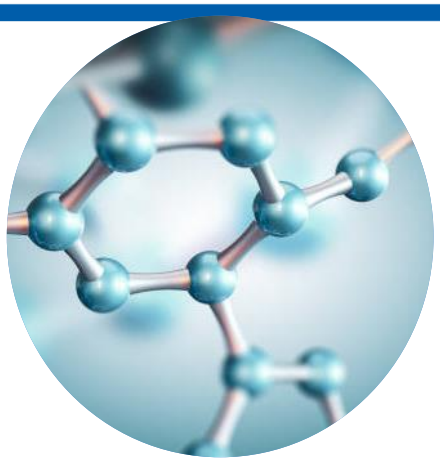

Meeting System Suitability for USP Amlodipine, Valsartan, and Hydrochlorothiazide Tablets Assay and Organic Impurities

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Overview

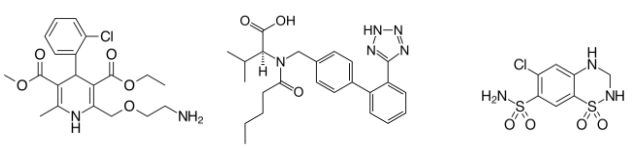
Amlodipine, Valsartan, and Hydrochlorothiazide tablets contain a combination of drugs used to treat high blood pressure. Amlodipine is a calcium channel blocker (CCB) that affects calcium movement into the cells of the heart and blood vessels, Valsartan is an angiotensin II receptor blocker (ARB) that relaxes blood vessels, and Hydrochlorothiazide is a thiazide diuretic that reduces the amount of water in the body by increasing the flow of urine and lowering blood pressure. In this application note, we report the separation of Amlodipine, Valsartan, and Hydrochlorothiazide and their related organic impurities per the USP monograph using a Luna Omega 3 µm C18 column as an alternative L1 column to the ACE 3 µm C18 column originally used to elucidate the monograph.

System suitability per USP monograph for Amlodipine, Valsartan, and Hydrochlorothiazide tablets Assay is a symmetry factor no more than (NMT) 2.0 for Amlodipine, Valsartan, and Hydrochlorothiazide and a percent relative standard deviation (%RSD) of NMT 2 % for Amlodipine, Valsartan, and Hydrochlorothiazide. System suitability per USP monograph for Amlodipine, Valsartan, and Hydrochlorothiazide tablets organic impurities is resolution no less than (NLT) 2.0 between any adjacent peaks of Benzothiadiazine related compound A, Hydrochlorothiazide, Amlodipine related compound A, Amlodipine, Valsartan related compound B, and Valsartan, a %RSD NMT 5.0 % for Amlodipine related compound A, Benzothiadiazine related compound A, Amlodipine, Valsartan, and Hydrochlorothiazide, and a signal-to-noise (S/N) ratio NLT 10 for Amlodipine, Valsartan, and Hydrochlorothiazide. All system suitability requirements for both Assay and Organic Impurities were met by both the Luna Omega C18 column and the ACE C18 column.

The Luna Omega C18 column gave comparable results and is therefore a suitable substitute for the ACE C18 column for the USP monograph for Amlodipine, Valsartan, and Hydrochlorothiazide Tablets Assay and Organic Impurities methods.

All solutions were prepared as indicated in the USP monograph for Amlodipine, Valsartan, and Hydrochlorothiazide tablets. USP Amlodipine Besylate RS (Catalog No. 1029501), UPS Amlodipine Related Compound A RS (Catalog No. 1029512), USP Benzothiadiazine Related Compund A RS (Catalog No. 1057507), USP Hydrochlorothiazide RS (Catalog No. 1314009), USP Valsartan RS (Catalog No. 1708762) and USP Valsartan Related Compound B RS (Catalog No. 1708784) were purchased from USP.

Figure 1. Drug Structures.



