Nota applicativa

Demonstration of the USP Quetiapine Fumarate Impurities Method Across a Wide Range of Liquid Chromatographic Systems

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Abstract

In this application the USP quetiapine fumarate impurity method is analyzed on three different LC systems including the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System. The successful execution of the method on each system will be evaluated based upon the system suitability requirements listed in the USP monograph.

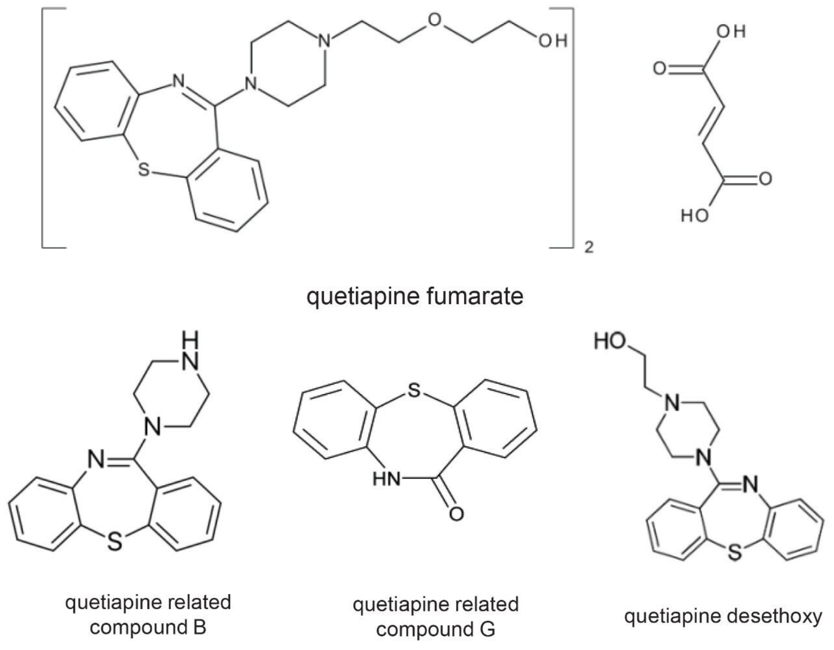
Benefits

- The USP quetiapine fumarate impurity method can be effectively analyzed on the Alliance HPLC, the ACQUITY Arc UHPLC, and the ACQUITY UPLC H-Class PLUS Systems.
- Gradient elution methods can be run on a variety of liquid chromatography systems.
- The impurity results of a sample can be replicated on the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System.

Introduction

Many pharmaceutical companies adhere to the United States Pharmacopeia (USP) methods when analyzing impurities contained within their active pharmaceutical ingredient (API). Many of these methods use gradient elution for the separation of impurity compounds. When a USP method contains a gradient elution it is important to consider which type of liquid chromatography system to use for the analysis. Based upon method conditions that consist of larger column dimensions and long run times, it may seem that the method needs to be run on a high performance liquid chromatography (HPLC) system, when in reality the method can be effectively run on a variety of systems. As long as the system suitability requirements of the USP method are met, the analysis can be completed on a liquid chromatography system that has lower dispersion and higher pressure specifications then an HPLC system, for example, UHPLC and UPLC systems.

In this application the USP quetiapine fumarate impurity (Figure 1) method1 will be analyzed on three different types of liquid chromatography systems, including the Alliance HPLC System, the ACQUITY Arc UHPLC System, and the ACQUITY UPLC H-Class PLUS System. The successful execution of the method on each system will be evaluated based upon the system suitability requirements listed in the USP monograph.



quetiapine fumarate

quetiapine related compound B

quetiapine related compound G

quetiapine desethoxy

Figure 1. Structure of quetiapine fumarate (API) and it's impurities of quetiapine related compound B, quetiapine related compound G, and quetiapine desethoxy.

