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Stability-indicating UPLC method for determination of Valsartan and their degradation products in active pharmaceutical ingredient and pharmaceutical dosage forms

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ABSTRACT

A simple, precise, accurate stability-indicating gradient reverse phase ultra-performance liquid chromatographic (RP-UPLC) method was developed for the quantitative determination of purity of Valsartan drug substance and drug products in bulk samples and pharmaceutical dosage forms in the presence of its impurities and degradation products. The method was developed using Waters Aquity BEH C18 (100 mm × 2.1 mm, 1.7 μm) column with mobile phase containing a gradient mixture of solvents A and B. The eluted compounds were monitored at 225 nm, the run time was within 9.5 min, which Valsartan and its seven impurities were well separated. Valsartan was subjected to the stress conditions of oxidative, acid, base, hydrolytic, thermal and photolytic degradation. Valsartan was found to degrade significantly in acid and oxidative stress conditions and stable in base, hydrolytic and photolytic degradation conditions. The degradation products were well resolved from main peak and its impurities, proving the stability-indicating power of the method. The developed method was validated as per international conference on harmonization (ICH) guidelines with respect to specificity, linearity, limit of detection, limit of quantification, accuracy, precision and robustness. This method was also suitable for the assay determination of Valsartan in pharmaceutical dosage forms.

1. Introduction

Though high-performance liquid chromatography (HPLC) is a well-established reliable technique used in controlling the quality and consistency of active pharmaceutical ingredients (APIs) and dosage forms, it is often a slow technique because of the complexity of some of the samples, it could still be improved.

Ultra-performance liquid chromatography (UPLC) is a new category of separation technique based upon well-established principles of liquid chromatography, which utilizes sub-2 μm particles for stationary phase. These particles operate at elevated mobile phase linear velocities to affect dramatic increase in resolution, sensitivity and speed of analysis. Owing to its speed and sensitivity, this technique is gaining considerable attention in recent years for pharmaceutical and biomedical analysis. In the present work, this technology has been applied to the method development and validation study of related substance and assay determination of Valsartan bulk drug and dosage forms.

The chemical formula of Valsartan is *N*-(1-oxopentyl)-*N*-[[2-(1H-tetrazol-5-yl) [1,1-biphenyl]-4-yl]methyl]-L-valine (Fig. 1A). Valsartan is a potent, highly selective, and orally active antagonist at the angiotensin II AT1-receptor that is used for the treatment of hypertension. Very few methods appeared in the literature for the determination of VAL individually based on high-performance liquid chromatography (HPLC) [1–3]. Sampath et al. [4] described identification and characterization of potential impurities of Valsartan AT1 receptor antagonist. There has been some of estimation of assays of analyte in human plasma including the use of liquid chromatography [5–8] and some combination with other drugs using high pressure liquid chromatography and derivative spectroscopy [9–14].

The European Pharmacopoeia (Ph.Eur.) and United States Pharmacopoeia (USP) monograph methods for Valsartan related compounds cannot separate all the potential impurities and degradation compounds of Valsartan. However, the Ph.Eur. and USP monograph methods can resolve Imp-C and Imp-F related compounds of Valsartan and total run time is about 40 min. To the best of our knowledge, none of the currently available analytical methods (including the Ph.Eur. and USP method) can separate and

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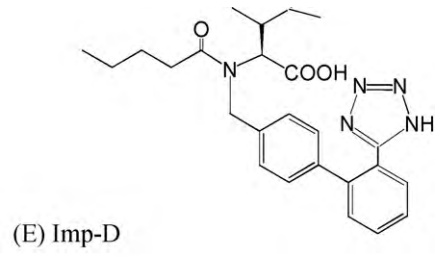
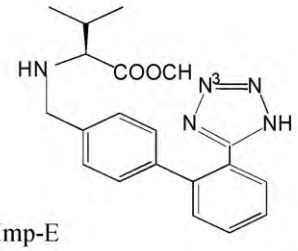
quantify all the known related compounds and degradation impurities of Valsartan API and dosage forms. Furthermore, there is no stability-indicating HPLC/UPLC method reported in the literature that can adequately separate and accurately quantify Valsartan API and dosage forms. It is, therefore, felt necessary to develop a new stability-indicating method for the related substance determination and quantitative estimation of Valsartan. We intend to opt for a faster chromatographic technique UPLC, for the said study. An attempt was made to determine whether UPLC can reduce analysis times without compromising the resolution and sensitivity.