Amlodipine Valsartan Hydrochlorothiazide

LC-UV Conditions

Columns: Luna™ Omega 3 µm C18 (00F-4784-E0)
ACE® 3 µm C18
Dimensions: 150 x 4.6 mm
Mobile Phase: A: Acetonitrile / Water / Phosphoric Acid (50:950:1, v/v/v)
B: Acetonitrile / Water / Phosphoric Acid (950:50:1, v/v/v)
Gradient:

Time (min)	%B
0.00	5
3.00	50
6.00	60
10.0	95
10.1	5
15.0	5

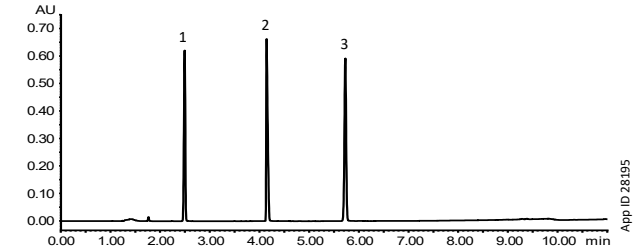
Flow Rate: 1.5 mL/min
Injection Volume: 10 µL
Temperature: 40 °C
LC System: Waters® ACQUITY® H-Class
Detection: UV @ 225 nm

Table 1. Preparation of Test Solutions. Use Amber Glassware for All Solutions Containing Drug Substances.

Solution	Composition
Diluent	Acetonitrile / Water (1000:1, v/v)
Standard Solution (Assay)	0.14 mg/mL of *USP Amlodipine Besylate RS*, 0.064 mg/mL of *USP Valsartan RS*, and 0.025 mg/mL of *USP Hydrochlorothiazide RS* in Diluent.
Standard Solution (Organic Impurities)	0.0005 mg/mL of *USP Amlodipine Related Compound A RS*, 0.0001 mg/mL of *USP Benzothiadiazine Related Compound A RS*, 0.0003 mg/mL of *USP Amlodipine Besylate RS*, 0.00015 mg/mL of *USP Valsartan RS*, and 0.00005 mg/mL of *USP Hydrochlorothiazide RS* in Diluent.
System Suitability Solution (Organic Impurities)	0.02 mg/mL each of *USP Benzothiadiazine Related Compound A RS* and *USP Valsartan Related Compound B RS*, 0.005 mg/mL of *USP Amlodipine Related Compound A RS*, 0.14 mg/mL of *USP Amlodipine Besylate RS*, 0.064 mg/mL of *USP Valsartan RS*, and 0.025 mg/mL of *USP Hydrochlorothiazide RS* in Diluent.
Sensitivity Solution (Organic Impurities)	0.14 µg/mL of *USP Amlodipine Besylate RS*, 0.064 µg/mL of *USP Valsartan RS*, and 0.025 µg/mL of *USP Hydrochlorothiazide RS* in Diluent.

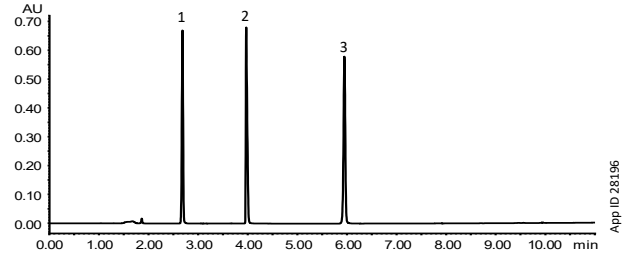
Figure 2. Standard Solution – Assay.

ACE® 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	%RSD	Symmetry Factor
1	Hydrochlorothiazide	2.49	1198889	1.65	0.9
2	Amlodipine	4.14	1378275	1.63	2.0
3	Valsartan	5.73	1430802	1.72	1.0
N=5 Injections					

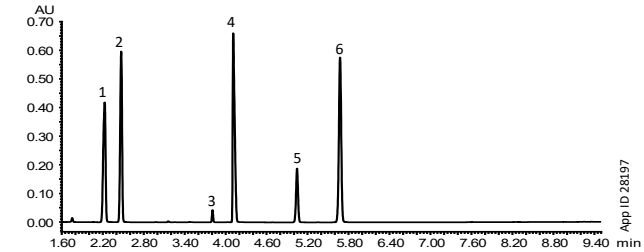
Luna™ Omega 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	%RSD	Symmetry Factor
1	Hydrochlorothiazide	2.68	1220034	0.05	0.9
2	Amlodipine	3.97	1404294	0.02	1.8
3	Valsartan	5.95	1455076	0.05	1.0
N=5 Injections					

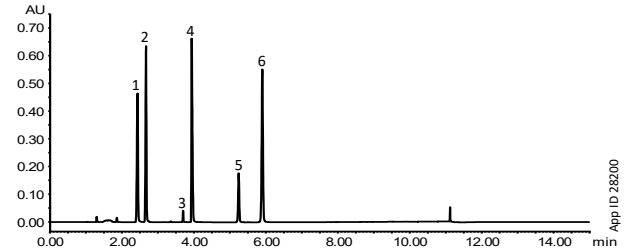
Figure 3. System Suitability Solution – Organic Impurities.

