestive heart failure. It blocks the blood pressure by increasing effects of AT2 via the renin-angiotensin- aldosterone system (RAAS). It is an orally active non-peptide Triazolederived antagonist of angiotensin (AT) II with antihypertensive properties. Valsartan specifically and competitively blocks the binding of AT2 to the AT1 subtype receptor in vascular smooth muscle and the adrenal gland, preventing AT II-mediated vasoconstriction, aldosterone synthesis & secretion, renal reabsorption of sodium, resulting in vasodilation, increased excretion of sodium & water, a reduction in plasma volume, and a reduction in blood pressure.

Lercanidipine and Valsartan in combination therapy resulted in significantly greater and earlier reduction in blood pressure than the monotherapy. Hence this combination is most effective and safe compared to monotherapy.

Table 1: Estimation of Lercanidipine by Uv- Spectrophotometry [5]

Sr. No	Drug	Method	Description
1	Lercanidipine in pharmaceutical formulation.	UV Spectroscopy	Detection wavelength: 236nm Solvent: Methanol Linearity range: 0.5-60µg/ml Correlation coefficient: 0.997

Table 2: Chromatographic Methods [6-18]

Sr. No	Drug	Method	Description
1	Lercanidipine Hydrochloride in Tablets	Stability indicating HPLC	Stationary phase: C_8 column Mobile phase: 0.02 M KH_2PO_4 buffer: methanol (35:65, v/v) Linearity range: 20-80 µg/ml Flow rate: 1ml/min Wavelength: 240nm
2	Lercanidipine HCl in pure form and nanosuspension formulation	RP-HPLC	Stationary phase: C_{18} Column. Mobile phase: Acetate buffer and Acetonitrile (10:90, v/v). Linearity range: 5.0–25.0 µg/ml Flow rate: 1ml/min Wavelength: 240nm
3	Lercanidipine Hydrochloride and Its Impurities in Tablets.	RP-HPLC	Stationary phase: C_{18} column. Mobile phase: Acetonitrile-Water-Triethylamine 55:44.8:0.2 (*v/v/v*) Flow rate: 1ml/min Wavelength: 240nm
4	Purity of Lercanidipine Hydrochloride in Tablet Dosage form	RP-HPLC	Stationary phase: C_{18} column. Mobile phase: K_3PO_4 buffer and acetonitrile(55:45,v/v) Linearity range: 0.04-150 µg per ml Flow rate: 1ml/min Wavelength: 240nm
5	Lercanidipine Hydrochloride in Tablets	RP-HPLC	Stationary phase: C_{18} column. Mobile phase: Methanol: Acetonitrile (70:30) Retention time: 9.2 min Linearityrange: 10-60µg/ml Flow rate: 1ml/min Wavelength: 219nm
6	Lercanidipine Hydrochloride	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Buffer solution and Acetonitrile (650 : 350 v/v)Linearity range: 0.1 µg/ml to 20 µg/ml Flow rate: 1ml/min Wavelength: 205nm
7	Lercanidipine hydrochloride in tablets	Stability-indicating HPLC method	Stationary phase: C_8 Column. Mobile phase: $NH_4H_2PO_4$: buffer: methanol (35:65, v/v) Linearity range: 20-80 µg/ml Wavelength: 240nm
8	Lercanidipine Hydrochloride in pharmaceuticals and in blood plasma.	HPTLC	Stationary phase: Pre-coated silica gel 60 F_{254} plates. Mobile phase: Methanol: Toluene (2.5:7.5, v/v) Linearity range: 100-600ng/band R_f Value: 0.70
9	Atorvastatin and Lercanidipine in rat plasma	HPLC	Stationary phase: C_{18} column Mobile phase: acetonitrile: 0.1M ammonium acetate buffer (50:50 v/v). Linearity range (AT and LER): 0.1 to 40 µg/ml Flow rate: 1.2ml/min Wavelength: 235nm
10	Atenolol and Lercanidipine in bulk and pharmaceutical dosage form.	Stability indicating RP-HPLC	Stationary phase: C_{18} column Mobile phase: Acetonitrile :Methanol: KH_2PO_4 (50:10:40) Linearity range (ATL): 208-624 µg/ml. Linearity range (LER): 40-120 µg/ml Flow rate: 1ml/min Wavelength: 226nm
11	Lercanidipine Hydrochloride And Atenolol in bulk and tablet dosage form.	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Methanol: Water (95:5 v/v) Linearity range: 4-24µg/ml Flow rate: 1ml/min

