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Pharmacological and Pharmaceutical Profile of Valsartan: A Review

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ABSTRACT

Angiotensin II Receptor type 1 antagonists have been widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Their beneficial effects are related to inhibition of Angiotensin II by blockade of AT₁ receptor. Valsartan is an orally active Angiotensin II receptor type 1 antagonist which causes reduction in blood pressure and is used in treatment of hypertension. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. The drug is a very good target for the generic industries. This review evaluates the pharmacological properties of Valsartan and its efficacy and tolerability in the treatment of patients with hypertension. A brief discussion has also been made on the current and future aspects of the drug in the market.

Key words: Valsartan, hypertension, diabetes mellitus, spectrophotometry, ACE inhibitors

INTRODUCTION

Valsartan is a potent, orally active nonpeptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 (Flesch et al., 1997) which causes reduction in blood pressure and is used in treatment of hypertension. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. The drug is a very good target for the generic industries. It is soluble in the neutral pH range. It belongs to the BCS class III drug classified as low permeability and high solubility drug. Valsartan is soluble in acetonitrile and methanol. The drug is rapidly absorbed orally and has limited volume of distribution and is extensively bound to plasma proteins. Valsartan is not extensively metabolized and is mainly excreted by non-renal routes. Valsartan is effective in treatment of pediatric, adolescents and the elderly patients with mild to moderate hypertension. Monotherapy with Valsartan with 80 mg as the starting dose has shown considerable efficacy in patients with CHF and renal impairment alongwith hypertension and add on therapy helped control BP in large population of patients with severe hypertension not responding sufficiently to β -blockers, ACE inhibitors or diuretics. The importance of aggressive blood pressure control is undisputed, but the therapeutic focus is now extending to end-organ protection as a treatment goal of equal importance to BP reduction. Thus, the value of ARBs like Valsartan in slowing the progression of kidney disease due to high blood pressure or diabetes has very positive medical as well as commercial implications. Many clinical trial studies like VALUE, VALIANT, VAL-Heft, PREVAIL and many more have been conducted of which valsartan administration is a part. From these studies comparison of valsartan with other antihypertensives

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have been made extensively. Valsartan was well tolerated in clinical studies and with most treatment related adverse effects related to the drugs of same category and ACE inhibitors. Many analytical methods have been developed for the quantitation and determination of valsartan in biological fluids and pharmaceutical dosage form.

HISTORY

Valsartan was first developed by Novartis and was sold under the brand name DIOVAN and it currently holds the largest market share for the drug of its kind in the market. In the USA, valsartan is registered by the Food and Drug Administration (FDA) for use in the treatment of hypertension in children of 6 years and older and adolescents in the December 2008.

Present and Future Scenario

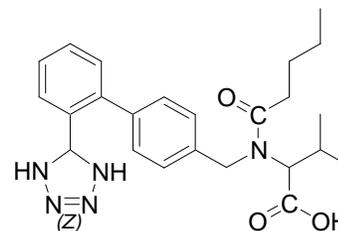
Diovan (valsartan) was labelled as the world's number-one selling high blood pressure medication and accounted for \$6 billion in sales in 2010 worldwide. In near future its patent protection on its active ingredient is ready to expire in most of the major territories. There are two types of dosage forms of valsartan available in the market. One comprising of single-active component valsartan and other comprising three dosage forms containing a combination of valsartan with one or more active ingredients hydrochlorothiazide, amlodipine besylate, aliskiren hemifumarate. Ranbaxy Laboratories filed a Paragraph IV certification in 2007 and claimed the US5399578 patent as invalid and thereby pledged not to make, use, sell, offer to sell, or import Valsartan until November 2012 expiry date. Ranbaxy along with Teva has got tentative approval for many strengths of the tablet and is expecting 180 days exclusivity and being first to file upon the expiry of the US5399578 patent. Data exclusivity (DE) delays generic competition even if the patented period has expired and hence is a cause for trouble for companies interested in developing a generic equivalent. As the DE periods for the combination periods by Novartis are scheduled to expire in US (Valsartan/Hydrochlorothiazide expiring in 2011; Valsartan/Hydrochlorothiazide/Amlodipine and Valsartan/ Aliskiren expiring in 2012). Similarly in Europe, data exclusivity for Valsartan alone has expired, and the combination products are scheduled to expire as follows: Valsartan/Aliskiren expiring in 2017 and Valsartan/Hydrochlorothiazide/Amlodipine expiring in 2019. Hence, the originator of Valsartan, 'Novartis' aims to secure its credentials in the market by focusing the combination products by convincing the medical practitioners and patients with their benefits.

