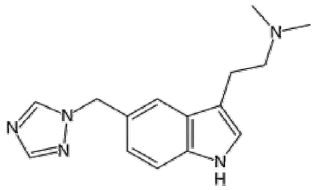
Rizatriptan and Related Substances (USP)

Purospher® STAR Phenyl



Rizatriptan

Rizatriptan is a 5-HT1 receptor agonist for the treatment of migraine headaches.
Common brand name is Maxalt.

The current USP monograph method for Rizatriptan and related substances as well as the assay method specifies the use of a 250x4.6 mm column with 5 µm L11 (Phenyl) packing as stationary phase. System suitability criteria in the assay method specify that the relative retention times for rizatriptan and benzoic acid are 1.0 and about 2.1, respectively., as well as a tailing factor NMT 3.5 for rizatriptan. System suitability requirements for related substances are; the relative retention times for rizatriptan, rizatriptan impurity C, and benzoic acid are 1.0, about 1.3, and about 2.1 RRT. The resolution is NLT 2.0 between rizatriptan and rizatriptan impurity C; and using the sensitivity solution the signal-to-noise ratio should be NLT 10 for the rizatriptain peak.

The following pages illustrate that the acceptance criteras are met for the assay and there is higher resolution and retention for the impurites in the Rizatriptan and related substances method by following the current USP monograph using a 250x4.6 mm Purospher® STAR Phenyl (5 µm) column.

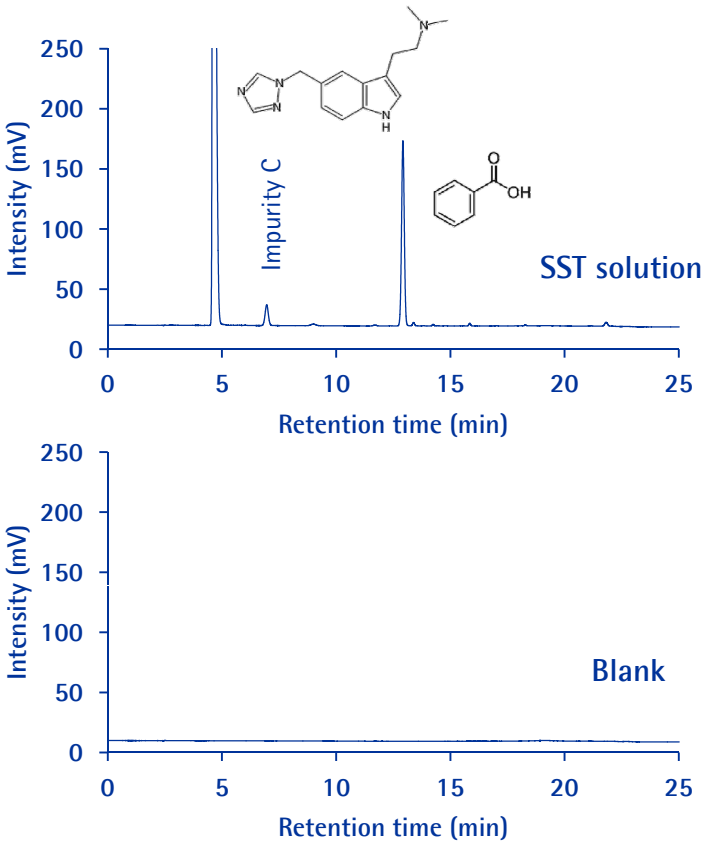
To address the current trend of monograph modernization, and improving the method in terms of selectivity, speed and sensitivity, we also scaled this method to a 100x2.1 mm UHPLC column; Purospher® STAR Phenyl (2 µm). Also in this example, all the system suitability critera are met. This is however, a non-allowed scaling and would require a complete revalidation of the new method for approval. For gradient separations, changes in length, column inner diameter and particle size are not allowed. This is new in USP 37.