Experimental

Sample description

The Quetiapine Fumarate Standard (Catalog#: 1592704), the Quetiapine System Suitability Standard (Catalog#: 1592715), Quetiapine Related Compound B (Catalog#: 1592737) and Quetiapine Related Compound G (Catalog#: 1592781) were purchased from the United States Pharmacopeia. The unknown quetiapine fumarate sample was purchased from Alibaba.com.

All solutions were prepared to the designated concentrations per the USP monograph. The system suitability, standard, and peak identification solutions were prepared in the diluents of solution A: solution B (86:14), where solution A is acetonitrile and buffer (25:75) and solution B is acetonitrile. The sample solution was prepared in solution A.

The concentrations of the solutions are 1.0 mg/mL for the system suitability solution, 0.001 mg/mL for the standard solution, and 1.0 mg/mL for the sample solution. The peak identification solution is 1 µg/mL of USP

Quetiapine Fumarate Standard, 10 µg/mL of USP Quetiapine Related Compound B, and 2 µg/mL of USP Quetiapine Related Compound G.

LC conditions

LC systems:	Alliance e2695 Separations Module with 100 µL syringe,2998 PDA Detector and CH-30 equipped with passive column preheater ACQUITY Arc System with active solvent preheating (CH-30A) and 2998 PDA Detector (Path 1) ACQUITY UPLC H-Class PLUS System with active solvent preheating (CH-30A), 50 µL extension loop and ACQUITY UPLC PDA Detector
Column:	XBridge BEH C8 Column, 3.5 µm, 4.6 mm × 150 mm (p/n: 186003055)
Column temp.:	45 °C
Sample temp.:	4 °C
Injection volume:	20 µL
Flow rate:	1.5 mL/min
Run time:	70 minutes
PDA wavelength:	250 nm at 4.8 nm resolution
Data rate:	2 points/sec (Hz)
Mobile phase A:	Acetonitrile and buffer (25:75)

Mobile phase B:	Acetonitrile
Buffer:	3.1 g/L of ammonium acetate in water. 2 mL of 25% ammonium hydroxide was added to each 1 L of solution. The final pH is not less than (NLT) 9.2

Gradient

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0.0	100.0	0.0
25.0	100.0	0.0
60.0	29.3	70.7
60.1	100.0	0.0
68.0	100.0	0.0

Table 1. Gradient

Data management

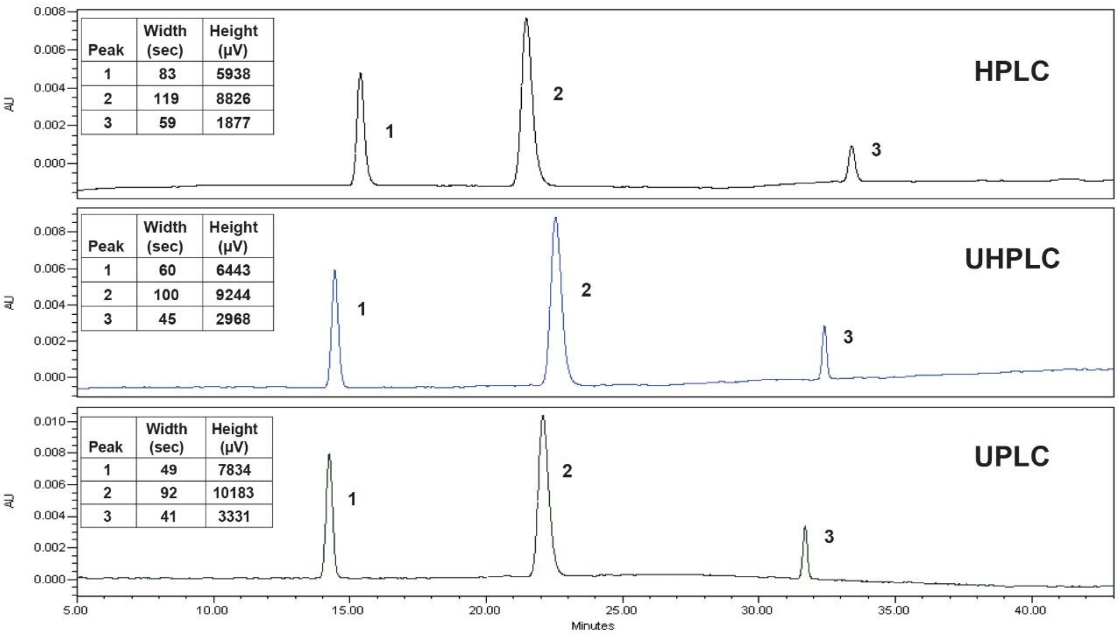
Empower 3 Chromatography Data Software, FR 3

