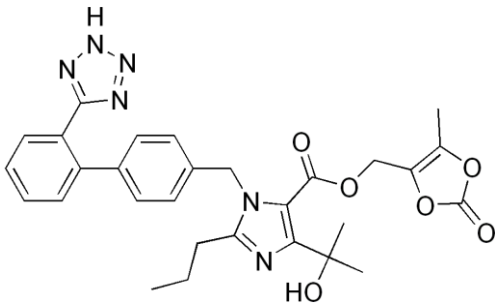
Olmesartan Medoxomil (USP)



Olmesartan medoxomil is an angiotensin II receptor antagonist.
It is an ester prodrug that is completely and rapidly hydrolyzed to the active acid form, olmesartan. It is used to treat high blood pressure.

Olmesartan medoxomil was developed by Daichii Sankyo in 1995.

Common commercial brand name: Benicar (US), Olmetec (EU, Canada and Japan), WinBP, Olsar, Golme (India) etc. Sales in 2010 were $2.5 billion globally.
Patent expiry in 2016

In this application compilation, we have followed the experimental conditions in USP37-NF32 for Olmesartan medoxomil.

Identification – FTIR (197K)
Assay – HPLC and UHPLC (isocratic methods)
Related Substances (RS) – HPLC (gradient method)
Karl Fischer – water content

The assay and RS methods have been carried out with HPLC using RP-8 and RP-18 endcapped columns. The assay method was, in addition, scaled to two shorter column dimensions with different particle sizes (3 and 2 µm particles).

Finally we have also included a new proposal for UHPLC analysis of olmesartan medoxomil related substances using LC-MS conditions (in-house method), and a proposal for heavy metal analysis per suggestions in the new general chapters USP 232/233 that will come active in 2018 using ICP-OES or ICP-MS analysis.

Olmesartan medoxomil (USP)

Definition:

Olmesartan Medoxomil contains NLT 98.5% and NMT 101.5% of $C_{29}H_{30}N_6O_6$, calculated on the anhydrous and solvent-free basis.

Identification: FTIR

A. Infrared Absorption 197K
B. The ratio of the retention time of the major peak to that of the internal standard of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

Assay: HPLC

Procedure
[Note—The Standard solution and Sample solution are stable for 24 h at 5.]

Diluted phosphoric acid: 0.2% phosphoric acid
Buffer: 0.015 M monobasic potassium phosphate. Adjust the solution with Diluted phosphoric acid (w/v) to a pH of 3.4.
Mobile phase: Acetonitrile and Buffer (17:33)
Diluent 1: Acetonitrile and water (4:1)
Diluent 2: Acetonitrile and water (2:3)
Internal standard solution: 0.5 mg/mL of 4-hydroxybenzoic acid isobutyl ester in Diluent 2.
[Note—This solution is stable for 1 month at room temperature.]
Standard stock solution: 1 mg/mL of USP Olmesartan Medoxomil RS in Diluent 1
Standard solution: 0.05 mg/mL of USP Olmesartan Medoxomil RS from the Standard stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2
Sample stock solution: 1 mg/mL of Olmesartan Medoxomil in Diluent 1
Sample solution: 0.05 mg/mL of Olmesartan Medoxomil from the Sample stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2

Chromatographic system (See Chromatography 621, System Suitability.)

Detector: UV 250 nm
Column: 4.6-mm × 15-cm; 5 µm packing L1
Column temperature: 40
Flow rate: 1 mL/min
Injection size: 10 µL

We have used: Purospher® STAR 5µm RP-18 endcapped 150x4.6 mm (1.51455)

Olmesartan medoxomil (USP)

System suitability
Sample: Standard solution

Suitability requirements
Resolution: NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
Relative standard deviation: NMT 0.5% for the peak ratio of olmesartan medoxomil and the internal standard

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of olmesartan medoxomil in the portion taken:

Result = (RU/RS) × (CS/CU) × 100

RU = ratio of the peak areas of olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester from the Sample solution
RS = ratio of the peak areas of olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester from the Standard solution
CS = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
CU = concentration of Olmesartan Medoxomil in the Sample solution (mg/mL)

Acceptance criteria: 98.5%–101.5% on the anhydrous and solvent-free basis

IMPURITIES:

Inorganic Impurities
- Residue on Ignition 281: NMT 0.1%. [Note—The ignition temperature range is 450 to 550.]
- Heavy Metals, Method II231: NMT 10 ppm

Organic Impurities
Procedure
Buffer: Prepare as directed in the Assay.
Solution A: Acetonitrile and Buffer (1:4)
Solution B: Acetonitrile and Buffer (4:1)
Mobile phase: See the gradient table.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	75	25
35	0	100
45	0	100

System suitability solution: 0.01 mg/mL each of USP Olmesartan Medoxomil RS and USP Olmesartan Medoxomil Related Compound A RS in acetonitrile
Standard solution: 0.01 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile
Sample solution: 1 mg/mL of Olmesartan Medoxomil in acetonitrile

Olmesartan medoxomil (USP)

Chromatographic system (See Chromatography 621, System Suitability.)
[Note—A guard column of 4.6-mm × 5-cm of packing L7 may be used.]

