World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Drug Profile of Valsartan: A Review

Babita Kumari and Rajeev Garg

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial (ASBASJSM) College of Pharmacy, BELA, Ropar, India

Received: 13-06-2015 / Revised: 20-07-2015 / Accepted: 21-07-2015

ABSTRACT

Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of Angiotensin II type I receptor antagonists. Angiotensin II receptor type I antagonists have been widely used in the treatment of hypertension, heart failure, myocardial infraction and diabetic nephropathy. It is a lipophilic drug and it was first developed by Novartis and has a wide market in the developed and developing countries. It is available as single and in combination with other antihypertensive drugs. Valsartan is rapidly absorbed after oral administration. Volume of distribution at steady state has been estimated 17L and mean absolute bioavailability is 23%. Food decreases the exposure of Valsartan by about 40% and peak plasma concentration by about 50%. 94%-97% of drug bound to serum protein mainly albumin. It is eliminated by non-renal route. Plasma clearance of Valsartan is 2L/hours and renal clearance is 0.62L/hour. In this paper, the physicochemical properties, analytical determination methods, pharmacokinetics and pharmacodynamics of Valsartan are reviewed.

Key words: Valsartan, Hypertension, Pharmacokinetics, Bioavailability, Angiotensin II receptors inhibitors

INTRODUCTION

Most cardiovascular events are attributed to high blood pressure. High blood pressure is quantitatively the largest single risk factor for premature death and disability due to its extremely high prevalence in industrialized countries [1, 2]. Hypertension currently affects approximately one billion adults globally. It is a major risk factor for cardiovascular disease and stroke and is associated with metabolic syndrome include insulin resistance and lipid abnormalities. The high prevalence of hypertension has contributed to the present pandemic of cardiovascular diseases, which now accounts for 30% of all death worldwide [3]. The risk of hypertension increases with age and is associated with gender and ethnicity [4]. To minimize or prevent hypertension adequate diet and physical exercise are recommended [5, 6]. Hypertension is one of the most prevalent chronic adult illness today and cannot be cured, but can be controlled. The pharmacological treatment for control of hypertension utilizes various drug therapies such as single dose or associates with diuretics, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitor and angiotensin receptor antagonist [7, 8].

Valsartan is a potent and highly selective type 1 antagonist that lowers blood pressure in hypertensive patients [9]. Valsartan has greater affinity for AT I receptor than AT II receptor. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme. Angiotensin II is the principal presser agent of renin angiotensin system, with effect that includes vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium [10].

PHYSICOCHEMICAL PROPERTIES

Valsartan is N-(1-oxopentyl)-N-[[2-(1H-tetrazol-5-yl) [1, 1-biphenyl]-4-yl] methyl]-l-valine [11-14]. It is a white powder with empirical formula $C_{24}H_{29}N_5O_3$ and molecular weight 435.52g/mol [15]. It is synthesized from L-valine methyl ester hydrochloride. Key step involves palladium-catalysed Suzuki coupling. Melting range of 105-110 °C and specific rotation [α]D/20 in methanol is 68° and partition coefficient of Valsartan is 0.033 (logP=1.499) indicating that the compound has a rather hydrophilic characteristic at physiological pH. Due to its fine particle size, Valsartan absorbs water reversibly from ambient atmosphere. The compound is stable when stored under dry

***Corresponding Author Address:** Babita Kumari, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial (ASBASJSM) College of Pharmacy, BELA, Ropar, India*

conditions [16]. For ionizable molecules, pH plays a crucial role. The charge state that a molecule exhibit at particular pH is characterized by ionization constant pKa of the molecules. Buffer affects pH gradients weakly acidic and weakly basic drug exhibit pH dependent solubility [17]. Valsartan is a tetrazole derivative that contains two weakly acidic function groups (acid and carboxylic acid) with pKa value of 4.7 and 3.9. These groups making compound stable in the neutral pH range [18]. It exists as solution at physiological pH value as the undissociated acid, the mono and di-anion. On increasing the pH from 4 to 6 the solubility of Valsartan increases by a factor of about 1000, but it favor the anionic form and decreases lipophilicity, since the solubility of Valsartan in the pH range 4-8 and lipophilicity decreases in the same range. The rate of absorption of Valsartan may be influenced by intestinal pH [16]. In a buffered solution, the solubility is increased because the di-anion salt is formed [16].