The combination of Valsartan and Hydrochlorothiazide is not protected by any patent but only the Valsartan molecule, hence the generic versions of this product is expected to be launched at the same time as the single active product.

From the past eight years, it has been observed that there has been an increase in the patent filing of Valsartan and its combination products clearly indicating the importance of the drug molecule.

PHYSICOCHEMICAL PROPERTIES

Valsartan is 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]amino]-butanoic acid (**Structure 1**) with empirical formula $C_{24}H_{29}N_5O_3$. Its molecular weight is 435.519g/mol (Flesch et al., 1997). Valsartan is a white coloured powder that is freely soluble in ethanol, methanol, acetonitrile and sparingly soluble in water. The drug is listed officially in USP monograph along with its three impurities (R)-N-valeryl-N-[[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl]valine, (S)-N-butryryl-N-[[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl]valine and (S)-N-valeryl-N-[[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl]valine benzyl ester. Valsartan appears in the melting range of 105-110°C and the specific rotation $[\alpha]_D^{20}$ in methanol being 68°. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. The compound is stable under storage in dry conditions (Saydam et al., 2007).



(structure 1: Valsartan)

Valsartan is a tetrazole derivative that contains acid ($pK_a=4.73$) and carboxylic ($pK_a=3.9$) groups making the compound soluble in the neutral pH range (Flesch et al., 1997). Hence, it exists as solution at physiological pH values as the undissociated acid, the mono-anion and the di-anion. On increasing the pH from 4 to 6 the solubility of valsartan increases by a factor of about 1000, but it favors the anionic form and decreases lipophilicity, hence the rate of absorption of valsartan is influenced by intestinal pH along the (GI)tract. *In vitro* dissolution is complete and rapid at pH 5.0 and above. As valsartan has pH dependent solubility it belongs to a special case in a proposed general classification system that categorises drugs with respect to their biopharmaceutical and absorption properties. In the biopharmaceutical classification system, valsartan has been classified as Class III drug with low permeability, poor metabolism and high solubility (Saydam et al., 2007). The pK_a of Valsartan varies with the percentage of acetonitrile in ACN:water mixtures, with 60% ACN, pK_a of carboxyl group is 5.321 and that of tetrazole is 6.189 with 55% ACN, pK_a of carboxyl group is 5.143 and tetrazole group has pK_a of 6.163. Under the influence of 50% ACN pK_a of carboxyl group is 4.982 and that of tetrazole is 6.6130. These studies help in selection of mobile phases for the development in RP-HPLC (Demiralay et al., 2010). Valsartan has bioavailability of about 25% due to its acidic nature. Being acidic in nature it is poorly soluble in the acidic environment of GIT and is absorbed from the upper part of GIT that is acidic in nature and where its solubility is low.

Valsartan is 0.18 g/L soluble in water at 25°C. In a buffered solution a dianion salt is formed due to which its solubility is increased. In phosphate buffer (pH 8.0), valsartan is 16.8 g/L soluble at 25°C (Saydam et al., 2007).

PHARMACOLOGY

Valsartan belongs to the family of angiotensin II type 1 receptor (AT₁) antagonists and possesses about 20,000 fold greater affinity for it than for the angiotensin II type 2 receptor (AT₂) (Saydam et al., 2007). This action exerts effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal function and also leads to reduction in progression of atherosclerosis lesions (Burnier et al., 2000). Also blockade of AT₁ receptor by valsartan leads to increase in local angiotensin II concentration that stimulates the unblocked AT₂ receptor (McInnes et al., 1999). The increase in AT₂ receptor stimulation causes vasodilation through local production of bradykinin which in turn leads to a signaling cascade that increases the production of nitric oxide and cyclic guanosine 3'-5'-monophosphate at the endothelial level that provides protection against vascular dysfunction (Verdechia et al., 2004).