Detector: UV 250 nm
Column: 4.6-mm × 10-cm; 3.5 µm packing L7
Column temperature: 40
Flow rate: 1 mL/min
Injection size: 10 µL

System suitability
Suitability requirements
Sample: System suitability solution

Resolution: NLT 5 between olmesartan medoxomil and olmesartan medoxomil related compound A
Relative standard deviation: NMT 2.0% for the olmesartan medoxomil peak

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Olmesartan Medoxomil taken:

Result = (rU/rS) × (CS/CU) × (1/F) × 100

rU = peak response of each impurity from the Sample solution
rS = peak response of olmesartan medoxomil from the Standard solution
CS = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
CU = concentration of Olmesartan Medoxomil in the Sample solution (mg/mL)
F = relative response factor (see the Impurity Table)

Acceptance criteria
Individual impurities: See the Impurity Table on the next page.
Total impurities: NMT 1.3%. *[Note—Disregard any peak below 0.05%.]*

Olmesartan medoxomil (USP)

Name	RRT	RRF	Acceptance Criteria, NMT (%)
Olmesartan[a]	0.2	1.0	0.5
Olmesartan medoxomil related compound A[b]	0.7	1.6	0.1
Olmesartan medoxomil	1.0	1.0	-
Olefinic impurity[c]	1.6	1.0	0.6
N-alkyl impurity[d]	3.4	0.7	0.1
Any other individual unidentified impurity	-	1.0	0.1

a 1-{[2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.
b 1-{[2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one.
c (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2¢-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1H- imidazole-5-carboxylate.
d (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2¢-(2-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate

SPECIFIC TESTS

Limit of Acetone (if present) – Not conducted because we only performed analysis of USP reference standards

Water Determination Method 921-Ic: NMT 0.5%

ADDITIONAL REQUIREMENTS

Packaging and Storage: Preserve in well-closed containers, protect from moisture, and store below 25.

USP Reference Standards
USP Olmesartan Medoxomil RS
USP Olmesartan Medoxomil Related Compound A RS
1-{[2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one.

Olmesartan medoxomil (USP)

Recommended Merck Millipore products:

FTIR – Identification (197K)
Potassium bromide for IR spectroscopy Uvasol® (1.04907)
KF – Water Determination (921 –Ia)
CombiCoulomat fritless Karl Fischer reagent for coulometric water determination for cells with and without diaphragm apura® 1.88002
CombiCoulomat fritless - Coulometric KF reagent for cells with or without diaphragm; 100 mL (1.09257)

HPLC Assay and Related Substances
Purospher® STAR RP-18 endcapped (5 µm) 150x4.6 mm (1.51455) for assay scaled to
Purospher® STAR RP-18 endcapped (3 µm) 100x2.1mm (1.50653) for assay
Purospher® STAR RP-18 endcapped (2 µm) 50x2.1mm (1.50651) for assay
Purospher ® STAR RP-8 endcapped (3 µm) 100x4.6 mm for RS analysis (1.50013.7220) for RS analysis
Sodium dihydrogen phosphate dihydrate for analysis EMSURE® Reag. Ph Eur 106342
ortho-Phosphoric acid 85% for analysis EMSURE® ACS,ISO,Reag. Ph Eur 100573
Acetonitrile (isocratic grade for liquid chromatography LiChrosolv® 1.14291)
Acetonitrile (gradient grade for liquid chromatography) LiChrosolv® Reag. Ph Eur 1.00030
Water (LiChrosolv® 1.15333 or water from a Milli-Q system)

LC-MS - Related Substances (proposal method)
Purospher® STAR RP-18 endcapped (3 µm) 100x2.1mm (1.50653)
Acetonitrile hypergrade for LC-MS LiChrosolv® 100029
Formic acid 98-100% for analysis EMSURE® ACS,Reag. Ph Eur 100264
Water (LiChrosolv® 1.15333 or water from a Milli-Q system)

ICP Analysis
Nitric acid 65% Suprapur® (1.00441)
Hydrochloric acid 30% Suprapur® (1.00318)
Hydrogen peroxide 30% Suprapur® (1.07298)

Elements: As, Cd, Cu, Hg, Mo, Ni, Pb, V
ICP Multi-element standard USP-I according to USP <232> oral dose. Certipur® (5.05101)
ICP Multi-element standard USP-II according to USP <232> parenteral dose. Certipur® (5.05102)

Elements: Ir, Os, Pd, Pt, Rh, Ru
ICP Multi-element standard USP-III according to USP <232> oral dose 100 mg/l. Certipur® (5.05103)
ICP Multi-element standard USP-IV according to USP <232> parenteral dose 10 mg/.Certipur® (5.05104)

Olmesartan medoxomil (USP)

