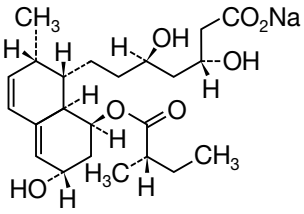

Pravastatin Sodium and Related Substances – Ph. Eur. monograph 2059

MACHEREY NAGEL application department · Dr. H. R. Wollseifen, T. Kretschmer, R. Nuessgen

Application benefits

- HPLC method with faster separations within allowable adjustments
- Shorter runtimes
- Lower solvent consumption
- Optimized system suitability

MN products

REF 760103.46
EC HPLC column (analytical), NUCLEODUR® C18 Gravity, 5 µm, 150x4.6 mm

REF 763134.46
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x4.6 mm

REF 763134.20
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x2 mm

REF 702107
Screw closure, N 9, PP, yellow, center hole, Silicone white/PTFE red, 1.0 mm

REF 702079
Screw neck vial, N 9, 11.6x32.0 mm, 1.5 mL, label, flat bottom, amber, silanized

MN application numbers

HPLC: 129230 HPLC: 129240
HPLC: 129250

Keywords

Pravastatin Sodium, Ph. Eur. monograph 2059, NUCLEOSHELL® RP 18, NUCLEODUR® C18 Gravity, L1, European Pharmacopeia

Introduction

The Ph. Eur. monograph 2059 describes the separation of Pravastatin Sodium from impurities. This work starts using a fully porous HPLC phase and shows the benefits using superficially porous particles. The method optimization was performed to achieve shorter run time and system suitability results within allowable adjustments.

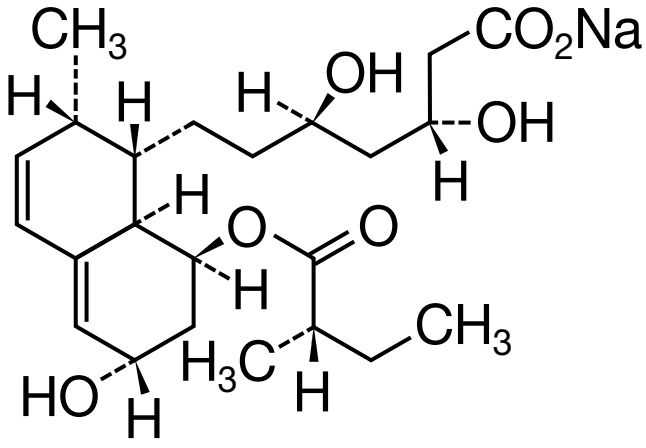

Figure 1: Pravastatin Sodium

Ph. Eur. Monograph 2059 method parameters

Method Parameter	Description
Test Solution	(a) Dissolve 0.1000 g of Pravastatin 1,1,3,3-tetramethylbutylamine CRS* in the solvent mixture (methanol R, water R (45:55 v/v)) and dilute to 100.0 mL with the solvent mixture (b) Dilute 10.0 mL of the test solution (a) to 100.0 mL with the solvent mixture
Reference Solution (a)	Dissolve the contents of a vial of Pravastatin Impurity A CRS* in 1.0 mL of test solution (b)
Column Size	150 x 4.6 mm
Stationary Phase	End-capped octadecylsilyl silica gel for chromatography R (5 µm)
Mobile Phase	Glacial acetic acid R, triethylamine R, methanol R1, water for chromatography (1:1:450:550 v/v/v/v).
Flow Rate	1.3 mL/min
Temperature	25 °C
Detection	UV, 238 nm
Injection	10 µL
Run Time	2.5 times the retention time of Pravastatin
Elution Order	1. Impurity A 2. Pravastatin
System Suitability Requirements Resolution (Reference Solution a)	Minimum resolution of 7.0 between peaks of Impurity A and Pravastatin

* Pravastatin 1,1,3,3-tetramethylbutylamine CRS (Y0000204) and Pravastatin Impurity A CRS (Y0000223) were purchased from European Directorate for the Quality of Medicines & HealthCare (EDQM) – Council of Europe; Postal address: 7 Allee Kastner CS 30026F - 67081 STRASBOURG (France).

Table 1: Ph. Eur. monograph 2059 details.