PHARMACOKINETIC PROFILE

The pharmacokinetics of valsartan had been examined in healthy male volunteers after administration of 20 mg of valsartan as an i.v bolus injection and 80 mg of valsartan as capsule formulation and as a buffered solution (Flesch et al., 1997). (Table 1)

Table 1: Pharmacokinetic Profile of Valsartan

Dose administered	C _{max} (mg/l)	T _{max} (h)	AUC (mg/l/h)	f(%)	t _{1/2} (h)	Ae(% of dose)
20mg of Valsartan administered as an i.v bolus	4.02	1	9.39	-	9.45	4.02
80mg of valsartan administered as an oral capsule	1.64	2	8.54	23	7.05	7.34
80mg of valsartan administered as an oral solution	3.25	1	14.32	0.39	7.50	12.55

C_{max}= maximum plasma Concentration
percentage bioavailability
t(max)= time to reach maximum terminal phase
plasma concentration
amount of drug
AUC= area under curve indicating unchanged) concentration of valsartan in body with time
f(%)=
t_{1/2}= half life in
Ae(% of dose)= excreted

Absorption

Valsartan is rapidly absorbed orally. After oral administration of Valsartan 80mg capsule and solution formulation in 12 healthy volunteers, maximum plasma concentrations (C_{max}) of Valsartan (1.64mg/l and 3.25 mg/l) were respectively reached in ~ 1-2 h. Plasma levels and the area under the plasma concentration-time curve were not linearly related to dose, indicating a saturable first pass metabolism (Flesch et al., 1997).

According to the AUC values obtained, the bioavailability of capsule was 23% and that of solution was 39%. The deconvolution results of the plasma levels, measured after administration of the two oral formulations with the i.v. bolus dose as three unit impulse response showed that valsartan was 24% absorbed from capsule and 41% from the solution. Valsartan is absorbed rapidly, 50% of it in capsule being absorbed within 1.6 h and 90% within 4.6 h. The absorption occurs by a passive diffusion process. Food has not been reported to affect the absorption of valsartan. Hence, it can be administered with or without food (Iqbal et al., 2010).

Distribution

Valsartan has only limited distribution outside the plasma compartment and is extensively bound to the plasma proteins (94-97%) and hence is only limited distributed outside plasma compartment. Because of the presence of carboxylic groups Valsartan is soluble in neutral pH range and is mainly present in the ionized form at physiological pH. The volume of distribution at steady state is about 17l (Flesch et al., 1997).

Metabolism and Elimination

Valsartan does not require any metabolism in the body to become active. After the oral administration of 80 mg of [¹⁴C]-radiolabelled valsartan (Waldmeier et al., 1997) only one pharmacologically inactive metabolite was found in plasma nearly about 11%. The primary metabolite was identified as valeryl 4-hydroxy Valsartan (M1) accounted for about 9% of the dose and is inactive in hypertension. M1 has about 200 fold lower affinity for the AT₁ receptor than valsartan (Waldmeier et al., 1997). Valsartan is mainly excreted in faeces via biliary excretion and hence it is not recommended for patients with hepatic dysfunction and biliary cirrhosis (Martin et al., 2005). After the administration of an i.v. dose in healthy volunteers, plasma clearance of Valsartan was found to be ~2 l/h (Iqbal et al., 2010). Renal Clearance (0.62 l/h) was found to be only 30% of the total plasma clearance. Hence, it is clear that Valsartan is eliminated mostly by non-renal routes. It is only slightly metabolized and excreted mainly unchanged in bile (<80%) and urine (20%). M1 is formed by oxidative biotransformation and accounts for 9±3 % of the dose in excreta. Dose adjustment is not needed based on age, but for an average 70year old patient, plasma concentration generally falls by 22% compared with an average 55 year old patient (Martin et al., 2005). Hence, dose reduction needs to be considered in this group.