Rizatriptan and Related Substances (USP)

Purospher® STAR Phenyl – HPLC

Chromatographic Conditions

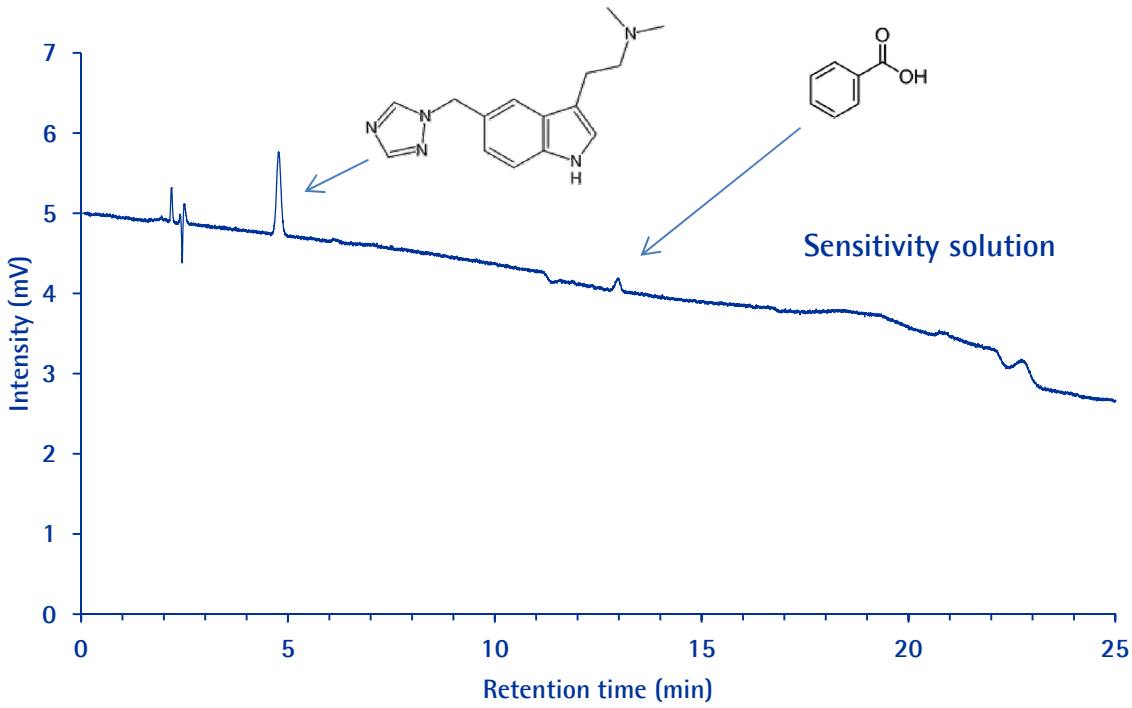
Column:	Purospher® STAR Phenyl (5µm) Hibar® RT 250x4.6 mm	1.51918.0001
Injection:	20 µL	
Detection:	UV 280 nm	
Cell:	10 µL	
Flow Rate:	1.5 mL/min	
Mobile Phase:	A: 1.0 mL of trifluroacetic acid to 1 L of a solution of acetonitrile and Water 4:21 (v/v), and mix. B: Acetonitrile and trifluroacetic acid 1000:1 (v/v) (or use our premixed product 4.80448)	
Gradient:	See table	
Temperature:	40°C	
Diluent:	Solution A	
Test Solution:	1 mg/mL of USP Rizatriptan Benzoate System Suitability Mixture in Solution A	
Resolution Solution:	0.5 µg/mL of Rizatriptan Benzoate obtained by suitable dilution of the Sample solution with Solution A	
Pressure Drop:	140 - 129 Bar (2030 - 1871 psi)	



Time (min)	A (%)	B (%)
0.0	100	0
8.0	100	0
17.0	70	30
20.0	70	30
20.1	100	0
23.0	100	0

Rizatriptan and Related Substances (USP)

Purospher® STAR Phenyl – HPLC



Chromatographic Data :

