Modernizing the USP Monograph for Impurity Profiling of Metoprolol Tartrate

Application Note

Small Molecule Pharmaceuticals and Generics

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Abstract

An HPLC method was developed for profiling related compounds of the drug metoprolol tartrate. The method was developed on Agilent Poroshell 120 EC-C18 and Poroshell 120 Phenyl-Hexyl columns, with a gradient using a mass-spectrometer friendly buffer of ammonium acetate in water and acetonitrile. The sample was degraded by exposure to ultraviolet light at 254 nm. Degraded compounds can be easily separated and detected by this method with both Poroshell 120 columns.

Introduction

The United States Pharmacopeia (USP) has embarked on a global initiative to modernize many current monographs across all compendia [1]. Many of the methods in existing monographs apply traditional methods, including spectrophotometry, thin-layer chromatography (TLC) and other techniques for determination of impurities, related compounds or assay analysis. However, HPLC is an effective technique for pharmaceutical analysis, and more and more HPLC methods are included in USP.

In the USP method for metoprolol tartrate, chromatographic purity is determined using TLC [2]. We developed a new HPLC method to analyze possible related compounds in metoprolol tartrate simultaneously, using 2.7-µm superficially porous particle columns, including Poroshell 120 EC-C18 and Poroshell 120 Phenyl-Hexyl. These columns have efficiencies similar to that of sub-2-µm totally porous columns. This is attributed primarily to a shorter mass-transfer distance and a narrower particle size distribution. Furthermore, the larger particle size results in lower backpressure of only 50% to 60% that of sub-2 µm totally porous particles, allowing these columns to be used on virtually any LC system. The benefits of using 2.7 µm Poroshell 120 columns include very significant time and cost savings, because superficially porous particles are optimally run at faster flow rates and achieve similar resolution with a much shorter column length.

Materials and Methods

All reagents and solvents were HPLC or analytical grade. The metoprolol tartrate standard was purchased from USP. Ammonium acetate was purchased from J&K Scientific Ltd, Beijing, China.

The test solution was 0.5 mg/mL metoprolol tartrate in the mobile phase. The reference solution was made from diluting 1.0 mL of the test solution to 20.0 mL with the mobile phase, then diluting 3.0 mL of the solution to 50.0 mL with the mobile phase.

The degraded solution was prepared by dissolving 10 mg metoprolol tartrate in 10 mL of 0.1 M hydrochloric acid and transferring this solution to an evaporating dish 10 cm id. The dish was placed so that the surface of the solution was 5 cm from a lamp emitting ultraviolet light at 254 nm for 6 hours. Finally, the degraded solution (0.5 mL) was diluted to 25 mL with the mobile phase [3].

The study was performed on an Agilent 1290 Infinity LC with a 1290 Infinity Binary Pump (G4220A), 1290 Infinity Autosampler (G4226A), 1290 Infinity Thermostatted Column Compartment (G1316C), and 1290 Infinity Diode Array Detector (G4212A).

Conditions for Figures 1 and 2

Columns:	Agilent Poroshell 120 EC-C18, 3.0 × 100 mm, 2.7 µm (p/n 695975-302), Agilent Poroshell 120 Phenyl-Hexyl, 3.0 × 100 mm, 2.7 µm (p/n 695975-312)	
Mobile phase:	A, 10 mM Ammonium acetate; B, acetonitrile	
Gradient:	Time (min)	B%
	0	10
	5	50
Stop time:	10 min	
Flow rate:	0.5 mL/min	
Column temperature:	30 °C	
Injection volume:	2 µL	
Detector:	UV, 280 nm	

Results and Discussion

The European Pharmacopoeia (EP) 5.0 includes an HPLC method for determination of related substances in metoprolol tartrate [3]. An isocratic method with an EP-recommended C18 column is used for separation of impurities. The isocratic method allows a very long analysis time with a broadening peak, which leads to low sensitivity of impurities. We developed a gradient method using ammonium acetate and acetonitrile on 3.0 x 100 mm, 2.7-µm columns for separating impurities from metoprolol tartrate.

Figure 1 shows the separation of reference, test, and degraded solutions using Poroshell 120 EC-C18 with a total analysis time of 10 minutes. Several small peaks were found in the test solution. These impurities could be separated from metoprolol tartrate. Compared to the test solution, additional peaks were found in the degraded solution treated by acid and UV. The degraded compounds were easily separated from metoprolol tartrate and each other, with good peak shapes and high sensitivities.

The same method was repeated using Poroshell 120 Phenyl-Hexyl. This phenyl-hexyl bonded column has improved selectivity for aromatic compounds. According to the EP metoprolol tartrate monograph, the degraded compounds from metoprolol tartrate are mostly aromatic. The lower chromatogram in Figure 2 shows the degraded compound separation using Poroshell 120 Phenyl-Hexyl. The highlighted compounds, especially the first two peaks, have better resolution than on EC-C18 column. However, the peaks on Poroshell 120 Phenyl-Hexyl have lower sensitivities than on EC-C18 due to peak tailing.