THERAPEUTIC EFFICACY

The therapeutic efficacy of valsartan has been evaluated in a number of dose ranging and comparative studies in patients with varying degrees of hypertension, diabetes and renal impairment.

Comparison of Valsartan with placebo Hypertension

Efficacy had been studied from nine double-masked, randomized, placebo-controlled, parallel studies on 4067 patients. Patients with mild-to-moderate hypertension were given a range of

doses of valsartan 10-320 mg once daily or placebo. The integrated analysis resulted in a linear relationship between increasing dose of valsartan 10 to 320 mg and blood pressure-lowering efficacy. (Placebo-subtracted mean changes from baseline to endpoint for valsartan were reported to be systolic diastolic blood pressure (SDBP), -1.3 to -9.0 mm Hg in a dose dependent manner).

The dose recommended for starting the medication is 80 mg o.d or hydrochlorothiazide may be added (Martin et al., 2005). In nine double-masked, randomized, placebo-controlled studies of similar design conducted on 4067 patients with mild-to-moderate hypertension, administration of valsartan doses ≥ 80 mg showed reduction in supine or seated diastolic blood pressure(SDBP) and systolic blood pressure (SSBP) as compared with placebo ($P<0.05$) (Pool et al., 1998).

Chronic Heart Failure

Valsartan had favourable acute and chronic neurohormonal and haemodynamic actions in CHF according to a large randomized, double blind placebo study (Val HeFT-Valsartan Heart Failure Trial) conducted on a 5010 group of patients and had no effect on mortality among patients but patients receiving valsartan showed 13.2% reduction in morbidity. This study proved the fact that valsartan is a good treatment for patients with hypertension receiving ACE inhibitors as Valsartan has shown to decrease hospitalization(27.5%) in such patients (Ferdinand et al., 2009).

Renal Impairment

A study was conducted in a randomized, double-blinded group of patients with chronic renal failure and hypertension. It showed that Valsartan (80 mg) considerably lowered the mean arterial blood pressure, when compared to placebo. It had no affect on the GFR (glomerular filtration rate) or renal blood flow when compared to placebo, but showed significant reduction in proteinuria(26%) and albuminuria(41%) (Martin et al., 2005).

Comparison 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 treatment of moderate hypertension 80 mg Valsartan is as effective as 20 mg Enalapril.

In elderly patients Valsartan 80-160 mg daily provides comparative short and long term anti-hypertensive efficacy as compared to lisinopril 10-20 mg (Malacco et al., 2004; Martin et al., 2005).

Valsartan (80 mg) has been as effective as Hydrochlorothiazide and amlodipine in treatment of mild-to-moderate hypertension.

In a clinical trial study VALUE (Valsartan Antihypertensive Long-term Use Evaluation) conducted on hypertensive patients ≥ 50 years of age, blood pressure reduction for valsartan and amlodipine based treatment strategies were compared for fatal or non-fatal myocardial infarction. It was shown

that valsartan gave almost same response as that of amlodipine (Ferdinand et al., 2009).

Another clinical trial study VALIANT (Valsartan in Acute Myocardial Infarction) conducted on about 10,000 patients, patients were treated beta blockers and ACE inhibitors or Valsartan or both. The resulted showed that there were no concerning differences between the two strategies (Ferdinand et al., 2009).

In the PREVAIL study conducted on about 1200 patients showed that 82.7% of the patients receiving valsartan showed control in BP than 81.6% patients with lisinopril therapy. Adverse effects were observed in about only 5.1% patients receiving Valsartan than with 10.7% patients receiving lisinopril (Malacco et al., 2004).

Chronic Heart Failure

In general, Angiotensin Receptor Blockers like Valsartan are more effective inhibitors of the rennin-angiotensin-aldosterone system than ACE inhibitors. Valsartan appears to be better tolerated in context with side effects like cough and angioedema as seen with the ACE inhibitors (Martin et al., 2005).