No.	Compound	Retention Time (min)	Resolution	RRT
1	Rizatriptan	4.6		1.00
2	Impurity C	7.0	9.1	1.52
3	Benzoic acid	12.9		2.80

	USP Specification	Observed value
S/N ratio of Sensitivity solution	NLT 10	12.6

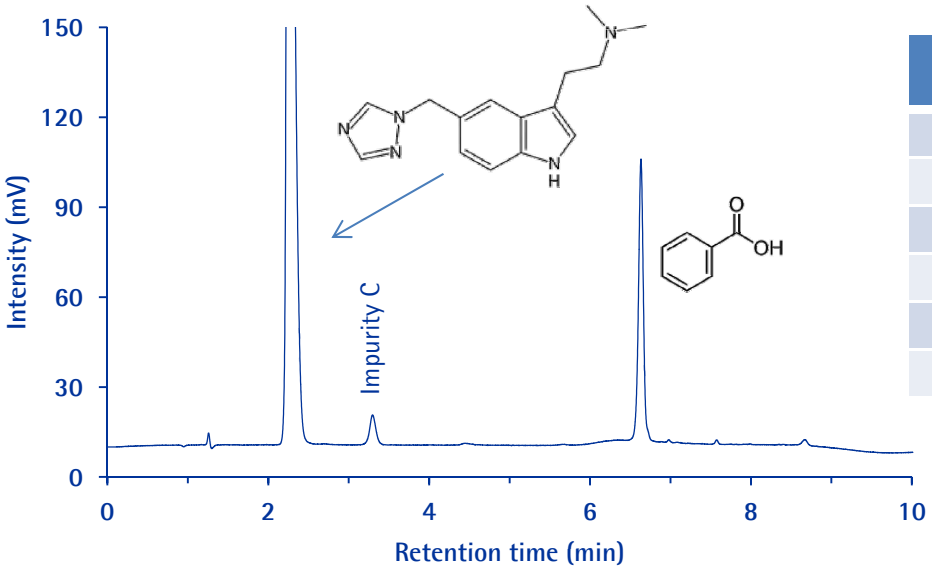
The benzoic acid retention time is somewhat larger than the specified value in the current monograph (and more than ± 10% of tabulated RRT). This deviation would most likely be approved benzoic acid is both well separated from the API and not interfering with the analysis of any other impurities.

Rizatriptan and Related Substances (USP)

Purospher® STAR Phenyl – UHPLC

Chromatographic Conditions

Column:	Purospher® STAR Phenyl (2µm) Hibar® HR 100x2.1 mm	1.51014.0001
Injection:	2 µL *(appropriate scaling per column tube volume reduction)*	
Detection:	UV 280 nm	
Cell:	2.5 µL	
Flow Rate:	0.25 mL/min *(not scaled according to linear velocity)*	
Mobile Phase:	A: Add 1.0 mL of trifluroacetic acid to 1 L of a solution of acetonitrile and water; 4:21 (v/v) B: Acetonitrile and trifluroacetic acid 1000:1 (v/v) (or use our premixed product 4.80448)	
Gradient:	See table	
Temperature:	40°C	
Diluent:	Solution A	
Test Solution:	1 mg/mL of USP Rizatriptan Benzoate System Suitability Mixture in Solution A	
Resolution Solution:	0.5 µg/mL of Rizatriptan Benzoate obtained by suitable dilution of the Sample solution with Solution A	
Pressure Drop:	205 - 195 Bar (2973 - 2828 psi)	



Time (min)	A (%)	B (%)
0.0	100	0
2.55	100	0
5.67	70	30
6.67	70	30
6.7	100	0
10.0	100	0

Chromatographic Data :

No.	Compound	Retention Time (min)	Resolution	RRT
1	Rizatriptan	2.2		1.00
2	Impurity C	3.3	6.7	1.50
3	Benzoic acid	6.6		3.00

Merck Millipore is a division of Merck KGaA, Darmstadt, Germany
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