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Judul Chapter: Valsartan

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Valsartan

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Contents

1. GENERAL INFORMATION

Valsartan is an antihypertensive drug which selectively inhibits angio-tensin receptor type II [1,2]. This tetrazole derivative was first developed by Novartis and marketed under brand name Diovan® [3]. This compound is orally active and is rapidly absorbed after oral doses, having a bioavailability of approximately 23% [4].

Valsartan appears as a white or almost white hygroscopic powder [5]. This compound must be kept in an air-tight container and should be protected from light and heat [6].

It is available in film-coated tablets containing valsartan 40, 80, 160, or 320 mg, and capsules with dosage of 80 or 160 mg. Tablet combinations of valsartan with hydrochlorothiazide or amlodipine are also available [3,7].

1.1 Solubility

Valsartan is practically insoluble in water, sparingly soluble in methylene chloride, and freely soluble in anhydrous ethanol and methanol [3,5]. Solubility of valsartan in water is affected by pH; solubility in pH 4.07, 7.02, 9.18, and 10.06 are 56.6, 62.8, 71.6, and 100.0 mg/100 mL, respectively [8].

1.2 Chemical Name

N-(1-Oxophentyl)-N-[[2′-(1H-tetrazole-5-yl)[1,1′-biphenyl]-4-yl] methyl]-L-valine

L-Valine, N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl] methyl]

N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine

(2S)-3-Methyl-2-[pentanoyl[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]amino]butanoic acid

3-Methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl] methyl]amino]butanoic acid

N-Pentanoyl-N-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-L-valine

(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine [2,4–6,9].

1.3 Synonym

CGP-48993, Diovan®, and Tareg® [1,4,9]

1.4 CAS Number

137862-53-4 [4–6]

1.5 pK_a and Partition Coefficient

The pK_a of valsartan is 4.9 [10]; partition coefficient in octanol–water system is 22.2; n-octanol–phosphate buffer is 0.033 [8,9]

1.6 Proprietary Preparations

Diovan®, Co-Diovan® (combination with hydrochlorothiazide), and Exforge (combination with amlodipine) [3,4]

1.7 Structural Formula
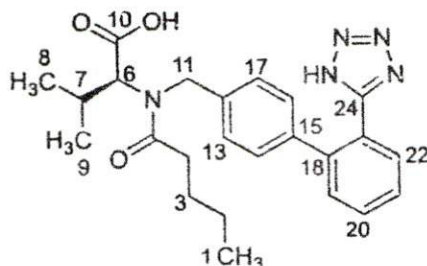
1.8 Molecular Formula, Molecular Weight, and Elementary Analysis

Molecular formula: $C_{24}H_{29}N_5O_3$ [4–6]

Molecular weight: 435.52 [6]

Elementary analysis: HRMS (calculated): 436.23432 $[M+H]^+$ [11]. C: 66.19%, H: 6.71%, N: 16.08%, and O: 11.02% [9].

2. THERMAL ANALYSIS

The melting point of valsartan crystallized from diisopropyl ether is 116–117 °C [9]. Unfortunately, the melting point measurement of the USP valsartan RS (lot L0L195) and valsartan raw material from TEVA, India (Control No. 761120512; using a Mettler Toledo MP 70 system) did not show sharp light intensity curves (see Figure 1), so their melting points cannot be determined accurately.
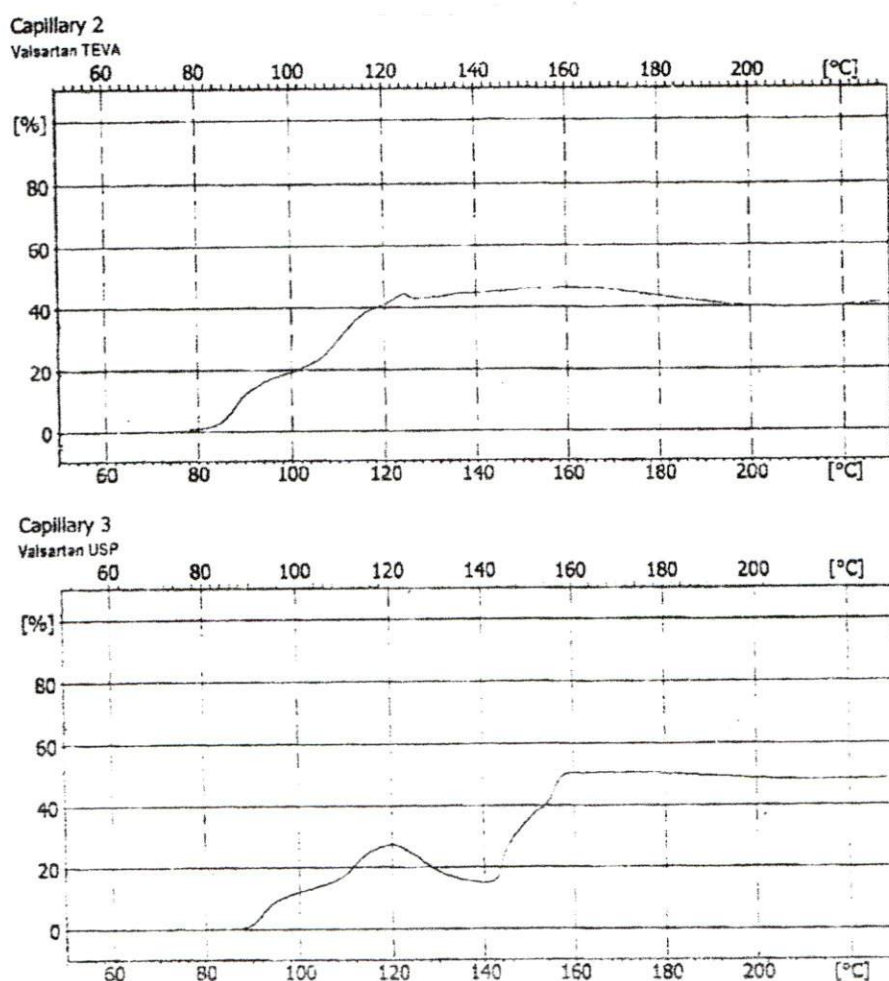
Figure 1 Light intensity curves of USP valsartan RS and valsartan bulk drug (TEVA, India) recorded on a Mettler Toledo MP 70. Y-axis: light intensity (%); X-axis: temperature (°C).

Nalluri *et al.* [12] reported that recrystallization of valsartan from methanol, ethanol, isopropanol, and acetonitrile could yield different endothermic (broad) peaks according to their DSC thermograms (75.2, 65.9, 64.6, and 80.6 °C, respectively). These results indicated that crystallization of valsartan from different solvents could yield different crystal forms. The broad endothermic peak of valsartan was reported at 102.8 °C [13] and 100.8 °C [14], while a sharp endothermic peak was reported at around 118 °C [15], 115 °C [16], and 115.77 °C [17]. Skotnicki *et al.* [18] reported that valsartan gave two endothermic peaks at approximately 80 °C (a small

DSC
mW

0.00

-10.00

-20.00

100.00   200.00
Temp (°C)
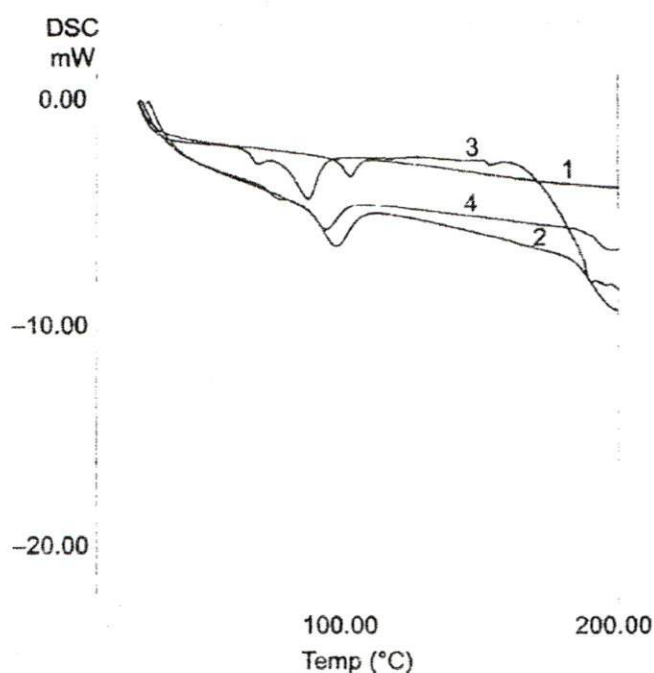
Figure 2 DSC curves of USP valsartan RS and valsartan bulk drug (TEVA, India) recorded on a DSC-60A Shimadzu Thermal Analyzer. (1) USP valsartan RS rate 20 °C/min, (2) USP valsartan RS rate 40 °C/min, (3) valsartan TEVA rate 20 °C/min, and (4) valsartan TEVA rate 40 °C/min.

broad peak) and at 100.6 °C (a sharp peak). These peaks are related to water evaporation and enthalpy relaxation. The glass transition of valsartan appeared at around 76 °C. Figure 2 shows the DSC thermograms of USP valsartan RS and valsartan TEVA measured by using a DSC-60A Shimadzu Thermal Analyzer. The DSC of valsartan TEVA exhibits two endothermic peaks (2 and 3), which are similar to that of DSC reported by Skotnicki et al. [18]. Based on our data and several published results, it can be suggested that crystal forms of valsartan available in the market are not identical.

3. POLYMORPH

Valsartan may occur in 12 different polymorphs and an amorphous form. X-Ray data of various crystal forms are presented in Table 1.

Burgbacher et al. [21] reported the invention of a highly crystalline form of valsartan. The crystal was characterized by its XRPD pattern that

Table 1 X-Ray Powder Diffraction of Valsartan Polymorphs

Polymorph	Scattering Angle (Degree 2θ)	Reference
Form I	(5.4; 13.0; 16.3; 19.5; 20.7; 23.4) $\pm 0.2°$	[19]
Form II	(5.8; 12.7; 14.0; 17.6; 20.8; 22.5) $\pm 0.2°$	[19]
Form III	(5.1; 10.1; 15.3; 18.6) $\pm 0.2°$	[19]
Form IV	(6.2; 10.7; 14.5; 15.7; 19.0; 23.5; 24.8) $\pm 0.2°$	[19]
Form VI	(5.5; 13.3; 14.3; 17.7; 21.1; 22.3) $\pm 0.2°$	[19]
Form VII	(5.2; 15.2; 15.9; 18.6; 22.8; 23.6) $\pm 0.2°$	[19]
Form VIII	(5.7; 13.6; 18.0)	[19]
Form IX	(6.3; 14.0; 17.9) $\pm 0.2°$	[19]
Form X	(5.6) $\pm 0.2°$ broad peaks: (15.0; 20.6) $\pm 0.2°$	[19]
Form XI	(5.2; 10.5; 12.9; 13.9; 18.8) $\pm 0.2°$	[19]
Form XIII	(5.1; 11.6; 15.8; 18.6; 26.2) $\pm 0.2°$	[19]
Amorphous	Very broad peak	[20]
Valsartan highly crystalline form	(9.308; 10.74; 11.643; 13.854; 15.136; 16.056; 16.686; 17.643; 18.561; 19.186; 20.024; 20.567; 21.335; 21.595; 21.858; 22.879; 24.597; 25.051; 26.292; 31.032) $\pm 0.2°$	[21]

had a scattering angle peak (2°θ) about (31.0 $\pm$ 10.2)°; its melting point was (140.8 $\pm$ 3)°C. The invention stated that this highly crystalline form of valsartan can be easily dried compared to other forms of valsartan. This crystal has less residual solvent, higher stability, and better purity compared to the other forms of valsartan. The highly crystalline form of valsartan can also be characterized with SEM that showed very low water content. The quasi flower-like conglomerates and the formation of spheroid conglomerates were assumed for high flowability of the highly crystalline valsartan.

4. RELATED COMPOUNDS AND IMPURITIES

Valsartan has one chiral center in the valine moiety, and usually the pure (S)-enantiomer is used for pharmaceutical purposes. This S enantiomer

is derived from the L-valine that is used in the synthesis [22]. Method for testing enantiomer impurity is described in BP 2013 [5].

There are three related compounds or impurities described in the USP 36 [6] and BP 2013 [5]. These compounds are impurities A, B, and C in BP 2013 [5] which are identical to USP valsartan-related compound A RS, USP valsartan-related compound B RS, and USP valsartan-related compound C RS.

Nie et al. [23] isolated three impurities from crude valsartan, and one of the impurities was identified as impurity A. This compound may be formed by hydrolysis of a methyl ester intermediate in the last step of valsartan synthesis; the methyl group can react with the nitrogen of the tetrazole acid isostere to form impurity A. Approximately 80% of valsartan could be recovered by dissolving impurity A in methanol (pH 11) over 24 h. Impurity A described by Nie et al. [23] is different from impurity A in BP 2013 [5].

Sampath et al. [24] detected five impurities, i.e., impurities I, II, III, IV, and V from crude drug valsartan. The characterization and structure elucidation of the impurities were achieved by spectroscopic methods (IR, NMR, and MS) as well as by synthesis. The mechanism of impurities formation has been described in detail.

Mehta et al. [25] reported three impurities (DP-1, DP-2, and DP-3) from the results of degradation studies using acidic (in 1 N HCl), alkaline (in 2 N NaOH), neutral (in water), oxidative (in 30% H_2O_2), and photolytic studies (exposure to UV radiation). The structure of DP-1 reported by Mehta and coworkers [25] was identical to that of impurity I described by Sampath et al. [24].

Bianchini et al. [26] reported two degradation products of valsartan (DP-1 and DP-2) from exposure of valsartan to UV–VIS radiation (320 nm). DP-1 was formed by light-induced decarboxylation of valsartan, while DP-2 could be formed by further decomposition of tetrazole moiety from the loss of nitrogen and cyclization. The chemical structures of DP-1 and DP-2 are not identical to those of DP-1 and DP-2 reported by Mehta et al. [25].

Table 2 summarizes known impurities and related substances of valsartan, and their chemical structures are presented in Figure 3. The compendial method of separation and analysis of the impurities are summarized in Table 3. Raw pharmaceutical substances are required to have related substances or impurities less than 0.05% [24].