Post myocardial infarction

A study named VALIANT (valsartan in acute myocardial infarction) conducted on patients with LV systolic dysfunction, HF, or both following an acute myocardial infarction, compares the efficacy and safety of long-term treatment with Valsartan, Captopril and their combination in 14,703 high risk patients after MI. It is a multi centre, double blind, randomized, active controlled parallel group study. The study showed no differences in mortality among patients being treated with captopril 50 mg TID, Valsartan 160 mg BID, or the combination of Valsartan 80 mg BID with Captopril 50 mg TID (Pool et al., 1998).

Diabetes Mellitus

Valsartan (80 mg) gives similar response as compared to Amlodipine (5 mg) in blood pressure reduction. But Valsartan shows a significantly greater reduction in urinary albumin excretion ratio when compared to amlodipine. (Spinola et al., 2009) A clinical trial study named MARVAL (MicroAlbuminuria Reduction with VALsartan) conducted on 332 patients, showed that Valsartan considerably decreased albuminuria in patients with diabetic nephropathy. Patients were randomized and received either valsartan or amlodipine in a 24-week period. Patients of the group receiving valsartan showed significant reduction in urinary albumin excretion (Pool et al., 1998).

Left Ventricular Hypertrophy

In a randomized double-blind study of 69 previously untreated hypertensive people, it was shown that Valsartan (80 mg daily for 8months) reduced left ventricular mass index by 21 g/m² as compared to 10 g/m² with atenolol (Martin et al., 2005).

Valsartan with other antihypertensives

In a randomized, double-blind, parallel-group superiority study conducted on 838 patients, it was found that combination of

valsartan 160 mg + simvastatin 40 mg was statically superior to that of valsartan 160 mg + simvastatin 20 mg in reduction of LDL-C (low density level cholesterol) in patients with hypercholesterolemia and essential hypertension (Verdechhia et al., 2008). (Table 2)

Table 2: Summary chart for clinical studies conducted with lsartan

Trial	Drug compared	No. of patients	Results
VALIANT	Valsartan(160mg BD) vs captopril(50mgTD) vs Valsartan(160mg BD)+captopril(50mgTD)	14703(with acute MI or Heart Failure)	Adverse events ↑ in valsartan/captopril vs valsartan group or captopril
VALUE	Valsartan(80mg) vs Amlodipine(5mg)	15245(with treated or untreated hypertension)	Valsartan group had lesser no. of incidences of diabetes as adverse effect and was better tolerated
PREVAIL	Valsartan(160mg) vs Lisinopril(20mg) (alone or combined with HCTZ)	1213(with mild to moderate hypertension)	Valsartan alone was better tolerated
VAL-Heft	Titrated doses from Valsartan 40mg BD to 160mg BD vs Placebo	5010(with history of heart failure)	Valsartan was well tolerated and mortality and morbidity was significantly reduced

SAFETY AND TOLERABILITY

The safety of antihypertensives deserves a special importance because they are likely to be used long term in general practice in a number of patients. Valsartan has a good tolerability profile consistent over the wide dose range (Verdechhia et al., 2004) with a side effect profile almost indistinguishable from placebo and is superior to that of other comparable antihypertensive drugs. Valsartan doesnot cause cough and angioneurotic oedema as associated with ACE inhibitors, the reason being the site specificity and the greater selectivity of the drug (Biswas et al., 2002).

In a Val-HeFt (the VALsartan Heart Failure Trial) study conducted on 2511 patients adverse drug reactions occurred in 9.9% of the patients receiving valsartan and 7.2 % occurred in patients receiving placebo and not the drug showing that the drug is generally safe for use in patients with hypertension (Malacco et al., 2004).

In one study conducted on 11191 patients valsartan was found to be 81.1% as effective as losartan that was 84.8% effective. Thus, both have almost same tolerability (Biswas et al., 2002). Valsartan is also well tolerated in children, adolescents and elderly both in males and females as proved by a post-marketing surveillance study conducted in England (Herder et al., 2010).