Chromatographic methodology improvements

Figure 2: a

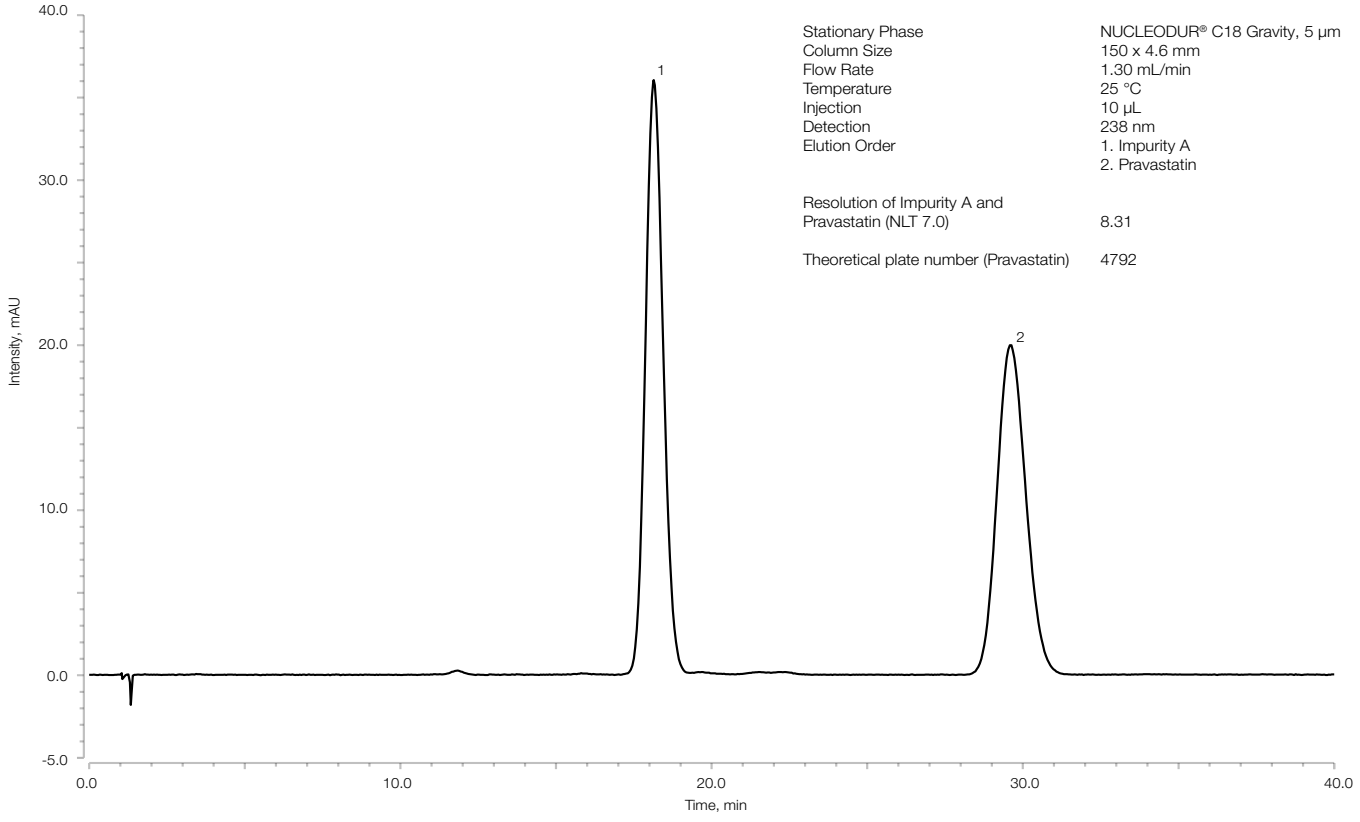

Figure 2: b

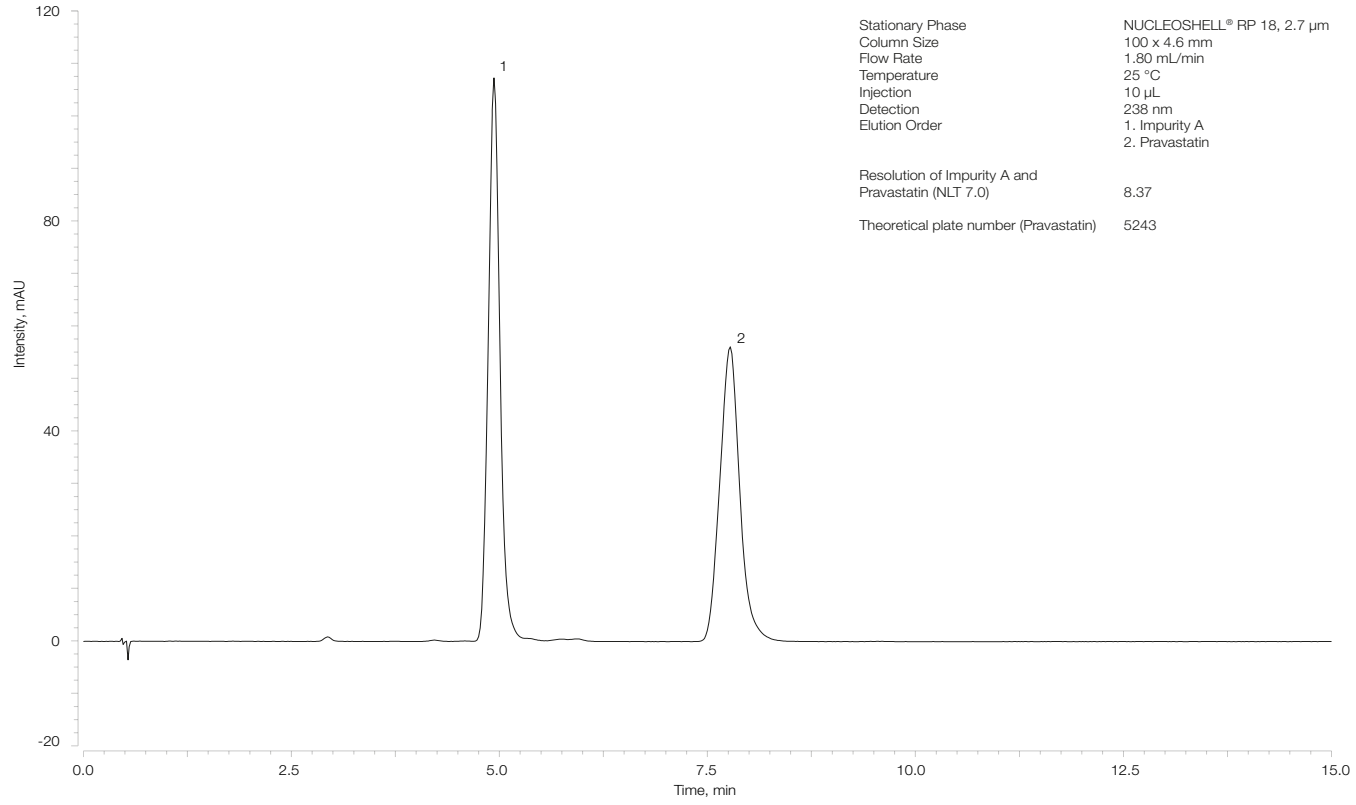

Figure 2: c

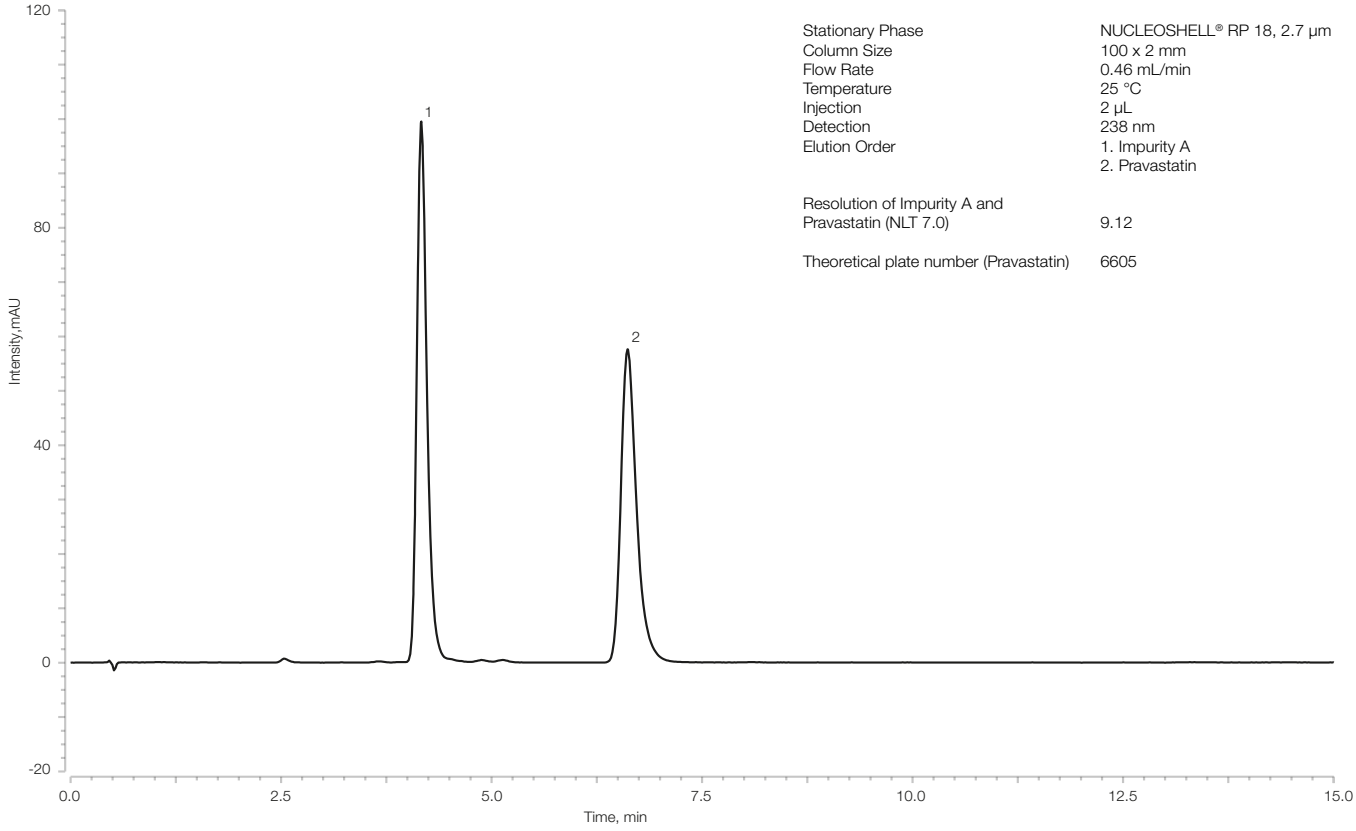

Figure 2: a: EC HPLC column (analytical), NUCLEODUR® C18 Gravity, 5 µm, 150x4.6 mm, b: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x4.6 mm, c: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x2 mm

Results

Method Parameter	Allowed Adjustments (isocratic elution)*	Method 1 (figure 2a)	Method 2 (figure 2b)	Method 3 (figure 2c)
Mobile phase pH	± 0.2 units	As specified	As specified	As specified
Concentration of salts in buffer	± 10%	As specified	As specified	As specified
Composition of the mobile phase	± 30% of the minor solvent component relative or 2% absolute, whichever is the larger. No other component is altered by more than 10% absolute.	As specified	As specified	As specified
Stationary phase	No change of C18 allowed	NUCLEODUR® C18 Gravity	NUCLEOSHELL® RP 18	NUCLEOSHELL® RP 18