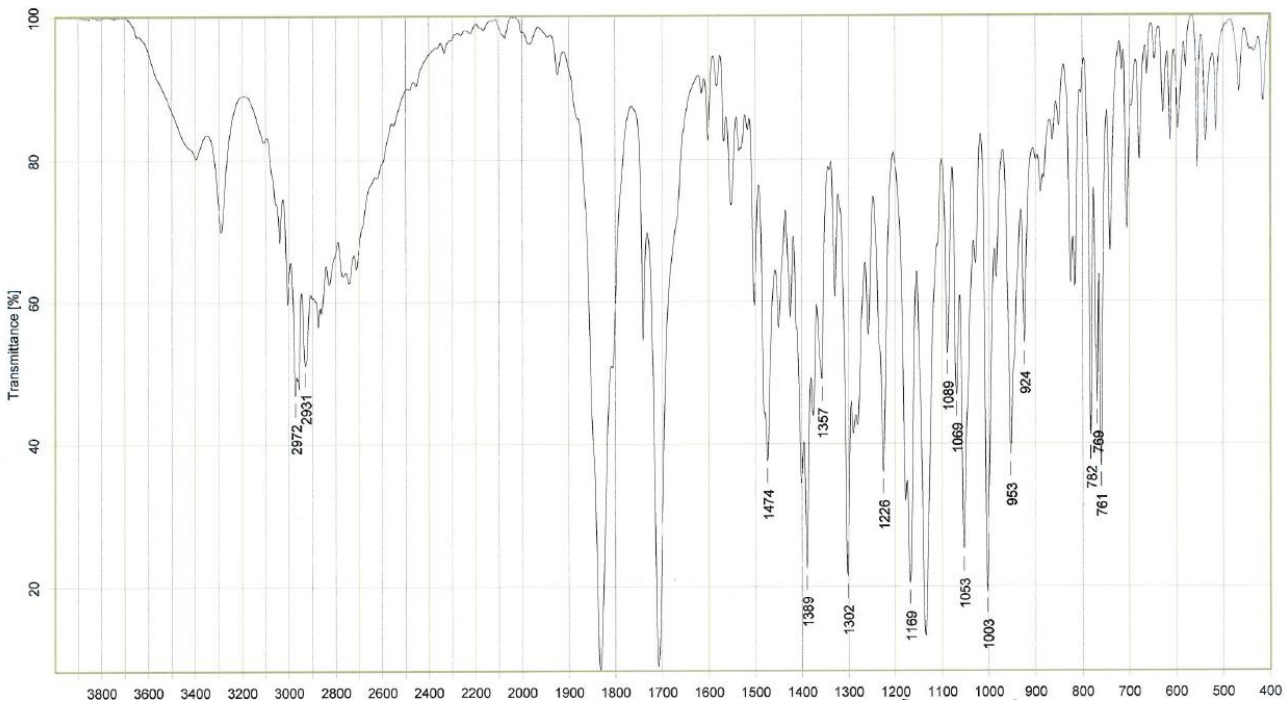
Identification

A. INFRARED ABSORPTION <197K> FTIR

The reference 197K in a monograph signifies that the substance under examination is mixed intimately with potassium bromide.
We recommend Potassium bromide for IR spectroscopy Uvasol® (1.04907) to be used.

B. HPLC (Assay)

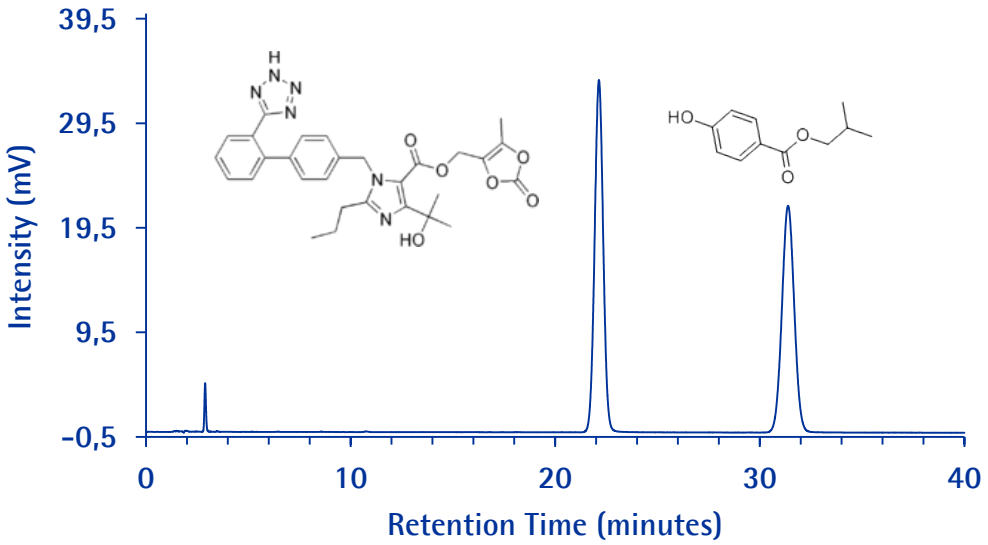
The ratio of the retention time of the major peak to that of the internal standard of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.



Olmesartan medoxomil (USP)

Purospher® STAR RP-18 endcapped HPLC - Assay

Column:	Purospher ® STAR RP-18 endcapped (5µm) 150x4.6 mm	1.51455.0001
Injection:	10 µL	
Detection:	UV, 250nm	
Cell:	11 µL	
Flow Rate:	1mL/min	
Solution A:	15mM monobasic potassium phosphate pH=3.4	
Solution B:	Acetonitrile (Gradient Grade 1.00030)	
Mobile Phase:	Buffer and acetonitrile 33:17 (v/v)	
Temperature:	40°C	
Diluent 1	Acetonitrile:Water 4:1	
Diluent 2	Acetonitrile:Water 2:3	
Standard solution:	0.05mg/mL of Olmesartan medoxomil RS of the Standard Stock solution and 0.025mg/mL of p-Hydroxybenzoic acid isobutyl ester from the internal Standard solution in Diluent 2	
Standard Stock soln.	1mg/mL of Olmesartan medoxomil RS in Diluent 1	
Internal Standard	0.5mg/mL of p-Hydroxybenzoic acid isobutyl ester in Diluent 2	
Pressure Drop:	63 Bar (907 psi)	



