

A REVIEW ON: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF UV SPECTROPHOTOMETRIC AND RP-HPLC METHODS FOR THE SIMULTANEOUS ESTIMATION OF VALSARTAN AND HYDROCHLOROTHIAZIDE IN BULK DRUG AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Valsartan and hydrochlorothiazide are commonly used together for the treatment of hypertension. Valsartan is an angiotensin II receptor blocker that reduces vasoconstriction and aldosterone-related sodium retention, while hydrochlorothiazide is a thiazide diuretic that promotes the excretion of sodium and water. Their combined action provides an effective antihypertensive effect and the combination is available in various pharmaceutical dosage forms. Therefore, reliable analytical methods are required for the identification, estimation, quality control, and validation of these drugs.

This review summarizes the reported analytical methods for the simultaneous estimation of valsartan and hydrochlorothiazide, with special emphasis on UV-visible spectrophotometric and reversed-phase high-performance liquid chromatographic (RP-HPLC) methods. Different spectrophotometric techniques, including simultaneous-equation, first-derivative, absorbance-ratio, and other multicomponent methods, have been reported. RP-HPLC methods have been developed using different reversed-phase columns, aqueous buffers, organic solvents, and UV detection wavelengths. Important validation parameters such as linearity, accuracy, precision, specificity, robustness, limit of detection, and limit of quantification are discussed.

UV spectrophotometric methods are generally simple, rapid, economical, and suitable for routine analysis. RP-HPLC methods provide better separation and selectivity, particularly in the presence of formulation excipients

and other interfering substances. This review provides a concise summary of reported analytical methods and serves as a useful reference for the development and validation of methods for valsartan and hydrochlorothiazide in bulk drugs and pharmaceutical dosage forms.

Keywords: Valsartan, Hydrochlorothiazide, UV spectrophotometry, RP-HPLC, Method Development and Validation.

1. INTRODUCTION

Hypertension represents one of the most prevalent cardiovascular conditions and typically necessitates therapeutic intervention utilizing multiple antihypertensive medications. Pharmaceutical therapy employing agents with synergistic mechanisms of action can enhance blood-pressure management. Valsartan and hydrochlorothiazide are frequently utilized in combination because valsartan inhibits the renin–angiotensin system whereas hydrochlorothiazide facilitates renal elimination of sodium and water. Valsartan (VAL) functions as an angiotensin II receptor blocker (ARB) that selectively inhibits the angiotensin II AT₁ receptor.

Hydrochlorothiazide (HCTZ) operates as a thiazide-class diuretic that diminishes sodium and chloride reabsorption within the distal renal tubule. The combined pharmaceutical formulation consequently delivers pharmacologically complementary therapeutic effects. From an analytical chemistry perspective, concurrent quantification of VAL and HCTZ presents considerable difficulty because these two substances exhibit distinct physicochemical and spectroscopic properties.

Analytical methodologies must therefore demonstrate the capacity to precisely measure both constituents amid mutual interference and formulation additives. Numerous analytical methodologies have been documented for VAL and HCTZ, encompassing UV-visible spectrophotometry, derivative spectrophotometry, HPLC/RP-HPLC, HPTLC, and LC-MS-based approaches. Satana et al. demonstrated concurrent quantification utilizing first-derivative UV spectrophotometry combined with an HPLC methodology in 2001.

Subsequent researchers established simultaneous-equation and absorbance-ratio UV methodologies as well as isocratic RP-HPLC techniques applicable to pharmaceutical tablets. UV spectrophotometry presents advantages for routine analytical work because it demands relatively uncomplicated instrumentation, economical solvents, and abbreviated analysis durations. Nevertheless, its discriminatory capability may be compromised when spectral interference transpires. RP-HPLC, conversely, accomplishes chromatographic separation of individual constituents and consequently can deliver superior selectivity and specificity.

The purpose of this review is to synthesize and evaluate published UV spectrophotometric and RP-HPLC methods for simultaneous estimation of VAL and HCTZ in bulk drug and pharmaceutical dosage forms, with emphasis on analytical conditions and validation as per ICH guidelines.