			Wavelength: 237nm Linearity range: 4-24µg/ml
12	Atenolol and Lercanidipine hydrochloride in Pharmaceutical dosage forms	RP-HPLC	Stationary phase: C_{18} column Mobile phase: ACN: phosphate buffer (60:40, v/v) Linearity range (ATL): 50-250 mg/ml Linearity range (LER): 10-50 mg/ml Flow rate: 0.5ml/min Wavelength: 235nm
13	Atenolol and Lercanidipine Hydrochloride in Tablets	Stability indicating HPLC	Stationary phase: C_{18} column Mobile phase: acetonitrile and buffer (potassium dihydrogen phosphate pH 3.5) (55:45,v/v) Linearity range (ATE): 40-160 µg/ml. Linearity range (LER): 8-32 µg/ml Flow rate: 1ml/min Wavelength: 235nm

Table 3: Hyphenated Techniques [19-20]

Sr. No	Drug	Method	Description
1	Lercanidipine in human plasma	LC-MS/MS	Stationary phase: C_{18} column Mobile phase: methanol and 0.1 % formic acid (75:25 v/v) Linearity range: 0.10-10.0 ng/ml Flow rate: 0.7ml/min Correlation coefficient: 0.992
2	Fixed-Dose Combination of Lercanidipine and Valsartan in Human Plasma	LC–MS-MS	Stationary phase: C_{18} column. Mobile phase: acetonitrile and ammonium acetate (53:47, v/v) *m/z (LER)* 612.1 → 280.2 *m/z (VAL)* 436.0 → 235.1 Internal Standard: diazepam Linearity range (LER):0.01504–10.07 ng/ml Linearity range (VAL): 5.025–6,030 ng/ml.

Table 4: Estimation of Valsartan by UV Spectrophotometry [21-39]

Sr. No	Drug	Method	Description
1	Valsartan in bulk and tablet dosage form	UV Spectrophotometric method	Detection wavelength : 250nm (Zero order spectra) Detection wavelength: 241nm (Second order spectra) Solvent: Methanol Linearity range: 10-50µg/ml Correlation coefficient: 0.999
2	Valsartan in pure and in formulations	UV-Spectrophotometric method	Detection wavelength: 250.80nm Solvent: Methanol Linearity range:5-30µg/ml Correlation coefficient: 0.996
3	Valsartan in Bulk and Pharmaceutical Dosage Form	UV-Spectrophotometric method	Detection wavelength: 248.20nm Solvent: Methanol Linearity range: 2-20µg/ml Correlation coefficient: 0.999
4	Valsartan in Bulk and Pharmaceutical Dosage Forms	UV-Spectrophotometric method	Detection wavelength: 250nm Solvent: Phosphate buffer pH7.4 Linearity range: 2-20µg/ml Correlation coefficient: 0.999
5	Valsartan in bulk and tablet dosage form	UV-Spectrophotometric method. Method 1: Absorption maxima method. Method 2: AUC Method. Method 3: Second Order Derivative Spectroscopy.	Detection wavelength: 250 nm (Method 1) Detection wavelength: 245-255 nm (Method 2) Solvent: Methanol Linearity range: 5-50µg/ml Correlation coefficient: 0.999 (Method 1) Correlation coefficient: 0.999 (Method 2) Correlation coefficient: 0.979 (Method 3)
6	Valsartan in Bulk and Pharmaceutical Dosage Form	UV Spectrophotometric Method	Detection wavelength: 248.21nm Linearity range:2-20µg/ml Solvent: Methanol LOD: 0.15 µg/ml LOQ: 0.45 µg/ml