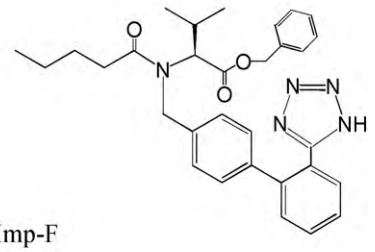
Hence a reproducible stability-indicating RP-UPLC method was developed for the quantitative determination of Valsartan and its seven impurities namely Imp-A, B, C, D, E, F and G (Fig. 1B–H). This method was successfully validated according to the International Conference Harmonization (ICH) guidelines (Validation of Analytical Procedures: Test and Methodology Q2). The method was also applied for study of in vitro dissolution profiles in pharmaceutical dosage forms.



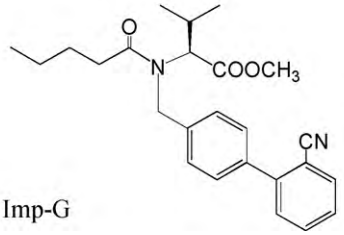
(E) Imp-D



(F) Imp-E

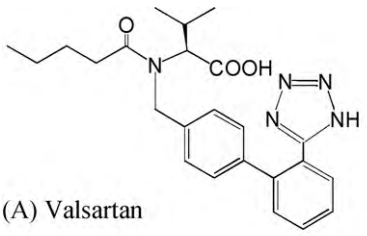


(G) Imp-F

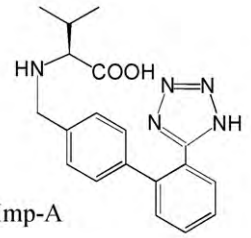


(H) Imp-G

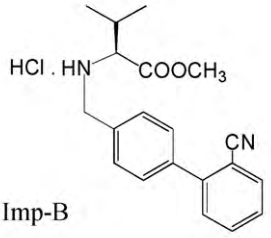
Fig. 1. Structures of Valsartan and its seven impurities. (A) Valsartan; (B) Imp-A; (C) Imp-B; (D) Imp-C; (E) Imp-D; (F) Imp-E; (G) Imp-F; and (H) Imp-G.



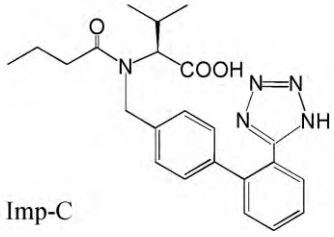
(A) Valsartan



(B) Imp-A



(C) Imp-B



(D) Imp-C

Fig. 1. *Continued.*

2. Experimental

2.1. Materials and reagents

Active pharmaceutical ingredient standards and samples were supplied by Dr. Reddy's Laboratories Limited, IPDO, Hyderabad, India. Commercially available Diovan tablets Novartis Pharmaceuticals Corporation, USA, were used for the dosage form analysis. The HPLC grade acetonitrile and analytical grade ortho phosphoric acid were purchased from Merck, Darmstadt, Germany. Water was prepared using Millipore Milli.Q Plus water purification system, Bedford, MA, USA.

2.2. Chromatographic conditions and equipments

LC was carried out on a Waters Aquity UPLC with photodiode array detector. The output signal was monitored and processed using empowers software. The chromatographic column used was acquity UPLC BEH C-18 100 mm, 2.1 mm, and 1.7 μm particle size. The separation was achieved on a gradient method. The solvent A contains a mixture of 1.0% acetic acid buffer, Acetonitrile in the ratio 90:10 (v/v); and the solvent B contains a mixture of 1.0% acetic acid buffer and acetonitrile in the ratio 10:90 (v/v), respectively.