Table 2 Impurities and Related Compounds of Valsartan

Compound Number	Chemical Name	Other Name	Chemical Formula	Degradation Process or Formation	Ref.
1	(R)-N-Valeryl-N-{[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl} valine	Compound A RS, impurity A	$C_{24}H_{29}N_5O_3$		[5,6]
2	(S)-N-Butyryl-N-{[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl} valine	Compound B RS, impurity C, CGP 55390	$C_{23}H_{27}N_5O_3$		[5,6,27]
3	(S)-N-Valeryl-N-{[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]-methyl} valine benzyl ester	Compound C RS, impurity B	$C_{31}H_{35}N_5O_3$		[5,6]
4	(S)-N-Valeryl-N-{[2'-(1-methyl-tetrazole-5-yl)biphenyl-4-yl]-methyl} valine	Impurity A[a]	$C_{25}H_{31}N_5O_3$	Hydrolysis of the methyl ester in the last step of crude synthesis	[23]
5	(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4ylmethyl]amine	Impurity I, DP-1[b]	$C_{19}H_{21}N_5O_2$	Intermediate product of valsartan Simple amide hydrolysis under acidic and neutral conditions	[24,25]
6	(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-(5-phenylthio)pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4ylmethyl] amine	Impurity II	$C_{30}H_{33}N_5O_3S$	Intermediate product of valsartan	[24]

7	(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-(5-phenyl)pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4ylmethyl] amine	Impurity III	$C_{30}H_{33}N_5O_3$	Condensation of impurity I with 5-phenylvaleroyl chloride in the presence of pyridin	[24]
8	(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-4-pentenoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4ylmethyl]amine	Impurity IV	$C_{24}H_{27}N_5O_3$	Condensation of impurity I with 4-pentanoic acid	[24]
9	(S)-N-(1-Carboxy-2-methylprop-1-yl)-N-(5-hydroxy)pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4ylmethyl] amine	Impurity V	$C_{24}H_{29}N_5O_4$	Condensation of impurity I with 5-chlorovaleric acid	[24]
10	n/a	DP-2[b]	$C_{19}H_{21}N_5O_3$	N-Dealkylation in photoneutral condition	[25]
11	n/a	DP-3[b]	$C_{24}H_{28}N_5O$	Cyclization of tetrazole ring in photo acidic condition	[25]
12	N-[2'-(1H-Tetrazol-5-yl)-biphenyl-4ylmethyl]-N-isobutylpentanamide	DP-1	$C_{23}H_{30}N_5O$ $[M+H]^+$	Photodegradation of valsartan	[26]
13	N-(Diazirinol[1,3-f]phenanthridin-4ylmethyl)-N-isobutylpentanamide	DP-2	$C_{23}H_{27}N_3O$	Photodegradation of valsartan	[26]

[a]Degradation product from Nie et al. [23].
[b]Degradation products from Mehta et al. [25].
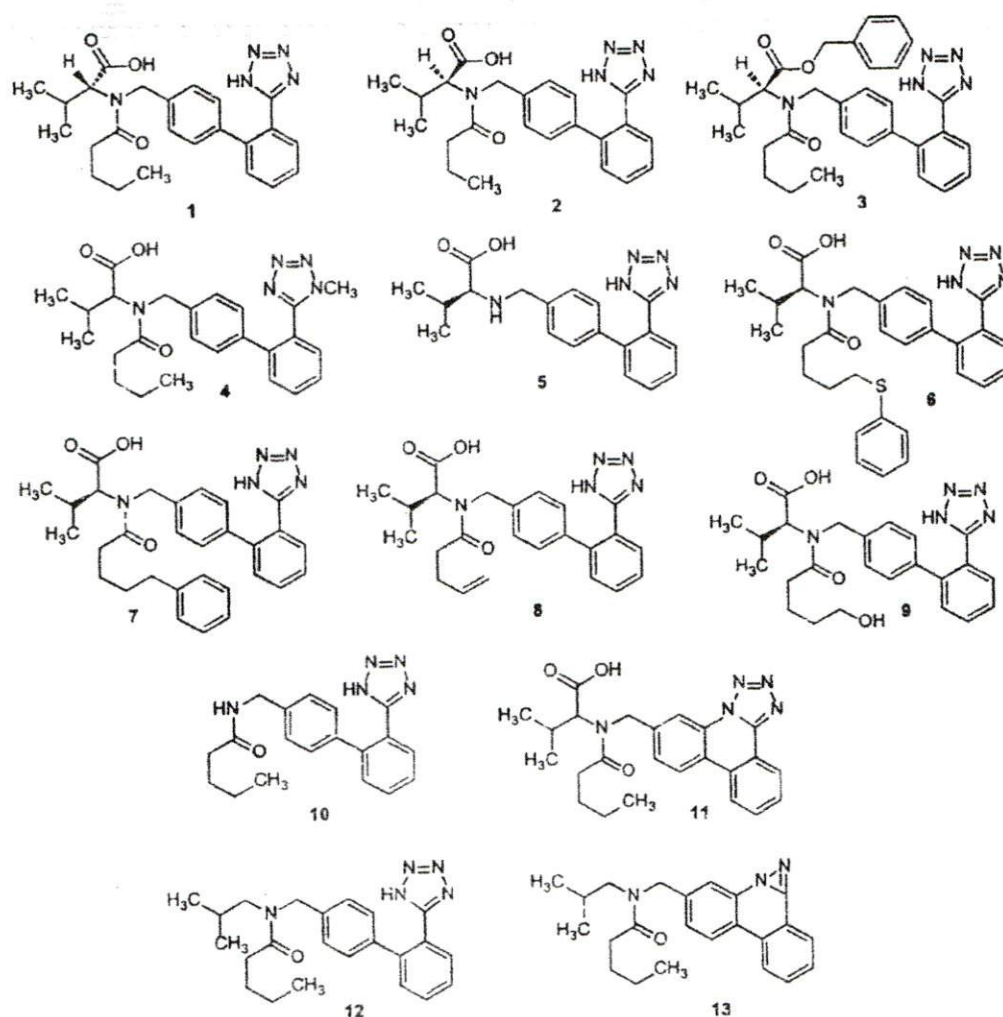
Figure 3 Chemical structures of impurities and related compound of valsartan. Compound numbers were described in Table 2.

5. SPECTROSCOPY

5.1 Ultraviolet Spectroscopy

The UV spectra of valsartan in methanol (10 ppm, scanned 200–400 nm) are presented in Figure 4. These spectra were recorded using a Spectrophotometer Shimadzu UV-1800 series; valsartan showed emission wavelength at 399 nm (excitation 259 nm), and the intrinsic fluorescence was decreased in basic pH [32].

Table 3 Compendial LC Methods and Their Validation Report

Analyte(s)	Sample	Test	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	Ref.
Valsartan	Raw material	Compendial USP assay method	Water:ACN: glacial acetic acid (500:500:1, v/v/v)	Column: L1 (125 mm × 3 mm; 5 µm) Temperature: n/a Detector: 273 nm	Water:ACN:glacial acetic acid (500:500:1, v/v/v) Flow rate: 0.4 mL/min Injection volume: 5 µL	[6]
Valsartan	Raw material	Assay method in USP/MC validation report	Water:ACN: glacial acetic acid (500:500:1, v/v/v)	Column: L10 Zorbax SB-CN (250 mm × 4.6 mm; 5 µm) Temperature: 25 °C Detector: 273 nm	Water:ACN:glacial acetic acid (500:500:1, v/v/v) Flow rate: 0.7 mL/min Injection volume: 10 µL	[28]
Valsartan-related compound A	Raw material	Compendial USP method for related compound A	n-Hexane:2-propanol: trifluoroacetic acid (85:15:0.1, v/v/v)	Column: L40 (250 mm × 4.6 mm; 5 µm) Temperature: n/a Detector: 230 nm	n-Hexane:2-propanol: trifluoroacetic acid (85:15:0.1, v/v/v) Flow rate: 0.8 mL/min Injection volume: 10 µL	[6]
Valsartan-related compounds B, C, and other related compounds	Raw material	Compendial USP method for related compounds B, C, and other related compounds	Water:ACN: glacial acetic acid (500:500:1, v/v/v)	Column: L1 (125 mm × 3 mm; 5 µm) Temperature: n/a Detector: 225 nm	Water:ACN:glacial acetic acid (500:500:1, v/v/v) Flow rate: 0.4 mL/min Injection volume: 5 µL	[6]

Table 3 Compendial LC Methods and Their Validation Report—cont'd

Analyte(s)	Sample	Test	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	Ref.
Valsartan	Raw material	Organic impurities test in USP/MC validation report	Water:ACN: acetic glacial acid (500:500:1, v/v/v)	Column: L10 Zorbax SB-CN (250 mm × 4.6 mm; 5 μm) Column oven temp: 25 °C Auto sampler temp: 4 °C Detector: 225 nm MS condition: Detector: MS Source: ES Scan (+ and −) Capillary (kv): 3.00 Cone (v): 20.0 Extractor (v): 2.0 RF lens (v): 0.1 Source temperature: 80 °C Desolvation temperature: 400 °C	Water:ACN:acetic glacial acid (500:500:1, v/v/v) Flow rate: 0.7 mL/min Injection volume: 10 μL	[28]
Valsartan	Tablet, organic impurities	Compendial USP assay method	ACN:water (1:1, v/v)	Column: L1 (250 mm × 4.6 mm; 10 μm) Column temperature: 30 °C Detector: 230 nm	Water:ACN:glacial acetic acid (50:50:1, v/v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	[6]
Valsartan	Tablet	Assay method in USP/MC validation report	Water:ACN: glacial acetic acid (500:500:1, v/v/v)	Column: L10 Zorbax SB-CN (250 mm × 4.6 mm; 5 μm) Column oven temp: 25 °C Auto sampler temp: 4 °C Detector: 225 nm	Water:ACN:glacial acetic acid (500:500:1, v/v/v) Flow rate: 0.7 mL/min Injection volume: 10 μL	[29]

Valsartan	Tablet	Organic impurities test in USP/MC validation report	Water:ACN: glacial acetic acid (500:500:1, v/v/v)	Column: L10 Zorbax SB–CN (250 mm × 4.6 mm; 5 µm) Column oven temp: 25 °C Auto sampler temp: 4 °C Detector: 225 nm MS condition: Detector: MS Source: ES Scan (+ and −) MS condition: Capillary (kv): 3.00 Cone (v): 20.0 Extractor (v): 2.0 RF lens (v): 0.1 Source temperature: 80 °C Desolvation temperature: 400 °C	Water:ACN:glacial acetic acid [29] (500:500:1, v/v/v) Flow rate: 0.7 mL/min Injection volume: 10 µL
Valsartan, hydrochlorothiazide	Tablet, organic impurities	Compendial USP assay method	ACN:water (1:1, v/v)	Column: L1 (125 mm × 3.0 mm; 5 µm) Column temperature: n/a Detector: 265 nm	Solution A: ACN:water: [6] trifluoroacetic acid (10:90:0.1, v/v/v) Solution B: ACN:water: trifluoroacetic acid (90:10:0.1, v/v/v) (gradient) Flow rate: 0.4 mL/min Injection volume: 10 µL

Table 3 Compendial LC Methods and Their Validation Report—cont'd

Analyte(s)	Sample	Test	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	Ref.
Valsartan, hydrochlorothiazide	Tablet	Assay method in USP/MC validation report	Solution A: 0.2% acetic acid in water Solution B: ACN Solvent: solution A: solution B (1:1, v/v)	Column: L10 Zorbax SB–CN (250 mm × 4.6 mm; 5 μm) Column oven temp: 25 °C Auto sampler temp: 10 °C Detector: 272 nm	Solution A: 0.2% acetic acid in water Solution B: ACN (gradient) Flow rate: 1 mL./min Injection volume: 10 μL	[30]
Valsartan, hydrochlorothiazide	Tablet	Organic impurities test in USP/MC validation report	Solution A: 0.2% acetic acid in water Solution B: ACN Solvent: solution A: solution B (1:1, v/v)	Column: L10 Zorbax SB–CN (250 mm × 4.6 mm; 5 μm) Column oven temp: 25 °C Auto sampler temp: 10 °C Detector: 272 nm MS condition: Detector: MS Source: ES Scan (+ and −) MS condition: Capillary (kv): 3.00 Cone (v): 25.0 Extractor (v): 2.0 RF lens (v): 0.1 Source temperature: 90 °C Desolvation temperature: 500 °C	Solution A: 0.2% acetic acid in water Solution B: ACN (gradient) Flow rate: 1 mL/min Injection volume: 10 μL	[30]

