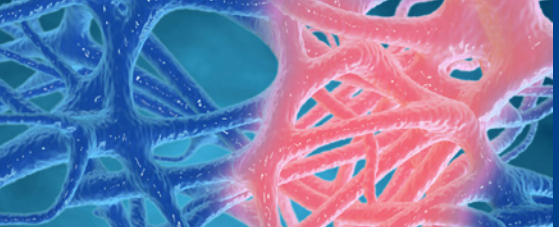

Diclofenac Sodium and Related Substances – Ph. Eur. monograph 1002

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

Application benefits

- HPLC method with faster separations within allowable adjustments.
- Shorter runtimes
- Optimized system suitability

MN products

REF 760101.46
EC HPLC column (analytical), NUCLEODUR® C18 Gravity, 5 µm, 250x4.6 mm

REF 763157.46
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 5 µm, 250x4.6 mm

REF 763156.46
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 5 µm, 150x4.6 mm

REF 763136.46
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 150x4.6 mm

REF 763134.46
EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x4.6 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: 129520 HPLC: 129550
HPLC: 129530 HPLC: 129560
HPLC: 129540

Keywords

Diclofenac Sodium, Ph. Eur. monograph 1002, NUCLEOSHELL® RP18, NUCLEODUR® Gravity C18, L1, European Pharmacopeia

Introduction

The Ph. Eur. Monograph 1002 describes the separation of Diclofenac 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.

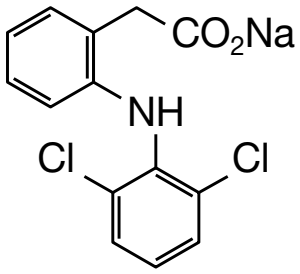

Figure 1: Diclofenac Sodium

Ph. Eur. Monograph 1002 method parameters

Method Parameter	Description
Test solution Reference solution (a) Reference solution (b)	Dissolved 50.0 mg of the substance to be examined in the mobile phase and diluted to 50.0 mL with the mobile phase. Diluted 2.0 mL of the test solution to 100.0 mL with the mobile phase. Diluted 1.0 mL of this solution to 10.0 mL with the mobile phase. Dissolved the contents of a vial of diclofenac for system suitability CRS (containing impurities A and F) in 1 mL of the mobile phase.
Column size	250 x 4.6 mm
Stationary phase	End-capped octadecylsilyl silica gel for chromatography R (5 µm)
Mobile phase	Mix 34 volumes of a solution containing 0.5 g/L of phosphoric acid R and 0.8 g/L of sodium dihydrogen phosphate R, previously adjusted to pH 2.5 with phosphoric acid R, and 66 volumes of methanol R.
Flow rate	1.0 mL/min
Detection	254 nm
Injection	20 µL
Run time	1.6 times the retention time of diclofenac (about 25 min)
Elution order	Impurity A Impurity F Diclofenac
System suitability Reference solution (b)	Minimum resolution of 4.0 between peaks due to Impurity F and Diclofenac

* Diclofenac for system suitability CRS* (Y0001635), and Diclofenac sodium CRS (S0765000) 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 1002 Diclofenac Sodium Method Details