According to the Summary of Product Characteristics, in the patients on valsartan alongwith with renal impairment, the elderly or those on potassium supplements, serum potassium levels should be monitored regularly as the clinical trials have shown incidences of hyperkalemia (Biswas et al., 2002).

Side-effects

According to a post marketing surveillance study conducted on 12881 patients in England (the largest safety study conducted on valsartan as reported from MEDLINE and EMBASE criteria), malaise was the most frequently reported event (13.7 percent per 1000 patient-months of exposure). Dizziness (11.7%), headache and migraine (10.3%) followed thereafter. Epistaxis (0.5%), fatigue (10%), rash (1.1%) appeared the labeled adverse drug reactions associated with Valsartan. Joint stiffness, muscle cramps, myalgia added to the list (Biswas et al., 2002).

Renal functions alongwith creatinine clearance, electrolyte excretion and uric acid excretion are not influenced on administration of valsartan (Saydam et al., 2007). Other reported side effects of the drug are dose-related orthostatic hypotension, rash, hyperkalemia(5%), respiratory tract disorders, nausea, vomiting(1.4%), intolerance, diarrrohea, dyspnoea, impotence/ejaculation failure, dyspepsia, oedema as listed in the Summary of Product Characteristics.(Figure 1)

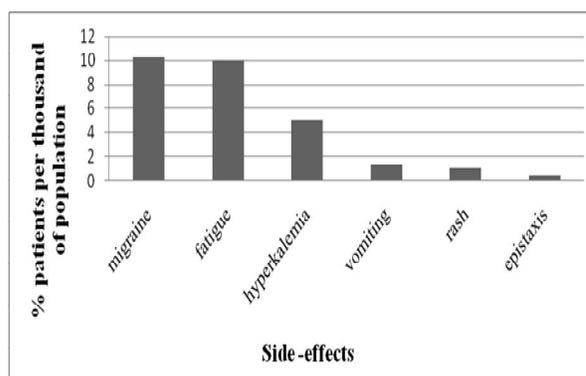


Fig 1: Various side-effects of Valsartan

Contraindications

Valsartan is contraindicated in patients with severe hepatic impairment, liver cirrhosis, and biliary obstruction. In a study conducted it was seen that liver function tests (LFTs), bilirubin levels were found to be raised after the valsartan administration in patients (Biswas et al., 2002).

Valsartan is contraindicated throughout pregnancy and lactation as the drug acts directly on the rennin-angiotensin system, so can cause some injury or even death to the developing foetus. Though no controlled studies have been conducted in women about the effect of valsartan on foetus, on detection of pregnancy the therapy should be discontinued as soon as possible and should only be used until it justifies the risk associated with it.

Drug Interactions

Valsartan is contraindicated with NSAIDs and ciclosporin as it causes increased risk of renal impairment and hyperkalemia. With general anaesthetics, clozapine, dopamine agonists and other hypertensives valsartan causes increased risk of hypotension. Hyperkalemia can be caused during valsartan therapy with potassium-sparing diuretics, potassium supplements, ACE inhibitors and heparin.

