

Modernization of the USP Monograph for the Analysis of Miconazole Nitrate Cream using CORTECS Phenyl 2.7 μm Columns

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GOAL

To demonstrate that smaller configuration, high efficiency solid-core CORTECS® Phenyl 2.7 μm Columns can be used to modernize methods that use larger, 5 μm HPLC columns. Comparable chromatographic selectivity and enhanced resolution was achieved with these columns to meet the criteria for an official USP monograph.

BACKGROUND

USP methods that were developed for traditional HPLC systems have typically used columns packed with relatively large diameter, fully-porous particles. Revalidation of these methods to include the use of high performance ACQUITY UPLC® Systems and modern, more efficient HPLC columns can be costly and time consuming. However, isocratic USP methods can be modernized in accordance to the recent changes in USP General Chapter <621>, which allow for scaling of constant L/d_p (column length per particle diameter) or -25% to +50% column efficiency. In this Technology Brief, an updated analysis for miconazole nitrate cream, using a CORTECS Phenyl 2.7 μm Column, is described. The modernization was achieved by reducing column dimension and particle size within the USP <621> allowed limits.

THE SOLUTION

A CORTECS Phenyl Column, 2.7 μm , 3.0 x 100 mm ([p/n 186008331](#)) was compared to an XBridge Phenyl Column, 5 μm , 4.6 x 250 mm ([p/n 186003353](#)), the recommended

Older USP methods typically use longer HPLC column lengths packed with larger diameter fully-porous particles. The modernization of a USP method can be achieved by reducing both column dimension and particle size. Solid-core particle packed columns offer higher efficiency per unit length, a distinct advantage over fully-porous particles of the same size.

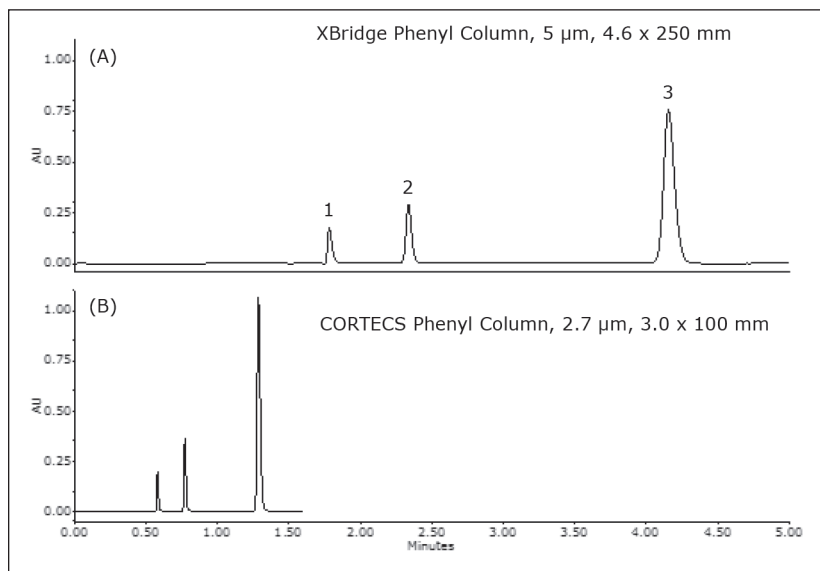


Figure 1. Separation of miconazole (3), benzoic acid (2), and miconazole related peak (1) on XBridge® Phenyl Column (A) and CORTECS Phenyl Column (B).

L11 column configuration and particle size for the separation of miconazole nitrate and benzoic acid, an anti-microbial preservative. The separation was achieved using the quaternary mobile phase system of methanol/acetonitrile/tetrahydrofuran/1% triethylamine, pH 2.5 (25/20/15/40, v/v) as given in the USP monograph.

A standard solution of 0.28 mg/mL of miconazole nitrate and 0.02 mg/mL of benzoic acid were prepared in mobile phase. A sample solution with a concentration of 0.28 mg/mL of miconazole nitrate and 0.02 mg/mL of benzoic acid was prepared by dispersing one applicator of an OTC (over-the-counter) cream preparation containing 100 mg of miconazole per dose in 357 mLs of mobile phase. The solution was heated for one hour at 40–45 °C in an ultrasonic bath, and then allowed to cool to room temperature. Twenty milliliters was filtered through a 0.45 µm Teflon® filter, and a 2 mL aliquot was transferred to a TruView™ LCMS Clear Glass Vial (p/n 186005666CV) for analysis.

