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Transfer of USP Assay for Quetiapine Fumarate Across Different Liquid Chromatographic Systems

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Abstract

In this study, the USP assay method for quetiapine fumarate, an anti-psychotic drug, will be evaluated on a range of systems including an Alliance HPLC System, an ACQUITY Arc UHPLC System and an ACQUITY UPLC H-Class PLUS System.

Benefits

- The Alliance HPLC, ACQUITY Arc UHPLC, and ACQUITY UPLC H-Class PLUS Systems can be used for the USP analysis of quetiapine fumarate, meeting all system suitability requirements.
- USP monographs can be successfully transferred between HPLC, UHPLC, and UPLC chromatographic systems.

Introduction

Pharmaceutical manufacturers often follow current United States Pharmacopeia (USP) methods for the analysis of raw materials and finished products. Many of the USP methods are high performance liquid chromatography (HPLC) methods which use larger particle size columns, typically equal to or greater than

5 µm, as well as larger column dimensions. This results in methods that use relatively high flow rates and require long runtimes. Since the column and method conditions are intended for HPLC systems, it is not commonly acknowledged that these methods can be run on lower dispersion and higher pressure systems such as UHPLC and UPLC systems, as long as the system suitability requirements of the monograph are met.[1]

In this study, the USP assay method for quetiapine fumarate, an anti-psychotic drug, will be evaluated on a range of systems including an Alliance HPLC System, an ACQUITY Arc UHPLC System and an ACQUITY UPLC H-Class PLUS System. This isocratic method will be evaluated under the conditions stated in the USP monograph: Quetiapine Fumarate.[2] The acceptance criteria of the method on each LC system was determined by evaluating both the system suitability requirements stated in the USP monograph and the reproducibility of an unknown sample across the systems.

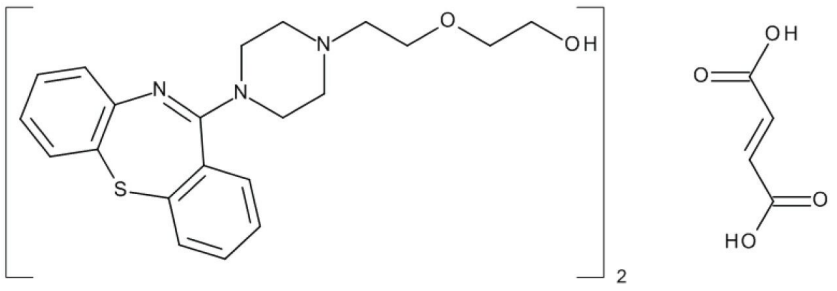

Figure 1. Structure of quetiapine fumarate.

Experimental

Sample description

Two reference standards were obtained from the USP: Quetiapine System Suitability (Catalog #: 1592715) and the Quetiapine Fumarate Standard (Catalog #: 1592704). The unknown sample was obtained from Alibaba.com. All samples were diluted per the USP monograph in mobile phase to the following concentrations: 1.0 mg/mL for the system suitability solution, 0.08 mg/mL for the standard solution, and 0.08 mg/mL for the sample solution.

Method conditions[1]

LC conditions

Systems:	Alliance e2695 Separations Module with 100 µL syringe (p/n: 176003519), 2998 PDA detector and CH-30 equipped with a passive preheater ACQUITY Arc System with 30-cm column heater with active solvent preheating (CH-30A) and 2998 PDA Detector (Path 1) ACQUITY UPLC H-Class PLUS with active solvent preheating (CH-30A) and ACQUITY UPLC PDA Detector
Column:	XBridge BEH C_8, 5 µm, 4.6 × 250 mm (p/n:186003018)
Column temp.:	25 °C
Sample temp.:	4 °C
Injection volume:	50 µL
Flow rate:	1.3 mL/min
Mobile phase:	Methanol, acetonitrile, and buffer (54:7:39) premixed
Buffer:	2.6 g/L of dibasic ammonium phosphate adjusted to pH 6.5 with phosphoric acid
Gradient:	Isocratic (premixed mobile phase filtered with 0.45 µm frit prior to analysis)
Run time:	15 min
PDA wavelength:	230 nm at 4.8 nm resolution
Data rate:	10 points/sec (Hz)

Data management

Chromatography data software: Empower 3 SR2 Hotfix 1

Results and Discussion

The USP quetiapine fumarate assay was evaluated on an Alliance HPLC System (Figure 2, top chromatogram), an ACQUITY Arc UHPLC System (Figure 2, middle chromatogram), and an ACQUITY UPLC H-Class PLUS System (Figure 2, bottom chromatogram). The system suitability solution, standard solution, and an unknown sample solution were prepared as described according to the USP monograph and were analyzed in six replicate injections on all three LC systems.