Table 3: Quantification and determination methods

S. no.	Sample	Column	Method	Mobile phase	Reference
1	Valsartan in human plasma		LC-MS/MS		Koseki et al., 2007
2	Valsartan in pharmaceutical dosage form	BEH C18(100mm X 2.1mm,1.7 μ)	RP-UPLC	Gradient mixture of solvent A and B	Krishnaiah et al., 2010.
3	Valsartan in tablet dosage form		UV		Gupta et al., 2010
4	Valsartan in Pharmaceutical dosage form	Venusil XBP C-18,5 μ	RP-HPLC	0.1 M Phosphate Buffer:Acetonitrile(20:80)	Thanusha et al., 2010
5	Valsartan in Tablet Dosage Form	Thermohypersil ODS (150mm x 4.4mm)5 μ	RP-HPLC	Water:acetonitrile:glacial acetic acid(500:500:01)	Reddy et al., 2010
6	Valsartan and its degradation products	HIQ sil C18 ODS (250mm X 4.6mm)5 μ	RP-HPLC	Methanol:water[70:30v/v]pH 7.2 Methanol:water[60:40v/v]pH 7.2	Bhatia et al., 2009
7	Valsartan and its metabolites in human plasma	Atlantis C18(100mm x 3.9mm)3 μ	SPE-HPLC-UV	Gradient: ACN with 0.025% TFA and 5mM phosphate buffer with 0.025% TFA pH 2.5	Iriarte et al., 2006
8	Valsartan or candesartan in human plasma		Tandem mass spectroscopy		Levi et al., 2009
9	Valsartan and other ATII antagonists in plasma	Bondapak C18	HPLC-flourescence	Gradient: Acetonitrile-5mM acetate buffer(pH4)	Gonzalez et al., 2002
10	Valsartan and HCTZ	Precoated silica gel 60F ₂₅₄	HPTLC	Chloroform:methanol:toluene :glacial acetic acid(6:2:1:0.1 v/v/v/v)	Shah et al., 2009.
11	Valsartan and HCTZ in tablets	Precoated silica gel G 60F ₂₅₄	HPTLC	Chloroform:ethyl acetate:acetic acid(5:5:0.2v/v)	Kadam et al., 2007.
12	Valsartan, Aliskiren, Ramipril,HCTZ	Purosphere Star RP 18(250mmX4.6mm)	HPLC	0.2%v/v TEA buffer(pH 3.0):ACN	Pachauria et al., 2010
13	Valsartan and HCTZ in tablet dosage form	HIQ sil ODS (250 mmX4.6mm)	Ion pair chromatography	Methanol:0.0025M orthophosphoric acid(70:30) pH 4.6: 0.1%hexane sulphonic acid	Bhatia et al., 2010
14	Valsartan and Amlodipine	Kromasil C18(250 X 4.6mm)	RP-HPLC	Acetonitrile:phosphate buffer(0.02M,pH3.0),(56:44v/v)	Chitlange et al., 2008.
15	Valsartan and Amlodipine	Precoated silica gel 60F ₂₅₄	TLC	Toluene:methanol:acetic acid(7:3:0.1 v/v/v)	Dhaneshwar et al., 2009
16	Valsartan and Amlodipine	HICHRROME Nucleosil 100-5,C18(250X4.5mm)	RP-HPLC	Phosphate buffer(pH 3.6;0.01M):acetonitrile:methanol(50:40:10v/v)	Celebier et al., 2008
17	Valsartan and Amlodipine	X Terra RP18, 5 μ , 150mm X 4.6mm	RP-HPLC	Mixture of solution A and solution B	Patel et al., 2009
18	Valsartan, HCTZ, Amlodipine	Hypersil C18 (250mm X 4.6mm)	RP-HPLC	ACN:Phosphate buffer pH6.8 (55:45)	Younus et al., 2010.

Dosage

Valsartan is available in the dose range of 10, 20, 40, 80, 160, and 320 mg. All doses of Valsartan have been found to be safe and tolerable (Oparil et al., 1996). Special care should be exercised when initiating treatment with Valsartan in the elderly or patients with mild to moderate renal or hepatic dysfunction, although dosage adjustments are not required in such patients. In general clinical practice, therapy is initiated with 80 mg once daily appropriate dosage in hypertensive patients as a functional blockade of AT₂ receptor has been shown to occur in humans after single doses of 80 mg valsartan in 2 to 24 h (Saydam et al., 2007). A randomized, double-blind, placebo-controlled study was conducted by Pool *et al* on 4067 adult hypertensive patients who received various oral doses of valsartan (10, 20, 40, 80, 160, 320 mg) for 4 weeks. It was found that the response to valsartan was dose related and clinically relevant and also clinically

significant as compared with placebo. As compared placebo changes in systolic BP (SBP) and diastolic BP (DBP) in response to valsartan 80, 160, 320 mg were found to be -6.8/-3.9, -8.6/-5.1, and -9.0/-6.4 mm Hg respectively (Verdechhia et al., 2004).