Valsartan, amlodipine	Tablet	Assay method in USP/MC validation report	Water:MeOH (3:7, v/v)	Column: L1 Purosphere Star RP18 (150 mm × 4.6 mm; 5 μm) Column oven temp: 40 °C Auto sampler temp: 10 °C Detector: 237 nm	Solution A: 25 mM ammonium acetate pH 7.5 Solution B: ACN (gradient) Flow rate: 1 mL/min Injection volume: 20 μL	[31]
Valsartan	Raw material	Organic impurities test in USP/MC validation report	Water:MeOH (3:7, v/v)	Column: L1 Purosphere Star RP18 (150 mm × 4.6 mm; 5 μm) Column oven temp: 40 °C Auto sampler temp: 10 °C Detector: 237 nm MS condition: Detector: MS Source: ES Scan (+ and −) MS condition: Capillary (kv): 3.00 Cone (v): 25.0 Source temperature: 90 °C Desolvation temperature: 500 °C	Solution A: 25 mM ammonium acetate pH 7.5 Solution B: ACN (gradient) Flow rate: 1 mL/min Injection volume: 20 μL	[31]
Valsartan	Raw material	Compendial BP method of enantiomer purity	Trifluoroacetic acid:2-propanol:hexane (0.1:15:85, v/v/v)	Column: silica gel OD for chiral separations (250 mm × 4.6 mm) Temperature: n/a Detector: 230 nm	Trifluoroacetic acid:2-propanol:hexane (0.1:15:85, v/v/v) Flow rate: 0.8 mL/min Injection volume: 5 μL	[5]
Valsartan	Raw material	Compendial BP method for related substances	Glacial acetic acid:ACN:water (1:500:500, v/v/v)	Column: end-capped octadecylsilyl silica gel (125 mm × 3.0 mm; 5 μm) Temperature: n/a Detector: 230 nm	Glacial acetic acid:ACN:water (1:500:500, v/v/v) Flow rate: 0.4 mL/min Injection volume: 10 μL	[5]
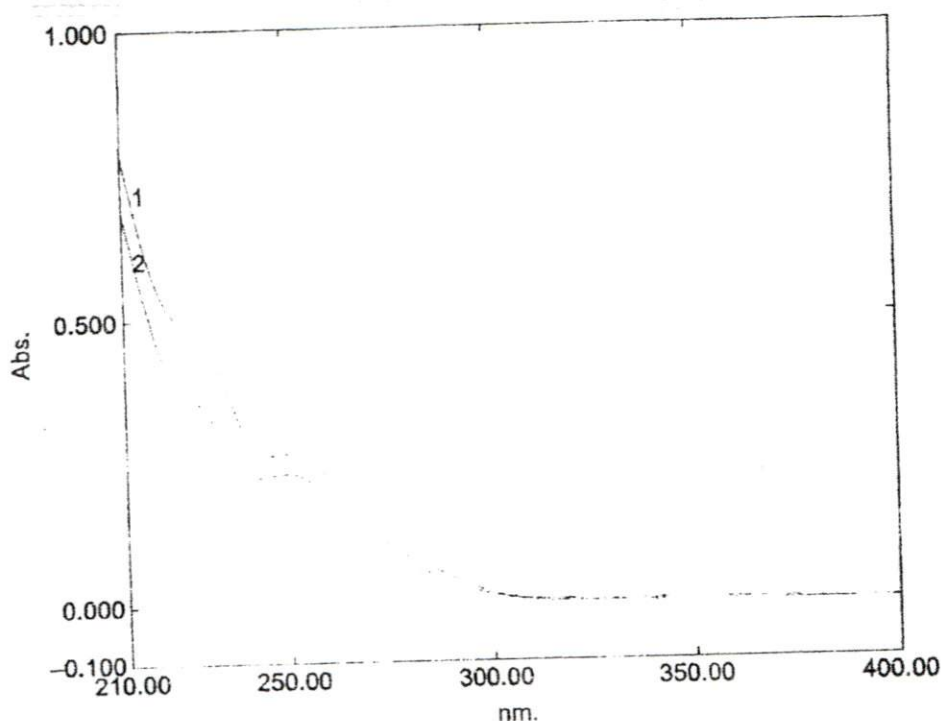
Figure 4 UV spectra of valsartan in methanol (10 ppm) recorded on a Shimadzu UV-1800 series spectrophotometer. (1) USP valsartan RS and (2) valsartan (TEVA, India).

5.2 Infrared Spectroscopy

The IR spectra of USP valsartan RS in KBr (2 mg/200 mg) pellets are shown in Figure 5. IR spectra were obtained by using a Shimadzu IR Prestige-21 Spectrophotometer. The principle peaks and their assignments are listed in Table 4.

Several authors used IR spectrum to characterize nanoparticles of valsartan with Eudragit® L 100 [33], solid dispersion of valsartan and cyclodextrin [34,35], and hydrogel formulations [13]. Data from these references suggested that the IR spectrum of valsartan bulk drug is not fully identical, which confirmed the results of DSC (see Section 2).

5.3 Mass Spectroscopy

The ESI-MS of valsartan (TEVA) is shown in Figure 6A. The ESI-M-S (positive ion mode) is measured by using a UPLC Waters H Class and MS: XEVO TQD (direct injection to MS; cone voltage 30 V), while MS/MS (collision; 20 V) is presented in Figure 6B. The important
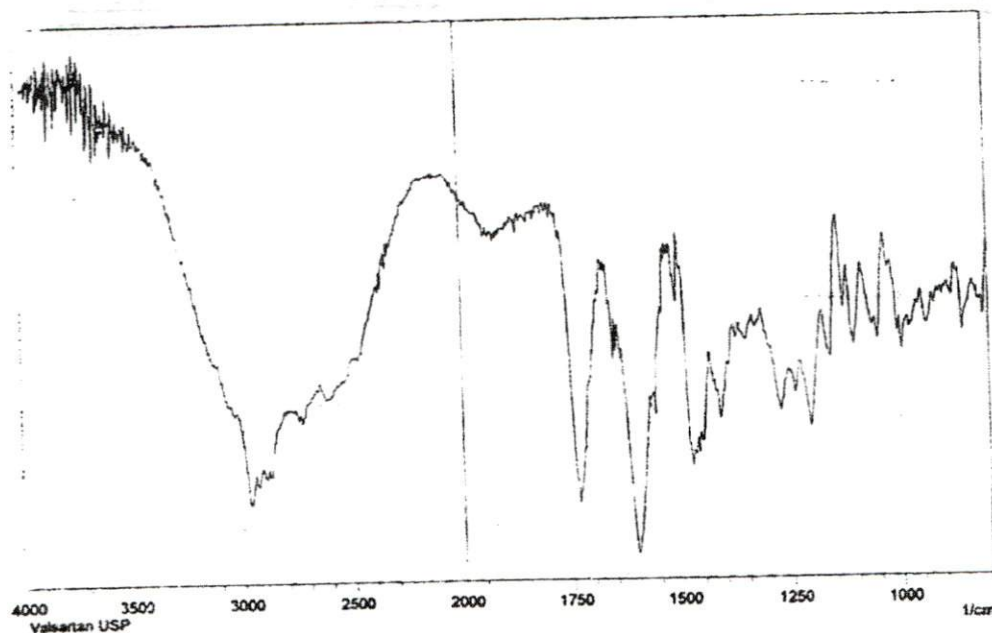
Figure 5 IR spectrum of USP valsartan RS recorded on a Shimadzu IR Prestige-21 spectrophotometer using KBr pellet sampling (2 mg/200 mg).

Table 4 IR Characteristic Band of USP Valsartan RS Lot L0L195[a]

Frequency (cm^{-1})	Assignment
3035.96	O—H stretch
2873.94	C—H stretch
2927.94	C—H stretch
1734.01	C=O stretch, acid
1602.85	C=O stretch, amide
1570.06	N—N bending
1473.62	C—OH plane bend
1448.54	C—OH plane band
1390.68	C—O stretch
995.27	C—N stretch

[a]Assignments were compared to previous published data [13,24].

A

B
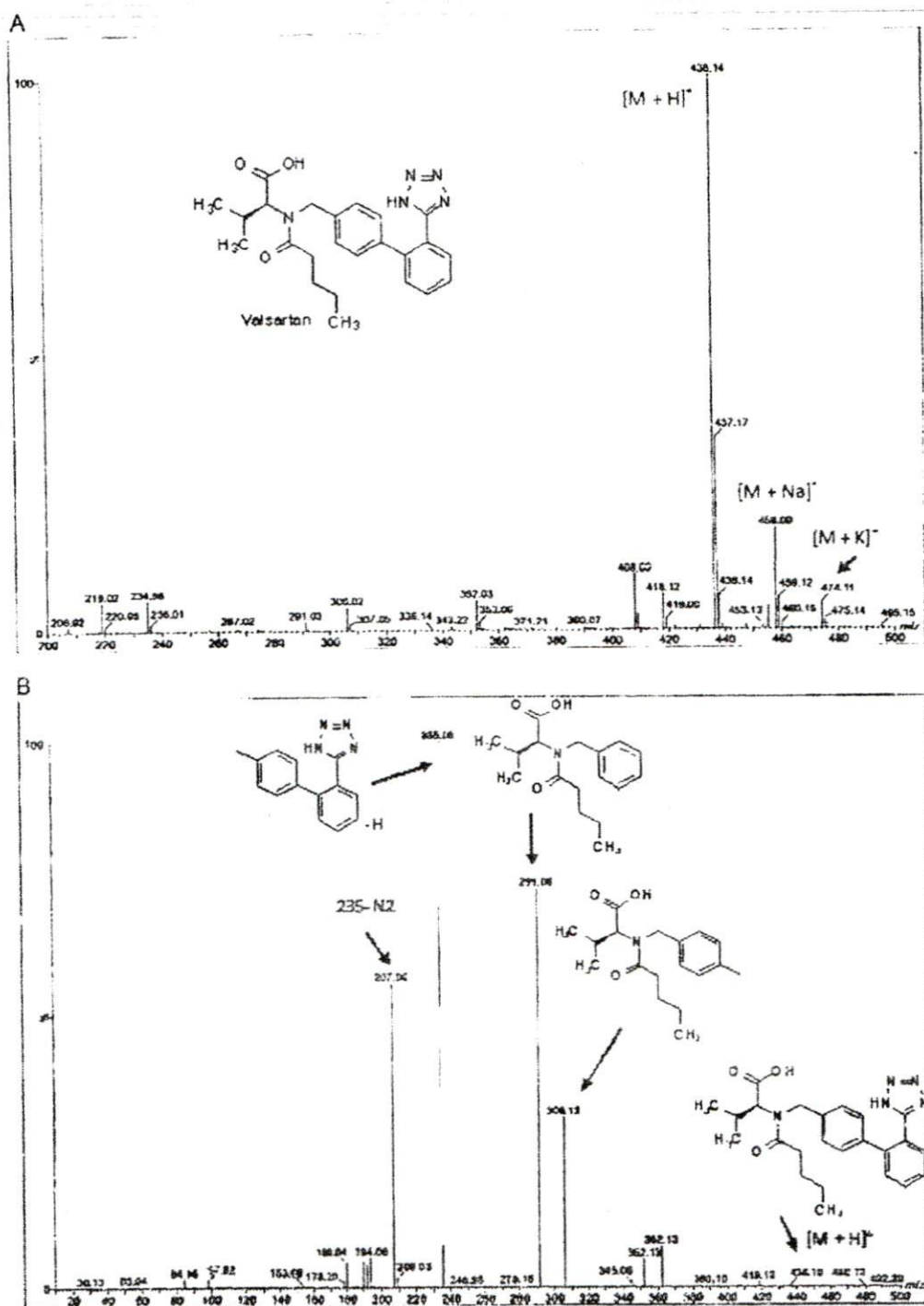
Figure 6 (A) ESI-MS spectrum of valsartan (TEVA) recorded on a UPLC Waters H Class and MS: XEVO TQD (direct injection to MS; cone voltage 30 V). (B) MS/MS spectrum of valsartan (precursor ion m/z 436, collision energy 20 V).

fragments are also described. The MS data are similar to that of described in the literature [36–39]. The ESI negative ion mode is also reported; the important fragments (m/z) are 434.25 (M–H⁻), 390.1, 350.1, and 179.2 [40,41]. Both positive and negative ion modes are used for determination of valsartan by LC–MS/MS (see Section 8).

The EI-MS of valsartan dimethyl ester was reported by Maurer *et al.* [42]. The important fragments (m/z) were 463 ([M]⁺, valsartan dimethyl ester), 378 [M–57], 320 [M–115], 268 [M–115- 57], and 250 [M–115–78].

5.4 Nuclear Magnetic Spectroscopy

Li *et al.* [43] reported two conformations for valsartan based on the result of 2D NOESY experiment and quantum chemistry calculations. The two conformers, namely conformers A (major) and B (minor), are presented in Figure 7 (ChemBio3D Ultra 13, energy minimization with MM2 software to an RMS gradient of 0.100). These *cis/trans* isomer existed as the result of the conformational interchange via rotation around the peptide C(O)—N bond. Potamitis and coworkers [44] as well as Li *et al.* [43] suggested that the two conformers can be distinguished by NOESY experiment. A NOESY experiment was conducted on valsartan sample. In the major conformer A, NOESY cross peaks were observed from H-2, H-3, and H-4 to the methylene protons at C-11 (Figures 7 and 8). Other NOESY correlation observed was between H-4 and the aromatic proton H-13/H-17.
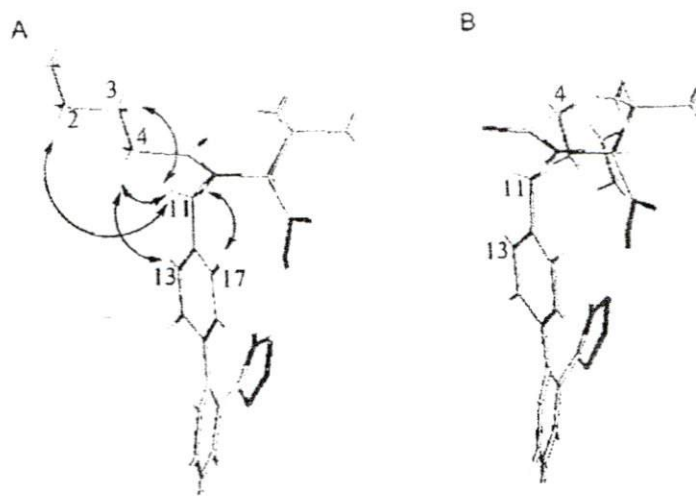
Figure 7 Conformers of valsartan and their NOESY correlation. Structures were drawn by ChemBio3D Ultra 13, energy minimization with MM2 software to an RMS gradient of 0.100: (A) major and (B) minor.
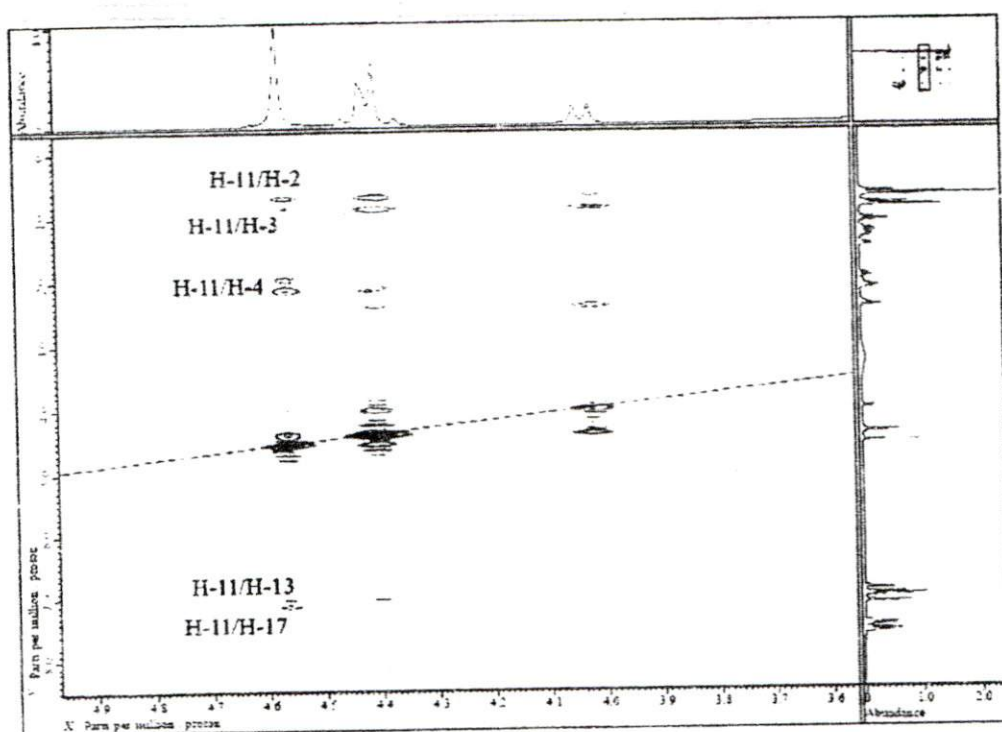
Figure 8 Selected 2D NOESY spectrum for valsartan (TEVA, India) recorded on a JEOL ECS-400, NMR spectrometer in DMSO-d_6 at 294 K with mixing time 500 ms.