Results and Discussion

The USP method for the impurities of quetiapine fumarate was analyzed on the Alliance HPLC, the ACQUITY

Arc UHPLC, and the ACQUITY UPLC H-Class PLUS systems using the conditions specified in the monograph. The peak identification solution, the system suitability solution, the standard solution and an unknown sample solution were prepared as described in the monograph and were analyzed in six replicates. Each system was evaluated based upon the system suitability requirements and the acceptance criteria for the sample impurities outlined in the monograph.

The peak identification solution provides proper identification of the three components, quetiapine, quetiapine related compound B, and quetiapine related compound G, contained in the solution. Identification was based on information provided in the monograph including relative retention times and peak size. An advantage of running the impurity method on the lower dispersion systems is the decrease in peak width resulting in an increase in the peak height,[2] which may be able to provide lower detection limits of the smaller impurity peaks. The system dispersion values determined for the systems are 44.5 µLs for the Alliance HPLC System, 21.5 µLs for the ACQUITY Arc UHPLC System, and 9.6 µLs for the ACQUITY UPLC H-Class PLUS System. The increase in peak height and decrease in peak width can be seen with the Peak ID solution (Figure 2). All three impurity compounds increase in peak height and decrease peak width as the dispersion of the LC system is decreased from the Alliance HPLC system to the ACQUTIY UPLC H-Class PLUS System (Figure 2).



Peak	Width (sec)	Height (µV)
1	83	5938
2	119	8826
3	59	1877

Peak	Width (sec)	Height (µV)
1	60	6443
2	100	9244
3	45	2968

Peak	Width (sec)	Height (µV)
1	49	7834
2	92	10183
3	41	3331

Figure 2. Peak ID solution chromatograms, with the corresponding peak width and peak heights, for the three impurity compounds obtained using each LC system. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as follows: 1: quetiapine related compound G 2: quetiapine related compound B, 3: quetiapine.

The resolution between two closely eluting peaks demonstrates the efficiency of a method on a system.[3] For the USP impurity method, the system suitability solution is used to evaluate the resolution between two different critical pairs. The monograph requires that the resolution between the quetiapine desethoxy and quetiapine peaks be not less than (NLT) 4.0 and the resolution is NLT 3.0 between the quetiapine related compound B and quetiapine related compound G peaks (Figure 3). The results of the system suitability solution on all three systems meet the USP requirements and can be found in Table 2.