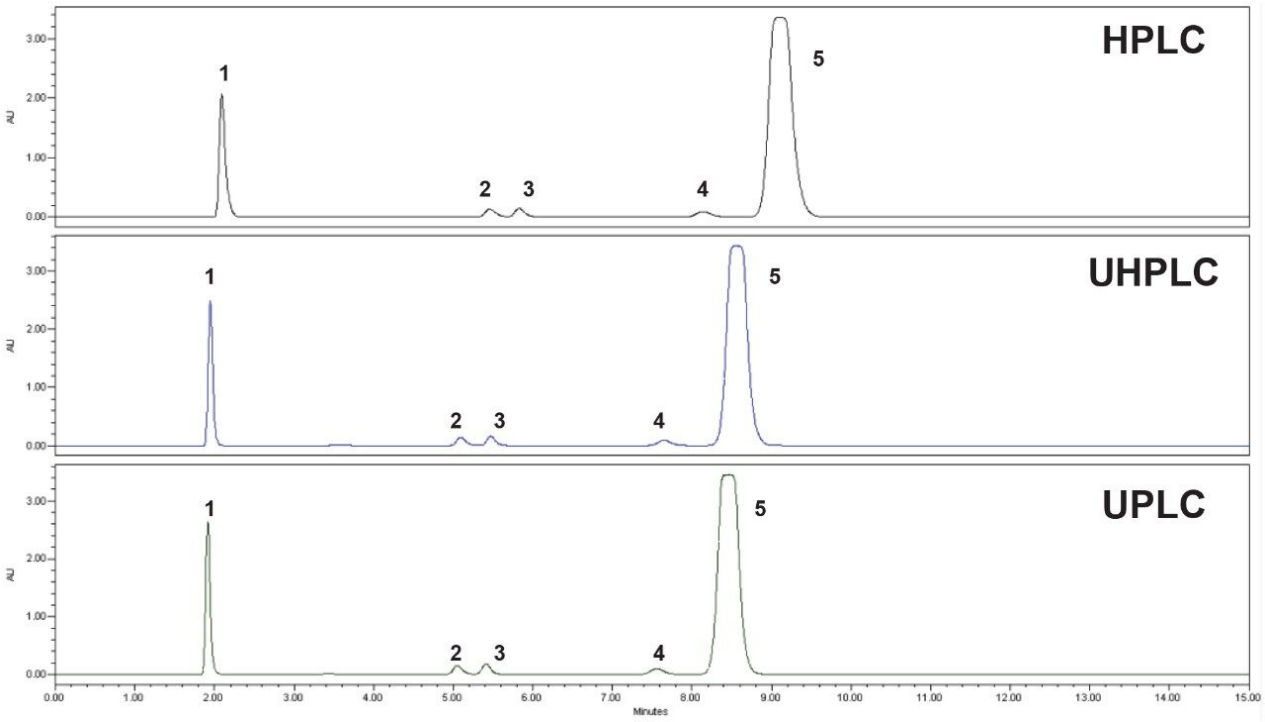

Figure 2. System suitability reference standard run on three LC instruments. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as: (1) fumaric acid, (2) quetiapine related compound G, (3) quetiapine related compound B, (4) quetiapine desethoxy, and (5) quetiapine.

System suitability tests are an important element of the USP monographs given that they determine whether or not a "chromatographic system is adequate for an intended analysis".[3] For this example, the USP monograph has requirements for both the system suitability solution as well as the standard solution.

For the system suitability solution, the USP monograph requires that the resolution between quetiapine desethoxy (Figure 2, peak 4) and quetiapine (Figure 2, peak 5) can be not less than (NLT) 1.5. Resolution, which is an assessment of the separation quality of the method, is often a requirement for two closely eluting peaks. In this study, the resulting resolution was 2.4, 2.7, and 2.6, on the Alliance HPLC System, the ACQUITY Arc System, and the ACQUITY UPLC H-Class PLUS System, respectively (Table 1). Based on these results for the system suitability sample, all three systems met the requirements.

The standard solution requires the tailing factor is not more than (NMT) 2.0 and the Relative Standard Deviation (RSD) is NMT 2.0% (Figure 3). Six replicate injections were used for the determination of RSD based upon the system suitability requirements stated in the USP General Chapter <621>.[3] The first peak in the standard chromatogram pertains to fumaric acid and was therefore not considered when evaluating the system suitability requirements for retention time and area.

