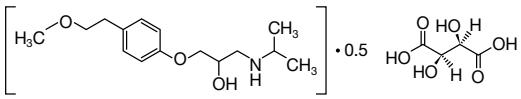


Metoprolol Tartrate and related substances – Ph. Eur. monograph 1028

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 720120.46
NUCLEOSIL® 100 – 5 C18, 5 µm, 150 × 4.6 mm

REF 763156.46
NUCLEOSHELL® RP 18, 5 µm, 150 × 4.6 mm

REF 763134.46
NUCLEOSHELL® RP 18, 2.7 µm, 100 × 4.6 mm

REF 763134.20
NUCLEOSHELL® RP 18, 2.7 µm, 100 × 2 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, 11.6 × 32.0 mm, 1.5 mL, label, flat bottom, amber, silanized

MN application numbers

HPLC: 129190
HPLC: 129200
HPLC: 129210
HPLC: 129220

Keywords

Metoprolol Tartrate, Ph. Eur. monograph 1028, NUCLEOSHELL® RP 18, NUCLEOSIL® 100 – 5 C18, L1, European Pharmacopeia

Introduction

The European Pharmacopeia (Ph. Eur.) monograph 1028 describes the separation of Metoprolol Tartrate 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 runtime and system suitability results within allowable adjustments.

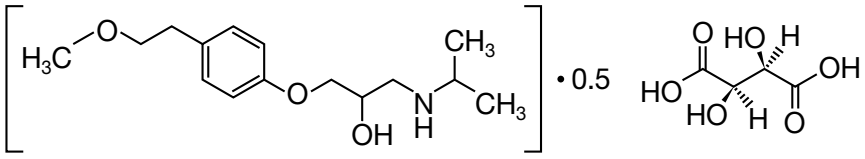


Figure 1: Metoprolol Tartrate

Ph. Eur. Monograph 1028 method parameters.

Method Parameter	Description
Reference Solution (a)	Dissolve 1.5 mg of Metoprolol Impurity A CRS*, 2.5 mg of Metoprolol Tartrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.
Column Size	150 × 3.9 mm
Stationary Phase	End-capped octadecylsilyl silica gel for chromatography R (5 µm)
Mobile Phase	Dissolve 3.9 g of ammonium acetate R in 810 mL of water R, add 2.0 mL of trimethylamine R, 10.0 mL of glacial acetic acid R, 3.0 mL of phosphoric acid R and 146 mL of acetonitrile R and mix
Flow Rate	1.0 mL/min
Detection	UV, 280 nm
Injection	20 µL
Run Time	3 times the retention time of Metoprolol Tartrate
Elution Order	1. Impurity A 2. Metoprolol Tartrate
System Suitability Requirements Resolution (Reference Solution a):	NMT 6.0 between Impurity A and Metoprolol

* Metoprolol impurity A CRS (Y0000145) and Metoprolol Tartrate CRS (M1830000) 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 1028 details.