The suitability measurements were determined using the standard solutions and an XBridge Phenyl Column, 5 µm, 4.6 x 250 mm (p/n 186003353), on an HPLC system, and were determined for the CORTECS Phenyl Column, 2.7 µm, 3.0 x 100 mm (p/n 186008331) on a UPLC® system. The chromatographic conditions for both columns are given in Table 1.

The high efficiency of CORTECS Phenyl Columns allows for the use of a smaller configuration column, reducing the analysis time threefold without the need for revalidation. The change in configuration did not impact the system suitability results (Table 2).

According to the USP method, the nominal amount of miconazole nitrate in the cream formulation is 0.28 mg/mL. Five injections of the sample solution were made on each column using the volumes given in Table 1. The percentage of the labeled amount of miconazole nitrate in the cream was calculated using the following formula:

$$\text{Result} = \left(\frac{r_u}{r_s} \right) \times \left(\frac{C_s}{C_u} \right) \times 100$$

r_u = peak response (area) from sample solution

r_s = peak response (area) from the standard solution

C_s = concentration of miconazole nitrate in standard solution

C_u = nominal concentration of miconazole nitrate in the sample solution

The acceptance criterion for the labeled amount is 90.0%-110.0% of the listed amount. The result for the XBridge Phenyl Column, 5 µm, 4.6 x 250 mm was 96.3% and for the CORTECS Phenyl Column, 2.7 µm, 3.0 x 100 mm, the result was 94.9%. The miconazole nitrate peak height on the more efficient CORTECS Phenyl 2.7 µm Column was 35% higher than on the XBridge Phenyl 5 µm Column. Figure 1 shows the separation of the prepared miconazole nitrate sample on each column.

| | XBridge Phenyl 5 µm | CORTECS Phenyl 2.7 µm |
|-------------------|---|-----------------------|
| I.D. x L: | 4.6 x 250 mm | 3.0 x 100 mm |
| dp, µm: | 5 | 2.7 |
| LC system: | Alliance® e2695 | ACQUITY UPLC |
| Detection: | 2489 UV/Vis Detector 225 nm | ACQUITY PDA 225 nm |
| Mobile phase: | methanol/acetonitrile/tetrahydrofuran/ 1% triethylamine, pH 2.5 with H3PO4 (25/20/15/40, v/v) | |
| Flow rate: | 1.5 mL/min | 0.64 mL/min |
| Column temp.: | 45 °C | |
| Injection volume: | 10 µL | 1.7 µL |

Table 1. Chromatographic conditions used for the separation of miconazole and benzoic acid.

| | | XBridge Phenyl | CORTECS Phenyl |
|----------------------------------|--|----------------|----------------|
| Resolution (HH): | No less than 13 between miconazole nitrate and benzoic acid. | 17.4 | 15.5 |
| Column efficiency (HH): | No less than 7,500 theoretical plates for the miconazole nitrate peak. | 14,147 | 15,175 |
| Tailing factor (USP): | No more than 2.0 for the miconazole nitrate peak. | 1.2 | 1.4 |
| Relative standard deviation, tR: | No more than 2.0% from the miconazole nitrate peak. | 0.03 | 0.04 |

Table 2. System suitability requirements for the standard solution.

SUMMARY

CORTECS Phenyl Columns deliver similar selectivity as other USP L11 designated columns, such as an XBridge Phenyl Column, allowing for modernization of USP methods. By utilizing the allowed limits for column length and particle diameter given in USP General Chapter <621>, the published miconazole nitrate method was performed three times faster with 35% higher sensitivity. The rapid analysis that met the USP method requirements of the miconazole nitrate cream monograph was easily achieved with a combination of the high performance ACQUITY UPLC System and high efficiency CORTECS Phenyl 2.7 μm Columns.

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