DETERMINATION METHODS

Many analytical methods have been developed for the determination of Valsartan in pharmaceutical formulations and in biological fluids. Such as UV-spectroscopy[13,19-23], HPLC[24-31], RP-HPLC[12,32-50], HPTLC[51-53], TLC[54], absorption ratio method[55,56] voltammetry[57] has been developed. Methods such as HPLC, Capillary electrophoresis and simultaneous UV spectroscopic methods of Valsartan are reported for estimation of Valsartan alone or in combination with other drugs. The advantages of UV-spectroscopic methods over HPLC is significantly shortening analysis time, low cost of analysis, widespread access to the apparatus, while the HPLC procedure is time consuming, require too many solvents and expensive apparatus. HPLC-MS/MS [58] and LC-MS/MS [59] methods have been developed for analysis of ACE inhibitors in plasma.

Table no. 1 Determination and Quantification Methods

S.no	Sample	Column	Method	Mobile phase	References
1	Valsartan, Losartan and Irbesartan pharmaceutical preparation	C_{18} column	RP-HPLC	Acetonitrile: phosphate potassium buffer (pH 3).	Youssef R *et al* (2014):
2	Valsartan in human plasma	Zorbax Extend-C18 (4.6 x 150 mm)	HPLC	Phosphate buffer - acetonitrile mixture (50:50 v/v) pH 3.0	Abdallah OM *et al* (2013)
3	Valsartan potassium & Amlodipine besylate in tablet formulation	C-18 Column (Inertsil ODS-2, 150 x 4.6 mm)	RP-HPLC	Methanol: Water (62:38), pH 3.0	Maheshwari N *et al* (2013):
4	Valsartan in tablet formulation	X terra ,RP-18(100mm X 4.6mm 5µm)	RP-HPLC	Degassed mixture of water, Acetonitrile & Glacial acetic acid in the ratio of 550:450:1v/v	Nissankararao S *et al* (2013)
5	Valsartan and hydrochlorothiazide in pure form and in tablets	Butyl-modified aleppo bentonite (BAC4)	TLC	Acetonitrile:water: acetic acid (49.35:49.35:1.3, v/v), at pH 3.2	Ramadan AA *et al* (2013)
6	Valsartan in pharmaceutical dosage forms.	X terra C18(150mm × 4.6mm × 5µm)	RP - HPLC	Potassium dihydrogen ortho-phosphate, pH 3.0	Reddy KNK *et al* (2012)
7	Losartan, Valsartan, Telmisartan and Irbesartan in the presence of the degradation products	C_{18} column (250 mm×4.6 mm, 5 µm)	RP-HPLC	65:35 % (v/v) potassium dihydrogen phosphate (0.025 M, pH 6.0): acetonitrile	Elshanawane AA *et al* (2012)
8	Valsartan/HCTZ in tablet formulation	C_{18} Column	HPLC	Mixture of Solvent A (0.20 M ammonium acetate, adjusted to pH 5.6 with glacial acetic acid) and Solvent B (acetonitrile)	Kharoaf M *et al* (2012)