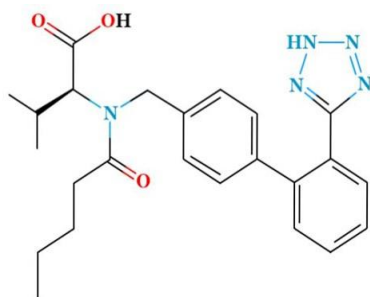


Fig 1 : Structure of Valsartan

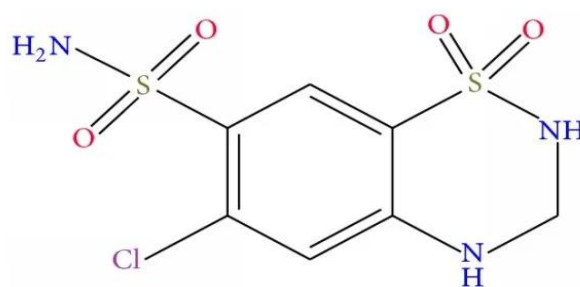


Fig 2 : Structure of Hydrochlorothiazide

Available Formulations of Valsartan + Hydrochlorothiazide In market in India

S. No	Brand Name	Valsartan (mg)	HCTZ (mg)	Pharmaceutical dosage form	Manufacturer / Marketer
1	Co-Diovan 80/12.5	80	12.5	Film-coated tablet	Novartis India Ltd.
2	Valent-H 80	80	12.5	Tablet	Lupin Ltd.
3	Valzaar-H 80	80	12.5	Tablet	Torrent Pharmaceuticals Ltd.
4	Valembic-H 80	80	12.5	Tablet	Alembic Pharmaceuticals Ltd.
5	Valfect-H 80	80	12.5	Tablet	AstraZeneca Pharma India Ltd.
6	Valsazem 80 H	80	12.5	Tablet	Zeelab Pharmacy Pvt. Ltd.
7	Valtan-H 80/12.5	80	12.5	Tablet	Knoll Healthcare Pvt. Ltd.
8	Valzaar-H 160	160	12.5	Tablet	Torrent Pharmaceuticals Ltd
9	Co-Diovan 160/25	160	25	Film Coated tablet	Novartis India Ltd

S. No	Brand Name	Valsartan (mg)	HCTZ (mg)	Pharmaceutical dosage form	Manufacturer / Marketer
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3	Valzaar-H 80	80	12.5	Tablet	Torrent Pharmaceuticals Ltd.
4	Valembic-H 80	80	12.5	Tablet	Alembic Pharmaceuticals Ltd.
5	Valfect-H 80	80	12.5	Tablet	AstraZeneca Pharma India Ltd.
6	Valsazem 80 H	80	12.5	Tablet	Zeelab Pharmacy Pvt. Ltd.
7	Valtan-H 80/12.5	80	12.5	Tablet	Knoll Healthcare Pvt. Ltd.
8	Valzaar-H 160	160	12.5	Tablet	Torrent Pharmaceuticals Ltd
9	Co-Diovan 160/25	160	25	Film Coated tablet	Novartis India Ltd

2.METHODS

2.1 Reported the UV Method of Valsartan.

S. No.	Title of the Article	Journal	Year	UV method / λ_{max}	Solvent/ Medium
1	Comparison of UV- and second derivative- spectrophotometric and LC methods for the determination of valsartan in pharmaceutical formulation	Journal of Pharmaceutical and Biomedical Analysis	2002	Zero-order UV: 205.6 nm; second derivative: 221.6 & 231.2 nm	Ethanol
2	UV- Spectrophotometric Methods for Estimation of Valsartan in Bulk and Tablet Dosage Form	International Journal of ChemTech Research	2010	Zero-order: 250 nm; second derivative: 241 nm	Methanol

3	Stress Degradation Studies on Valsartan and Development of a Validated Method by UV Spectrophotometric in Bulk and Pharmaceutical Dosage Form	Journal of Pharmaceutical and Biomedical Sciences	2011	249 nm	Methanol
4	Development and Statistical Validation of Spectrophotometric Methods for the Estimation of Valsartan in Tablet Dosage Form	Asian Journal of Chemistry	2012	Absorption maxima: 250 nm; AUC: 245–255 nm; second derivative method	Methanol
5	Development and Validation of New UV-Spectrophotometric Assay Method for Valsartan in Pure and in Formulations	Journal of Chemical and Pharmaceutical Research	2013	Approximately 250.8 nm	Methanol–water
6	Development and Validation of Spectrophotometric Methods for Simultaneous Estimation of Valsartan and Hydrochlorothiazide in Tablet Dosage Form	International Journal of Spectroscopy	2014	VAL: 249.4 nm	0.1 N NaOH
7	New UV-Spectrophotometric Method Development and Validation of Valsartan in Bulk and Pharmaceutical Dosage Forms	Asian Journal of Research in Chemistry	2016	250 nm	Phosphate buffer pH 7.4
8	UV Spectrophotometric Method Development	Asian Journal of	2016	248.21 nm	Methanol:water (50:50)

	and Validation for the Estimation of Valsartan in Bulk and Pharmaceutical Dosage Form	Pharmaceutical Analysis			
9	Development and Validation of UV Spectroscopic Method for Estimation of Valsartan in Tablet Dosage Form	American Journal of Pharm Tech Research	2019	250 nm	Methanol:water (50:50)
10	Quantification of Valsartan in Tablets by Validated UV-Spectrophotometric Method	IJRDO-Journal of Applied Science	2019	252 nm in ethanol; 250 nm in methanol	Ethanol/ Methanol