ACE 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	Resolution	
1	Benzothiadiazine related compound A	2.23	1003193	4.2	-
2	Hydrochlorothiazide	2.47	1148293		32.0
3	Amlodipine related compound A	3.81	50605	6.8	
4	Amlodipine	4.11	1317665		16.8
5	Valsartan related compound B	5.05	382561	10.7	
6	Valsartan	5.68	1372433		-

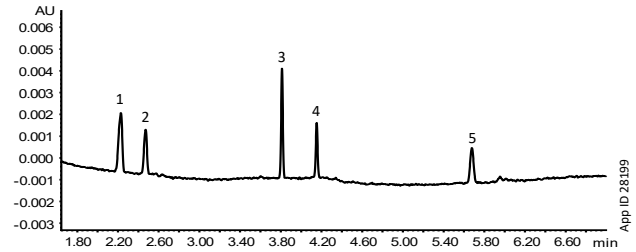
Luna Omega 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	Resolution	
1	Benzothiadiazine related compound A	2.43	1014133	4.4	-
2	Hydrochlorothiazide	2.67	1155816		25.7
3	Amlodipine related compound A	3.70	49951	5.4	
4	Amlodipine	3.94	1325691		22.9
5	Valsartan related compound B	5.24	385825	10.8	
6	Valsartan	5.90	1384201		-

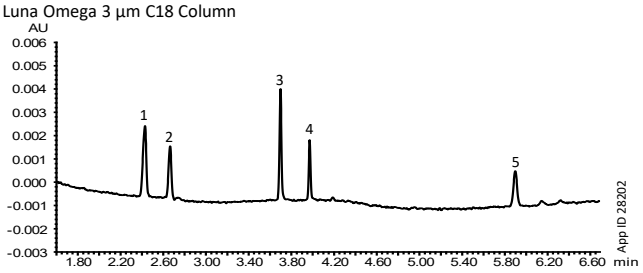
Figure 4. Standard Solution – Organic Impurities.

ACE 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	%RSD
1	Benzothiadiazine related compound A	2.23	6857	1.36
2	Hydrochlorothiazide	2.47	4096	2.49
3	Amlodipine related compound A	3.81	6031	1.35
4	Amlodipine	4.15	3208	0.92
5	Valsartan	5.68	3832	2.99
N=6 Injections				

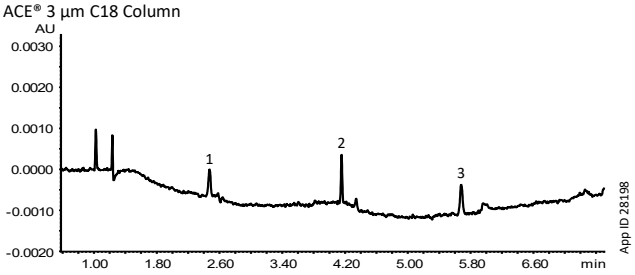
Luna Omega 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	%RSD
1	Benzothiadiazine related compound A	2.43	6695	1.83
2	Hydrochlorothiazide	2.67	4212	1.94
3	Amlodipine related compound A	3.70	6107	0.96
4	Amlodipine	3.98	2937	3.32
5	Valsartan	5.90	3639	3.65
N=6 Injections				

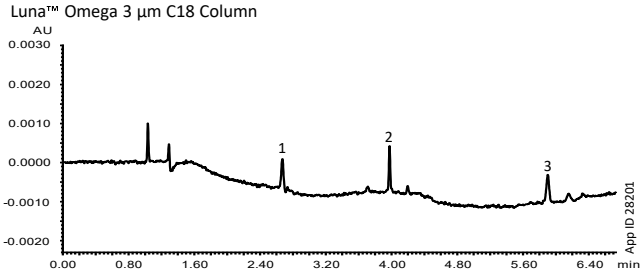
Figure 5. Sensitivity Solution – Organic Impurities.

ACE® 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	S/N
1	Hydrochlorothiazide	2.47	1381	10
2	Amlodipine	4.15	1447	19
3	Valsartan	5.68	1813	12

Luna™ Omega 3 µm C18 Column



Peak No.	Analyte	Retention Time (min)	Area	S/N
1	Hydrochlorothiazide	2.67	1648	13
2	Amlodipine	3.98	1469	18
3	Valsartan	5.90	1580	11

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