9	Valsartan in tablet formulations	Precoated silica gel G 60 F254 HPTLC plates	HPTLC	Chloroform: acetonitrile: toluene: glacial acetic acid, in the ratio 1:8:1:0.1 (v/v) (v/v)	Parambi DGT *et al* (2011)
10	Valsartan in pure and pharmaceutical dosage form	-	UV	-	Nataraj KS *et al* (2011)
11	Valsartan in pure and tablet formulation.	X-terra C18 column (100×4.6 mm I.D., 5µm particle size)	RP-HPLC	mixture of phosphate buffer pH 3 and acetonitrile in the ratio of 50:50 v/v	Raju VB *et al* (2011)
12	Valsartan and ezetimibe in pharmaceuticals		UV		Ramachandran S *et al* (2011)
13	Valsartan in pure and tablet forms		RP-HPLC	0.01 M $NH_4H_2PO_4$ (pH 3.5) buffer: methanol [50:50]	Patro SK *et al* (2010)
14	Valsartan in human plasma	Chromolith Performance (RP-18e, 100×4.6 mm)	HPLC	0.01 M disodium hydrogen phosphate buffer-acetonitrile (60:40 v/v) pH 3.5	Zarghi A *et al* (2008)
15	Valsartan and Amlodipine from their combination dosage form.	X Terra® RP8, 5 µm, 100 mm × 4.6 mm	RP-HPLC	0.05M Ammonium Acetate and 0.5% TEA buffer having pH 5.5 and Acetonitrile in the ratio of 68:32 v/v	Prasad CVN *et al* (2011)
16	Valsartan in tablet dosage form	Microbondapak, C18, 5µm, 25cmx4.6mm	HPLC	Methanol: phosphate buffer of pH 3 (65:35)	Patnaik A *et al* (2011)
17	Valsartan and losartan potassium degradation behavior in pharmaceutical dosage form	C18 (250mm X 4.6mm X 5µ).	RP-HPLC	Acetonitrile: phosphate buffer (0.02M, pH 3.5), (60: 40 v/v)	Ibrahim MM *et al* (2015)
18	Valsartan and Amlodipine besylate in microcrystalline cellulose and starch Matrix		UV		Jadhav ML *et al* (2015)
19	Valsartan and Amlodipine besylate in microcrystalline cellulose and starch Matrix	X terra C_{18} column	RP-HPLC	Valsartan and Amlodipine besylate in microcrystalline cellulose and starch Matrix	Sarigomula P *et al* (2013)
20	Atenolol, HCTZ losartan and Valsartan in the pharmaceutical dosage form	Nucleodur 100 C–18 column having 250 x 4.6mm	RP-HPLC	Potassium dihydrogen phosphate buffer pH 3.0 and acetonitrile (50:50 v⁄v)	Havaldar FH *et al* (2010)
21	Valsartan in bulk drug and pharmaceutical dosage forms	Symmetry C18 (250mm × 4.6mm × 5µ) column	RP-HPLC	0.02 M sodium dihydrogen ortho-phosphate, pH adjusted to 2.5 using ortho-phosphoric acid (solvent A), and acetonitrile (solvent B) in the ratio of 58:42 %v/v.	Rao KS *et al* (2010)

22	Amlodipine and Valsartan in their combined dosage forms	C_{18} column (ODS 2, 10 µm, 200 x 4.6 mm)	HPLC	Phosphate buffer (pH 3.6 , 0.01 mol L^{-1}) :acetonitrile: methanol (46:44:10 v/v/v)	Çelebier M *et al* (2010)
23	Amlodipine besylate, Valsartan, Telmisartan, Hydrochlorothiazide and Chlorthalidone commercially available drug products	Cosmosil PAQ (150 mm × 4.6 mm) 5 µm	HPLC	0.05 M sodium dihydrogen phosphate buffer and acetonitrile	Mhaske RA *et al* (2011)
24	Valsartan and Atorvastatin from their combination dosage form	Hypersil BDS C18, 5 µm, 250 mm× 4.6 mm	RP-HPLC	0.1% acetic acid and acetonitrile in the ratio 50:50 v/v	Prasad CVN *et al* (2011)
25	Amlodipine (AMD) and Valsartan (VSN) in plasma	25 cm × 4.6 mm 5-µm particle, C18 column	RP-HPLC	47:53 (v/v) Acetonitrile: 20mM phosphate buffer, pH 3.5	Devi R *et al* (2010)
26	Valsartan and hydrochlorothiazide in combined dosage forms	Aluminum plates pre-coated with silica gel 60 F254	HPTLC	Chloroform: Methanol: Formic acid (4:1:0.05 v/v/v)	Jadhav ML *et al* (2015)
27	Valsartan in tablet dosage form	symmetry C_{18} column	RP-HPLC	Methanol: water: THF 60:35:05 (v/v/v)	Manoranjani M *et al* (2011)
28	Valsartan and Nebivolol dosage forms	C-18 column	RP-HPLC	Acetonitrile: methanol: pH4.0 0.02M Potassium hydrogen phosphate buffer in the ratio of 50:20:30 v/v	Nekkala K *et al* (2014)
29	Valsartan and hydrochlorothiazide in tablets		Absorpti-on ratio method		Chaudhary AB *et al* (2010),
30	Valsartan and Amlodipine Besylate in Human Serum and Pharmaceutical Dosage Forms		Voltamm-etry		Erden PE *et al* (2014)
31	Ramipril (RAM) and Valsartan (VST) from pharmaceutical formulation	C-18 column	RP-HPLC	Acetonitrile: acetate buffer, 1% TEA and pH adjusted to 3.55 with 0.5% Glacial acetic acid in the ratio (60:40v/v)	Balap AR *et al* (2012)
32	Determination of Amlodipine, Valsartan, HCTZ in Dosage Form and Spiked Human Plasma	C18 chromatographic column, Phenomenex Kinetex (150 mm × 4.6 mm	HPLC	Acetonitrile-phosphate buffer (0.05 M) with pH 2.8 in the propor-tion of (40/60, v/v)	El-Gizawy SM *et al* (2012)
33	Valsartan in tablet dosage form	Phenomenox C18, 5µm,25cm x 4.6 mm	RP-HPLC	Methanol & phosphate buffer pH 3.0 in ratio of 65:35(v/v)	Haque MA *et al* (2012)
34	Valsartan in tablet dosage form.	Thermo-hypersil ODS column (150 mm × 4.6 mm	RP-HPLC	Water: acetonitrile: glacial acetic acid (500:500:01)	Vinzuda DU *et al* (2010)