System Suitability criteria:
Resolution: NLT 4 between Olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester

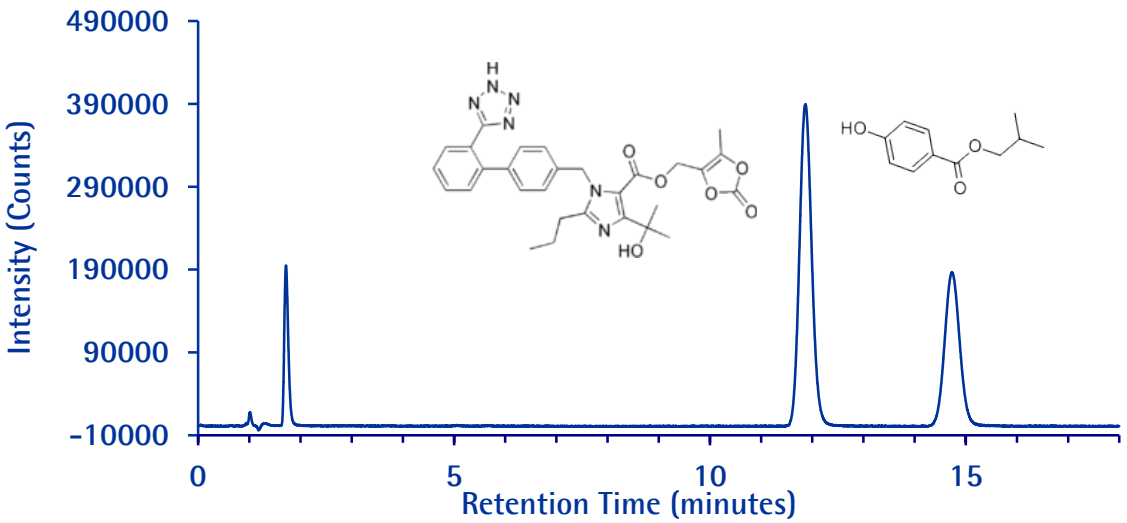
Chromatographic Data: (Standard solution)

Compound	Retention Time (min)	Resolution	Plates	Tailing Factor
t0 void volume	2.9			
Olmesartan RS	22.1		13101	1.02
p-HBA i-But ester	31.3	9.8	12822	1.01

Olmesartan medoxomil (USP)

Purospher® STAR RP-18 endcapped HPLC - Assay

Column:	Purospher® STAR RP-18 endcapped (3 µm) 100x2.1mm	1.50653.0001
Injection:	2.1 µL	
Detection:	UV; 250nm	
Cell:	11 µL	
Flow Rate:	1mL/min	
Solution A:	15mM monobasic potassium phosphate pH=3.4	
Solution B:	Acetonitrile (Gradient Grade 1.00030)	
Mobile Phase:	Buffer and Acetonitrile 33:17 (v/v)	
Temperature:	40°C	
Diluent 1	Acetonitrile:Water 4:1	
Diluent 2	Acetonitrile:Water 2:3	
Standard solution:	0.05mg/mL of Olmesartan medoxomil RS of the Standard Stock solution and 0.025mg/mL of p-Hydroxybenzoic acid isobutyl ester from the internal Standard solution in Diluent 2	
Standard Stock soln:	1mg/mL of Olmesartan medoxomil RS in Diluent 1	
Internal Standard	0.5mg/mL of p-Hydroxybenzoic acid isobutyl ester in Diluent 2	
Pressure Drop:	76 Bar (1102 psi)	



System Suitability criteria:
Resolution: NLT 4 between Olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester

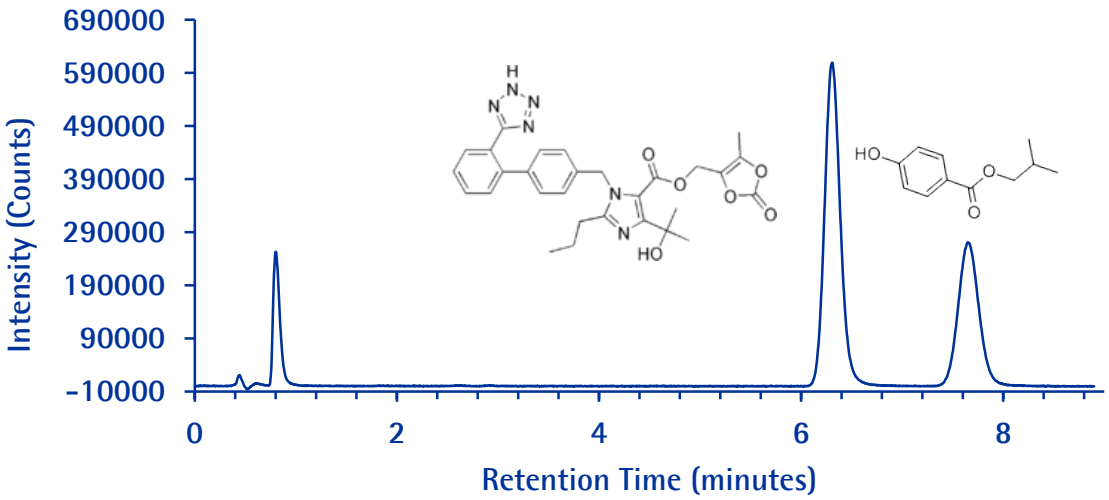
Chromatographic Data: (Standard solution)