Chromatographic methodology improvements

Figure 2: a

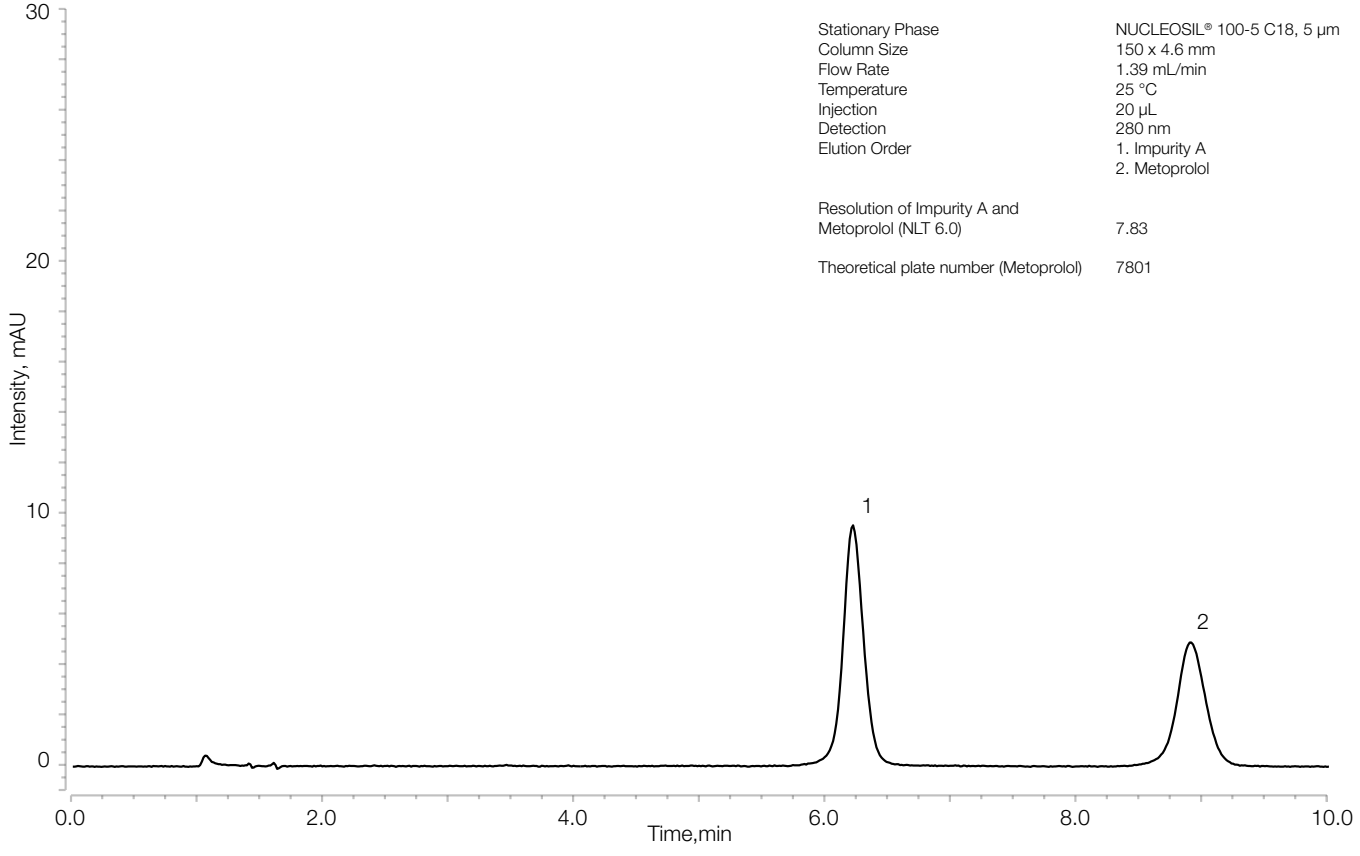