		i.d., 5 µm particle size)			
35	Valsartan and hydrochlorothiazide in tablets		Absorpti-on ratio method		Banerjee T *et al* (2012)
36	Amlodipine and Valsartan in Samples for Liver Perfusion	C18 column (250mm x 4.6 mm I.D.)	HPLC	Phosphate buffer (pH 3.6; 0.01 M): acetonitrile: methanol (50:40:10 v/v)	Celebier M *et al* (2008)
37	Amlodipine and Valsartan in tablet formulation		UV		Mohamed NG *et al* (2011)
38	Nebivolol Hydrochloride and Valsartan and Nebivolol Hydrochloride and Hydrochlorothiazide in Pharmaceutical Formulations		UV		Meyyanathan SN *et al* (2010)
39	Valsartan and Ramipril in the combined solid dosage form.		UV		Rajesh V *et al* (2011)
40	Nebivolol and valsartan in bulk and pharmaceutical dosage form	Altima C18 (4.6 x 150mm, 5µ)	RP-HPLC	Phosphate buffer and acetonitrile (52:48 v/v) adjusted to pH 4.8	Siddartha B *et al* (2014)
41	Ramipril & Valsartan in Tablets	10 cm × 10cm aluminum-backed TLC plates, coated with 0.2 mm layers of silica gel 60 F254	HPTLC	ethyl acetate : chloroform: glacial acetic acid, (8:2:0.2, v/v)	Gaikwad A V *et al* (2011)
42	Quantification of Valsartan in Rat plasma	Thermo Hypurity C18 (4.6mm x 150 mm, 5.0 mm)	HPLC-MS/MS	0.1% formic acid: methanol (25:75, v/v).	Venkata SP *et al* (2011)
43	Analysis of angiotensin II receptor antagonist and protein markers at microliter level plasma	C18 nano-flow column.	LC–MS/MS	ACN:1% FA= 20:80 (v/v)	Chi-Yu Lu *et al* (2009)

PHARMACOLOGY

Valsartan belong to the family of angiotensin II type I receptor (AT 1) antagonists and possess about 20,000 fold greater affinities for it than for the angiotensin type II receptor. This action exert effect on blood pressure reduction, as well as decreases vascular smooth muscle contraction, inhibit sympathetic outflow, improve renal function and also leads to reduction in progression of artherosclerosis lesion. Also blockade of AT1 receptor by Valsartan leads to increase in local AT II concentration that stimulates the unblocked AT II receptor. The increase in AT II receptor stimulation cause vasodilation through local production of bradykinin which in turn leads to a signaling cascade that increase the production of nitric oxide and cyclic guanosine 3'-5'-monophosphate at the endothelial level that provides protection against vascular dysfunction [60].

PHARMACOKINETICS

Absorption: Valsartan is rapidly absorbed after oral dose. Absorption occurs by passive diffusion process [61]. Peak plasma concentration occurs 2 to 4 hours and its half-life is 7.5 hours after an oral

dose [62]. Absolute bioavailability of Valsartan is about 23% [63]. Food decreases the bioavailability of Valsartan by about 40% and peak plasma concentration (C_{max}) by about 50% [10].

Distribution: Valsartan has only limited distribution outside the plasma compartment. It is highly bound to plasma protein i.e 94% to 97% mainly serum albumin and hence limited distribution outside the plasma compartment. Volume of distribution has been estimated at 17L [16].

Metabolism: Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolite. A hydroxy metabolite has been identified in plasma at low concentration (less than 10% of Valsartan). This metabolite is pharmacologically inactive. The primary metabolite accounting for 9% of dose is Valeryl 4 hydroxy Valsartan. The metabolite is formed by oxidative biotransformation. The enzymes responsible for Valsartan metabolism have not been identified but do not seems to be CYP 450 isoenzymes. [16, 61] *In vitro* metabolism studies involving recombinant CYP 450 enzyme indicated that CYP2C9 isoenzymes is responsible for the formation of Valeryl 4 hydroxy Valsartan.