Compound	Retention Time (min)	Resolution	Plates	Tailing Factor
t0 void volume	1.3			
Olmesartan RS	11.9		11270	1.10
p-HBA i-But ester	14.7	5.7	11345	1.08

Olmesartan medoxomil (USP)

Purospher® STAR RP-18 endcapped UHPLC - Assay

Column:	Purospher® STAR RP-18 endcapped (2 µm) 50x2.1mm	1.50651.0001
Injection:	2.1 µL	
Detection:	UV; 250nm	
Cell:	1.4 µL	
Flow Rate:	0.21mL/min	
Solution A:	15mM monobasic potassium phosphate pH=3.4	
Solution B:	Acetonitrile (Gradient Grade 1.00030)	
Mobile Phase:	Buffer and Acetonitrile 33:17 (v/v)	
Temperature:	40°C	
Diluent 1	Acetonitrile:Water 4:1	
Diluent 2	Acetonitrile:Water 2:3	
Standard solution:	0.05mg/mL of Olmesartan medoxomil RS of the Standard Stock solution and 0.025mg/mL of p-Hydroxybenzoic acid isobutyl ester from the internal Standard solution in Diluent 2	
Standard Stock soln:	1mg/mL of Olmesartan medoxomil RS in Diluent 1	
Internal Standard	0.5mg/mL of p-Hydroxybenzoic acid isobutyl ester in Diluent 2	
Pressure Drop:	48 Bar (696 psi)	



System Suitability criteria:
Resolution: NLT 4 between Olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester

Chromatographic Data: (Standard solution)

Compound	Retention Time (min)	Resolution	Plates	Tailing Factor
t0 void volume	0.7			
Olmesartan RS	6.4		7962	1.13
p-HBA i-But ester	7.8	4.0	6527	1.09

Olmesartan medoxomil (USP)

Validation and Verification HPLC – Assay

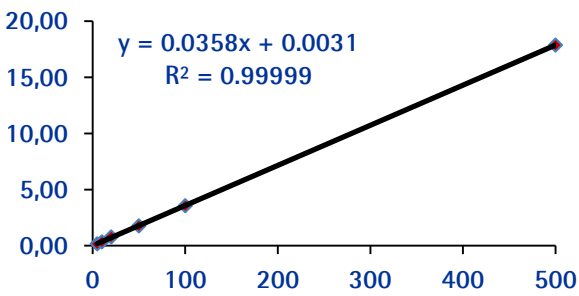
1. **Specificity**
   Determined by injection of SST Solution and determination of the retention time and relative retention time for Olmesartan medoxomil RS A and Olmesartan medoxomil RS using a Purospher® STAR RP-18 endcapped (5µm) 150x4.6 mm column.

Compound	Retention Time (min)	RRT	Tailing factor	Resolution
Olmesartan medoxomil	22.1	-	1.0	-
p-HBA i-Butyl ester	31.4	0.70	1.0	9.8

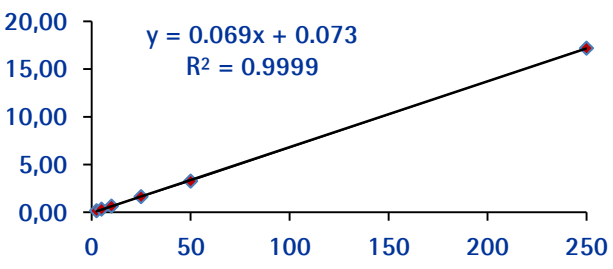
2. **Linearity, Limit of Detection (LOD) and Limit of Quantitation (LOQ).**
   Determined by injecting six (6) concentration levels from 5-500 ppm of Olmesartan medoxomil RS, and six (6) concentration levels ranging from 2.5-250 ppm of p-Hydroxybenzoic acid isobutyl ester

	[Olmesartan medoxomil] (ppm)	Area (mAU*min)	[p-HBA i-Butyl ester] (ppm)	Area (mAU*min)
	5	0.17	2.5	0.15
	10	0.35	5.0	0.33
	20	0.79	10	0.65
	50	1.77	25	1.63
	100	3.56	50	3.26
	500	17.88	250	17.20
STEYX		0.0031		0.0734
SLOPE		0.0358		0.0690
LOD		3.5		3.5
LOQ		10.7		10.7