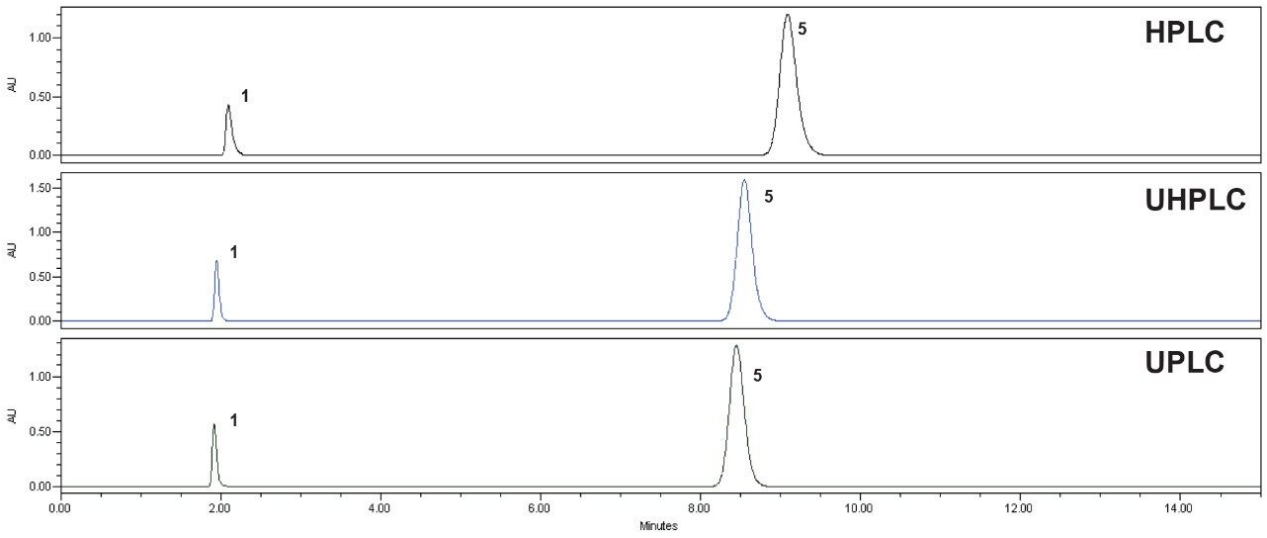

Figure 3. Quetiapine fumarate standard on the three LC systems. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as: (1) fumaric acid and (5) quetiapine.

Peak tailing, or symmetry factor,[3] is a measure of how symmetrical a peak is with an ideal peak shape having a tailing factor equal to 1.0. The peak tailing measurement can provide information on the performance of the LC system, method, and column;3 as well as, enables the user to successfully track any changes in peak shapes over time.[4] The results for quetiapine peak tailing on the Alliance HPLC System, the ACQUITY Arc System, and the ACQUITY UPLC H-Class PLUS System were 1.2, 1.1, and 1.1, respectively (Table 1). The measured tailing factors on all three systems were well within the USP requirement.

	Resolution	Quetiapine tailing	Quetiapine area %RSD	Quetiapine retention time %RSD
Alliance HPLC	2.4	1.2	0.09	0.16
ACQUITY Arc UHPLC	2.7	1.1	0.01	0.27
ACQUITY UPLC H-Class PLUS	2.6	1.1	0.07	0.16
USP requirements	NLT 1.5 *System suitability*	NMT 2.0 *Standard*	NMT 2.0% *Standard*	NMT 2.0% *Standard*

Table 1. Assay results for the system suitability and standard solutions run on the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System.

The relative standard deviations for area and retention time are a measure of the reproducibility of a chromatographic system and method for a particular assay. The area and retention time repeatability for quetiapine in the standard solution for all three systems can be found in Table 1. The area and retention time RSDs are substantially lower than the required value of NMT 2.0% for all three systems, highlighting the reproducibility and precision of all three LC systems.

An unknown sample was analyzed for the percent quetiapine fumarate along with the system suitability solution and the standard solution on all three systems (Figure 4). In order to determine the percent of quetiapine fumarate contained within the sample, the following calculation was used:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

where r_u is the peak response from the sample solution, r_s is the peak response from the standard solution, C_s is the concentration of USP Quetiapine Fumarate Standard in the standard solution (mg/mL), and C_u is the concentration of quetiapine fumarate in the sample solution (mg/mL).[2] The calculated results were 107.7%, 107.1%, and 107.5% (Table 2) for the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System, respectively. Although the percent quetiapine fumarate did not fall within the USP acceptance criteria of 98.0% to 102.0%, the unknown sample results were reproducible across all three LC systems, showing that reproducible and accurate data is obtained regardless of which LC system is used.