Elimination: Valsartan shows multiexponential kinetics ($t_{1/2\alpha}$<1h and $t_{1/2\beta}$ about 9h) is primarily eliminated by biliary excretion in faeces about 83% of dose and renally about 13% of dose mainly as unchanged drug. It is not recommended for patients with hepatic dysfunction and biliary cirrohosis [61]. After oral dosing, 83% of the dose is excreted in the faeces and 13% in the urine. Following iv administration, plasma clearance of Valsartan is about 2L/h and its renal clearance is 0.62L/h (about 30% of total clearance). Hence it is clear that the Valsartan is eliminated by non-renal routes.

Comparasion of Valsartan with other agents: The antihypertensive efficacy of Valsartan is quite similar to that of the other antihypertensive agents like thiazide diuretics, beta blockers, ACE inhibitors and calcium channel blockers. In the treatment of moderate hypertension 80 mg of Valsartan is as effective as 20 mg enalapril. Valsartan 80-160 mg daily provides comparative short and long term anti-hypertensive efficacy as compared to lisinopril 10-20mg. Valsartan 80 mg has been as effective as hydrochlorothiazide and amlodipine in treatment of mild-to-moderate hypertension. Fewer side effects of Valsartan as compared to ACE inhibitors which are used in the treatment of hypertension. In clinical trials, where Valsartan was compared with an ACE inhibitors, the incidence of dry cough was significantly ($p<0.05$) less in patient treated with Valsartan than in those treated with ACE inhibitors. When resistance developed by another antihypertensive dugs, Valsartan may be used to treat hypertension. In hypertensive patients with type 2 diabetes and microalbuminuria, Valsartan has been shown to reduce the urinary excretion of albumin (dose 160mg-320mg). The onset of action of Valsartan was more rapid than that of losartan, which underwent hepatic transformation into a more active metabolite before the full effect is produced.

In a study, effect of 160mg/day Valsartan and 80mg Telmisartan were compared, and it was found that Valsartan was also more effective in lowering arterial pulse pressure.

In a comparison study with losartan and Telmisartan, Valsartan induced significantly greater blood pressure reductions than did losartan and Telmisartan at 2 weeks ($p<0.01$) and after 4 weeks ($p<0.05$) of treatment.it was concluded that treatment with Valsartan resulted in earlier, greater and smoother antihypertensive effect compared with treatment with Losartan and Telmisartan.

FORMULATION TYPES

The conventional tablet dosage forms and capsule of Valsartan exist in commercially available forms. In addition, transdermal patches [10], SMEDDS [63] microspheres [64], has been prepared. The prepared system SMEDDS contains captex 200P, Capmul MCM, tween 80, Cremophore EL, PEG 400. Transdermal patch of Valsartan contains HPMC, PEG 200, tween 80 and microsphere of Valsartan contains eudragit, ethylcellulose, polyvinyl alcohol, and tween 80, dichloromethaneand ethanol.

SIDE EFFECTS

- Blood and lymphatic system disorder: Neutropenia, thrombocytopenia
- Immune system disorder: Hypersensitivity including serum sickness
- Metabolism and nutrition disorder: Hyperkalaemia
- Psychiatric disorder: Insomnia
- Nervous system disorder: Postural dizziness, dizziness, headache
- Cardiac disorder: Cardiac failure
- Vascular disorder: Hypotension
- Respiratory disorder: Cough
- Gastrointestinal disorder: Diarrhoea, nausea
- Skin and subcutaneous tissue disorder: Angioneurotic oedema, rash, pruritus
- Musculoskeletal and connective tissue disorder: Back pain
- Renal and urinary disorder: Renal impairement, acute renal failure
- General disorder: Fatigue

CONTRAINDICATION

- Treatment with Valsartan is contraindicated in the following cases:
- In sodium and / or volume depleted patients (hypotension)
- Renal artery stenosis
- Impaired renal functions (creatinine clearance <30ml/min)
- Impaired hepatic function (Hepatic impairement, biliary cirrhosis, cholestasis)
- Hepatic injury (Hepatitis)
- Heart failure / post myocardial infraction
- Angioedema
- Dual blockade of RAS
- Patients receiving potassium sparing diuretics or potassium containing products
- Primary hyperaldosteronism
- In pregnancy
- In lactation

INTERACTIONS

- Combination use of ACE inhibitors or angiotensin receptor antagonist, thiazide diuretics and anti-inflammatory drugs (NSAIDs, COX-2 inhibitors)
- Dual blockade of renin angiotensin system with ARBs, ACEIs or aliskiren.
- Potassium sparing diuretics
- Lithium salts

OVERDOSE

Overdose with Valsartan may result in marked hypotension which could lead to depressed level of consciousness, circulatory collapse and shock. The patient should always be given a sufficient amount of activated charcoal.