These data indicated the closeness of the aliphatic *n*-butyl side chain to the aromatic ring. In the minor conformer, these NOESY correlations were absent. The composition of the two conformers was calculated at different temperature ranging from 293 to 313 K by using ^{1}H NMR spectroscopy. The data suggested that population of the minor conformer B increased as the temperature increased. Potamitis *et al.* [44] suggested that between 50 and 65 °C the ratio of isomer A:B is ~60:40. The ^{1}H and ^{13}C NMR spectra also indicated two sets of data which are presented in Table 5.

6. COMPENDIAL METHOD

6.1 Identification Test

USP 36 [6] described two methods for identification of valsartan bulk drug, i.e., IR absorption and LC system (by comparison of the retention time). This LC method has also been applied for identification of valsartan in tablets (valsartan tablets, valsartan, and hydrochlorothiazide tablets;

Table 5 NMR Data of Two Conformers of Valsartan

	Major Conformer						Minor Conformer			
	δ_C			δ_H			δ_C		δ_H	
#	CD$_3$OD[a,b]	DMSO-d_6[b]	DMSO-d_6[c]	CD$_3$OD[a,b]	DMSO-d_6[b]	DMSO-d_6[c]	CD$_3$OD[a,b]	DMSO-d_6[b]	CD$_3$OD[a,b]	DMSO-d_6[b]
1	14.5	13.6	14.1	0.84 (t, 7.4)	0.75	0.74 (t, 7.2)	14.5	13.6	0.95 (t, 7.4)	0.88
2	23.7	21.6	22.1	1.24	1.15	1.10–1.18	23.8	21.7	1.38	1.31
3	28.8	26.7	28.0	1.51	1.37; 1.39	1.52 (sextet, 6.9)	28.9	26.9	1.66	1.54
4	34.8	32.4	32.9	2.19; 2.33	2.04; 2.20	2.41–2.51 (m)	34.7	32.4	2.50; 2.64	2.46
5	177.5	173.4	172.4	--	—	—	177.3	173.4	—	—
6	65.2	62.9	63.4	4.58 (d, 10.1)	4.45	4.03 (d, 6.5)	68.2	65.7	4.14 (d, 10.7)	4.08
7	29.6	27.5	27.2	2.31	2.21	2.17 (septet, 6.5)	29.5	27.5	2.24	2.13
8	19.7	18.7	19.2	0.84 (d, 6.5)	0.75	0.73 (d, 6.5)	19.6	18.4	0.79 (d, 6.7)	0.70
9	20.9	20.0	20.5	1.00 (d, 6.5)	0.93	0.91 (d, 6.5)	20.3	19.3	1.01 (d, 6.5)	0.93
10	173.9	171.8	174.2	—	—	—	173.3	171.5	—	—
11	50.9	48.7	49.1	4.62; 4.80	4.62	4.41(d, 13.6) 4.49 (d, 13.6)	47.6	45.5	4.60	4.47
12	139.1	137.7	138.1	—	—	—	139.8	137.1	—	—
13	128.1	126.2	126.7	7.24	7.20	7.05 (br d, 8.0)	129.0	126.9	7.18	7.09
14	130.6	128.7	128.2	7.10	7.06	7.18 (d, 8.0)	130.1	128.2	7.02	6.97

Continued

Table 5 NMR Data of Two Conformers of Valsartan—cont'd

| | Major Conformer | | | | | | Minor Conformer | | | |
| | δ_C | | δ_H | | | | δ_C | | δ_H | |
#	CD₃OD[a,b]	DMSO-d₆	DMSO-d₆	CD₃OD[a,b]	DMSO-d₆	DMSO-d₆	CD₃OD[a,b]	DMSO-d₆	CD₃OD[a,b]	DMSO-d₆
15	140.0	137.7	138.2	–	–	–	139.1	138.2	–	–
16	130.6	128.7	128.7	7.10 (d, 8.3)	7.06	6.95 (d, 8.0)	130.1	128.2	7.02 (d, 8.3)	6.97
17	128.1	126.2	128.7	7.24 (d, 8.3)	7.20	7.08 (d, 8.0)	129.0	126.9	7.18 (d, 8.3)	7.09
18	143.4	141.1	141.6	–	–	–	143.6	141.3	–	–
19	132.1	130.5	129.2	7.55	7.53	7.48–7.59 (m)	132.1	130.5	7.53	7.53
20	131.9	130.5	131.0	7.67	7.63	7.59–7.71 (m)	132.8	130.5	7.66	7.63
21	129.3	127.6	127.4	7.56	7.57	7.48–7.59 (m)	129.2	127.6	7.54	7.57
22	132.8	130.9	131.6	7.65	7.68	7.59–7.71 (m)	132.0	130.9	7.64	7.68
23	124.7	123.5	123.8	–	–	–	124.5	123.5	–	–
24	156.9	155.0	155.0	–	–	–	157.0	155.0	–	–
NH	–	–	–	–	–	1.97 (s)				

[a]Data from Li et al. [43].
[b]Data from Potamitis et al. [44].
[c]Data from Bianchini et al. [26].

see Table 3). In addition, a TLC method has also been used for identification of valsartan and hydrochlorothiazide tablets ⟨201⟩. The sample ground tablets (the weight is equivalent to a single tablet) was dissolved in a 2 mL of acetone by sonication for 5 min, followed by centrifugation. The mobile phase was a mixture of EtOAc:dehydrated alcohol:3.6 M ammonium hydroxide. The R_f of the samples should be identical to that of the standard solutions.

British Pharmacopeia 2013 [5] described three methods (A, B, and C) for identification of valsartan, i.e., (A) IR absorption, (B) enantiomeric purity, and (C) specific optical rotation. The identification must be conducted by using either methods A and B or A and C. Method B should be performed by using LC system (see Table 3). The sample used in this method contains impurity A, and the area of the impurity should not be more than the area of the principle peak in the standard solution. For method C, 0.2000 g sample was dissolved in 20 mL methanol, and the value should be between −64.0 and −69.0.

6.2 Related Compounds

USP 36 [6] described two limit tests for valsartan-related compounds using LC methods. Test 1 is the limit test for related compound A (RS A), while test 2 is for related compound B (RS B), related compound C (RS C), and other related compounds. The percentage of the related compounds can be calculated by using the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which C_s is the concentration (mg/mL) of the valsartan-related compound A RS in the standard solutions, while C_u is the concentration of valsartan (mg/mL) in the test solutions; r_u and r_s are the peak responses of RS A from the test and standard solutions, respectively. The acceptability limit is 1%. Details of LC methods are described in Table 3.

British Pharmacopeia 2013 [5] described an LC method for determination of the impurity in bulk drugs (see Table 3). The area of impurity C should not be more than twice the area of the principle peak in the chromatogram of reference solution A (0.2%). The area of each unspecified impurity should be less than that of reference solution A (0.1%), and the area of total impurities must not be more than the reference solution A (0.3%).

6.3 Assay

USP 36 [6] described LC methods for the determination of valsartan bulk drugs, valsartan tablets, and valsartan and hydrochlorothiazide tablets. All three LC methods used the same material for column (L1) but with different dimensions and particle sizes, while mobile phases are identical. A gradient elution was applied for analysis of valsartan and hydrochlorothiazide. Details of LC conditions are presented in Table 3.

British Pharmacopeia 2013 [5] used potentiometry for assay of valsartan in bulk drugs. The sample (0.170 g) in 70 mL of 2-propanol R was then titrated with 0.1 M tetrabutylammonium hydroxide in 2-propanol. Analyses were performed under nitrogen, and the end point was determined potentiometrically. In this method, 1 mL of 0.1 M tetrabutylammonium hydroxide in 2-propanol is equivalent to 21.78 mg $C_{24}H_{29}N_5O_3$.

6.4 Dissolution Test

6.4.1 Valsartan Tablets

USP 36 [6] described the determination of valsartan in dissolution medium (phosphate buffer pH 6.8) by using spectrophotometer at UV 250 nm against blank (medium). The percentage of dissolved valsartan can be calculated by using the equation:

$$\text{Result} = (A_u/A_s) \times (C_s/L) \times V \times 100$$

A_u = absorbance of sample solution; A_s = absorbance of standard solution; C_s = concentration of USP valsartan RS in standard solution (mg/mL); L = label claim (mg/tablet); V = volume medium (1000 mL); tolerance is not less than 80% (Q value).

6.4.2 USP Valsartan and Hydrochlorothiazide Tablets
6.4.2.1 Spectrophotometer

The determination of valsartan and hydrochlorothiazide in dissolution medium (phosphate buffer pH 6.8) was performed by using spectrophotometer at UV 250 nm (valsartan) and at 272 nm (hydrochlorothiazide) against blank (medium). The percentage of the dissolved valsartan and hydrochlorothiazide can be calculated using equations:

$$\text{Valsartan}: \text{Result} = [(AT_2 \times D) - (AT_1 \times E)/(C \times D) \\ -(B \times E)] \times 12,500$$

$$\text{Hydrochlorothiazide}: \text{Result}: [(AT_1 \times C) - (AT_2 \times B)/(D \times C) \\ -(E \times B)] \times 80,000$$

AT_1 = absorbance of sample solution at 272 nm; AT_2 = absorbance of sample solution at 250 nm; B = A1% V_{272} absorptivity (1%, 0.2 cm, 272 nm) valsartan in medium; C = A1% V_{272} absorptivity (1%, 0.2 cm, 250 nm) valsartan in medium; D = A1% V_{272} absorptivity (1%, 0.2 cm, 272 nm) hydrochlorothiazide in medium; E = A1% V_{272} absorptivity (1%, 0.2 cm, 250 nm) hydrochlorothiazide in medium.

6.4.2.2 Liquid Chromatography

Valsartan and hydrochlorothiazide can be analyzed in dissolution medium using an LC method. The sample diluents are ACN:water (1:1). Details of the LC condition are described in Table 3. The percentage of dissolved valsartan and hydrochlorothiazide can be calculated by equation:

$$Result = (r_u/r_s) \times (C_s/L) \times D \times V \times 100$$

r_u = peak response valsartan or hydrochlorothiazide in the sample solution; r_s = peak response valsartan or hydrochlorothiazide in the standard solution; C_s = concentration of valsartan or hydrochlorothiazide in standard solution; L = label claim of valsartan or hydrochlorothiazide in tablet (mg/tablet); D = dilution factor (if applicable); V = volume of medium (1000 mL). Tolerance is 80% (Q value).

7. METHOD OF ANALYSIS

7.1 Spectrophotometer

Gupta et al. [45] described analysis of valsartan in bulk drugs and tablets. The standard and samples were dissolved in methanol, and the determination of analytes in samples was performed by comparing with standards and value of A (1%, 1 cm). Comparison with standards was performed by using two methods, i.e., zero-order absorption (at 250 nm) and second-order spectra (at 241 nm). Calibration ranges were linear in the range of 10–50 μg/mL (r = 0.999). Recovery studies were in the range of 99.08–100.31%. A statistical evaluation showed no significant difference among three methods of estimation. A similar spectrophotometric method was proposed by Kumar et al. [46]; in this case, the analysis was performed at λ 249 nm (in methanol), and recovery showed good values (97.77–101.4%).

Dinç et al. [47] reported two simultaneous spectrophotometric determination of valsartan and hydrochlorothiazide in tablets. The first method applied ratio derivative method; in this case, first amplitude derivates were at λ 231.5 and 260.5 nm (valsartan) and 270.6 nm (hydrochlorothiazide);

mean recover for valsartan was 100.4% (RSD = 1.76%). Second method applied inverse least square absorbance matrix of zero-order spectra in the range of 225–280 nm ($\Delta\lambda = 5$ nm, at 12 wavelengths). Spectra were measured in various binary mixtures; in this case, recovery of valsartan was 101.2% (RSD = 1.58%).

Chaudhary et al. [48] determined valsartan and hydrochlorothiazide simultaneously in tablets by using absorption ratio method. Molar absorptivity was calculated at both wavelengths 270.5 nm (λ_{max} of hydrochlorothiazide) and 231.5 nm (isoabsorptive point). The recovery showed satisfactory results (valsartan: 99.05–102.23%; hydrochlorothiazide: 97.42–100.22%). RSD of intra- and interday precision was below 2%.

Gupta et al. [49] reported analysis of valsartan and amlodipine in tablets by using simultaneous equation method and absorption correction method. A simultaneous equation method was developed by using λ_{max} of valsartan (250 nm, MeOH) and amlodipine (238 nm, MeOH), while absorption correction method applied at iso-bestic wavelength of the drugs (236 nm). Recoveries were in the range of 99.48–100.13% for both spectrophotometric methods.