Olmesartan medoxomil



p-Hydroxybenzoic acid isobutyl ester

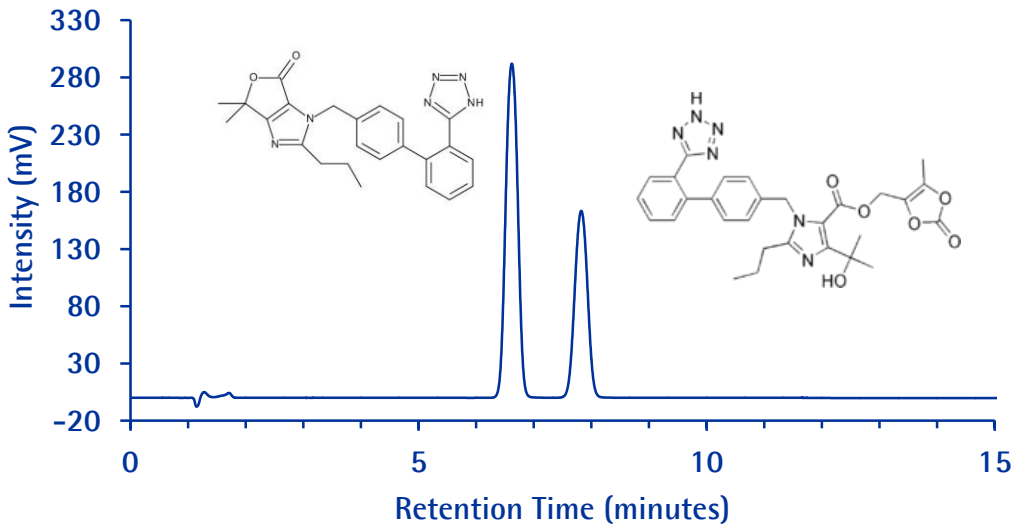


Olmesartan medoxomil (USP)

Purospher® STAR RP-18 endcapped HPLC – RS

Column:	Purospher® STAR RP-8 endcapped (3 µm) 100x4.6 mm	1.50013.7220
Injection:	10 µL	
Detection:	UV; 250nm	
Cell:	11 µL	
Flow Rate:	1mL/min	
Solution A:	15mM monobasic potassium phosphate pH=3.4	
Solution B:	Acetonitrile (Gradient Grade 1.00030)	
Mobile Phase:	A : Solution A : Solution B 4:1 (v:v) B : Solution A : Solution B 1:4 (v:v)	
Gradient:	See table	
Temperature:	40°C	
Diluent	Acetonitrile	
Standard for Impurity	0.01mg/mL of Olmesartan medoxomil RS in Acetonitrile	
Sample for Impurity	1mg/mL of Olmesartan medoxomil RS in Acetonitrile	
SST for Impurity	0.01mg/mL each of Olmesartan medoxomil RS and related compound A in Acetonitrile	
Pressure Drop:	48-108 Bar (696-1566psi)	

Time (min)	A (%)	B (%)
0	75	25
10	75	25
35	0	100
45	0	100



System Suitability criteria:
Resolution: NLT 5 between Olmesartan medoxomil and Olmesartan medoxomil RS A

Chromatographic Data: (SST solution)

Compound	Retention Time (min)	Resolution	Plates	Tailing Factor
t0 void volume	1.3			
Olmesartan RS A	6.6		5004	1.00
Olmesartan RS	7.8	5.7	5926	1.00

Olmesartan medoxomil (USP)

Validation and Verification HPLC – RS

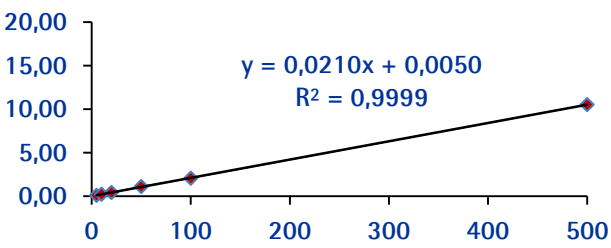
1. **Specificity**
   Determined by injection of SST Solution and determination of the retention time and relative retention time for Olmesartan medoxomil RS A and Olmesartan medoxomil RS using a Purospher® STAR RP-8 endcapped (3 µm) 100x4.6 mm column.

Compound	Retention Time (min)	RRT	Tailing factor	Resolution
Olmesartan medoxomil RS A	6.6	-	1.0	-
Olmesartan medoxomil	7.8	0.85	1.0	5.7

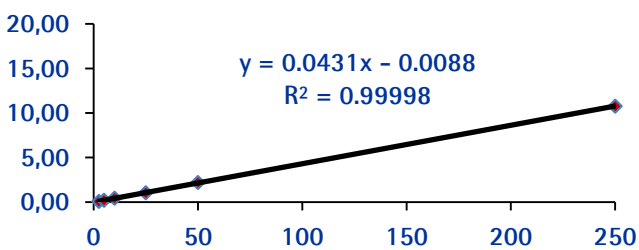
2. **Linearity, Limit of Detection (LOD) and Limit of Quantitation (LOQ).**
   Determined by injecting six (6) concentration levels from 5-500 ppm of Olmesartan medoxomil RS, and six (6) concentration levels ranging from 2.5-250 ppm of Olmesartan medoxomil RS A

	[Olmesartan medoxomil] (ppm)	Area (mAU*min)	[Olmesartan medoxomil RS A] (ppm)	Area (mAU*min)
	5	0.10	2.5	0.08
	10	0.21	5.0	0.21
	20	0.43	10	0.43
	50	1.10	25	1.05
	100	2.07	50	2.19
	500	10.51	250	10.77
STEYX		0.0050		-0.0088
SLOPE		0.0210		0.0431
LOD		5.1		2.0
LOQ		15.3		6.2