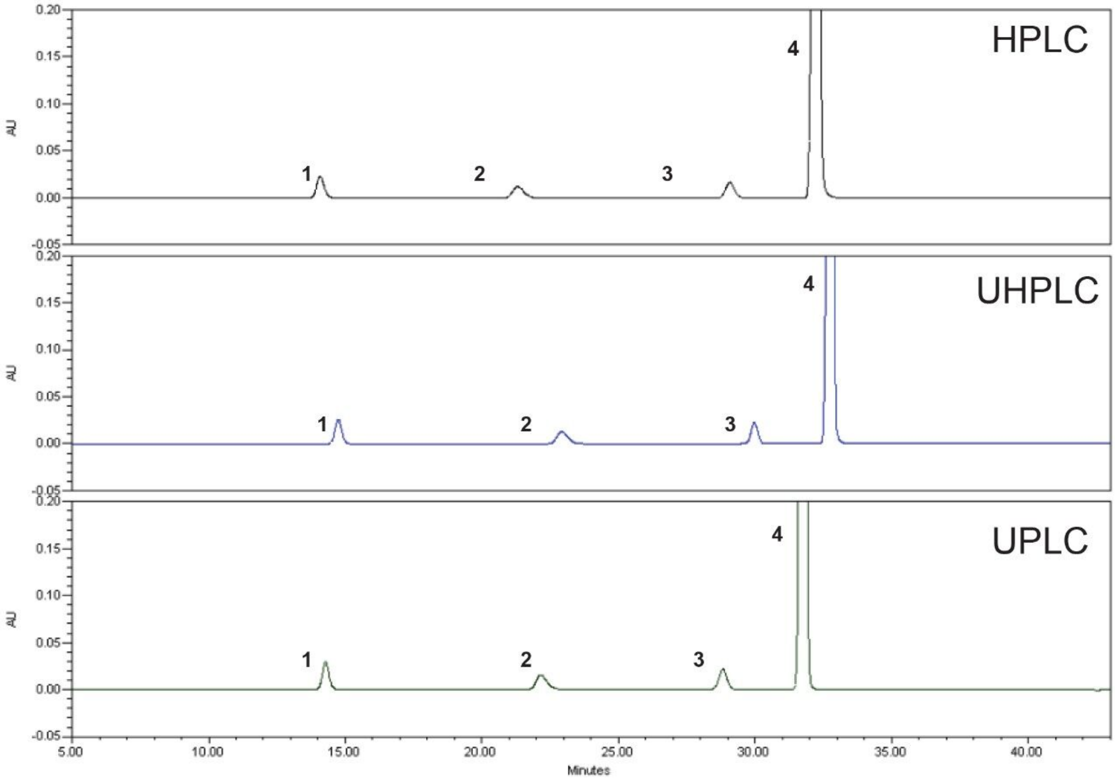


Figure 3. System suitability solution run on three LC instruments. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as follows: 1: quetiapine related compound G, 2: quetiapine related compound B, 3: quetiapine desethoxy, and 4: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

	Resolution between quetiapine desethoxy and quetiapine peaks	Resolution between compound B and compound G peaks
Alliance HPLC System	6.6	11.0
ACQUITY Arc UHPLC System	7.4	13.3
ACQUITY UPLC H-Class PLUS System	6.9	13.4
USP requirements	NLT 4.0	NLT 3.0

Table 2. Resolution results for the system suitability solution on all three LC systems.

The reproducibility of a system and peak symmetry are evaluated by examining the percent relative standard deviation (%RSD) and tailing factor of six replicate injections.[4] The monograph requires a tailing factor of not more than (NMT) 2.0 and %RSDs for area and retention time be NMT 5.0% for the quetiapine peak contained in the standard solution (Figure 4). The results from each system for the standard solution can be found in Table 3, and all systems successfully met the tailing factor and %RSD criteria.

	Tailing factor	Retention time %RSD	Area %RSD
Alliance HPLC System	1.0	0.14	0.84
ACQUITY Arc UHPLC System	1.0	0.05	1.14
ACQUITY UPLC H-Class PLUS System	1.0	0.10	1.18
USP requirements	NMT 2.0	NMT 5.0%	NMT 5.0%

Table 3. Tailing factor and RSD results for the standard solution on the three systems.

The analysis of the unknown sample requires injection of the standard solution at a known concentration (Figure 4). The percent impurity contained within the unknown sample is determined using the following equation:

$$\text{Result} = (r_u/r_s) \text{ x } (C_s/C_u) \times (1/F) \times 100$$

Where r_u is the peak response of each impurity for the sample solution, r_s is the peak response of quetiapine from the standard solution, C_s is the concentration of USP quetiapine fumarate standard in the standard solution (mg/mL), C_u is the concentration of quetiapine fumarate in the sample (mg/mL), and F is the relative response factor provided in the monograph.[1] Analysis of the unknown sample yielded twoimpurity peaks. One was identified as quetiapine desethoxy, while the other peak could not be identified. The % impurity was calculated using the response factor provided in the monograph where applicable. The calculated amount of the quetiapine desethoxy impurity and the unknown impurity are both below the acceptance criteria value set in the monograph. Additionally, the calculated concentration of the quetiapine desethoxy impurity and the unknown impurity are consistent and reproducible across all three chromatographic systems (Table 4).