Valsartan is not removed by Haemodialysis.

STORAGE

Store below 30°C

CONCLUSION

Valsartan is new potent, effective, highly selective, orally active and well tolerated antihypertensive agent in patient with mild to moderate hypertension. Valsartan is belonging to the family of angiotensin II type I receptor antagonists. The drug may reduce BP when used in patients with severe hypertension or when used in patient with resistant hypertension. The most important property of Valsartan is pH dependent solubility and decrease in absorption when it is taken with food. Rise in pH 4 to 6 increase solubility of Valsartan. Valsartan is an appropriate choice for first line treatment of patient with mild to moderate hypertension. It is concluded that Valsartan will become a more forthcoming drug in the angiotensin II type I receptor antagonist class of drugs and used to treat Hypertension, Recent Myocardial Infraction and heart failure.

REFERENCES

1. McVeigh GE et al, Goals of antihypertensive therapy, Drugs. 1995; 49(2):161-175
2. Li H et al, A liquid chromatography/tandem mass spectrometry method for the simultaneous quantification of valsartan and hydrochlorothiazide in human plasma, J Chromatogr B Analyt Techno Bio Life Sci. 2007; 852(1-2):436-442
3. Kearney PM et al, Global burden of hypertension: analysis of worldwide data, Lancet. 2005; 365(9455):217-223.
4. Hyman DJ, Pavlik VN, Characteristics of patients with uncontrolled hypertension in the United State, N Engl J Med. 2001;345(7):479-486
5. Lewington S et al, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies, Lancet. 2000; 360(9349):1903-1913.
6. Lotufo PA, Stroke in Brazil: a neglected disease. Sao Paulo Medi J, 2005,123(1):3-4
7. Masmoudi S et al, Evaluation of diuretic activity of hydrochlorothiazide - γ-cyclodextrin inclusion complex in wistar rats, World J Pharm Res, 2014; 3(6):1146-1155.
8. Mahmud A, Feely J, Low-dose quadruple antihypertensive combination more efficacious than individual agents – a preliminary report. Hypertension, 2007; 49: 272-275
9. Séchaud R et al, Bioequivalence study of a valsartan tablet and a capsule formulation after single dosing in healthy volunteers using a replicated crossover design, Int J Clin Pharmacol Ther. 2002; 40(1):35-40
10. Gottipati DB et al, Design & evaluation of Valsartan transdermal patches, Int J Res Ayur Pharm, 2012;3(3):461-464
11. Zaid AN et al, Formulation and Bioequivalence of Two Valsartan Tablets After a Single Oral Administration, Sci Pharm, 2011;79(1): 123–135.
12. Elshanawane AA et al, Stability Indicating HPLC Method for Simultaneous Determination of Several Angiotensin-II-Receptor Antagonists in Their Dosage Forms, Pharm Analytica Acta, 2012;3(8):1-11
13. Nataraj KS et al, Simple quantitative method development and validation of Valsartan in pure form and pharmaceutical dosage form by UV- spectroscopy, Int J Pharm & Bio Sci, 2011;1(2): 67-73
14. Julio TA et al, Compatibility and stability of Valsartan in a solid pharmaceutical formulation, Brazil J Pharm Sci, 2013; 49(1):645-651.
15. Yan J et al, Electrochemical behavior of valsartan and its determination in capsules, Colloids Surf B Biointerfaces. 2008;67(2):205-209
16. Saydam M, Takka S, Bioavailability file :Valsartan, Fabad J pharm.sci 2007;32:185-196
17. Avdeef A, Physicochemical profiling (solubility, permeability and charge state), Curr Top Med Chem 2001;1(4): 277-351
18. Flesch G et al, Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man, Euro J Clin Pharmacol. 1997;52(2):115-120
19. Ramachandran S et al, Simultaneous spectrophotometric determination of valsartan and ezetimibe in pharmaceuticals, Tropical J pharm res, 2011;10(6):809-815