7	Nebivolol HCL and Valsartan in bulk and its pharmaceutical formulations	UV Spectrophotometric Method	Detection Wavelength: Nebivolol: 246 nm Valsartan: 280 nm Linearity range: Nebivolol: 0.5-2.5 µg/ml Valsartan: 1-20 µg/ml Correlation coefficient: Nebivolol: 0.998 Valsartan: 0.999
8	Valsartan and Nifedipine in synthetic mixture	UV Spectrophotometric Method	Detection Wavelength: 227nm(isoabsoraptive point) Solvent: methanol Linearity range: 2-20µg/ml LOD: Valsartan: 0.20 µg/ml Nifedipine: 0.15 µg/ml LOQ: Valsartan: 0.62 µg/ml Nifedipine: 0.47 µg/ml Correlation coefficient: valsartan: 0.9994 Nifedipine: 0.9988
9	Valsartan in pure and in pharmaceutical dosage forms	UV Spectrophotometric Method	Detection wavelength: 530 nm Solvent: Methanol Linearity range: 5-50µg/ml Correlation coefficient: 0.9976
10	Valsartan and Ezetimibe in pharmaceutics	UV Spectrophotometric Method	Detection Wavelength: Valsartan: 425 nm Ezetimibe: 250 nm Linearity range: Valsartan: 4-40µg/ml Ezetimibe: 1-50 µg/ml Correlation coefficient: Valsartan: 0.9950 Ezetimibe: 0.9990
11	Nefidipine and valsartan in synthetic mixture	UV Spectrophotometric Method	Detection Wavelength: Valsartan: 262.5 nm Nifedipine: 327.5 nm Linearity range: 2-20µg/ml LOD: Valsartan: 0.24 µg/ml Nifedipine: 0.19 µg/ml LOQ: Valsartan: 0.74 µg/ml Nifedipine: 0.58 µg/ml
12	Valsartan and Hydrochlorothiazide in their combination dosage form	UV Spectrophotometric Method	Detection Wavelength: Valsartan: 270.60 nm Hydrochlorthiazide:250.20 nm Linearity range: Valsartan: 2-14 µg/ml Hydrochlorothiazide: 4-20 µg/ml LOD: Valsartan: 1.157 µg/ml Hydrochlorothiazide: 0.634 µg/ml LOQ: Valsartan: 3.50 µg/ml Hydrochlorothiazide: 1.92 µg/ml
13	Valsartan and Ramipril	UV Spectrophotometric Method	Detection Wavelength: Valsartan: 289.36 nm Ramipril: 226.89 nm Correlation coefficient: Valsartan: 0.9973 Ramipril: 0.9987 Linearity range: 2-16µg/ml
14	Ramipril and valsartan in pharmaceutical dosage form	UV Spectrophotometric Method	Detection Wavelength: Valsartan: 218 nm Ramipril: 236 nm

			Solvent: Methanol: 0.1 N HCL (1:9) Linearity range: 10-40 µg/ml
15	Amilodipinbesylate, valsartan and hydrochlorothiazide in bulk and tablet formulation	UV- spectrophotometry	Detection Wavelength: Amilodipin: 359 nm Hydrochlorothiazide: 317 nm Valsartan: 250 nm Solvent: Methanol Linearity range: Amilodipin: 5-25µg/ml Hydrochlorothiazide: 10-50µg/ml Valsartan: 5-25µg/ml Correlation coefficient: Amilodipin: 0.999 Hydrochlorothiazide: 0.999 Valsartan: 0.999
16	Valsartan and hydrochlorothiazide in combined tablet dosage form	UV- spectrophotometry	Detection Wavelength: Valsartan: 250 nm Hydrochlorothiazide: 270 nm Solvent: Water Linearity range: Valsartan: 6-36µg/ml Hydrochlorothiazide: 2-12 µg/ml Correlation coefficient: Valsartan: 0.998 Hydrochlorothiazide: 0.999
17	Aliskiren Hemifumarate (ALK) and Valsartan in their combined tablet dosage form.	UV-spectrophotometric method	Detection wavelength (ALK): 275nm Detection wavelength (VAL): 250nm Solvent: Methanol Linearity range(ALK): 30-80µg/ml Linearity range(VAL): 5-25µg/ml LOD(ALK): 4.0749µg/ml LOQ(ALK):12.3482µg/ml LOD(VAL): 3.51µg/ml LOQ(VAL):10.6551µg/ml
18	Valsartan and Hydrochlorothiazide in pharmaceutical dosage form	UV-Spectrophotometric method.	Detection Wavelength: 270.5 nm Linearity range: 2-20µg/ml LOD: Valsartan: 0.628 µg/ml Hydrochlorothiazide: 0.413 µg/ml LOQ: Valsartan: 1.902 µg/ml Hydrochlorothiazide: 1.251 µg/ml
19	Valsartan and Hydrochlorothiazide in Tablet Dosage Form.	UV-Spectrophotometric method. Method-1: Simultaneous Equations. Method-2: Q-Absorbance equation	Detection wavelength (VAL): 249.4 nm (Method 1) Detection wavelength (HCT): 272.6 nm (Method 1) Detection wavelength: 258.4 nm (Is absorptive point) Solvent: 0.1 N NaOH Linearity range: (VAL): 5–30 µg/mL Linearity range: (HCT): 4–24 µg/Ml Correlation coefficient (VAL): 0.998 (Method 1) Correlation coefficient (VAL): 0.998 (Method 2) Correlation coefficient (HCT): 0.999 (Method 1) Correlation coefficient (HCT): 0.999 (Method 2)