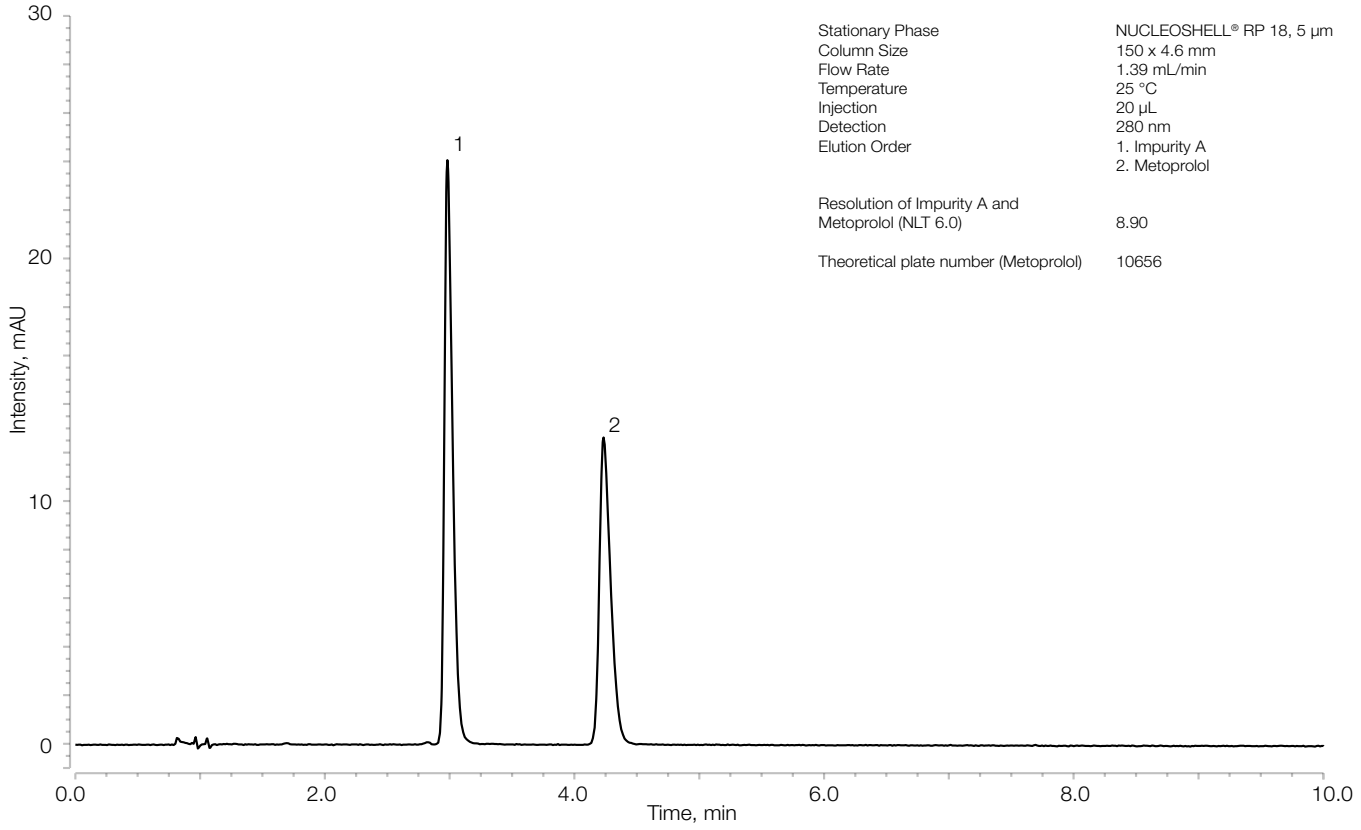
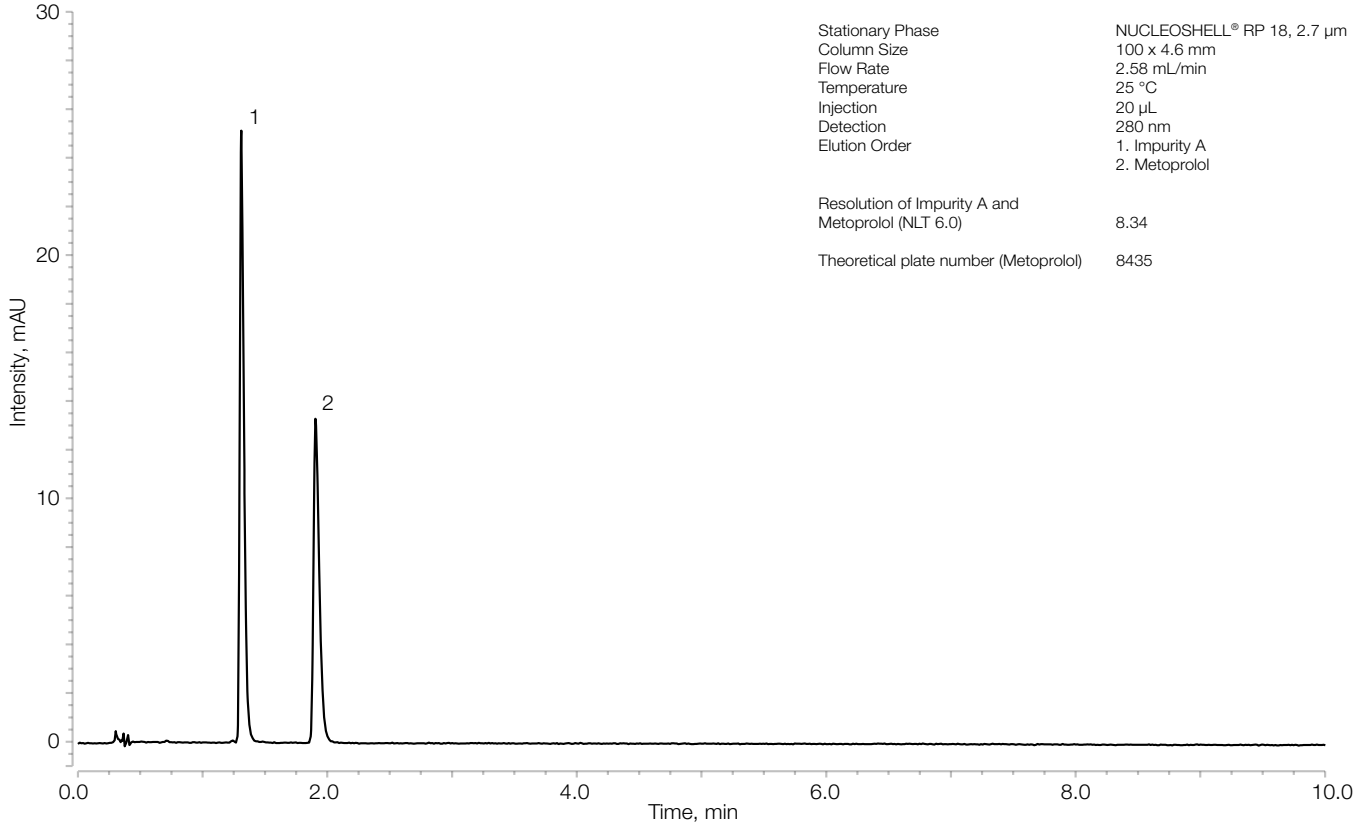