Chromatographic methodology improvements

Figure 2: a

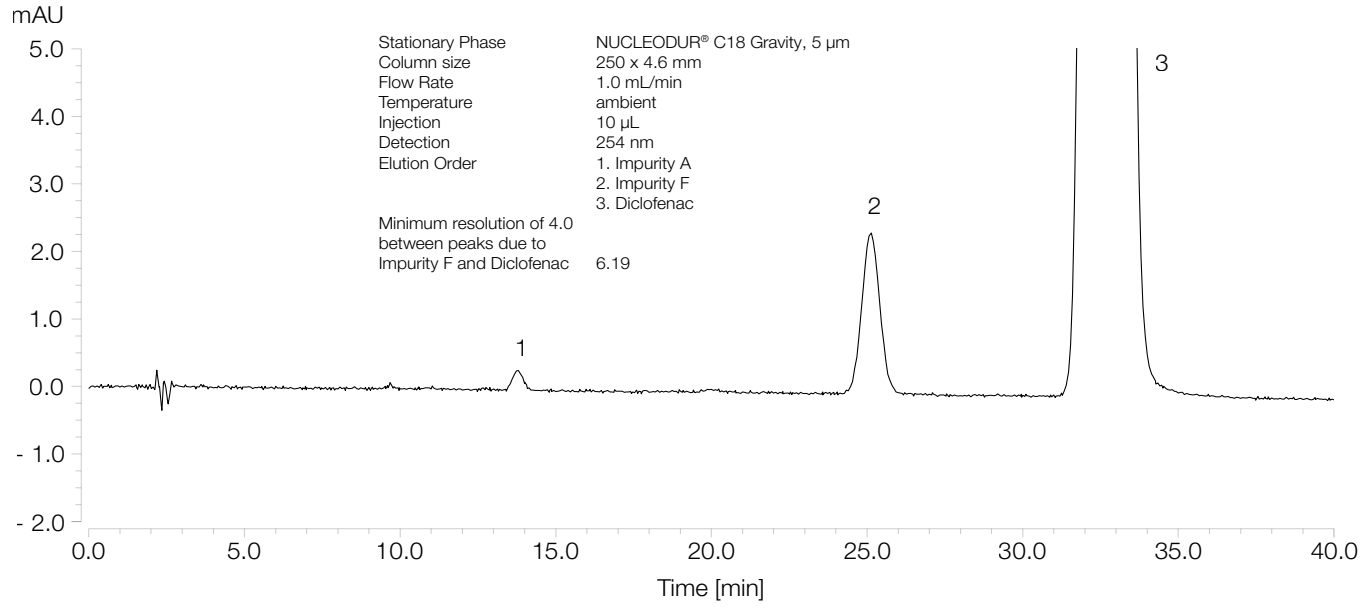

Figure 2: b

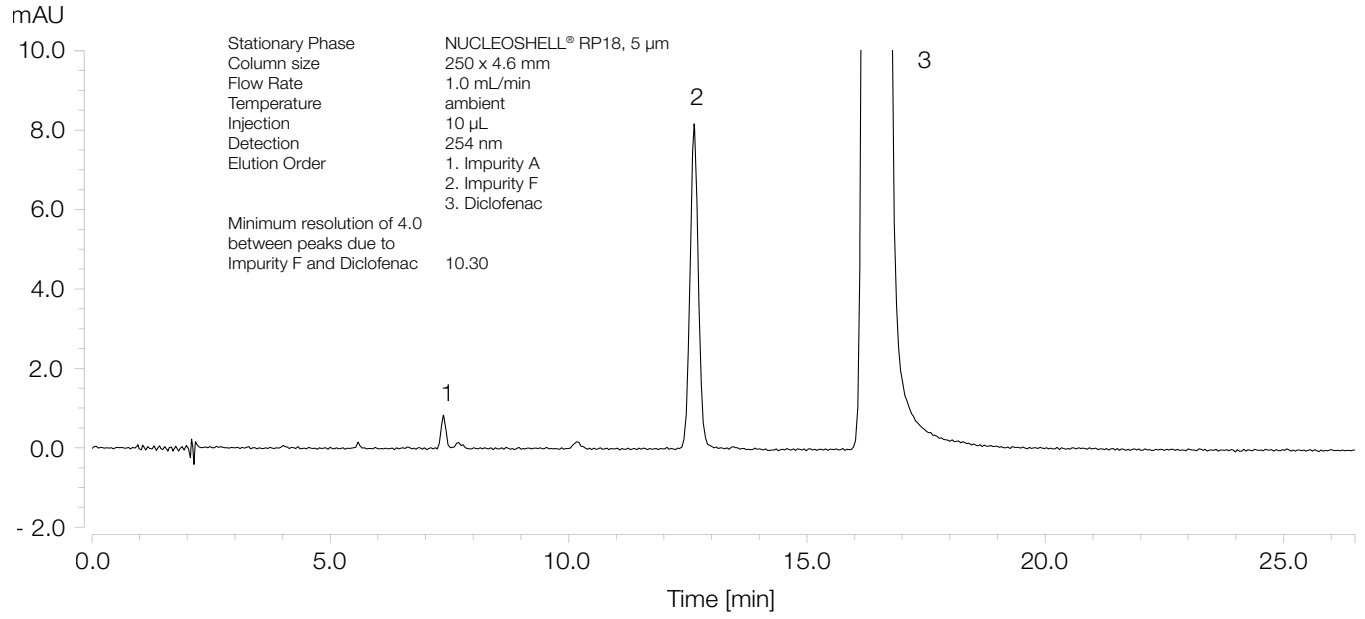

Figure 2: c

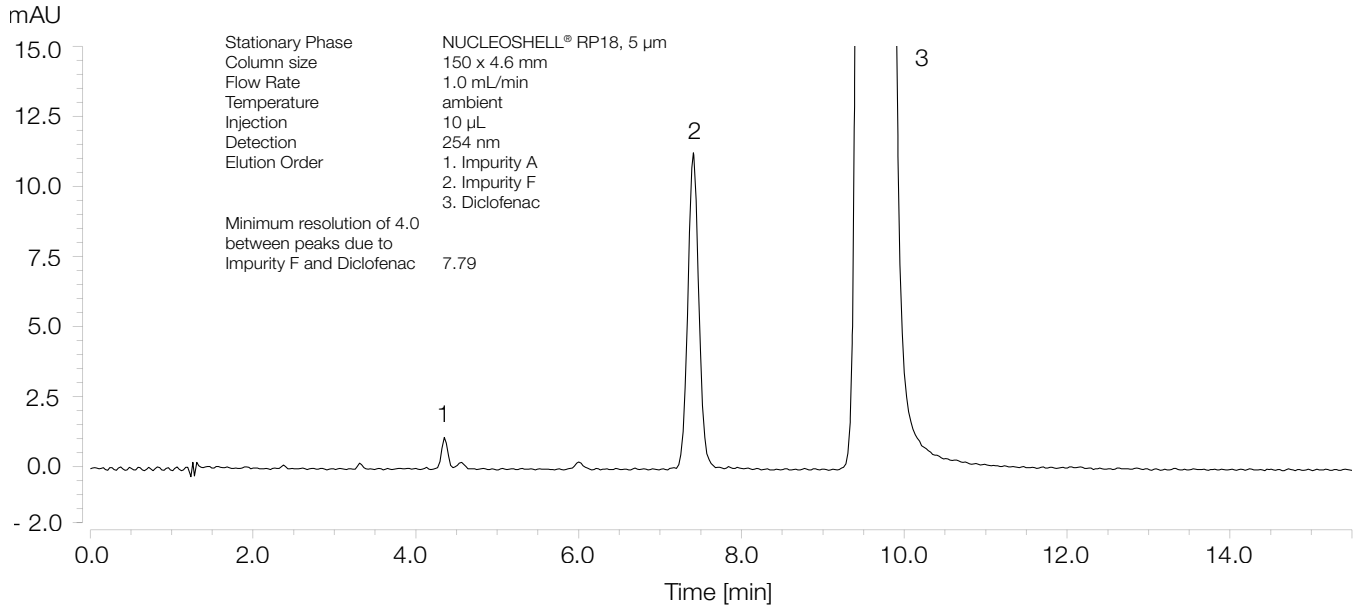

Figure 2: d