Ramachandran et al. [50] developed method for simultaneous determination of valsartan and ezetimibe in tablets by using complex formation with bromophenol blue (BPB) and bromocresol green (BCG). Valsartan–dye complex shows λ_{max} at 425 and 428 nm, respectively, while ezetimibe cannot react with both BPB and BCG. The analysis was then performed by using two wavelengths for each method of complexation (λ 425 or 428 for valsartan) and at λ_{max} for ezetimibe (250 nm). Good recovery was achieved using this method (99.3–100.3%).

Birajdar et al. [51] reported simultaneous determination of valsartan and nebivolol in tablets using Q method of analysis and simultaneous equations (at λ 280.2 and 246.6 nm). Isoabsorptive point of valsartan and nebivolol (at λ 275 nm) and λ 246.6 nm were selected for Q method. Recoveries for both analytes were in the range of 98.80–101.2% by using both spectrophotometric methods.

7.2 Capillary Electrophoresis

Hillaert and van den Bossche [52] described the separation of six ARA-IIs, i.e., valsartan, candesartan, eprosartan mesylate, irbesartan, losartan potassium, and telmisartan, by using capillary zone electrophoretic method

(CZE). Best separation was achieved by using 60 mM phosphate buffer pH 2.5. In 2003, these authors reported the separation of the same six ARA-IIs by using micellar electrokinetic capillary chromatography (MEKC) in a 55 mM sodium phosphate buffer solution (pH 6.5) containing 15 mM SDS. Both CZE and MEKC methods were performed in a fused silica capillary column and detected by using UV 214 nm.

Hillaert and van den Bossche [53] also reported simultaneous analysis of combination of the six ARA-IIs and hydrochlorothiazide by using CZE and MEKC methods. The experiments were conducted on a fused silica capillary (total length was 85 cm, 33 cm to the detector; 50 μm i.d.) and by UV 214 nm detection. The running buffers were similar to that of in the previous publications [52,54]. Sulfanilamide (CZE) and eprosartan mesylate (MEKC) were used as internal standard for a quantitative evaluation. The recovery of valsartan, losartan potassium, and irbesartan at three-level concentrations for both methods was in the range of 96.1–102.3%.

7.3 High-Performance Liquid Chromatography

Table 6 summarizes HPLC analysis of valsartan and other drugs in pharmaceutical preparations and raw materials. Most of the methods used C18 as the stationary phase.

7.4 Thin-Layer Chromatography

Silica gel has been reported as the stationary phase in most of the analysis of valsartan by (HP)TLC. The mobile phase usually contains a small amount of acid or base (ammonia), and UV was used for detection. Summary of these works is presented in Table 7.

Inglot and coworkers [102,103] reported the retention behavior of several antihypertension drugs on diol, silica, RP-8, RP-18, and CN plates in various mobile phases. The best separation on diol plate was achieved by using hexane:dioxane:formic acid (3:7:0.1, v/v/v), while a mixture of hexane:isopropanol:formic acid (4:6:0.1, v/v/v) was the best mobile phase for CN plate. An effective separation on RP-8 and RP-18 plates can be achieved by using simple mobile phase containing DMSO:phosphate buffer pH 5 (8:2, v/v). The detection limit of valsartan as determined by using densitometry at 254 nm and video densitometry were 0.1 and 0.2 μg/spot, respectively.

Table 6 Summary of HPLC Analysis of Valsartan

Analyte (s)	Sample	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	LOD, LOQ, Recovery (Rec) Valsartan	Ref.
Valsartan, hydrochlorothiazide	Tablet	ACN:acetate buffer (pH 4.0, 0.1 M; 40:60, v/v)	Column: RP Hypersil ODS (200 mm × 4.6 mm, 5 µm) Temperature: (20–25) °C Detector: 220 nm	ACN:acetate buffer (pH 4.0, 0.1 M; 40:60, v/v) Flow rate: 1.0 mL/min Injection volume: n/a	LOD: 1.0 µg/mL LOQ: n/a Rec: 99.75%	[55]
Valsartan, hydrochlorothiazide	Tablet, synthetic mixtures	MeOH	Column: Supelcosil C18 (150 mm × 4.6 mm; 5 µm) Temperature: n/a Detector: 225 nm	0.02 M Phosphate buffer pH 3.2:ACN (55:45, v/v) Flow rate: 0.9 mL/min Injection volume: 20 µL	LOD: 0.017 µg/mL LOQ: 0.058 µg/mL Rec: Tablet: 102.2% Synthetic mixtures: 100.8%	[56]
Valsartan,	Capsule	Std: ACN, diluted with mobile phase Sample: ACN	Column: Shim-pack C18 (250 mm × 4.6 mm; 10 µm) Temperature: room Detector: 265 nm	ACN:PO$_4$ buffer pH 2.7 (45:55, v/v) Flow rate: 1.3 mL/min Injection volume: 20 µL	LOD: 0.2 µg/mL LOQ: 1 µg/mL Rec: 99.91%	[57]
Valsartan	Crude valsartan	MeOH	Column: ODS Hypersil C18 (200 mm × 4.6 mm; 5 µm); Temperature: ambient Detector: 254 nm MS: ESI (−) ion mode Scan range: 80–600 m/z 434.2 m/z valsartan	Acetic acid 0.2%:water (55:45, v/v) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: n/a LOQ: n/a Rec: n/a	[23]
Valsartan, hydrochlorothiazide	Tablet, impurities	ACN:water (4:6; v/v)	Column: Hypersil 120-5 ODS (250 mm × 4.6 mm; 5 µm) Column temperature: 25 °C Detector: 256 nm	Mobile phase A: ACN: water = 10:90 (v/v, pH 2.5) Mobile phase B: ACN: water = 90:10 (pH 2.5) Gradient time program Flow rate: 1.0 mL/min Injection volume: 50 µL	LOD: 0.02 µg/mL LOQ: 0.004 µg/mL Rec: (103.7–105.3)%	[27]

Drug	Formulation	Extraction solvent	Chromatographic conditions	Mobile phase	Validation parameters	Ref.
Valsartan, amlodipine	Capsule	ACN:phosphate buffer (0.02 M, pH 3.0; 56:44, v/v)	Column: Kromasil RP18 (250 mm × 4.6 mm) Column temperature: 25 °C Detector: 234 nm	ACN:phosphate buffer (0.02 M, pH 3.0; 56:44, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.018 μg/mL LOQ: 0.054 μg/mL Rec: (99.09–101.79)%	[58]
Valsartan, nebivolol hydrochloride	Capsule	MeOH:1-hexanesulfonic acid monohydrate sodium salt (80:20, v/v)	Column: HIQ sil C18 ODS (250 mm × 4.6 mm, 5 μm) Temperature: ambient Detector: 289 nm	MeOH:1-hexanesulfonic acid monohydrate sodium salt (80:20, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 17.58 μg/mL LOQ: 53.29 μg/mL Rec: (99.08 ± 1.05)%	[59]
Valsartan, hydrochlorothiazide	Tablet	MeOH:ACN:water: isopropyl alcohol (22:18:68:2, pH 8.0, v/v/v/v)	Column: Diamonsil C18 (250 mm × 4.6 mm; 5 μm) Temperature: n/a Detector: 270 nm	MeOH:ACN:water: isopropylalcohol (22:18:68:2, pH 8.0, v/v/v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: n/a LOQ: n/a Rec: n/a	[60]
Valsartan	Raw material	n/a	Column: Kromasil C18 (250 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 265 nm	ACN:water:0.5% orthophosphoric acid (40:60, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.25 μg/mL LOQ: 1.0 μg/mL Rec: (98.76–101.30)%	[61]
Valsartan, amlodipine	Tablet	Water:ACN (50:50, v/v)	Column: Xterra RP18 (150 mm × 4.6 mm, 5 μm) Temperature: 25 °C Detector: Valsartan: UV 265 nm	A: 1000 mL water + 0.2 mL trifluoroacetic acid B: Water:ACN:trifluoroacetic acid (400:600:1, v/v/v) Flow rate: 1.5 mL/min Injection volume: 10 μL	LOD: 0.95 μg/mL LOQ: 1.6 μg/mL Rec: (99.76–99.91)%	[62]

Table 6 Summary of HPLC Analysis of Valsartan—cont'd

Analyte (s)	Sample	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	LOD, LOQ, Recovery (Rec) Valsartan	Ref.
Valsartan	Tablet	$NH_4H_2PO_4$ 0.01 M, pH 3.5:MeOH (50:50, v/v)	Column: Phenomenex Gemini C18 (250 mm × 4.6 mm; 5 µm) Temperature: 25 °C Detector: 210 nm	$NH_4H_2PO_4$ 0.01 M, pH 3.5: MeOH = 50:50 Flow rate: 1.0 mL min Injection volume: 20 µL	LOD: 0.0388 µg/mL LOQ: 0.1176 µg/mL Rec: (99.63–100.587)%	[63]
Valsartan	Degradation product	MeOH	Column: HIQ sil C18 (250 mm × 4.6 mm; 5 µm) Temperature: ambient Detector: 250 nm	MeOH:water (pH 7.2; 70:30, v/v) Flow rate: 1.2 mL/min Injection volume: 20 µL	LOD: n/a LOQ: n/a Acid hydrolysis (valsartan) (98.50–100.20)% Oxidation (valsartan): (98.70–101.50)%	[64]
Valsartan, ramipril	Synthetic mixture, degradation studies	ACN:water (55:45, v/v) pH 3.6	Column: Hypersil C18 (250 mm × 4.6 mm, 5 µm) Temperature: (25±2) °C Detector: 215 nm	ACN:water = 55:45 pH 3.6 Flow rate: 1 mL/min Injection volume: 20 µL	LOD: 0.0280 µg/mL LOQ: 0.0849 µg/mL Rec: (98.42–99.34)%	[65]
Valsartan, amlodipine besylate	Tablet	ACN:phosphate buffer (50:50, v/v)	Column: Zorbax ODS (250 mm × 4.6 mm, 5 µm) Temperature: room Detector: 210 nm	ACN:phosphate buffer (50:50, v/v) Flow rate: 1.0 mL/min Injection volume: n/a	LOD: 0.36 µg/mL LOQ: 1.28 µg/mL Rec: 100.48%	[66]
Valsartan	Capsule	0.1 M phosphate buffer:ACN (20:80, v/v)	Column: Venusil XBP C18 (250 mm × 4.6 mm, 5 µm) Temperature: ambient Detector: 273 nm	0.1 M Phosphate buffer:ACN (20:80, v/v) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 0.5 µg/mL LOQ: 1.5 µg/mL Rec: 100.57–100.80%	[67]
Valsartan	Tablet	Water:ACN (50:50, v/v)	Column: Thermo-Hypersil ODS (150 mm × 4.6 mm; 5 µm) Temperature: 25 °C Detector: 273 nm	Water:ACN:glacial acetic acid (500:500:01, v/v/v) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 2.72 µg/mL LOQ: 8.25 µg/mL Rec: (99.0–100.4)%	[68]

Drug	Dosage form	Diluent	Chromatographic conditions	Mobile phase	Validation	Ref.
Valsartan, nebivolol HCl	Capsule	ACN:water (1:1, v/v)	Column: Phenomenex RP C18 (250 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 275 nm	Ammonium acetate 50 mM, pH 3.5:ACN (30:70, v/v) Flow rate: 0.8 mL/min Injection volume: 50 μL	LOD: 0.032 μg/mL LOQ: 0.095 μg/mL Rec: 99.58%	[51]
Valsartan, hydrochlorothiazide	Tablet	MeOH	Column: Phenomenex Luna C18 (150 mm × 4.6 mm; 5 μm) Temperature: $(20 \pm 1)\,^\circ$C Detector: 250 nm	ACN:MeOH:PO$_4$ buffer 50 mM pH (3 ± 0.1) (20:50:30, v/v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.2077 μg/mL LOQ: 0.6294 μg/mL Rec: (100.73–102.22)%	[69]
Valsartan, atorvastatin	Tablet	Diluent 1: ACN: MeOH (50:50, v/v) Diluent 2: Water: MeOH (50:50, v/v)	Column: Hypersil BDS C18 (250 mm × 4.6 mm, 5 μm) Temperature: 40 °C Detector: 225 nm	0.1% Acetic acid:ACN (50:50, v/v) Flow rate: 2.0 mL/min Injection volume: 10 μL	LOD: n/a LOQ: n/a Rec: 99.2%	[70]
Valsartan	Pure, tablet	Phosphate buffer pH 3:ACN (50:50, v/v)	Column: Xterra C18 (100 mm × 4.6 mm, 5 μm) Temperature: ambient Detector: 210 nm	Phosphate buffer pH 3:ACN (50:50, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.012 μg/mL LOQ: 0.040 μg/mL Rec: 100.2%	[71]
Valsartan	Tablet	MeOH	Column: C18 (250 mm × 4.6 mm; 5 μm) Temperature: n/a Detector: 265 nm	Ammonium dihydrogen phosphate:MeOH (33.5:66.5, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 6 ng/mL LOQ: 18 ng/mL Rec: (99.4–100.6)%	[72]
Valsartan, amlodipine	Tablet	MeOH	Column: Microbondapak C18 (250 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 210 nm	MeOH:potassium dihydrogen phosphate 0.1 M, pH 3.0 (65:35, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.02 μg/mL LOQ: 0.06 μg/mL Rec: (98.95–99.76)%	[73]