Ratio column length/ particle size	Column length to particle size diameter ratio can be adjusted between –25% and + 50%	150 mm / 5 µm as specified	100 mm / 2.7 µm (+ 23.5%*)	100 mm / 2.7 µm (+ 23.5%*)
Column internal diameter	± 25%	4.6 mm as specified	4.6 mm as specified	2 mm
Flow rate	± 50% after adjustment due to a change in column dimensions	1.30 mL as specified	1.80 mL/min (– 25.3% after adjustments)	0.46 mL/min (± 0% after adjustments)
Column temperature	± 10 °C	25 °C as specified	25 °C as specified	25 °C as specified
Injection volume	May be decreased, provided detection and repeatability of the peak(s) to be determined are satisfactory	10 µL as specified	10 µL as specified	2 µL
Detection [nm]	No change permitted	238 nm as specified	238 nm as specified	238 nm as specified
Retention time (Pravastatin)		29.570 min	7.750 min (– 73.8%**)	6.610 min (– 77.6%**)
Theoretical plate number (Pravastatin)	Within – 25% to 50%, relative to the prescribed column***	4792	5243 (+ 9.4%**)	6605 (+ 37.8%)
System suitability requirements Resolution:	NLT 7.0 between Impurity A and Pravastatin	8.31	8.37	9.12

* Change in comparison to European Pharmacopeia 11.0, Chapter 2.2.46. Chromatographic separation techniques
** Change in comparison to method 1
*** Column used in method 1

Conclusion

The fully porous NUCLEODUR® C18 Gravity, 5 µm, 150x4.6 mm HPLC column from MACHEREY NAGEL fulfills all requirements of the Ph. Eur. monograph 2059. By using superficially porous NUCLEOSHELL® analytical columns the runtime of the method can be reduced by up to 77.6% (with NUCLEOSHELL® RP 18, 2.7 µm, 100x2 mm) compared to fully porous NUCLEODUR® silica gel, while keeping all method parameters well within the allowed adjustment range of the European Pharmacopeia. The reduction in runtime and flow rate leads to a lower solvent consumption optimizing the analysis of Pravastatin with regard to the guidelines of green chemistry. We were also able to reduce the required injection volume, while improving the resolution as well as the peak intensity with NUCLEOSHELL® columns compared to the original method with fully porous silica gel.

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