Figure 2: b



Stationary Phase	NUCLEOSHELL® RP 18, 5 µm
Column Size	150 x 4.6 mm
Flow Rate	1.39 mL/min
Temperature	25 °C
Injection	20 µL
Detection	280 nm
Elution Order	1. Impurity A 2. Metoprolol
Resolution of Impurity A and Metoprolol (NLT 6.0)	8.90
Theoretical plate number (Metoprolol)	10656

Figure 2: c



Stationary Phase	NUCLEOSHELL® RP 18, 2.7 µm
Column Size	100 x 4.6 mm
Flow Rate	2.58 mL/min
Temperature	25 °C
Injection	20 µL
Detection	280 nm
Elution Order	1. Impurity A 2. Metoprolol
Resolution of Impurity A and Metoprolol (NLT 6.0)	8.34
Theoretical plate number (Metoprolol)	8435

Figure 2: d

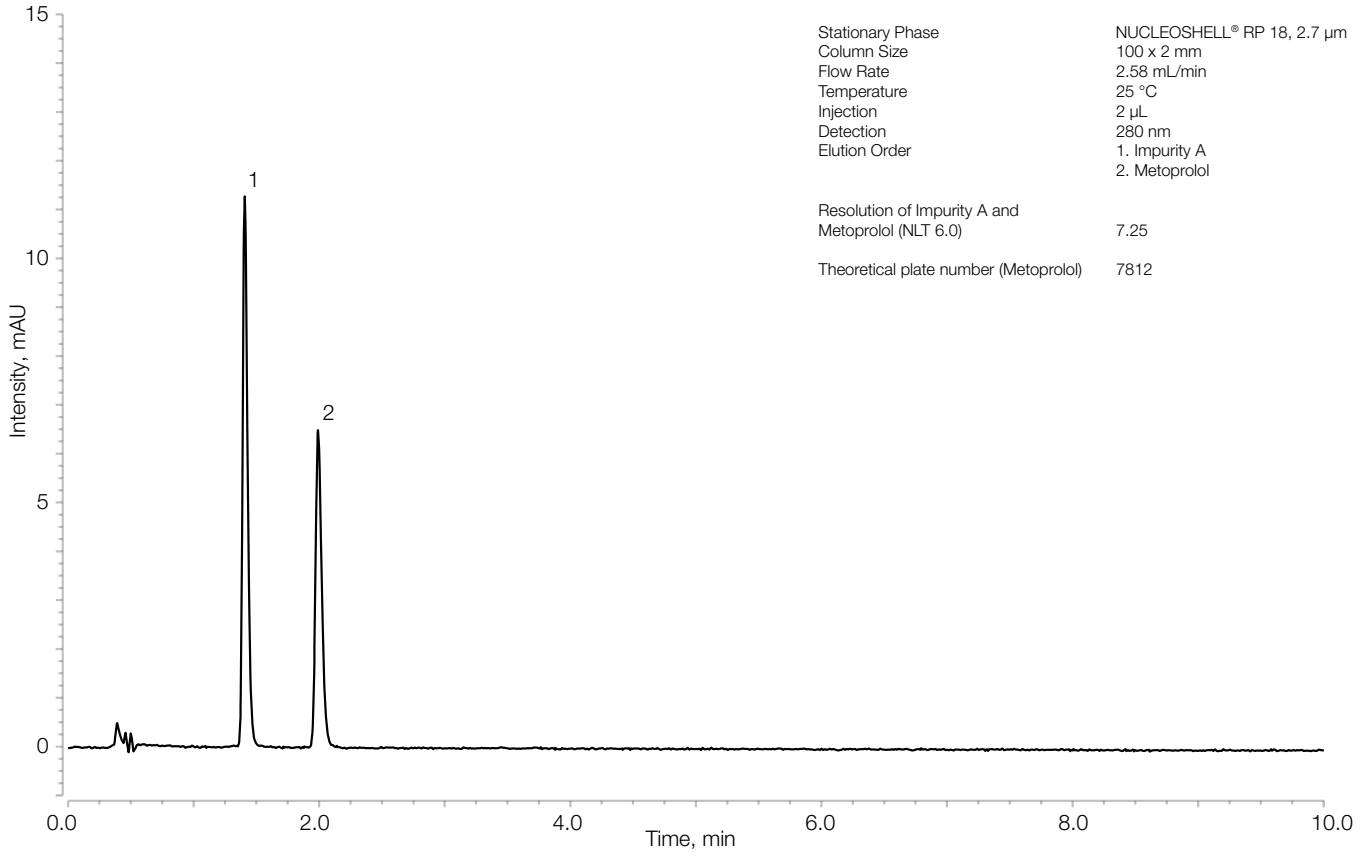


Figure 2: a: EC HPLC column (analytical), NUCLEOSIL® 100 – 5 C18, 5 µm, 150 × 4.6 mm, b: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 5 µm, 150 × 4.6 mm, c: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100 × 4.6 mm, d: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100 × 2 mm

Results

Method Parameter	Allowed Adjustments (isocratic elution)*	Method 1 (figure 2a)	Method 2 (figure 2b)	Method 3 (figure 2c)	Method 4 (figure 2d)
Mobile phase pH	± 0.2 units	As specified	As specified	As specified	As specified
Concentration of salts in buffer	± 10%	As specified	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	As specified
Stationary phase	No change of C18 allowed	NUCLEOSIL® C18 Gravity	NUCLEOSHELL® RP 18	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	150 mm / 5 µm as specified	100 mm / 2,7 µm (+ 23.5%)	100 mm / 2,7 µm (+ 23.5%)
Column internal diameter	Can be adjusted so long as linear velocity is maintained	4.6 mm	4.6 mm	4.6 mm	2 mm
Flow rate	± 50% after adjustment due to a change in column dimensions	1.39 mL/min	1.39 mL/min	2.58 mL/min a	0.49 mL/min
