Ph. Eur. Monograph 2423: Valsartan Related Substances with Ph. Eur. Method Modernization

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Overview

Valsartan is an antihypertensive drug which selectively inhibits angiotensin receptor type II. The European Pharmacopeia (Ph. Eur.) monograph method for the LC-UV determination of related compounds for Valsartan is based on an end-capped octadecylsilyl silica gel column run under isocratic mobile phase conditions. This application note demonstrates the potential method improvements that can be achieved within the allowed adjustments of chromatographic conditions. Different dimensions of a Luna™ Omega C18 column were used for evaluating the related substances method, within the new allowable adjustments published by European Pharmacopeia, Chapter 2.2.46, updated July 2022.

System suitability per Ph. Eur. Monograph 2423 for Valsartan Related Substances is a minimum resolution of 3.0 between the peaks due to impurity C and Valsartan. The results in the three methods show that the system suitability criteria were met. The use of a Luna Omega 3 µm C18, 100 x 3.0 mm column, a Luna Omega 5 µm C18, 100 x 4.6 mm column, and a Luna Omega 1.6 µm C18, 50 x 2.1 mm column is an allowed adjustment to the original column dimension with the flow rates scaled accordingly to accommodate the adjustments to column length (L), internal diameter (ID), and particle size (dp). With the Luna Omega 1.6 µm C18, 50 x 2.1 mm column, we demonstrated a reduction in total analysis time by 75% (from 20 minutes to 5 minutes with a 0.6 mL/min flow) over the Luna Omega 3 µm C18, 100 x 3.0 mm column, and of 83.3% compared to the original column dimensions (5 µm, 125 x 3.0 mm) specified in the monograph.

All the reference solutions were prepared as indicated in Ph. Eur. monograph 2423 for Valsartan. The following certified reference standards (CRS) were purchased from the European Directorate for the Quality of Medicines & HealthCare (EDQM) – Council of Europe; Postal address: 7 Allee Kastner CS 30026 F - 67081 Strasbourg (France):

- Y0001132, Valsartan CRS
- Y0001145, Valsartan for System Suitability CRS

Figure 1. Valsartan Structure

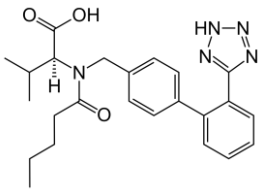


Table 1. Ph. Eur. Adjustments of Chromatographic Conditions and Method Comparison.

Method Parameter	Allowable Adjustments (Isocratic)	Method 1	Method 2	Method 3
Stationary Phase	No change of the identity of the substituent permitted	As Specified	As Specified	As Specified
Column Length (L), Column Particle Size (dp), L/dp	The particle size and/or length of the column may be modified provided that the ratio of L/dp remains constant or in the range of -25 % to +50 % of the prescribed ratio.	Length = 100 mm Particle Size = 3 µm L/dp = 33.3 Deviation = +33.3 % (Allowed)	Length = 100 mm Particle Size = 5 µm L/dp = 20.0 Deviation = -20.0 % (Allowed)	Length = 50 mm Particle Size = 1.6 µm L/dp = 31.25 Deviation = +25.0 % (Allowed)
Column Internal Diameter (dc)	In the absence of a change in particle size and/or length of the column, the internal diameter of the column may be adjusted.	3.0 mm (As Specified)	4.6 mm (Allowed)	2.1 mm (Allowed)
Flow Rate (F)	Flow rate is adjusted for changes in column diameter and particle size using the following equation: $F_2 = F_1 x \left(\frac{dc_2^2 x\ dp_1}{dc_1^2 x\ dp_2}\right)$ F_2 = flow rate indicated in the monograph, in mL/min F_2 = adjusted flow rate, in mL/min dc_1 = internal diameter of the column indicated in the monograph, in mm dc_2 = internal diameter of the column used, in mm dp_1 = particle size indicated in the monograph, in µm dp_2 = particle size of the column used, in µm After an adjustment due to a change in column dimensions, an additional change in flow rate of ± 50 per cent is permitted.	0.6 mL/min Deviation = -10.45 % (Allowed)	0.9 mL/min Deviation = -4.26 % (Allowed)	0.6 mL/min Deviation = -1.64 % (Allowed)
Column Temperature	± 10 °C	As Specified	As Specified	As Specified
Composition of Mobile Phase	The amount of the minor solvent components may be adjusted by ± 30 % relative; no component is altered by more than 10 % absolute.	As Specified	As Specified	As Specified
Detection Wavelength	No adjustment permitted	As Specified	As Specified	As Specified
Injection Volume	When column dimensions are changed, it may be adjusted with the equation: $V_{inj2} = Vi_{nj1} x \left(\frac{L_2 x\ dc_2^2}{L_1 x\ dc_1^2}\right)$ V_{inj} = injection volume indicated in the monograph, in µL V_{inj} = adjusted injection volume, in µL dc_1 = internal diameter of the column indicated in the monograph, in mm dc_2 = internal diameter of the column used, in mm L_1 = column length indicated in the monograph, in mm L_2 = new column internal diameter, in mm	8 µL	19 µL	2 µL

LC-UV Conditions

Columns: Luna™ Omega 3 µm C18, 100 x 3.0 mm (00D-4784-Y0) – Method 1
Luna Omega 5 µm C18, 100 x 4.6 mm (00D-4785-E0) – Method 2
Luna Omega 1.6 µm C18, 50 x 2.1 mm (00B-4742-AN) – Method 3

Mobile Phase: Mobile Phase (**Table 1**)

Flow Rate: 0.6 mL/min (Isocratic) – Method 1 and 3
0.9 mL/min (Isocratic) – Method 2

