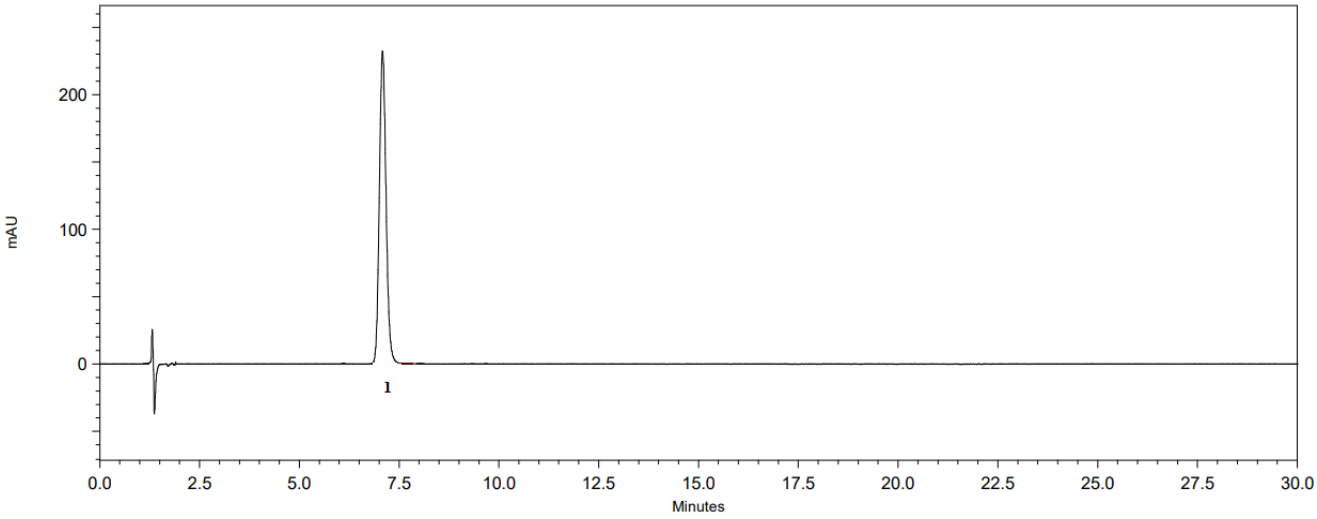
Atorvastatin Tablets – BP 2023

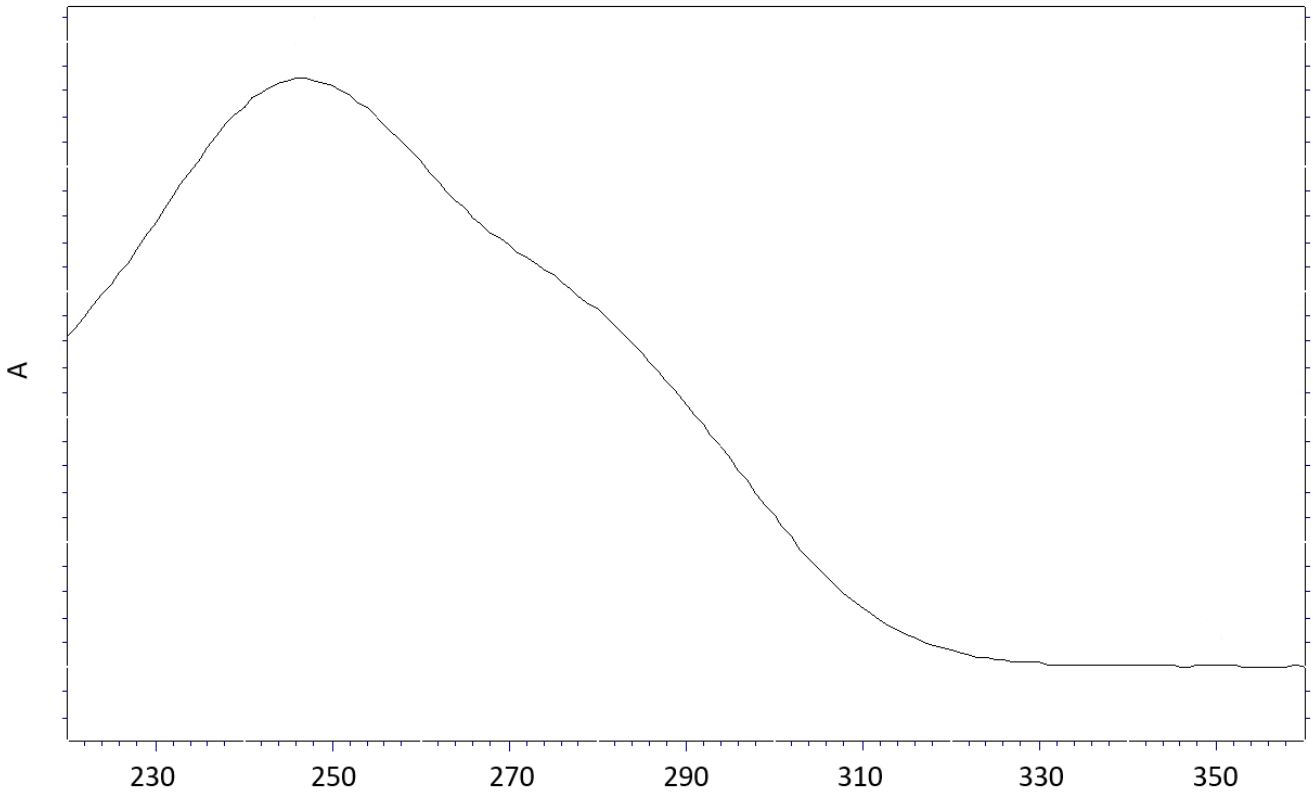
This spectrum is provided for information only as an aid to analysts and is intended as guidance for the interpretation and application of BP monographs.