20. Jadhav ML et al, Spectrophotometric Estimation of Valsartan and Amlodipine Besylate in Microcrystalline Cellulose and Starch Matrix, Int J Pharm Pharm Res, 2015;2(3): 154-167
21. Mohamed NG, Simultaneous Determination of Amlodipine and Valsartan, Ana Chem Insights, 2011;6; 53–59
22. Meyyanathan SN et al, Simultaneous Estimation of Nebivolol Hydrochloride and Valsartan and Nebivolol Hydrochloride and Hydrochlorothiazide in Pharmaceutical Formulations by UV Spectrophotometric Methods, Int J Pharm Edu Res, 2010;44(2):156-159
23. Rajesh V et al, Simultaneous Spectrophotometric estimation of Valsartan and Ramipril by derivative method, Int J Pharm Health Sci, 2010; 1(2):132-135
24. Abdallah OM, Zeid KA, HPLC- fluorescence determination of Valsartan in human volunteers and its application in bioequivalence study of two Valsartan tablets, Life Sci J, 2013;10(2):583-590
25. Kharoaf M et al, Tablet formulation and development of a validated stability indicating HPLC method for quantification of Valsartan and hydrochlorthiazide combination, Int J Pharm Pharm Sci, 2012;4(3):284-290
26. Zarghi A et al, Rapid Quantification of Valsartan in Human Plasma by Liquid Chromatography using a Monolithic Column and a Fluorescence Detection: Application for Pharmacokinetic Studies, Sci Pharm.2008;76: 439–450
27. Patnaik A et al, A new RP-HPLC method for the determination of valsartan in bulk and its pharmaceutical formulations with its stability indicative studies, Int J Pharm Sci, 2011; 2(3): 43-53
28. Celebier M et al,, HPLC method development for the simultaneous analysis of amlodipine and valsartan in combined dosage forms and in vitro dissolution studies, Brazil J Pharm Sci, 2010;46(4):761-768
29. Mhaske RA et al, RP-HPLC method for simultataneous determination of amlodipine besylate, valsartan, telmisartan, hydrochlorothiazide and chlorthalidone: application to commercially available drug products, Int J Pharm Sci Res, 2012;3(1): 141-149
30. El-Gizawy SM et al, Development and Validation of HPLC Method for Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma, Am J Ana Chem, 2012;3(1): 422-430
31. Çelebier M et al, Validated HPLC Method Development: The Simultaneous Analysis of Amlodipine and Valsartan in Samples for Liver Perfusion Studies, J Faculty Pharm, 2008; 28(1):15-30
32. Youssef R et al, Development and Validation of RP-HPLC Method for the Estimation and Separation of Valsartan, Losartan and Irbesartan in Bulk and Pharmaceutical Formulation, Int J Pharm Sci Rev Res, 2014;24(2): 311-314
33. Maheshwari N, Validated reverse phase high performance liquid Chromatography method for simultaneous estimation of Valsartan Potassium and Amlodipine Besylate in tablet dosage form, Int J drug Div & res, 2013;5(3):237-244
34. Nissankararao S et al, Method development and validation for the estimation of Valsartan in bulk and tablet dosage forms by RP-HPLC, Scholars res lib, 2013;5(2):206-211
35. Reddy KNK et al, Isocratic RP-HPLC method validation of valsartan in pharmaceutical research formulation with stress test stability evaluation of drug substance, J Chem & Pharm Sci, 2012;5(1):8-12
36. Raju VB, Rao AL, Reversed Phase HPLC Analysis of Valsartan in Pharmaceutical Dosage Forms, Int J Chem Environ and Pharm Res, 2011;2(1):56-60
37. Patro SK et al, Stability Indicating RP-HPLC Method for Determination of Valsartan in Pure and Pharmaceutical Formulation, Euro J Chem, 2010;7(1):246-252
38. Prasad CVN et al, A stability indicating RP-HPLC method with shorter runtime for simultaneous estimation of valsartan and amlodipine from their combination drug product, Int J Res Pharm Chem, 2011; 1(2): 102-110
39. Ibrahim MM et al, Application of a RP-HPLC method for comparative study on the degradation behavior of two angiotensin II receptor antagonists, valsartan and losartan potassium, Int J Pharm Chem Bio Sci, 2015; 5(2):417-426
40. Sarigomula P et al, Analytical methods development and validation for simultaneous estimation of fluvastation sodium and valsartan by RP-HPLC technique, Int J pharm & Ind Res, 2013;3(2):152-157
41. Havaldar FH, Dharmendra VL, Simultaneous estimation of atenolol, hydrochlorothiazide, losartan and valsartan in the pharmaceutical dosage form, Int J pharm & Life Sci, 2010; 1(5):282-289
42. Rao KS et al, Development and Validation of a Specific Stability Indicating High Performance Liquid Chromatographic Method for Valsartan, A young pharmacist group of India, 2010; 2(2): 183-189
43. Prasad CVN et al, A stability indicating RP-HPLC method for simultaneous estimation of valsartan and atorvastatin from their combination drug product, Int J Pharm Res & Ana, 2011;1(1):26-31
44. Devi R et al, Simultaneous determination and stability evaluation of amlodipine besylate and valsartan in rat plasma by RP-HPLC method, Int J Biopharm, 2010; 1(1): 31-38
45. Manoranjani M , Bhagyakumar T, RP-HPLC method for the estimation of valsartan in pharmaceutical dosage forms, Int J Sci Inno and Discov, 2011;1(2),101-108
46. Kalpana NK et al, Method development and validation of stability indicating RP-HPLC method for simultaneous estimation of nebivolol HCl and valsartan in bulk and its pharmaceutical formulations, Am J Adv Drug Deliv, 2014;2(5):624-637
47. Balap AR et al, Development and validation of RP-HPLC method for simultaneous determination of ramipril and valsartan in its pure and pharmaceutical dosage forms, Int J Uni Pharm & Life Sci, 2012; 2(3): 206-212
48. Haque MA et al, Stability indicating RP-HPLC method for the estimation of Valsartan in pharmaceutical dosage form, IOSR J Pharm, 2012;2(4):12-18
49. Vinzuda DU et al, RP-HPLC Method for Determination of Valsartan in Tablet Dosage Form, Int J Chem Tech Res, 2010;2(3):1461-1467
50. Siddartha B et al, Analytical method development and validation for simultaneous estimation of nebivolol and valsartan in bulk and pharmaceutical dosage form by RP-HPLC method, Int J Pharm, 2014; 4(1): 340-346
51. Parambi DGT et al, Quantitative analysis of Valsartan in tablets formulations by High Performance Thin-Layer Chromatography, J Applied Pharm Sci, 2011;1(4):76-78
52. Jadhav ML et al, Development and validation of HPTLC method for simultaneous estimation of Valsartan and Hydrochlorothiazide in tablet dosage form, Int J pharm & Biosci 2015;2(1):20-25
53. Gaikwad AV et al, Simultaneous Estimation of Ramipril & Valsartan in Tablets by HPTLC, Indo-Global J Pharm Sci, 2011;1(1): 99-112
54. Ramadan AA, et al, TLC simultaneous determination of valsartan and hydrochlorothiazide in pure form and in tablets using butyl-modified aleppo bentonite, Int J Pharm Pharm Sci, 2013;5(3):762-769
55. Chaudhary AB et al, Estimation of valsartan and hydrochlorothiazide in pharmaceutical dosage forms by absorption ratio method, Int J Applied Bio and Pharm Techno, 2010;1(2):455-464