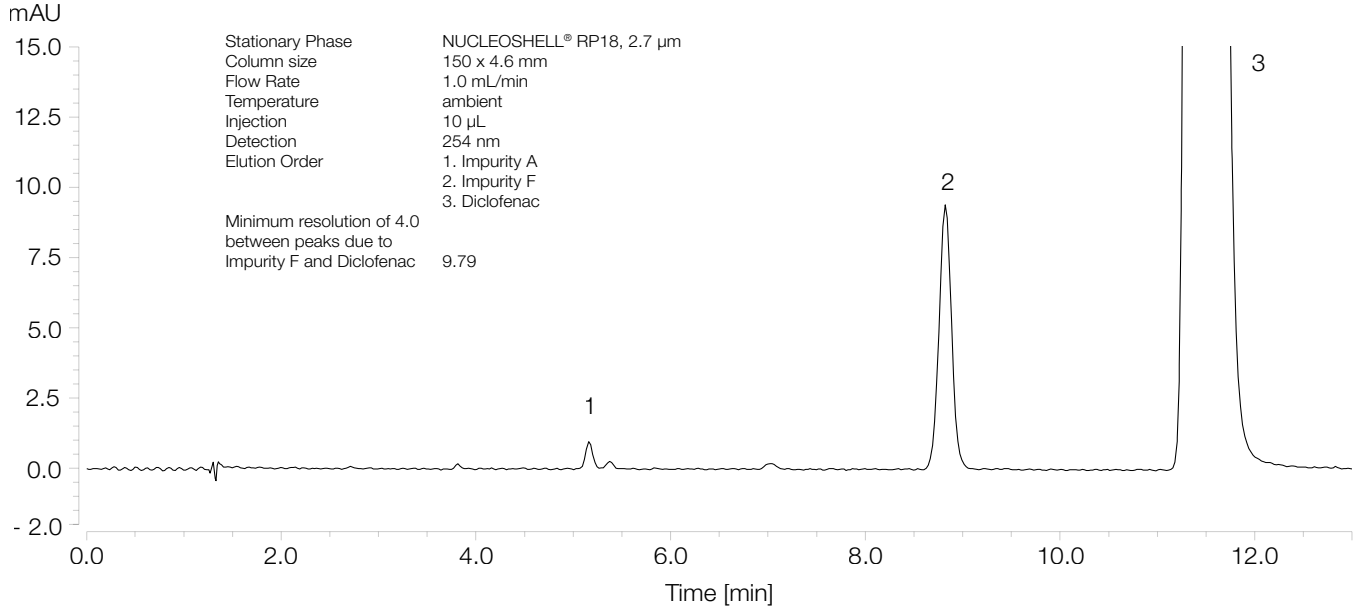

Figure 2: e

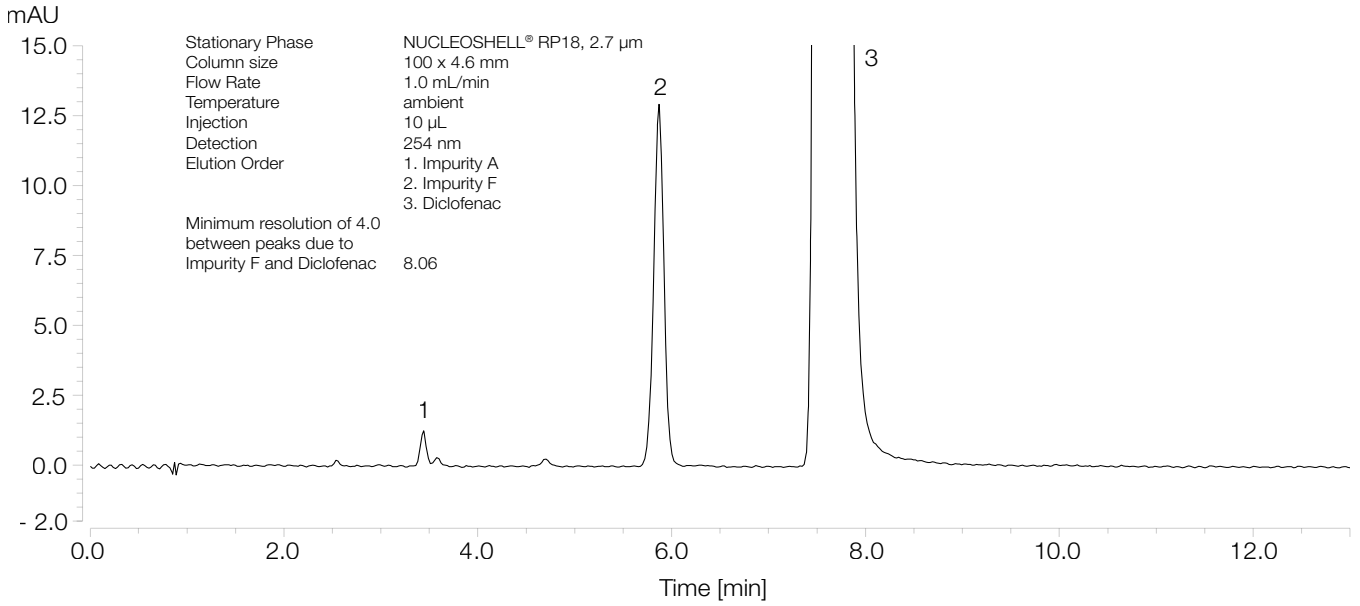

Figure 2: a: EC HPLC column (analytical), NUCLEODUR® C18 Gravity, 5 µm, 250x4.6 mm, b: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 5 µm, 250x4.6 mm, c: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 5 µm, 150x4.6 mm, d: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 150x4.6 mm, e: EC HPLC column (analytical), NUCLEOSHELL® RP 18, 2.7 µm, 100x4.6 mm