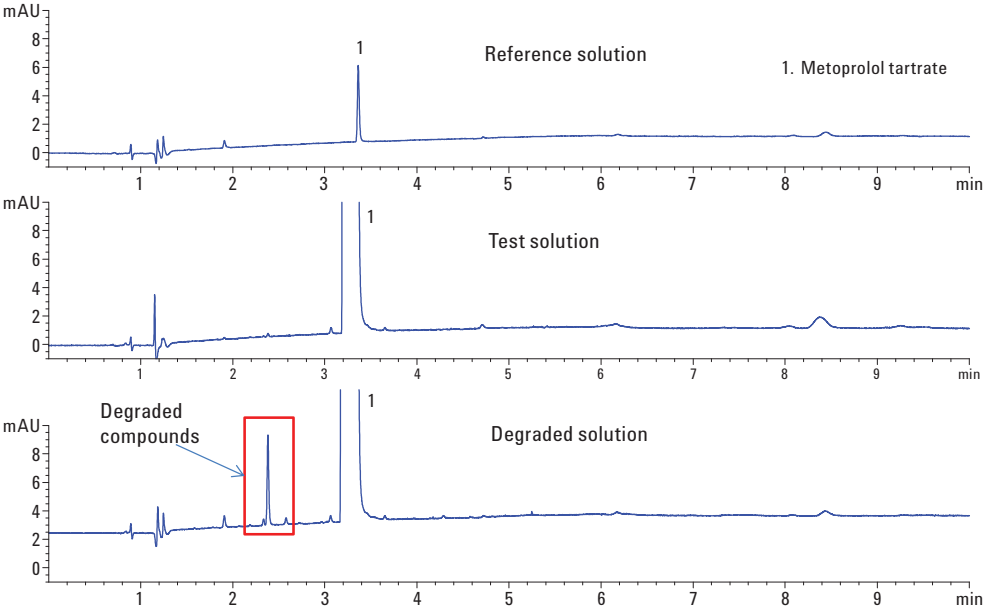

Figure 1. Overlay chromatograms of reference, test, and degraded solutions of metoprolol tartrate using Agilent Poroshell 120 EC-C18.

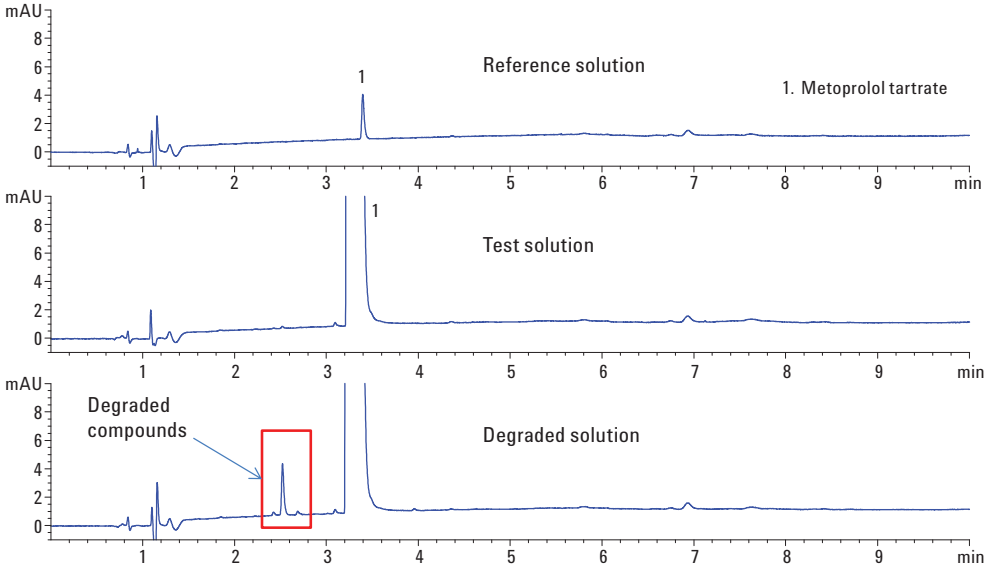

Figure 2. Overlay chromatograms of reference, test, and degraded solutions of metoprolol tartrate using Agilent Poroshell 120 Phenyl-Hexyl.

Conclusions

HPLC methods can easily profile impurities in metoprolol tartrate, replacing current TLC methods in USP by using two Poroshell 120 phases. Agilent Poroshell 120 EC-C18 provides the best peak shapes and separation for this analysis, while Agilent Poroshell 120 Phenyl-Hexyl provides unique selectivity for several related compounds.

References

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Published in the USA
May 6, 2014
5991-4564EN

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