56. BanerJee T et al, An ecofriendly estimation of valsartan and hydrochlorothiazide in pharmaceutical dosage form by absorption ratio method, Scholars Res Lib, 2012;4(2):593-599
57. Erden PE et al, Simultaneous Determination of Valsartan and Amlodipine Besylate in Human Serum and Pharmaceutical Dosage Forms by Voltammetry, Int J electrochemical sci, 2014,9(1): 2208 – 2220
58. Venkata SP et al, Bio- analytical method development and validation of Valsartan by precipitation method with HPLC-MS/MS: Application to a pharmacokinetic study, J Chem and Pharm Res, 2013;5(7):7-20
59. Chi-Yu Lu et al, Analysis of angiotensin II receptor antagonist and protein markers at microliter level plasma by LC–MS/MS, J Pharm and Biomedi Ana, 2009;49(1):123–128
60. Tripathi KD, Essentials of medical pharmacology, sixth edition 2006, Jaypee brothers medical publishers(P) ltd, Reprint 2010, pp 479-492
61. Siddiqui N et al, Pharmacological and pharmaceutical profile of Valsartan, J applied pharm sci, 2011;01(4):12-19
62. Jain C.P, Naruka PS, Formulation and evaluation of fast dissolving tablet of Valsartan, Int J Pharm Pharm Sci, 2009,1(1):219-226
63. Dixit RA et al, Preparation and Bioavailability Assessment of SMEDDS Containing Valsartan, American association of Pharm Sci Tech,2010:1-8
64. Kaushik AY et al, Preparation of floating microspheres of valsartan & *in-vitro* characterization, Int J Res Ayur Pharm, 2015;6(1):124-130