2.2 Reported the UV Method of Hydrochlorothiazide

S. No	Title of the Article	Journal	Year	UV method	Wavelength / λ_{max}
1.	UV Spectrophotometric Determination of Hydrochlorothiazide and Olmesartan Medoxomil in Pharmaceutical Formulation	Journal of Chemistry	2010	Simultaneous-equation method	271.5 nm
2.	Derivative and Q-analysis Spectrophotometric Methods for Estimation of Hydrochlorothiazide and Olmesartan Medoxomil in Tablets	Indian Journal of Pharmaceutical Sciences	2010	Q-analysis and first-derivative	264 nm, 271 nm; derivative: 254.5 nm
3.	Spectrophotometric and HPLC Methods for Simultaneous Estimation of Amlodipine Besilate, Losartan Potassium and Hydrochlorothiazide in Tablets	Indian Journal of Pharmaceutical Sciences	2010	Simultaneous-equation and AUC methods	271 nm; AUC 266–276 nm

4.	Development and Validation of a UV Spectrophotometric Method for the Simultaneous Estimation of Eprosartan Mesylate and Hydrochlorothiazide in Bulk and Formulations	Indian Journal of Pharmaceutical Sciences	2011	Absorbance-ratio method	249.1 nm and 274.5 nm
5.	Estimation of Amlodipine Besylate, Valsartan and Hydrochlorothiazide in Bulk Mixture and Tablet by UV Spectrophotometry	Indian Journal of Pharmaceutical Sciences	2012	Simultaneous equation, Q-analysis and AUC	317 nm
6.	Development and Validation of Spectrophotometric Methods for Simultaneous Estimation of Valsartan and Hydrochlorothiazide in Tablet Dosage Form	International Journal of Spectroscopy	2014	Simultaneous-equation and absorbance-ratio methods	272.6 nm; isoabsorptive 258.4 nm
7.	Simultaneous determination of cilazapril and hydrochlorothiazide in tablets by chemometric methods	Journal of Pharmaceutical and Biomedical Analysis	2002	CLS, ILS, PCR and PLS spectrophotometry	222–276 nm spectral region
8.	UV Spectrophotometric Determination of Hydrochlorothiazide and Olmesartan Medoxomil in Pharmaceutical Formulation	E-Journal of Chemistry	2010	Simultaneous equation, absorbance-ratio and three-wavelength methods	271.5, 261.5, 263.8, 278.4, 316.5 nm
9.	Computer aided greenness by design approach for resolving and quantifying Triamterene and Hydrochlorothiazide	Scientific Reports	2025	Derivative / multivariate UV methods	HCTZ: 266.8, 271, 283, 299 nm depending on method

10.	Spectrophotometric Estimation of Olmesartan Medoxomil and Hydrochlorothiazide in Tablet	Indian Journal of Pharmaceutical Sciences	2010	UV spectrophotometry	HCTZ wavelength reported in study
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2.3 Reported the Simultaneous UV Methods of Valsartan and Hydrochlorothiazide

S. No	Title of the Article	UV Spectrophotometric method	Journal	Year	Wavelength(s)
1	Simultaneous determination of valsartan and hydrochlorothiazide in tablets by first-derivative ultraviolet spectrophotometry and LC	First-derivative UV spectrophotometry	Journal of Pharmaceutical and Biomedical Analysis	2001	VAL: 270.6 nm; HCTZ: 335 nm
2	Spectrophotometric analysis of valsartan and hydrochlorothiazide	UV spectrophotometry	Analytical Letters	2002	VAL: 270.6 nm; HCTZ: 316 nm
3	Simultaneous Spectrophotometric Estimation of Valsartan and Hydrochlorothiazide in Tablet Formulations	Simultaneous-equation (Vierordt's) method	Research Journal of Pharmacy and Technology	2009	VAL: 250 nm; HCTZ: 271 nm
4	Development and validation of spectrophotometric and ion pair chromatographic technique for estimation of valsartan and hydrochlorothiazide	Multi-wavelength UV spectrophotometry	Journal of Pharmaceutical Research and Health Care	2010	VAL: 245 nm, correction at 301 nm; HCTZ: 316 nm
5	Estimation of valsartan and hydrochlorothiazide in pharmaceutical dosage forms by absorption ratio method	Absorbance-ratio / Q-analysis	International Journal of Applied Biology and Pharmaceut	2010	231.5 nm and 270.5 nm