Olmesartan medoxomil



Olmesartan medoxomil RS A



Olmesartan medoxomil (USP)

New LC-MS Compatible Related Substances Method

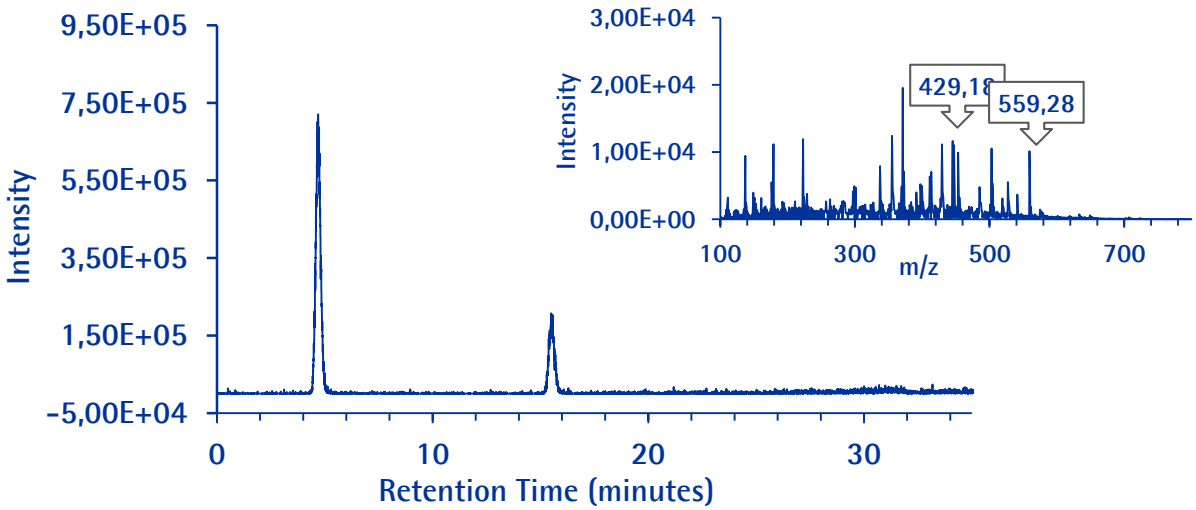
On the following pages, you will find presented a new alternative approach for the analysis of Olmesartan medoxomil and its related substance RS A (*1-{[2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one)* using LC-MS. The new procedure is both MS and UV compatible.

Column: Purospher® STAR RP-8 endcapped (2 µm) 100x2.1 mm 1.50653.0001
Injection: 2 µL
Detection: ESI-(+)-MS (m/z 100-800) Nebu.405 psi, Dry Gas 12L/min, Dry Temp.365°C, Scan mode - normal
Flow Rate: 210 µL/min

Mobile Phase:
Solution A: A : 90% Water + 10% Acetonitrile + 0,1% formic acid
Solution B: B: 10% Water + 90% Acetonitrile + 0,1% formic acid
Gradient: See table
Temperature: 40°C

Time (min)	A (%)	B (%)
0	75	25
10	75	25
35	0	100
45	0	100

Diluent Acetonitrile
SST for Impurity 0.01mg/mL each of Olmesartan medoxomil RS and related compound A in Acetonitrile
Pressure Drop: 51-102 Bar (734-1469 psi)



Chromatographic Data: (SST solution)

Compound	Retention Time (min)	Molecular Weight	m/z
Olmesartan RC A	4.8	428.5	429.2
Olmesartan RS	15.3	558.5	559.4

Merck Millipore is a division of Merck KGaA, Darmstadt, Germany
www.merckmillipore.com/perfect-solution

Olmesartan medoxomil (USP)

New LC-MS Compatible Related Substances Method

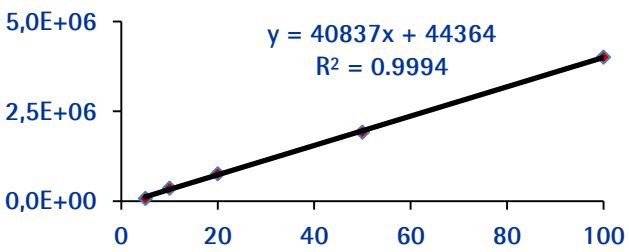
1. **Specificity**
   Determined by injection of SST Solution and determination of the retention time and relative retention time for Olmesartan medoxomil RS A and Olmesartan medoxomil RS using a Purospher® STAR RP-8 endcapped (2 µm) 100x2.1 mm column.