Results

Method Parameter	Allowed Adjustments (isocratic elution)	Method 1 (figure 2: a)	Method 2 (figure 2: b)	Method 3 (figure 2: c)	Method 4 (figure 2: d)	Method 5 (figure 2: e)
Mobile phase pH	± 0.2 units	As specified	As specified	As specified	As specified	As specified
Concentration of salts in buffer	± 10%	As specified	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 com-ponent is altered by more than 10% absolute.	As specified	As specified	As specified	As specified	As specified
Stationary phase	No change of C18 allowed	NUCLEODUR® C18 Gravity	NUCLEOSHELL® RP 18	NUCLEOSHELL® RP 18	NUCLEOSHELL® RP 18	NUCLEOSHELL® RP 18
Particle size	– 50%	5 µm as specified	5 µm as specified	5 µm as specified	2.7 µm (– 46%)	2.7 µm (– 46%)
Column length	± 70%	250 mm as specified	250 mm as specified	150 mm (– 40%)	150 mm (– 40%)	150 mm (– 40%)
Column internal diameter	± 25%	4.6 mm as specified	4.6 mm as specified	4.6 mm as specified	4.6 mm as specified	4.6 mm as specified
Flow rate	± 50%	1.0 mL as specified	1.0 mL as specified	1.0 mL as specified	1.0 mL as specified	1.0 mL as specified
Column temperature	± 10 °C	ambient as specified	ambient as specified	ambient as specified	ambient as specified	ambient as specified

Method Parameter	Allowed Adjustments (isocratic elution)	Method 1 (figure 2: a)	Method 2 (figure 2: b)	Method 3 (figure 2: c)	Method 4 (figure 2: d)	Method 5 (figure 2: e)
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	20 µL as specified
Detection [nm]	No change permitted	254 nm as specified	254 nm as specified	254 nm as specified	254 nm as specified	254 nm as specified
Run time	1.6 times the retention time of Diclofenac	52.2 min	26.2 min (– 49,8%**)	15.4 min (– 70.6%**)	18.3 min (– 64.9%**)	12.2 min (– 76.6%**)
System suitability Reference solution (b)	Minimum resolution of 4.0 between peaks due to Impurity F and Diclofenac	6.19	10.30	7.79	9.79	8.06

* European Pharmacopeia 9.0, Chapter 2.2.46. Chromatographic separation techniques, ** runtime reduction in comparison to method 1.

Conclusion

The fully porous NUCLEODUR® C18 Gravity, 5 µm, 250x4.6 mm HPLC column from MACHEREY-NAGEL fulfills all requirements of the Ph. Eur. monograph 1002. By using superficially porous NUCLEOSHELL® analytical columns the runtime of the method can be reduced by up to 76.6% (with NUCLEOSHELL® RP 18, 2.7 µm, 100x4.6 mm) compared to fully porous NUCLEODUR® silica gel, while keeping all method parameters well within the allowed adjustment range of the European Pharmacopeia. We were also able to improve 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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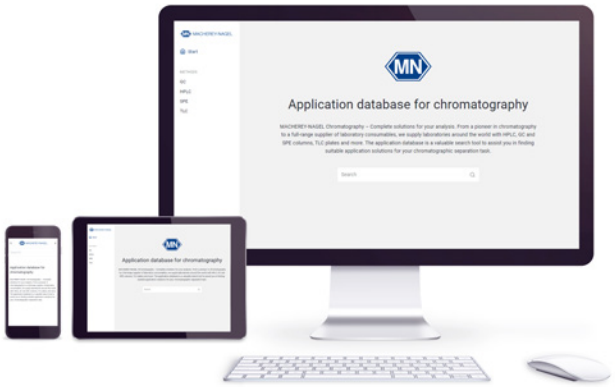

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