			ical Technology		
6	Validated Eco-Friendly Derivative Spectrophotometric Method for Valsartan and Hydrochlorothiazide Combined Tablet Dosage Form	First-derivative UV spectrophotometry	Asian Journal of Research in Chemistry	2012	VAL: 271.9 nm; HCTZ: 333 nm
7	Concurrent estimation of amlodipine besylate, hydrochlorothiazide and valsartan by RP-HPLC, HPTLC and UV-spectrophotometry	Simultaneous-equation UV method	Journal of Chromatographic Science	2014	VAL: 249.2 nm; HCTZ: 270.2 nm
8	Development and Validation of Spectrophotometric Methods for Simultaneous Estimation of Valsartan and Hydrochlorothiazide in Tablet Dosage Form	Simultaneous-equation and absorbance-ratio methods	International Journal of Spectroscopy	2014	Simultaneous equation: VAL 249.4 nm, HCTZ 272.6 nm; Q-analysis: 258.4 and 272.6 nm
9	Simultaneous spectrophotometric determination of valsartan and hydrochlorothiazide by H-point standard addition method and partial least squares regression	H-point standard addition and PLS regression	Journal of Pharmaceutical and Biomedical Analysis	2011	VAL: 216 and HCT: 228 nm
10	Estimation of amlodipine besylate, valsartan and hydrochlorothiazide in bulk mixture and tablet by UV spectrophotometry	Simultaneous equation, Q-analysis and AUC	Indian Journal of Pharmaceutical Sciences	2012	VAL: 250 nm; HCTZ: 317 nm

2.4 Reported the RP-HPLC Methods of Valsartan

S. No.	Title of Article	Journal	Mobile Phase	Column	Wavelength
1	Stability Indicating RP-HPLC Method for Determination of Valsartan in Pure and Pharmaceutical Formulation	E-Journal of Chemistry	0.01 M NH ₄ H ₂ PO ₄ buffer (pH 3.5): Methanol (50:50, v/v)	Phenomenex Gemini C18	210 nm
2	Development and Validation of a Specific Stability Indicating High Performance Liquid Chromatographic Method for Valsartan	Journal of Young Pharmacists	Sodium dihydrogen orthophosphate buffer (pH 2.5): Acetonitrile (58:42, v/v)	Symmetry C18 (250 × 4.6 mm, 5 µm)	227 nm
3	Development and Validation of RP-HPLC Method for Quantification of Valsartan and its Pharmaceutical Formulations	International Journal of Drug Development & Research	Acetonitrile: Phosphate buffer (70:30, v/v)	Agilent ODS UG 5 C18 (250 × 4.5 mm)	273 nm
4	New Stability Indicating Liquid Chromatographic Method for the Estimation of Valsartan in Pharmaceutical Dosage Forms	Journal of Pharmaceutical and Biomedical Analysis	Reported phosphate-buffer/organic-solvent RP-HPLC system	C18 RP column	UV detection
5	Stability-Indicating RP-HPLC Method for the Determination of Valsartan in Pharmaceutical Dosage Forms	Pharmaceutical analysis literature	Phosphate buffer: organic solvent	C18	UV detection
6	RP-HPLC Method for the Determination of Valsartan in Bulk Drug and Pharmaceutical Dosage Forms	Pharmaceutical analytical literature	Buffer: Acetonitrile	C18	UV detection

2.5 Reported the RP-HPLC Methods of Hydrochlorothiazide

S. No.	Article Name	Journal & Year	Mobile Phase	Column	Wavelength
1	Estimation of Hydrochlorothiazide in Pure and Pharmaceutical Dosage Forms by RP-HPLC	Journal of Chemical and Pharmaceutical Sciences, 2011	Potassium dihydrogen orthophosphate : Acetonitrile (35:65, v/v)	ZORBAX C18, 150 × 4.6 mm, 5 μm	270 nm
2	Development and Validation of RP-HPLC Method for the Determination of Hydrochlorothiazide in Bulk Drug and Pharmaceutical Dosage Form	Chromatography Research International, 2016	Acetonitrile : Water (50:50, v/v)	Inertsil ODS-3 C18, 250 × 4.6 mm, 5 μm	272 nm