Table 6 Summary of HPLC Analysis of Valsartan—cont'd

Analyte (s)	Sample	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	LOD, LOQ, Recovery (Rec) Valsartan	Ref.
Valsartan	Capsule	Ammonium dihydrogen orthophosphate pH 3.5:MeOH (50:50, v/v)	Column: Inertsil C18 (250 mm × 4.6 mm, 5 μm) Temperature: room temp Detector: 210 nm	Ammonium dihydrogen orthophosphate pH 3.5: MeOH (50:50, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.056 μg/mL LOQ: 0.156 μg/mL Rec: (100.01–100.04)%	[74]
Valsartan, hydrochlorothiazide	Tablet	MeOH and mobile phase	Column: C18 Inertsil (250 mm × 4.6 mm; 10 μm) Temperature: room Detector: 259 nm	0.02 M potassium dihydrogen orthophosphate:MeOH: triethylamine (25:75:0.2, v/v/v, pH 6.0) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 16 μg/mL LOQ: 48 μg/mL Rec: (99.39–100.05)%	[75]
Valsartan	Tablet	Phosphate buffer: ACN = 55:45	Column: Kromasil C18 (250 mm × 4.6 mm, 5 μm) Temperature: ambient Detector: 233 nm	Phosphate buffer:ACN (55:45, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.034 μg/mL LOQ: 0.104 μg/mL Rec: 99.97%	[76]
Valsartan, aliskiren hemifumarate	Tablet	ACN:0.05 M potassium dihydrogen PO$_4$ buffer pH 3.5 (45:55, v./v)	Column: Hyperchrom ODS BP (200 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 224 nm	ACN:0.05 M Potassium dihydrogen PO$_4$ buffer pH 3.5 (45:55, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.93 μg/mL LOQ: 2.84 μg/mL Rec: (99.32–99.92)%	[77]
Valsartan, ramipril	Capsule	MeOH	Column: RP 18 (250 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 225 nm	Phosphate buffer 1%:ACN (40:60, v/v, pH 3.2) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 1 μg/mL LOQ: 3 μg/mL Rec: (97.67–100.23)%	[78]

Valsartan, irbesartan, losartan potassium, telmisartan	Tablet	MeOH	Column: ACE RP–C18 (250 mm × 4.6 mm, 5 μm) Temperature: 40 °C Detector: 220 nm	Potassium dihydrogen phosphate 0.025 M, pH 6.0 (65:35, v/v) Flow rate: 1.5 mL/min Injection volume: 50 μL	LOD: 0.13 μg/mL LOQ: 0.4 μg/mL Rec: (99.87–101.35)%	[79]
Valsartan, amlodipine, hydrochlorothiazide	Tablet	ACN:phosphate buffer (0.05 M) pH 2.3 (40:60, v/v)	Column: Phenomenex Kinetex (150 mm × 4.6 mm, 5 μm) Temperature: (22–25) °C Detector: 227 nm	ACN:phosphate buffer (0.05 M) pH 2.8 (40:60, v/v) Flow rate: 0.8 mL/min Injection volume: 20 μL	LOD: 1.42 μg/mL LOQ: 4.31 μg/mL Rec: (98.9–101.0)%	[80]
Valsartan	Tablet	MeOH	Column: Phenomenex Luna C18 (250 mm × 4.6 mm; 5 μm) Temperature: n/a Detector: 210 nm	MeOH:PO_4 buffer pH 3.0 (65:35, v/v) Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: 0.02 μg/mL LOQ: 0.06 μg/mL Rec: (98.79–99.81)%	[81]
Valsartan	Tablet	MeOH	Column: Kromasil C18 (250 mm × 4.6 mm, 5 μm) Temperature: n/a Detector: 250 nm	Gradient condition of ACN and PO_4 buffer pH 3.5 Flow rate: 1.0 mL/min Injection volume: 20 μL	LOD: n/a LOQ: n/a Rec: (99.27–99.92)%	[82]
Valsartan, hydrochlorothiazide	Tablet	ACN:water (1:1, v/v)	Column: Xterra (250 mm × 4.6 mm, 5 μm) Temperature: room Detector: 265 nm	Ammonium acetate 0.20 M, pH 5.6:ACN (gradient elution) Flow rate: 1.5 mL/min Injection volume: 20 μL	LOD: 0.0375 μg/mL LOQ: 0.064 μg/mL Rec: (100.1–102.3)%	[83]
Valsartan	Tablet	Water:ACN (1:1, v/v)	Column: Phenomenex C18 (250 mm × 4.6 mm; 5 μm) Temperature: ambient Detector: 240 nm	ACN:5 mM ammonium acetate pH 4.5 (75:25, v/v) Flow rate: 1.0 mL/min Injection volume: 50 μL	LOD: 10 ng/mL LOQ: 28 ng/mL Rec: (99.85 ± 1.03)%	[84]

Table 6 Summary of HPLC Analysis of Valsartan—cont'd

Analyte (s)	Sample	Solvent	Column and Condition	Mobile Phase, Flow Rate, Injection Volume	LOD, LOQ, Recovery (Rec) Valsartan	Ref.
Valsartan, amlodipine besylate	Capsule	MeOH	Column: Waters Symmetry C18 (150 mm × 4.6 mm; 5 µm) Temperature: 25 °C Detector: 238 nm	MeOH:KH_2PO_4 buffer 0.01 M, pH 2.5 (60:40, v/v) Flow rate: 1.0 mL/min	LOD: 44 ng/mL LOQ: 300 ng/mL Rec: (98.97–99.97)%	[85]
Valsartan, hydrochlorothiazide	Tablet	0.02 M Phosphate buffer:ACN: MeOH = 50:40:10	Column: Supelcosil C18 (150 mm × 4.6 mm; 5 µm) Temperature: ~25 °C Detector: 225 nm	0.02 M Phosphate buffer pH 2.9:ACN:MeOH (50:40:10, v/v/v) Flow rate: 1.4 mL/min Injection volume: 50 µL	LOD: n/a LOQ: n/a Rec: 99.94%	[86]
Valsartan	Tablet	KH_2PO_4 buffer: ACN (pH 3.0±0.1, 55:45, v/v)	Column: Xterra C18 (150 mm × 4.6 mm; 5 µm) Temperature: 23±1 °C Detector: 286 nm	KH_2PO_4 buffer:ACN (pH 3.0±0.1, 55:45, v/v) Flow rate: 0.7 mL/min Injection volume: 20 µL	LOD: 0.0180 µg/mL LOQ: 0.1016 µg/mL Rec: (99.40–99.68)%	[87]
Valsartan, ramipril	Capsule	n/a	Column: Hypersil C18 (150 mm × 4.6 mm, 5 µm) Temperature: n/a Detector: 220 nm	20 mM Phosphate buffer: ACN (35:65, v/v) Flow rate: 0.8 mL/min Injection volume: 20 µL	LOD: n/a LOQ: n/a Rec: (98.4–99.6)%	[88]
Valsartan, amlodipine besilate, olmesartan medoxomil, hydrochlorothiazide	Tablet	MeOH diluted with ACN MeOH water (7:13:80, v/v/v)	Column: CN (200 mm × 4.6 mm, 5 µm) Temperature: 30 °C Detector: 235 nm	ACN:MeOH:10 mM phosphoric acid (pH 2.5, 7:13:80, v/v/v) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 0.1 µg/mL LOQ: 0.3 µg/mL Rec: 95.8%	[89]

Valsartan, amlodipine hydrochlorothiazide	Tablet	MeOH	Column: Zorbax SB-C8 (250 mm × 4.6 mm; 5 µm) Temperature: 25 °C Detector: 225 nm	0.025 M phosphoric acid: ACN (gradient) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 0.24 µg/mL LOQ: 0.80 µg/mL Rec: 100.65 ± 1.23%	[90]
Valsartan, amlodipine besylate, hydrochlorothiazide	Tablet	MeOH	Column: Kromasil KR-5 C18 (250 mm × 4.6 mm; 5 µm) Temperature: n/a Detector: 232 nm	50 mM KH_2PO_4 pH 3.7: ACN (56:44, v/v) Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 1.1 µg/mL LOQ: 3.3 µg/mL Rec: 99.69 ± 0.63% to 100.20 ± 0.07%	[91]
Valsartan, propranolol hydrochloride	Raw material, gel formulation	ACN: MeOH:0.01 M Na_2PO_4 pH 3.5 = 50:35:15	Column: Hypersil ODS C18 (250 mm × 4.6 mm, 5 µm) Temperature: 25 ± 0.2 °C Detector: 250 nm	ACN:MeOH:0.01 M Na_2HPO_4 pH 3.5 = 50:35:15 Flow rate: 1.0 mL/min Injection volume: 20 µL	LOD: 0.45 µg/mL LOQ: 1.39 µg/mL Rec: (99.79–102.93)%	[92]

Table 7 Summary of TLC Analysis of Valsartan

Analyte(s)	Sample	Stationary Phase	Mobile Phase, Solvent	Detection	LOD, LOQ, Recovery, Precision (Valsartan)	Ref.
Valsartan, amlodipine	Bulk drug, tablet	Silica gel F254	Mobile phase: toluene: MeOH:acetic acid (7:3:0.1, v/v/v) Solvent: MeOH	UV 244 nm	LOD: 50 ng/spot LOQ: 100 ng/spot Recovery: $(98.72 \pm 0.5)\%$ RSD precision: Intraday: (0.14–0.39)% Interday: (0.19–0.52)%	[93]
Valsartan, ramipril	Capsules	Silica gel F254	Mobile phase: ethyl acetate: chloroform:glacial acetic acid (8:2:0.2, v/v/v) Solvent: MeOH	UV 220 nm	LOD: 42.4 ng/spot LOQ: 1400.8 ng/spot Recovery: (98.92–101.22)% RSD precision: Intraday: 0.037% Interday: 0.046%	[94]
Valsartan, telmisartan	Tablets	Silica gel F254	Mobile phase:1,4-dioxane: hexane:formic acid 99% (5:5:0.1, v/v/v) Solvent: MeOH	Video scanning	LOD: n/a LOQ: n/a Recovery: (99.62–101.59)% Intermediate precision (RSD): 5.14%	[95]
Valsartan, ramipril	Capsule	Silica gel $60F_{254}$	Mobile phase: chloroform: ethyl acetate:methanol: glacial acetic acid (5:5:1:0.2, v/v/v/v) Solvent: n/a	UV 210 nm	LOD: 100 ng/spot LOQ: 330 ng/spot Recovery: 99.099.7% RSD precision: Intraday: 0.136–0.277% Interday: 0.172–0.259%	[96]

			Mobile phase	Detection	Validation parameters	Ref.
Valsartan, hydrochlorothiazide	Tablet	Silica gel 60F$_{254}$	Mobile phase: CHCl$_3$: MeOH:NH$_4$OH (8:2:1, v/v/v) Solvent: MeOH	UV 225 nm	Recovery: 99.94% RSD precision: Intraday: 1.22% Interday: 1.59%	[86]
Valsartan, telmisartan, potassium losartan	Tablet	Silica gel 60F$_{254}$	Mobile phase: CHCl$_3$: MeOH:acetone:toluene: acetic acid (7.5:1.5:5:5:0.01:0.003, v/v/v/v/v) Solvent: mobile phase	UV 254 nm	Recovery: 98.74–101.1% Precision (RSD): 0.85%	[97]
Valsartan	Bulk drug, formulation	Silica gel 60F$_{254}$	Mobile phase: toluene: ethyl acetate:MeOH: formic acid (60:20:20:1, v/v/v/v) Solvent: MeOH	UV 250 nm	LOD: 25 ng/band LOQ: 150 ng/band Recovery: 99.30–101.09% RSD precision: Intraday: 0.76–1.52% Interday: 0.40–1.35%	[98]
Valsartan, hydrochlorothiazide	Tablets	Silica gel 60F$_{254}$	CHCl$_3$:MeOH:acetone: toluene:acetic acid (6:2:1:0.1, v/v/v/v) Solvent: MeOH	UV 260 nm	LOD: 100 ng/spot LOQ: 300 ng/spot Precision: 0.27–1.19%	[99]

Table 7 Summary of TLC Analysis of Valsartan—cont'd

Analyte(s)	Sample	Stationary Phase	Mobile Phase, Solvent	Detection	LOD, LOQ, Recovery, Precision (Valsartan)	Ref.
Valsartan, losartan, irbesartan, candesartan, eprosartan mesylate, telmisartan	Tablets	HPTLC F_{254}	CH_2Cl_2:EtOA:EtOH: Glacial acetic acid:H_2O (45:40:5:1:0.5, v/v/v/v/v) Solvent: n/a	UV 260 nm	LOD: 0.02 μg/spot LOQ: 0.5 μg/spot Recovery: 98–102% Precision: n/a	[100]
		RP-Diphenyl-F	ACN:MeOH:0.1 M ammonium acetate:25% ammonia (30:20:50:0.5, v/v/v/v) Solvent: n/a			
Valsartan, nebivolol HCl	Dosage form	Silica gel	EtOA:MeOH:25% ammonia (12:2:1, v/v/v) Solvent: n/a	UV 280 nm	LOD: n/a LOQ: n/a Recovery: n/a Precision: n/a	[101]
Valsartan, hydrochlorothiazide, amlodipine besylate	Tablets	Silica gel	EtOA:MeOH:10% ammonia (17:4:2, v/v/v) Solvent: n/a	UV 320 nm	LOD: 3200 ng/zone LOQ: 6400 ng/zone Recovery: (98–101)% Precision (RSD): Intraday and interday: <0.8%	[101]

8. ANALYSIS OF VALSARTAN IN BIOLOGICAL FLUIDS AND HERBAL PREPARATION

HPLC is the most common method used in the analysis of valsartan and related compounds, biological fluids, and samples. In this technique, an RP-18 column is normally fitted, and detection was performed by various methods including UV, fluorescent, and MS (SIM and MRM (multiple reaction monitoring)).

Maurer and coworkers [42] reported the analysis of the methylation product of valsartan and other drugs in human urine by using GC-EIMS. The GC conditions used were splitless injection, column 12 mm × 0.2 mm i.d. HP column, injection temperature of 280 °C, column temperature of 100–310 °C at 30 °C/min, carrier gas He 1 mL/min, EI mode (70 eV, source 220 °C, interface 260 °C).

Valsartan is metabolized by CYP-450 isoenzyme into valeryl-4-hydroxy-valsartan in human. This metabolite has 200-fold lower affinities to the AT1 receptor than valsartan. The renal clearance of valsartan has reported only 30% of the total plasma clearance. The recovery of valsartan are 83% in feces and 13% in urine from oral solution administration of valsartan [2,3,104].

In the quantitative analysis of valsartan in a complex matrix, it is recommended to use an LC–MS technique with MRM due to its low LOQ and specificity. In this method, two daughter ions should be selected: one ion for qualification and the other for quantification purposes. The intensity ratio of qualifier and quantification ions must be compared between standard and samples. The qualifier and quantification ions as described by Ref. [105] in MS–MS Agilent (precursor ion m/z 436.2; ESI positive mode; fragmentation voltage: 98 V; collision energy: 14 eV; dwell time: 20 ms) for valsartan are m/z 235 and 291.1, respectively.