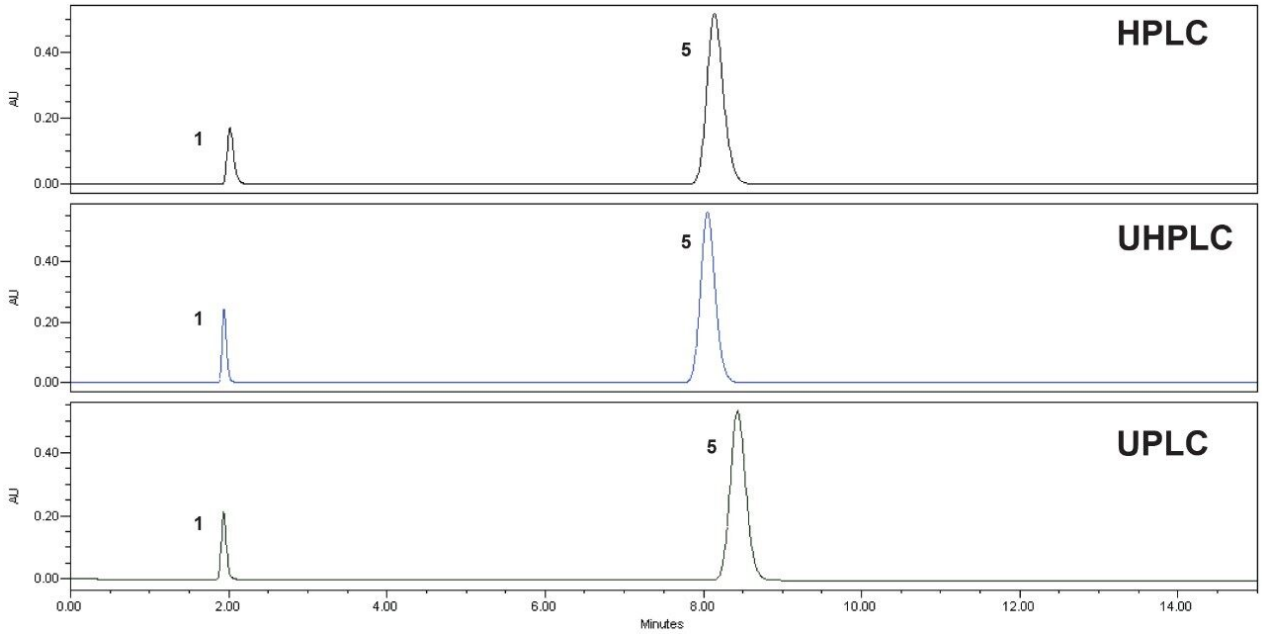

Figure 4. Quetiapine fumarate unknown sample solution on the three LC systems. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as: (1) fumaric acid and (5) quetiapine.

	Sample result (%)
Alliance HPLC	107.7
ACQUITY Arc UHPLC	107.1
ACQUITY UPLC H-Class PLUS	107.5

Table 2. Assay results for the sample solution run on the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System.

In order to determine the source of the considerably large calculated amount of quetiapine fumarate, further analysis would need to be performed. This may include examining the peak purity to identify any co-elutions, or the sample could be analyzed by another detection technique, such as mass spectrometry (MS), to provide further information.

Conclusion

The proof of the transferability of a USP method between various types of LC systems is important because many laboratories have varied instrumentation in terms of both performance level and vendor. The USP method for quetiapine fumarate was successfully transferred across three systems: an Alliance HPLC System, an ACQUITY Arc UHPLC System, and also an ACQUITY UPLC H-Class PLUS System. All three instruments were able to reproduce the percent of quetiapine fumarate in an unknown sample and meet system suitability requirements, including resolution, tailing factor, and repeatability specifications required by the USP quetiapine fumarate assay method.

References

1. Hong, P.; McConville, P. Dwell Volume and Extra-Column Volume: What Are They and How Do They Impact Method Transfer. Waters White Paper, 720005723EN, October 2016.
2. Official Monographs, Quetiapine Fumarate, USP 40 NF35 S1, United States Pharmacopeia and National Formulary (USP 40-NF35 S1) Baltimore, MD: United Book Press, Inc., 2017; p 5939.
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4. Snyder, L. R.; Kirkland, J.; Dolan, J. W. *Introduction to Liquid Chromatography*, 3rd Edition. Hoboken: Wiley and Sons, 2010; Section 2.4.2, pp 51–52.

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