Table 5: Chromatographic Methods [40-56]

Sr. No	Drug	Method	Description
1	Valsartan in bulk and tablet dosage forms	RP-HPLC	Stationary phase: C_{18} Column. Mobile phase: Water: acetonitrile: glacial acetic acid (550:450:1 v/v/v) Linearity range: 2-14 µg/ml Flow rate: 2.0ml/min Detection wavelength: 248 nm

2	Valsartan in pharmaceutical dosage form	Stability indicating method RP-HPLC	Stationary phase: C_{18} column Mobile phase: methanol: Phosphate buffer pH-3.0 (65:35 v/v) Retention time: 6.22 min Flow rate: 1 ml/min Detection Wavelength: 210 nm
3	Valsartan in pure and tablet dosage form	RP-HPLC	Stationary phase: C_{18} column Mobile phase: acetonitrile: phosphate buffer (55:45 v/v) Retention time: 3.943 min Detection Wavelength: 233nm
4	Valsartan and its degradation products	HPLC	Stationary phase: C_{18} column Mobile phase: Methanol: water (70/30 v/v). Detection Wavelength: 250 nm Retention time: 0.40 min (Acid hydrolysis), 0.27 min (Oxidation) Flow rate: 1.2 ml/min
5	Valsartan in solid oral dosage form	RP-HPLC	Stationary phase: C_{18} Column. Mobile phase: acetate buffer: acetonitrile: methanol (38/24/38 v/v/v/) Retention time: 4.6 ± 0.06 min Flow rate: 1.2 ml/min Detection wavelength: 248 nm
6	Valsartan in tablet dosage form	RP-HPLC	Stationary column: C18 Column. Mobile phase: ammonium dihydrogen phosphate buffer: methanol (33.5: 66.5 v/v) Flow rate: 1.0 ml/min Retention time: 11.6 min Detection Wavelength: 265 nm
7	Valsartan in human plasma	Liquid chromatography	Stationary phase: C_{18} Column. Mobile phase: 0.01M disodium hydrogen phosphate buffer: acetonitrile (60/40 v/v) Linearity range: 20-2000 ng/ml Flow rate: 2 ml/min Detection wavelength: 230 nm, 295 nm.
8	Valsartan and Atorvastatin in their combination drug product	Stability indicating RP-HPLC Method.	Stationary phase: C_{18} column Mobile phase: 0.1% acetic acid: Methanol (50:50 v/v) Linearity range: Valsartan: 40-120 µg/ml Atorvastatin: 5-15 µg/ml Retention time: Valsartan: 3.33 min Atorvastatin: 5.44 min Detection Wavelength: Valsartan: 225 nm Atorvastatin: 246 nm Flow rate: 2.0 ml/min
9	Valsartan and Hydrochlorothiazide in Tablets	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Methanol: Acetonitrile: Water: Isopropyl alcohol (v/v) Linearity range (VAL): 5-150µg/ml Linearity range(HCT): 78-234 µg/ml Flow rate: 1ml/min Detection wavelength: 270 nm.
10	Valsartan potassium (VP) and Amlodipine besylate (AB) in tablet dosage form.	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Methanol: Water (62:38) Linearity range (VP): 112µg/ml to 208µg/ml Linearity range(AB): 07µg/ml to 13µg/ml Flow rate: 1.4ml/min Detection wavelength: 230 nm
11	Propranolol and Valsartan in Bulk drug and Gel Formulation	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Acetonitrile: Methanol:0.01M disodium hydrogen phosphate (50:35:15 v/v) Linearity range(PROP):5-50 µg/ml Linearity range(VAL): 4-32 µg/ml Flow rate: 1ml/min
12	Amlodipine, Valsartan and Hydrochlorothiazide in dosage forms and spiked human plasma	RP-HPLC	Stationary phase: C_{18} column Mobile phase: Acetonitrile: phosphate buffer pH-2.8 (40/60 v/v) Flow rate: 0.8 ml/min Retention time:

			hydrochlorothiazide: 2.26 min Amlodipine: 3.16 min Valsartan: 11.19 min Detection Wavelength: 227 nm
13	Sacubitril and Valsartan in bulk and pharmaceutical dosage form	RP-HPLC	Stationary phase: C_{18} column Mobile phase: phosphate buffer: Methanol: Acetonitrile (30:50:20 % v/v) Linearity range: Sacubitril: 58.8-137.2 µg/ml Valsartan: 61.2-142 µg/ml Flow rate: 1 ml/min Detection Wavelength: 241 nm
14	Valsartan & Hydrochlorothiazide in Drug products	UPLC	Stationary phase: C_{18} column Mobile phase: Triethylamine buffer (0.1% v/v) and Methanol (75:25 v/v) Linearity range: Valsartan: 56-104 µg/ml Hydrochlorothiazid: 7-13 µg/ml Flow rate: 0.6 ml/min Detection Wavelength: 225 nm
15	Valsartan and Hydrochlorothiazide in Tablet Dosage Form	HPTLC	Stationary phase: precoated silica gel $60F_{254}$. Mobile phase: chloroform: methanol: toluene: glacial acetic acid (6:2:1:0.1 v/v/v/v) Linearity range: Valsartan: 300-800 ng/spot Hydrochlorothiazid: 100-600ng/spot Detection of Spots: 260 nm
16	Sacubitril and Valsartan in Its Bulk and Tablet Dosage Form	Force Degadation Studies by RP-UPLC	Stationary phase: Inertsil ODS (1.7 × 150mm, 3µm size) column. Mobile phase: phosphate buffer: acetonitrile (50:50%v/v) Linearity range: Valsartan: 13-65 µg/ml Sacubitril: 12-60 µg/ml Flow rate: 0.4 ml/min Detection Wavelength: 271 nm
17	Amlodipine Besylate and Valsartan in Bulk Drug and Formulation	Validated TLC Method.	Stationary phase: precoated silica gel $60F_{254}$. Mobile phase: toluene: methanol: acetic acid 7:3:0.1 *(v/v/v)* Linearity range: Amlodipine Besylate: 100-600 ng/spot Valsartan: 1,600–9,600 ng/spot Detection of Spots: 244 nm R_F value: Amlodipine Besylate: 0.41 ± 0.02 Valsartan: 0.54 ± 0.02

Table 6: Hyphenated Techniques [58]

Sr. No	Drug	Method	Description
1	Amlodipine and Valsartan in Human Plasma	LC-MS/MS	Stationary phase: C_{18}column. Mobile phase: acetonitrile: 5 mm ammonium format solution (80:20, v/v) Linearity range: Valsartan: 6.062–18060.792 ng/mL Amlodipine: 0.302–20.725 ng/mL Flow rate: 0.8 ml/min

Conclusion

This review portray the reported Spectroscopic and Chromatographic methods developed and validated for estimation of Lercanidipine and Valsartan. According to this review it was concluded that for Lercanidipine and Valsartan different Spectroscopic and Chromatographic methods are available for single and combination. The mobile phase containing Phosphate buffer, Methanol and Acetonitrile were common for most of the chromatographic method to provide more resolution. For chromatographic method flow rate is observed in the range 0.6 - 2 ml/min to get good resolution time. For most of the Spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

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