Typical chromatogram for solution (2) for the Identification test for Atorvastatin Tablets as published in BP 2023.



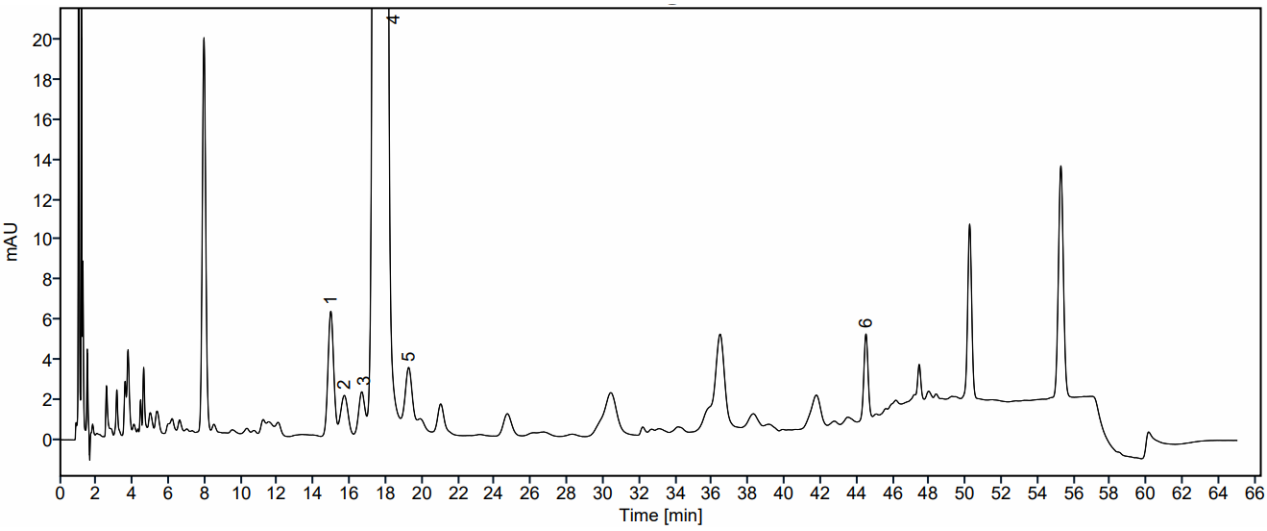
Peak ID: 1: Atorvastatin

Typical spectrum for the Identification test for Atorvastatin Tablets by LC-DAD as published in BP 2023.



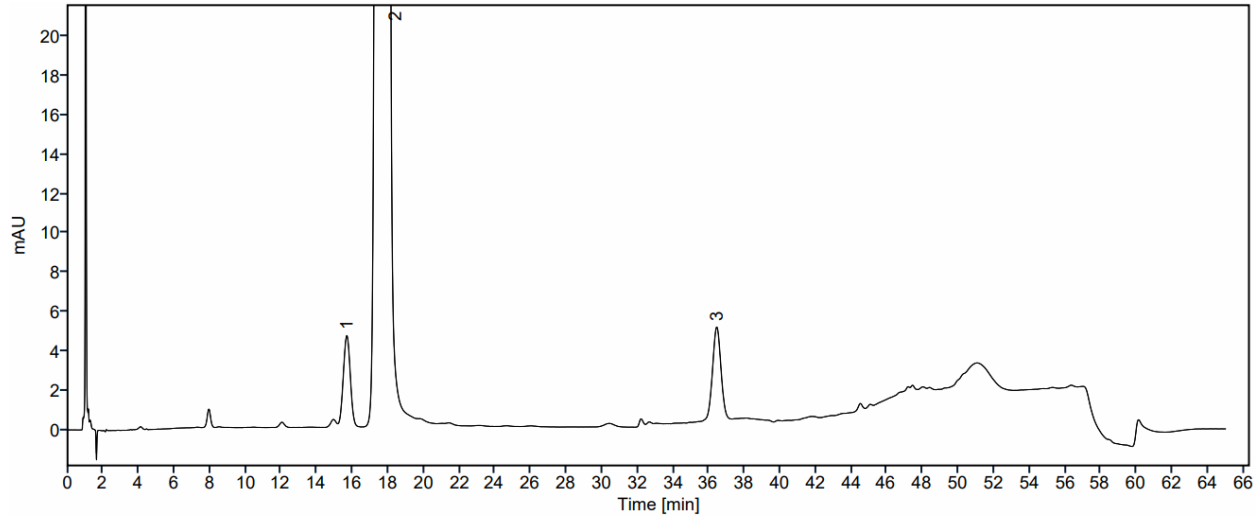
Column	Ultremex C18 (250 mm x 4.6 mm, 5 µm)
Method Ref.	Identification for the Atorvastatin Tablets monograph from BP 2023
Mobile Phase	Acetonitrile: tetrahydrofuran: buffer (27:20:53, v/v/v)
Buffer	0.962% w/v citric acid, adjusted to pH 4.0 with ammonium hydroxide
Diluent	Acetonitrile: 0.05M ammonium citrate solution (pH 7.4) (50:50, v/v)
Flow rate	1.5 mL/min
Column Temp	25 °C
Injection Volume	20 µL
Detection	244 nm