2.6 Reported the RP- HPLC Methods for Simultaneous of Valsartan and Hydrochlorothiazide

S.NO	Article Name	Journal & Year	Mobile Phase	Column	Wavelength
1	Simultaneous Determination of Valsartan and Hydrochlorothiazide in Tablets by RP-HPLC	Indian Journal of Pharmaceutical Sciences, 2008	Methanol : Acetonitrile : Water : Isopropyl alcohol (22:18:68:2, v/v); pH adjusted to 8.0 with triethylamine	Diamonsil C18, 200 × 4.6 mm, 5 μm	270 nm
2	Validated RP-HPLC Method for the Simultaneous Determination of Amlodipine Besylate, Valsartan, and Hydrochlorothiazide in Bulk and in Pharmaceutical Formulation	Acta Chromatographica, 2012	Acetonitrile : Methanol : 50 mM phosphate buffer, pH 3 (20:50:30, v/v/v)	RP-C18	239 nm

3	Development and Validation of an HPLC Method for the Simultaneous Determination of Amlodipine, Hydrochlorothiazide, and Valsartan in Tablets of Their Novel Triple Combination and Binary Pharmaceutical Associations	Journal of Liquid Chromatography & Related Technologies, 2011	Amlodipine + Valsartan + HCTZ	30 mM phosphate buffer pH 5.5 : Methanol (38:62)	C18
4	Validated RP-HPLC Method for the Simultaneous Determination of Amlodipine Besylate, Valsartan, and Hydrochlorothiazide in Bulk and in Pharmaceutical Formulation	Acta Chromatographica, 2012	Amlodipine + Valsartan + HCTZ	Acetonitrile : Methanol : 50 mM phosphate buffer pH 3 (20:50:30)	RP-C18
5	Simple RP-HPLC Method for Determination of Triple Drug Combination of Valsartan, Amlodipine and Hydrochlorothiazide in Human Plasma	Acta Pharmaceutica, 2012	Valsartan + Amlodipine + HCTZ	Gradient: Acetonitrile + 10 mM ammonium formate buffer pH 3.5	Gemini C18
6	Concurrent Estimation of Amlodipine Besylate, Hydrochlorothiazide and Valsartan by RP-HPLC, HPTLC and UV-Spectrophotometry	Journal of Chromatographic Science, 2014	Amlodipine + Valsartan + HCTZ	50 mM KH ₂ PO ₄ buffer pH 3.7 + 0.2% TEA : Acetonitrile (56:44)	C18

7	Validated Stability-Indicating HPLC-DAD Method of Analysis for the Antihypertensive Triple Mixture of Amlodipine Besylate, Valsartan and Hydrochlorothiazide in Their Tablets	Arabian Journal of Chemistry, 2013	Amlodipine + Valsartan + HCTZ	0.025 M phosphoric acid + Acetonitrile, gradient	Zorbax SB-C8
8	High Performance Liquid Chromatographic Assay of Amlodipine, Valsartan and Hydrochlorothiazide Simultaneously and its Application to Pharmaceuticals, Urine and Plasma Analysis	Journal of Chromatography B, 2020	Amlodipine + Valsartan + HCTZ	Ammonium acetate buffer + Acetonitrile:Methanol (20:80), gradient	Hibar RP-18e, 250 × 4.6 mm, 5 µm

CONCLUSION

The existing body of research demonstrates that ultraviolet-visible spectrophotometric analysis and reversed-phase high-performance liquid chromatography (RP-HPLC) techniques have been extensively employed for quantifying valsartan and hydrochlorothiazide in pharmaceutical raw materials and finished dosage forms. Numerous ultraviolet spectrophotometric approaches have been documented, encompassing simultaneous-equation methodology, absorbance-ratio techniques, derivative analysis, and additional multicomponent analytical strategies. These analytical approaches are typically characterized by their simplicity, rapid execution, cost-effectiveness, and suitability for standard laboratory analysis when adequate resolution of individual drug absorption spectra is achieved.

Reversed-phase HPLC techniques have similarly received considerable attention in scientific literature for the concurrent determination of valsartan and hydrochlorothiazide. Various octadecyl-bonded silica columns, phosphate buffer systems, ammonium acetate formulations and alternative aqueous mobile phase components, in combination with organic modifiers including methanol, acetonitrile, and isopropyl alcohol, have been utilized to accomplish effective separation of both pharmaceutical compounds. These methodologies have demonstrated acceptable linearity, accuracy, precision, and specificity, confirming that RP-HPLC represents a dependable analytical tool for standard laboratory analysis and pharmaceutical quality assurance of these active pharmaceutical ingredients in medicinal preparations.

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