Column Temperature	± 10 °C	25 °C as specified	25 °C as specified	25 °C as specified	25 °C as specified

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Method Parameter	Allowed Adjustments (isocratic elution)*	Method 1 (figure 2a)	Method 2 (figure 2b)	Method 3 (figure 2c)	Method 4 (figure 2d)
Injection volume	May be decreased, provided detection and repeatability of the peak(s) to be determined are satisfactory	20 µL as specified	20 µL as specified	20 µL as specified	20 µL as specified
Detection (UV)	No change permitted	As specified (280 nm)	As specified (280 nm)	As specified (280 nm)	As specified (280 nm)
Retention time (Metoprolol)		8.91 min	4.24 min (– 52.5%**)	1.91 min (– 78.6%**)	1.99 min (– 77.6%**)
Theoretical plate number (Metoprolol)	Within – 25% to 50%, rela-tive to the prescribed column***	7801	10656 (+ 36.6%**)	8435 (+ 8.1%**)	7812 (+ 0.1%**)
System suitability requirements Resolution	NLT 6.0 between Impurity A and Metoprolol	7.83	8.90	8.34	7.25

* 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 NUCLEOSIL® 100 – 5 C18, 5 µm, 150 × 4.6 mm HPLC column from MACHEREY NAGEL fulfills all requirements of the Ph. Eur. monograph 1028. By using superficially porous NUCLEOSHELL® analytical columns the runtime of the method can be reduced by up to 78.6% (with NUCLEOSHELL® RP 18, 2.7 µm, 100 × 4.6 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 Metoprolol with regard to the guidelines of green chemistry. We were also able to reduce the required injection volume with NUCLEOSHELL® columns compared to the original method with fully porous silica gel.

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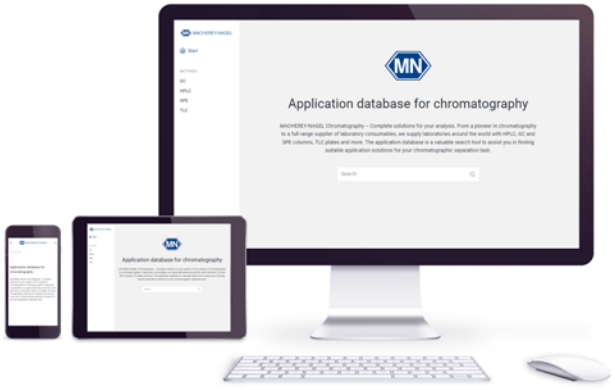

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