Compound	Retention Time (min)	Tailing factor	Resolution
Olmesartan medoxomil RS A	4.8	1.1	-
Olmesartan medoxomil	15.3	1.1	>>5

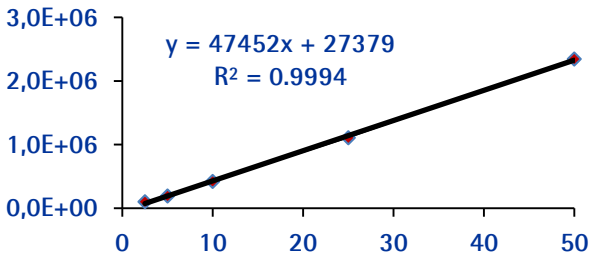
2. **Linearity, Limit of Detection (LOD) and Limit of Quantitation (LOQ).**
   Determined by injecting six (6) concentration levels from 5-500 ppm of Olmesartan medoxomil RS, and six (6) concentration levels ranging from 2.5-250 ppm of Olmesartan medoxomil RS A

	[Olmesartan medoxomil] (ppm)	Counts	[Olmesartan medoxomil RS A] (ppm)	counts
	5	75999	2.5	101188
	10	362596	5.0	191738
	20	764244	10	420902
	50	1920491	25	1108372
	100	4009862	50	2345859
STEYX		44364		27379
SLOPE		40837		47452
LOD		3.6		1.9
LOQ		10.9		5.8

Olmesartan medoxomil



Olmesartan medoxomil RS A



Olmesartan medoxomil (USP)

Water Determination <USP 921>

Pharmaceutical products are often characterized by complex formulations. Difficulties observed during Karl Fischer determination are often caused by the limited solubility. In some cases side reactions have to be considered. In dependence of composition and properties of the formulations, various measures are necessary for an undisturbed Karl Fischer determination.

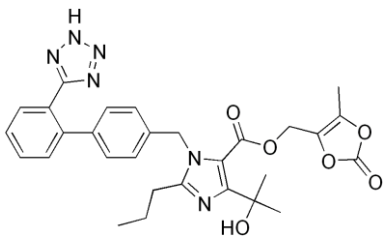
In the case of Olmesartan Medoxomil the water determination can be carried out without problems according to standard methods.

In pharmaceutical guidelines (USP, Ph Eur, DAB) the Karl Fischer titration is described as common method for water determination. For some substances special procedures can be found. The determination of mass loss as method for water determination is not recommended.

Titration one component system

Working Medium: apura® - CombiCoulomat fritless - Coulometric KF reagent for cells with or without diaphragm; 100 mL (1.09257)

Titration parameters
Stirring time: 60s
Default coulometer settings for cell without diaphragm:
For end point indication, e.g.:
I(pol) = 5 - 10 µA, U(EP) = 50 - 100 mV
Stop criterion for fast titration: drift < 20 µg/min
Sample size: 0.4 g (we used Olmesartan medoxomil RS)



Result:
Measured water content in Olmesartan: 0,054% (USP - requirement: < 0,5%)

Procedure
The Karl-Fischer reagent is placed into the titration cell without diaphragm. The coulometer is started and the solvent is titrated dry. After preliminary titration and stabilization of drift the sample is added into the titration cell with a weighing boat (exact sample weight determination by weighing of weighing boat before and after injection) and the water determination is started. For complete dissolution of the sample a stirring time of 60 seconds is recommended.

Product	P/N
CombiCoulomat fritless Karl Fischer reagent for coulometric water determination for cells with and without diaphragm apura®	1.88002

Olmesartan medoxomil (USP)

ICP-MS (USP 232/233)

The sample was tested on a high resolution ICP-MS instrument.
The following metal impurities were measured: Cd, Pb, As, Hg, Ir, Os, Pd, Pt, Rh, Ru, Cu, Mo, Ni, V.

Sample preparation:
0.1 g sample was digested (closed microwave digestion) in 3 mL HNO_3 with 1 mL HCl and 2 mL H_2O_2.

Calibration (using ICP multi-element standards):

For both oral dosage and parenteral dosage the impurities were tested.
Thus, the calibration of the HR-ICP-MS was performed for oral and parenteral dosage.

The limits of impurities are:

Oral dose			Parenteral dose		
Element		PDE*	Element		PDE*
Iridium	Ir	100	Iridium	Ir	10
Osmium	Os	100	Osmium	Os	10
Palladium	Pd	100	Palladium	Pd	10
Platinum	Pt	100	Platinum	Pt	10
Rhodium	Rh	100	Rhodium	Rh	10
Ruthenium	Ru	100	Ruthenium	Ru	10
Cadmium	Cd	25	Cadmium	Cd	2,5
Lead	Pb	5	Lead	Pb	5
Arsenic	As	1,5	Arsenic	As	1,5
Mercury	Hg	15	Mercury	Hg	1,5
Copper	Cu	1000	Copper	Cu	100
Molybdenum	Mo	100	Molybdenum	Mo	10
Nickel	Ni	500	Nickel	Ni	50
Vanadium	V	100	Vanadium	V	10

*PDE: Permissible Daily Dose based on a person of 50 kg [µg/day]

The calibration standards were diluted in either nitric acid or hydrochloric acid.
For oral dose the ICP multi-element standards (5.05101.0100 and 5.05103.0100) were used.
The multi-element standard (5.05101) that contains Cd, Pb, As, Hg, Cu, Mo, Ni, V was diluted in nitric acid.
The multi-element standard (5.05103) that contains Ir, Os, Pd, Pt, Rh, Ru was diluted in hydrochloric acid.

For parenteral dose the ICP multi-element standards 5.05102.0100 and 5.05104.0100 were used.
The multi-element standard 5.05102 that contains Cd, Pb, As, Hg, Cu, Mo, Ni, V was diluted in nitric acid.
The multi-element standard 5.05104 that contains Ir, Os, Pd, Pt, Rh, Ru was diluted in hydrochloric acid.