Quantification and Determination Methods

There have been reports in the literature regarding the determination of valsartan in pharmaceutical dosage forms and biological fluids using various analytical techniques including spectrophotometry. Many UV and second derivative spectrophotometric and high-performance liquid chromatographic techniques for the determination of valsartan in pharmaceutical dosage forms have been developed and presented. It is reported that the proposed second derivative spectrophotometric method provided a better precision and accuracy, and also determined a lower concentration of valsartan capsules than the UV-spectrophotometric method. The main advantage of this method is shorter analysis time, the low cost of analysis and widespread

availability of the apparatus. The HPLC methods used for routine analysis are rather time consuming, cumbersome and require too many solvents and are expensive (Tatar et al., 2002).

Various analytical methods have been developed for the determination of valsartan in the biological fluids and they mainly use the liquid chromatographic techniques. Various HPLC methods have been described in the literature for determination of valsartan in biological fluids with photometric (Soldner et al., 1998), fluorimetric (Kondo et al., 1996; Gonzalez et al., 2002) or mass spectrometric (Danaeshtalab et al., 2002) detection after extraction from plasma.

Very few methods have been reported in literature for the determination of valsartan in pharmaceutical dosage form that are based on liquid chromatography-tandem mass spectrometry(LC-MS/MS) (Koeski et al., 2007; Selvan et al., 2007; Levi et al., 2009).

Direct UV-Vis spectrophotometric method did not give much impressive results for the simultaneous determination of drugs with spectral overlapping. Application of derivative technique of spectrophotometry has reported a powerful tool for quantitative analysis of multi-component mixtures (Rojas et al., 2009).

Over the years, many methods have been developed for the determination of valsartan in pharmaceutical dosage forms based on HPLC (Agrahari et al., 2009; Thanusha et al., 2010; Bhatia et al., 2009; Reddy et al., 2010) and UV-derivative spectrophotometry (Gupta et al., 2010) and have been reported.

Many methods for the simultaneous determination of valsartan and hydrochlorothiazide in biological matrices and pharmaceutical dosage forms have been reported by the use of HPLC (Satana et al., 2001; Carlucci et al., 2000; Li et al., 2007) and UV-derivative spectrophotometry (Satana et al., 2001; Carlucci et al., 2000).

LC-MS/MS and capillary electrophoresis methods have been developed and reported for simultaneous determination of valsartan and hydrochlorothiazide in pharmaceutical dosage forms (Li et al., 2007; Hillaert et al., 2003) Some reverse phase high-performance liquid chromatography(RP-HPLC) methods have also been developed of the simultaneous for determination valsartan and amlodipine (Celebier et al., 2008; Chitlange et al., 2008). (Table 3)

Formulation Types

A variety of conventional dosage forms are commercially available consisting of tablets and capsules. A constant programmable chronotherapeutic controlled delivery pulsatile capsule dosage form has been prepared. It consists of a pre-coated capsule consisting of a drug tablet and erodible tablet (L-hydroxypropyl cellulose (L-HPC) or guar gum) made of swellable polymer (L-HPC), xanthan gum, polyethylene oxide or sodium alginate (Saydam et al., 2007).

Fast dissolving tablets of Valsartan were also prepared using different disintegrants. It was found that drug release increased with increasing concentrations of the disintegrant with Crospovidone showing the highest amount of drug release.

CONCLUSION

Valsartan is an effective and well tolerated once daily antihypertensive agent in patients with mild to moderate hypertension. In addition, the drug may reduce BP when used as monotherapy in patients with severe hypertension or when used adjunctively in patients with resistant hypertension. Importantly, Valsartan appears to be at least as effective and well tolerated as other commonly used antihypertensive agents. The drug therefore represents a useful therapeutic option in the management of patients with hypertension and will be particularly useful in patients not responding to, or intolerant of, anti-hypertensive agents from other drug classes. Valsartan is an appropriate choice for first-line treatment of patients with mild-to-moderate hypertension, and its predictable dose-responsive efficacy provides a rational basis for titration in clinical practice.

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