Injection: 8 µL – Method 1
19 µL – Method 2
2 µL – Method 3

Temperature: 25 °C

Detector: UV @ 225 nm

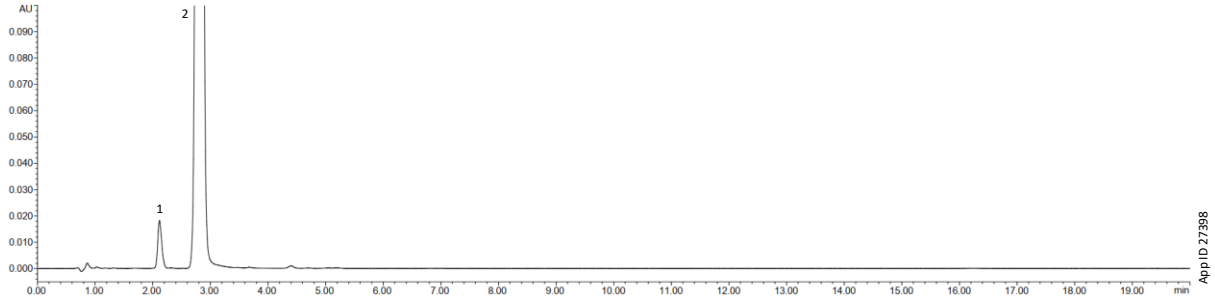
System: Waters® ACQUITY Arc® HPLC – Method 1 and 2
Waters ACQUITY® H-Class UHPLC – Method 3

Table 1. Preparation of Test and Reference Solutions

Solution	Composition
Mobile Phase	Glacial Acetic Acid / Acetonitrile / Water (1:500:500, v/v/v)
Test Solution	Dissolve 50 mg of Valsartan CRS in Mobile Phase and dilute to 100 mL with Mobile Phase.
Reference Solution (a)	Dilute 1.0 mL of Test Solution to 100.0 mL with Mobile Phase. Dilute 1 mL of the solution to 10 mL with Mobile Phase.
Reference Solution (b)	Dissolve the contents of a vial of Valsartan for System Suitability CRS (containing impurity C) in 1.0 mL of the Mobile Phase.

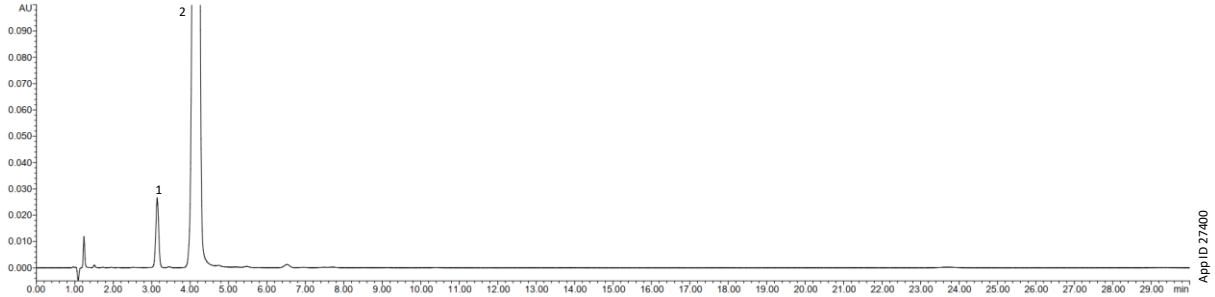
Figure 2. System Suitability Test for Related Substances Using Reference Solution (b).

Method 1 on Luna Omega 3 µm C18, 100 x 3.0 mm Column



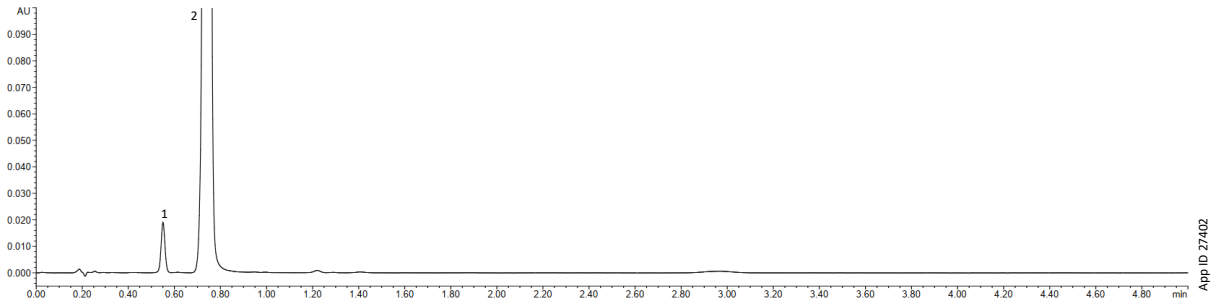
Peak No.	Analyte	Retention Time (min)	Area	Area %RSD	Height	Resolution	Symmetry Factor
1	Impurity C	2.12	87428	0.09	18145	5.04	1.22
2	Valsartan	2.80	8668323	0.05	1604221		1.18
N = 6 Injections							

Method 2 on Luna Omega 5 µm C18, 100 x 4.6 mm Column



Peak No.	Analyte	Retention Time (min)	Area	Area %RSD	Height	Resolution	Symmetry Factor
1	Impurity C	3.15	139779	0.53	26688	6.39	1.01
2	Valsartan	4.16	13774523	0.44	203527		0.98
N = 6 Injections							

Method 3 on Luna Omega 1.6 µm C18, 50 x 2.1 mm Column



Peak No.	Analyte	Retention Time (min)	Area	Area %RSD	Height	Resolution	Symmetry Factor
1	Impurity C	0.55	22526	0.17	19114	5.58	1.01
2	Valsartan	0.74	2210696	0.11	1560256		0.99
N = 6 Injections							

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