The HPLC methods that applied for analysis of valsartan and related compounds in biological fluids and samples are summarized in Table 8.

Kesting and coworkers [11] investigated the presence of adulterant in the Chinese herbal medicines which were used for the treatment of hypertension. The identification of adulterant was conducted by using LC–HRMS and LC–MS–SPE–NMR. The results showed the presence of valsartan, amlodipine, indapamide, and other drugs used for antihypertension as the commercial soft capsules of herbal drug preparations [11].

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
Valsartan, hydrochlorothiazide	Column: Zorbax SB-Aq C-18 (150 mm × 4.6 mm; 5 µm) Mobile phase: ACN:10 mM ammonium acetate (60:40, v/v; pH 4.5) Flow rate: 1.2 mL/min Column temperature: 35 °C Detection: MRM (negative ion mode): valsartan (m/z, quantification: 434.2 → 350.2; identification: 434.2 → 179.1) HCT (m/z quantification: 295.9 → 268.9; identification: 295.9 → 204.9) Probenecid: (m/z 283.9 → 239.9)	Human plasma	Probenecid	Standard solutions: Stock solutions of valsartan (4 mg/mL), HCT (1 mg/mL), and probenecid (5 mg/mL) were prepared by dissolving in ACN:water (80:20, v/v); working solution IS (150 ng/mL) Samples: 100 µL IS + 100 µL plasma sample + 300 µL ACN vortex-mixed 1 min, then centrifuged 10 min (10,000 × g), upper layer collected; 15 µL aliquot was injected into LC–MS/MS	Accuracy: ±7.85% Precision: Intraday: (1.92–4.81)%; Interday: (2.21–7.12)% LOD: n/a LOQ: 4 ng/mL	[106]
Valsartan	SPE column (20 mm × 2.1 mm) packed with OASIS MAX 30 µm; SPE was connected 10-port switching valve Samples (40 µL) was flushed from sample loop at 2 mL/min using water:acetic acid (85:15), after loading in SPE, and then SPE was washed with water and THF for 0.5 min. Elution was performed using THF:water:formic acid (95:5:5, v/v/v)	Human plasma and urine	Candesartan	Standard solutions: Stock solutions, valsartan (4 mg/mL) and candesartan (1 mg/mL), were dissolved in MeOH with 0.5% NH₄OH. Calibration and QC samples were prepared by spiking matrices with standard solutions Samples: Samples were centrifuged 5 min (2400 × g); 50 µL sample then deposited in 96-well polypropylene plate; after	Accuracy: Plasma: (101–108)% Urine: (41.7–46.4)% Precision: Intraday: Plasma: (2.0–8.5)% Urine: (0.6–9.3)% Interday: Plasma: (2.1–16.9)% Urine: (2.7–5.0)% LOD: n/a LOQ: n/a	[107]

| | | | | addition of 50 μL acetic acid (15%, v/v) and 10 μL IS solutions, the plates were sealed and vortexed at 1000 rpm (10 s), and kept 4 °C until injection | | |

Analyte	Conditions	Matrix	IS	Sample preparation	Validation	Ref.
	Detection: MRM (positive ion mode): valsartan: (m/z 436.2 → 291.2.1) Candesartan: (m/z: 441.2 → 263.2)			addition of 50 μL acetic acid (15%, v/v) and 10 μL IS solutions, the plates were sealed and vortexed at 1000 rpm (10 s), and kept 4 °C until injection		
Valsartan	Column: Phenomenex C18 (10 mm × 4.6 mm; 5 μm) equipped with guard column NovaPak C8 Column temperature: ambient Mobile phase: phosphate buffer pH 2.8:ACN (70:30, v/v) Flow rate: 1.3 mL/min Detection: fluorescent Excitation: 265 nm Emission: 378 nm	Human plasma	Losartan	Standard solutions: Stock solutions of valsartan (50 μg/mL) were prepared by dissolving in 0.1 M KOH and pH was adjusted to 8 with 1 M HCl. IS was prepared with same method (2 μg/mL) Samples: – 1 mL Human plasma + 100 μL IS, acidified with 125 μL phosphoric acid to pH 2.5, add 10 mL methyl-tert-butyl ether (MTBE) then vortex-mixed and centrifuged (1800 × g for 5 min) – Organic layer was transferred to tube containing 200 μL 0.05 M NaOH and then the mixture was vortexed and centrifuged (1800 × g for 5 min) – Organic layer was discarded, aqueous layer neutralized with 75 μL 0.2 M phosphoric acid, 125 μL was injected into HPLC	Accuracy and precision: Intraday: (91.8–100.6)% RSD: (0.7–10.8%) Interday: (88.3–100.6)% RSD: (0.8–8.9%) LOD: n/a LOQ: 10 ng/mL	[108]

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
Valsartan, losartan, irbesartan, candesartan cilexetil, and candesartan M1	Column: µBondapak C18 (300 mm × 3.9 mm; 10 µm) +guard column Novapak C18 (20 mm × 3.9 mm; 4 µm) Mobile phase: gradient elution 5 mM acetate buffer pH 4 and ACN Column temperature: room Detection: Fluorescence detector Excitation: 250 nm Emission: 375 nm	Human plasma	Bumetanide	Standard solutions: Stock solutions were prepared in MeOH and ACN Samples: – 0.25 mL plasma was spiked with appropriate amount of stock solutions and IS, then acidified with 0.25 mL 1 M H_3PO_4 and the mixture was then shaken and centrifuged 5 min ($10,000 \times g$ at 4 °C) – Clean up was performed using Bond Elut C8 that was conditioned with 2 mL MeOH followed by 1 mL 0.1 M phosphate buffer pH 2 – Samples was slowly passed into the cartridge (0.5 mL) – Column was washed with 0.5 mL MeOH–1 M phosphate buffer pH 2 (50:50, v/v) and dried. – Analyte then eluted with 0.5 mL MeOH – 0.1 mL ethylene glycol 10% (v/v) was added	Accuracy and precision: Intraday: Relative errors: −2.6% to +3.7% RSD: 3.4–5.4% Interday: Relative error: −4.6% to +6.7% RSD: 5.0–8.0% LOD: n/a LOQ: 51.5 ng/mL	[32]

				− The eluate was vortexed and dried under N_2 at 40 °C − The residue was dissolved in starting mobile phase (0.25 mL) − 20 μL solution was injected to the HPLC system	
Valsartan, amlodipine	Column: HICHROM Nucleosil 100-5 C18 (250 nm × 4.6 mm) Temperature: room Mobile phase: phosphate buffer (0.01 M, pH 3.6):ACN: MeOH (50:40:10, v/v/v) Flow rate: 1.0 mL/min Detection: UV 240 nm	Rat liver perfusate	n/a	Standard solutions: Standard solutions were prepared in MeOH (100 μg/mL) Samples: Spiked samples were prepared by adding 50 μL standard solutions into blank liver perfusate (100 μL) and then making up into 1000 μL by mobile phase, after filtering (0.45 μm) then injected into HPLC	Accuracy and precision [109] Intraday: Bias: −1.03% to +12.67%; RSD: 2.20–4.19% Interday: Bias: +0.89% to +12.33%; RSD: 2.93–4.74% LOD: 0.02 μg/mL LOQ: 0.05 μg/mL
Valsartan	Column: Nucleosil C18 (50 mm × 4 mm) + guard column Phenomenex (4 mm × 3 mm) Mobile phase: ACN:15 mM $KH_2(PO_4)_3$ pH 2.0 (45:55, v/v) Flow rate: 1 mL/min Column temperature: 40 °C Detection: fluorescence Excitation: 234 nm Emission: 374 nm	Human plasma	n/a	Standard solutions: Stock solutions were prepared by dissolving standard (20 mg) in 25 mL MeOH; calibration, and QC samples were prepared by spiking standard solutions into drug-free plasma Samples: 0.2 mL plasma + 1 mL MeOH then vortex-mixed 30 s (2000 rpm) and then centrifuged 3 min (2500 × g); 5 μL supernatant injected into HPLC system	Intraday: [110] Bias: +1.8% to +7.2%; RSD: 1.1–3.0% Interday: Bias: −0.8% to +1.4%; RSD: 1.3–4.9% LOD: 25 pg/mL LOQ: 97.9 ng/mL

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
Valsartan	Column: Chromolith RP-18e (100 mm × 4.6 mm) Mobile phase: 0.01 M Na_2HPO_4 buffer:ACN (60:40, v/v, adjusted to pH 3.5) Flow rate: 2 mL/min Column temperature: n/a Detection: fluorescence Excitation: 230 nm Emission: 295 nm	Human plasma	Atorvastatin	Standard solutions: Stock solutions (2 mg/mL) were prepared in MeOH Samples: 450 µL plasma + 50 µL IS (12 µg/mL) + 500 µL ACN then mixed and centrifuged for 10 min (8000 rpm); 20 µL was injected into HPLC	Recovery (average): 96.3 ± 1.3% Precision (%CV) Intraday: 2.6–4.3% Interday: 3.0–5.2% LOD: n/a LOQ: 20 ng/mL	[111]
Valsartan, losartan, telmisartan	Column: Chromolith RP-18e monolithic (25 mm × 4.6 mm) Mobile phase: 5 mM phosphate buffer pH 3.8:ACN:MeOH (65:20:15, v/v/v) Flow rate: 3.0 mL/min Temperature: room Detection: fluorescent Excitation: 259 nm Emission: 399 nm	Human urine	n/a	Standard solutions: Individual stock solution (1000 µg/mL) were prepared in MeOH Samples: -- 1 mL sample were transferred into 16 mm × 125-mm disposable glass tubes and 3 mL of extraction solvent 1 (2% MeOH in 5 mM phosphate buffer pH 3.8) and then vortexed and centrifuged 10 min (2500 × g) — 2 mL of supernatant was transferred into glass screw-cap vials, then processed by using SPE (LiChrocart 25-4 LiChrospher RP-18 ADS (25 mm × 4 mm; 25 µm)), and extracted using solvent 1	Recovery: (92.9–102 5)% Precision (CV) Intraday: <3.5% Interday: <3.5% LOD: 0.001 µg/mL LLOQ: 0.003 µg/mL	[112]

Valsartan, hydrochlorothiazide	Column: Betabasic C8 (50 mm × 4.6 mm; 5 μm) Mobile phase: ACN:MeOH:0.001% aqueous ammonia (75:15:10, v/v/v) Flow rate: 0.5 mL/min Column temperature: 50 °C MRM: Valsartan: (negative ion mode: m/z 434.25 → 179.22) HCT: m/z 295.85 → 204.86 Clonazepam: m/z: 314.0 → 278.27	Human plasma	Clonazepam	Standard solutions: Stock solutions (5 mg/mL) and IS (1 mg/mL) were prepared in MeOH:water (50:50, v/v). This stock solution can be used for spiking in plasma Samples: — 500 μL plasma + 25 μL IS + 500 μL orthophosphoric acid 2% in 1.7-mL microtube then vortexed — The mixture then applied to HLB cartridge (30 mg, 1 cm^3) previously conditioned with 1 mL MeOH and 2 mL water — The loaded cartridge was washed with 2 mL water, then 1 mL 5% MeOH in water, then eluted with 1.0 mL MeOH:ACN (90:10, v/v), and loaded into autosampler vial	Mean recovery: 90.28% CV: 0.12% Precision: Intraday: <10.0% Interday: <10.0% LOD: n/a LLOQ: 50.0 ng/mL	[41]
Valsartan	Column: Zorbax SB-C18 (50 mm × 4.6 mm; 3.5 μm) Mobile phase: ammonium formate 8 mM, pH 3:MeOH (30:70, v/v) Flow rate: 1 mL/min Temperature: room Detection: MS/MS (no detailed data reported)	Human blood	Valsartan-d_9	Standards: not reported Samples: — Plasma samples were vortexed (3000 rpm) and centrifuged (1900 × g, 5 min, 4 °C); — 100 μL aliquot + 600 μL solution of IS in MeOH were vortexed (3000 rpm)	Accuracy: 98.66% Precision: 3.51% LLOQ: 20.18 ng/mL	[113]

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
				and then centrifuged $(1900 \times g g, 10$ min, 4 °C). – 400 µL supernatant was evaporated into dryness with N_2 – Residue was reconstituted in 200 µL in mobile phase and measured with LC–MS/MS		
Valsartan, nebivolol	Column: Gemini–C18 (50 mm × 2.0 mm; 3 µm) Guard column C18 (4 mm × 3 mm) Mobile phase: ACN:0.05 mM formic acid buffer (50:50, v/v, pH 3.5) Flow rate: 0.25 mL/min Column temperature: 20 °C	Human plasma	Tamsulosin	Standard solutions: Analytes and IS were prepared individually in ACN (100.0 µg/mL). The stocks were diluted with water to give serial of standard solutions; QC samples were prepared by spiking standards into plasma	Accuracy: 101.1–103.7% Precision: Intrarun (RSD): 1.6–2.5% Interrun (RSD): 2.9–4.8% LOD: n/a LLOQ: 1.0 ng/mL	[114]
	Detection: Valsartan (negative ion mode) m/z: 434.2 → 179.0 nebivolol (positive ion mode) m/z: 406.1 → 150.9 IS (positive ion mode) m/z 409.4 → 228.1			Samples: 200 µL plasma + 400 µL ACN contained IS (240 ng/mL), then vortexed (1 min) and centrifuged (14,000 rpm; 10 min); aliquots were filtered through 0.2 µm and injected into LC–MS–MS system		

| Valsartan, valeryl-4-hydroxy-valsartan | Column: Waters Atlantis dC18 (100 mm × 3.9 mm; 3.9 μm) Guard column: μBondapak C18 (10 μm) Mobile phase: gradient elution using 0.025% TFA in ACN and 0.025% TFA in buffer phosphate buffer (5 mM, pH 2.5) Flow rate: 1.3 mL/min Temperature: 40 ± 0.2 °C Detection: fluorescence Excitation: 234 nm Excitation: 378 nm | Human plasma | Candesartan M1 | Standard solutions: Stock solutions valsartan, metabolite, and IS were prepared in MeOH with concentrations 107, 186, and 99.26 μg/mL, respectively. Working solutions prepared by diluting the stock solution Samples:

− 1 mL blank samples were spiked with valsartan, metabolite, and IS to achieve concentrations 1.1 μg/mL (analytes) and 1.2 μg/mL (IS) and then 1 mL of H_3PO_4 (0.5 M) was added, vortexed, and centrifuged (5 min, 10,000 rpm)
− The mixtures were applied to a C8 SPE (conditioned with 2 mL MeOH and 1 mL phosphate buffer pH 2, 60 mM)
− SPE was washed by 1 mL MeOH:phosphate buffer (40:60, v/v)
− After drying for 8 min, SPE was eluted using solution of | Recovery: Valsartan: (96.6–101.2)% (RSD: 1.2–3.1%) Metabolite: 94.6–108.8% (RSD: 0.7–1.6%) LOD: n/a LLOQ: 5 ng/mL (valsartan and metabolites) |

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
				10% ethylene glycol in MeOH (0.1 mL) – The compounds were eluted using 0.5 mL diethylether. – Evaporated with N_2 stream at 60 °C – Residue + 100 µL mobile phase was reconstituted, vortexed, mixed, and filtered with polypropylene membrane $\varnothing = 13$ mm, 0.45 µm – 20 µL was injected into HPLC system		
Valsartan, valeryl-4-hydroxy-valsartan	Same with Iriarte 2006	Human plasma	Candesartan M1	Same with Iriarte 2006 (except the nominal concentrations were different). This work reported the application of Iriarte 2006 for bioavailability studies	LOQ for both of analytes was 5 ng/mL Accuracy and precision of analytes: <15%	[115]
Valsartan, amlodipine, hydrochlorothiazide	Column: Gemini C18 (250 mm × 4.6 mm; 5 µm), protected with guard column C18 (4 mm × 2 mm) Column temperature: 35 °C Mobile phase: ACN:10 mM ammonium formate pH 3.5, v/v (gradient from 20:80 to 70:30)	Human plasma	Telmisartan	Standard solutions: Stock solutions (100 µg/mL) of the analytes were prepared in MeOH Samples: Plasma samples + 1 mL mixture of MeOH:ACN (50:50, v/v) + 15 µL IS solution, vortexed (3 min) and centrifuged 10,000 rpm (10 min),	Recovery: 76.5 ± 2.1%; Precision: Intraday: 101.1–101.8%; Interday: 101.7–107.0% LOD: 7 ng/mL LOQ: 20 ng/mL	[116]

	Flow rate: 1 mL/min Detector: PDA (254 nm)			supernatant filtered, and evaporated with N_2 Dried residue + 0.5 mL mobile phase reconstituted, filtered, and then injected into HPLC		
Valsartan	Column: Hypersyl BDS C18 (250 mm × 4.6 mm; 5 μm) Mobile phase: buffer triethylamine pH 3.0:ACN (45:55, v/v) Flow rate: 0.7 mL/min Column temperature: 25 °C Detection: UV 215 nm	Human plasma	Losartan potassium	Standard solutions: not reported Samples: 0.2 mL plasma was transfered into 2-mL centrifuge tube + 25 μL IS (1 mg/mL), vortexed 30 s (2000 rpm) + 1 mL MeOH, vortexed for 10 min (2000 rpm), then centrifuged 10 min (2500 rpm), and 20 μL supernatant injected into HPLC	Accuracy: n/a Precision: n/a LOD: n/a LOQ: n/a	[117]
Valsartan, gliclazide, benazepril	Column: Shimadzu VP-ODS C18 (250 mm × 2.0 mm, 5 μm) Temperature: 40 °C Mobile phase: gradient elution of MeOH and 0.05% formic acid Flow rate: 0.2 mL/min Column temperature: n/a Detection: SRM: Valsartan (m/z 436 → 207) Gliclazide (m/z 324 → 110) Benazepril (m/z 425 → 351) IS (m/z 531 → 489)	Human plasma	Ketoconazole	Standard solutions: Stock solutions were prepared in MeOH (valsartan 500 μg/mL; gliclazide and benazepril 50 μg/mL); calibration and QC samples were prepared by spiking into human blank samples Samples: 100 μL + 10 μL IS (125 μg/mL) + 500 μL MeOH, then vortexed and centrifuged for 10 min (40,000 × g), supernatant transferred into another clean test tube, centrifuged again for 10 min (40,000 rpm), 10 μL clear supernatant was injected into LC–MS	Recovery: (93.52–99.94)% Precision: Intraday: 6.2% Bias: 0.1% Interday: 10.4% Bias: 9.0% LOD: n/a LOQ: 20 ng/mL	[38]

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
Valsartan, verapamil, losartan, telmisartan, irbesartan, flecainide, beta blocker drugs	Column: Atlantis dC18 (150 nm × 2.1 mm; 3 μm) Mobile phase: gradient elution. Solvent A: 10 mM ammonium formate pH 3.1; B: ACN linear gradient from 90% A and 10% B to 10% A ad 90% B in 10 min, then held 3 min Column temperature: 25 ± 0.8 °C Flow rate: 0.3 mL/min Detection: SIM (m/z): Valsartan (207.3); telmisartan (276.3); losartan (207.3); irbesartan (207.3)	Post mortem whole blood	Diazepam-d5	Standard solutions: Two stock solutions were prepared in MeOH (2500 μM); aqueous calibration solutions and aqueous control solutions were prepared from stock solutions; IS was dissolved in ACN (155 μM) and water (18.5 μM). Spiked calibration and QC samples were prepared by adding aqueous solutions into drug-free sodium fluoride whole blood Samples: 0.5 mL whole blood + 50 μL (18.5 μM IS), then this mixture was precipitated with 1 mL ice cold mixture of ACN:MeOH (85:15, v/v), then frozen for 30 min (−20 °C), and centrifuged (2260 × g, 4 °C, 10 min). Supernatant was decanted and mixed with 0.2 mL 4.5 M HCl before diluting with water, and the samples were applied to SPE (Oasis MCX)	Accuracy: n/a Precision: intraday Bias: −7.3%, and −22%; RSD: 21% and 4% for theoretical concentration 5 and 1 μM, respectively Interday: Bias: −20%, and −21%; RSD: 13% and 28% for theoretical concentration 5 and 1 μM LOD: n/a LOQ: n/a	[118]

Valsartan	Column: XTerra MS (50 mm × 2.1 mm; 3.5 μm), guard column: Opti guard-mini C18 (15 mm × 1 mm) Mobile phase: 0.1% trifluoroacetic acid:MeOH:ACN (45:30:25, v/v/v) Flow rate: 0.2 mL/min Column temperature: 50 °C Detection: SRM (positive ion mode): Valsartan: m/z 436.2 and 291.2 IS: m/z 429.2 and 401.2	Human plasma	CGP48791	Standard solutions: Stock solutions were prepared in MeOH; Calibration standards and QC samples were prepared by spiking into heparinized human plasma Samples: Mixture of 500 μL plasma + 50 μL IS solution (500 ng/mL in MeOH:H_2O (50:50, v/v) + 250 μL 2% trifluoroacetic acid) was placed in 96-well collection plates, then the entire volume was transferred into 96-well Empore SPE that pretreated with 100 μL MeOH and 500 μL 1% trifluoroacetic acid, rinsed with various solvent, then the analytes were eluted using 500 μL mixture of MeOH:H_2O (90:10, v/v) Eluate dried under N_2, residue reconstituted with 100 μL MeOH/0.1% trifluoroacetic acid (50:50, v/v), filtered then centrifuged for 1900 × g (10 min) at 4 °C. Filtrate applied to LC–MS/MS	Recovery: (63.0–73.0)% Precision: Intraday: Precision (RSD): 2.19–5.40% Accuracy: 94.8–107% Interday: Precision (RSD): 1.87–5.67% Accuracy: 93.5–105% LOQ: 2 ng/mL LOQ: n/a	[37]

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
Valsartan, amlodipine, indapamide	Column: Zorbax Eclipse Plus C18 (50 mm × 3 mm; 3 μm) Mobile phase: Solvent A: ACN; B: H_2O with 0.1% formic acid (gradient elution): A:B (10:90) to (95:5) in 5 min, then held 1 min Detection: Qualitative: HRMS and NMR Quantitative: UV (valsartan: 250 nm; amlodipine: 360 nm; and indapamide: 240 nm)	Capsules of Chinese herbal medicine	n/a	Standard solutions: Analytes were dissolved in ACN:H_2O (1:1) Samples: Capsules were cut and emptied into 100 mL volumetric flask + 30 mL H_2O, stirred 30 min + 30 mL ACN stirred 30 min, and then diluted to volume with ACN:H_2O (1:1)	Recovery: 108.51 ± 3.40% Precision: n/a LOD: n/a LOQ: n/a	[11]
Valsartan, amlodipine, hydrochlorothiazide	Column: Aquasil C-18 (50 mm × 2.1 mm; 5 μm) Column temperature: 20 °C Flow rate: 0.2 mL/min Mobile phase: ACN:H_2O containing 0.1% formic acid (50:50, v/v, for separating valsartan and amlodipine) ACN:H_2O containing 0.1% glacial acetic acid (60:40, v/v, for separating hydrochlorothiazide) Detection: MRM (positive ion mode): valsartan (m/z 436 → 418); losartan (m/z 423 → 406); amlodipine (m/z 409 → 238) Negative ion mode: hydrochlorothiazide (m/z 296 → 268); furosemide (m/z 328 → 285	Rat plasma	Losartan Furosemide (only for hydrochlorothiazide)	Standard solutions: Stock solutions were prepared by dissolved analytes in ACN (10 mg/10 mL). Calibration and QC samples were prepared by spiking diluted stock solutions into drug-free rat plasma Samples: Analytes were extracted from plasma by adding ACN as precipitating agent, by vortexing (1 min), and centrifugating 10,000 rpm (10 min) Separated supernatant layer filters with 0.45-μm syringe, 20 μL was injected into LC–MS/MS	Recovery: Intraday: 87.9–106.3% Interday: 85.7–110% Precision: Intra- and interday: <14.3% LOQ: 1 ng/mL (all analytes)	[119]

Valsartan, amlodipine, olmesartan medoxomil, hydrochlorothiazide	Column: CN column (200 mm × 4.6 mm; 5 µm) Mobile phase: ACN: MeOH:10 mM phosphoric acid pH 2.5 (7:13:80, v/v/v) Flow rate: 1.0 mL/min Detection: UV 235 nm	Human plasma	n/a	Standard solutions: Stock solutions (1 mg/mL) were prepared in MeOH; dilution was performed using a mixture of ACN:MeOH:H$_2$O (7:13:80, v/v/v) Samples: – 1 mL plasma was spiked with various concentrations of working solutions and then basified with 0.5 mL NaOH – Analytes were extracted by vortex mixer (2 min) using mixture of 5 mL n-hexane: EtOA:isoamyl alcohol (88:10:2, v/v/v) – Samples were then centrifuged for 1 min (1500 rpm), and the organic layer was taken, evaporated, and then dissolved with 0.5 mL mobile phase	Recovery: 75.8–100.3% Precision: <5.8% LOD: 0.1 ng/mL LOQ: 0.3 µg/mL	[89]
Valsartan	The system comprised of 3-µL level pumps (A, B, C), an in-line degasser, a sample cooler, a syringe pump, and a switch valve Separation was performed in a 5 cm micro RP-C18 nano-flow column (150 µm i.d. and 375 µm o.d.; 3 µm).	Human plasma (microliter sample)	Losartan	Standard solutions: Stock solutions of valsartan were prepared in MeOH (1 mg/mL); IS solutions were prepared (10 µg/mL) in solutions of 100 g/L HFBA Samples: Human plasma samples (10 µL) were added in 500-µL vials and	Bias (relative error): Intraday: −4.69% to +4.50% Interday: −2.75% to 3.00% Precision: Intraday: 4.47–6.70%; Interday: 4.71–6.43% LOD: n/a LOQ: 1 µg/mL	[39]

Table 8 Summary of Analysis of Valsartan, Other Compounds, and Their Metabolite in the Biological Fluids and Samples—cont'd

Analyte(s)	Chromatography Conditions	Sample	Internal Standard (IS)	Preparation of Standards, Sample Extraction, and Cleanup	Accuracy, Precision (RSD), LOD, and LOQ Valsartan	Ref.
	Mobile phase: samples loading (pump A): ACN:1% formic acid (20:80, v/v) Flow rate: 3 μL/min For sample analysis (pump B: pump C) 1% formic acid:ACN (20:80, v/v) Flow rate: 1 μL/min Detection: SIR: valsartan m/z 436 ($[M+H]^+$)			then 5 μL solutions were added. Samples were vortexed (30 s) and centrifuged 10,000 rpm (2 min) 1 μL of supernatant was injected into the nanoscale LC–MS/MS		
Valsartan, losartan, irbesartan, candesartan cilexetil, candesartan cilexetil M1	Column: μBondapak C18 (300 mm × 3.9 mm; 10 μm) Guard column: Novapak C18 Mobile phase: ACN and sodium acetate 5 mM, pH 4 (gradient elution) Temperature: room Detector: UV 254 nm		Nimodipine	Standard solutions: Stock solutions (1000 μg/mL) prepared in MeOH and ACN Working solution were made daily by dilution with the same solvent Samples: 1. Frozen human urine (−20 °C) thawed 2. 1 mL vortexed and mixed urine + PO₄ buffer (0.5 mL, 0.1 M, pH 2) → shaken and centrifuged (3500 rpm) for 5 min 3. BondElut C8 cartridges + MeOH and 1 mL PO₄ buffer (0.1 M, pH 2)	Recovery (RSD): 1.85–2.27% Precision (RSD): Intraday: 0.82–0.97% Interday: 2.63–4.30% LOD: n/a LOQ: 0.43 μg/mL	[120]

4. Cartridges do not dry before application of 1 mL acidified sample under low vacuum (<5 mmHg)
5. Column conditioned with MeOH:PO_4 buffer pH 2 (40:60, v/v) → dried at vacuum (>200 mmHg) for 20 min
6. Analytes eluted with 1 mL MeOH
7. Eluate dry at 40 °C with N_2
8. Remaining residue dissolved with 0.5 mL mobile phase
9. 20 µL injected into HPLC system

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