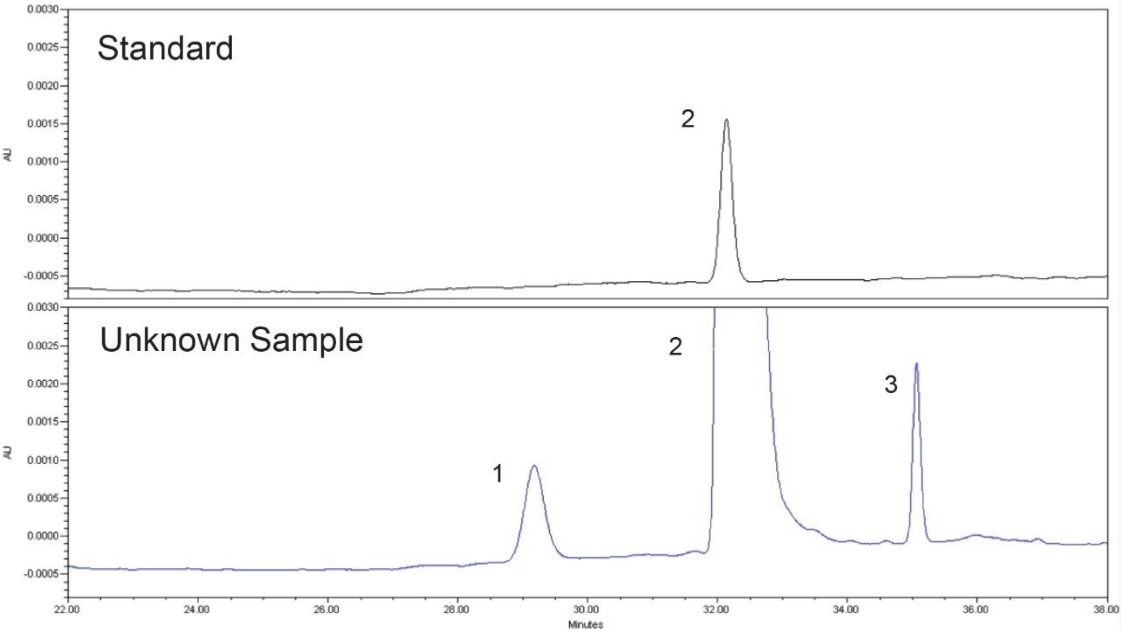


Figure 4. Standard solution (0.001 mg/mL) containing quetiapine (top) and the unknown sample solution (1.0 mg/mL) (bottom) run on the Alliance HPLC System. The compounds were identified based on the relative retention time provided in the USP method. The compounds are identified as follows: 1: quetiapine desethoxy 2: quetiapine and 3: unknown impurity.

	Quetiapine desethoxy	Unknown impurity
Alliance HPLC System	0.10%	0.07%
ACQUITY Arc UHPLC System	0.13%	0.08%
ACQUITY UPLC H-Class PLUS System	0.12%	0.08%
USP acceptance criteria	NMT 0.15%	NMT 0.10%

Table 4. Calculated percent of the impurity of quetiapine desethoxy and the unknown impurity peak in the unknown sample on the three LC systems.

Conclusion

Many USP gradient elution methods use columns with packing material of >3 µm particle size that can be effectively analyzed on a variety of LC systems. The USP quetiapine fumarate impurity method was successfully analyzed on three different LC systems: an Alliance HPLC System, an ACQUITY Arc UHPLC System and an ACQUITY UPLC H-Class PLUS System. The analysis on all three LC systems met the system suitability requirements and provided consistent and reproducible impurity concentration values for an unknown sample.

References

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