Typical chromatogram for solution (3) for the related substances test for Atorvastatin Tablets as published in BP 2023.



Peak ID: 1: Impurity A. 2: Impurity 1. 3: Impurity B. 4: Atorvastatin.
5: Impurity C. 6: Impurity D.

Typical chromatogram for solution (4) for the related substances test for Atorvastatin Tablets as published in BP 2023.



Peak ID: 1: Impurity 1. 2: Atorvastatin. 3: Impurity H.

Column	Kromasil C18 (250 mm x 4.6 mm, 5 µm)
Method Ref.	Related Substances for the Atorvastatin Tablets monograph from BP 2023
Solution B	75 volumes of tetrahydrofuran and 925 volumes of acetonitrile
Mobile Phase A	Solution B: 0.05M ammonium dihydrogen orthophosphate pH 4.3 (42:58, v/v)
Mobile Phase B	0.05M ammonium dihydrogen orthophosphate pH 4.3: Solution B: methanol (20:20:60, v/v/v)
Diluent	Acetonitrile: 0.05M ammonium citrate solution (pH 7.4) (50:50, v/v)
Column Temp	30 °C
Injection Volume	20 µL
Detection	244 nm

Gradient programme:

Time (minutes)	**Mobile phase A (% v/v)**	**Mobile phase B (% v/v)**	**Flow rate (mL per minute)**	**Comment**
0 – 30	100	0	1.8	isocratic
30 – 45	100 → 25	0 → 75	1.8	linear gradient
45 – 50	25	75	1.5	isocratic
50 – 55	25 → 20	75 → 80	1.5	linear gradient
55 – 58	20 → 100	80 → 0	1.8	linear gradient
58 – 65	100	0	1.8	re-equilibration

Additional information on the ranges for sample preparation and chromatographic parameters and method performance generated by our AQbD (Analytical Quality by Design) approach to method verification

The Assay for the BP 2023 Atorvastatin Tablets monograph was assessed using Analytical Quality by Design concepts to investigate the robustness of the method against its system suitability criteria at normal operating conditions. Further information on this case study, which was also intended to broaden the MHRA's understanding of, and put into practice the application of AQbD concepts, can be found in the Technical report published on GOV.UK.

SC X Supplementary Chapter on the use of Analytical Quality by Design concepts for Analytical procedures, published in the BP 2022, provides an overview of available tools and processes for quality risk management and generation of method understanding, as well as guidance on establishing an analytical control strategy and method trending.

In line with commitments included in our Strategy for the Application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines, the following additional data is provided to facilitate knowledge transfer of method understanding gained by the process outlined in the technical report.

This data does not define a method operable design region (MODR) but is the scope of our knowledge space for this method.

The performance of the method, at an intermediate precision and its normal operating conditions, has been demonstrated to quantify Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value with an accuracy of 99.0% - 101.0% and a precision coefficient of variation (CV) of not more than 1.5%.

We would be grateful for any feedback you have on the content of this additional information which can be submitted at the following link - https://forms.office.com/r/RD6ahQPkbd

Data from a Design of Experiments investigating impact of sample preparation factors on accuracy of the method.

The sample preparation factors detailed in table 1 were assessed to carry the greatest risk to method performance and so were the subject of a Design of Experiments (DoE) investigation to determine impact on method accuracy.

Table 1: Variation of sample preparation factors around the Normal Operating Conditions (NOC)

Factor	Lower level studied	NOC	Upper level studied
Shaking Time	10	15	20
Filter Type	GMF	PTFE	GF/C
Buffer pH	7.2	7.4	7.6
Solvent Mixture (Buffer/Acetonitrile)	45/55	50/50	55/45

From the DoE, the % Assay results for the 12 preparations of a control sample were between 96.9-98.9%, with a mean % Assay of 97.6% and % RSD of 0.40%.

It was concluded that the Normal Operating Conditions for sample preparation were appropriate and that no significant effects were observed from any of the changes made to the extraction parameters.

Data from Design of Experiments investigating the impact of chromatographic factors on method suitability

The chromatographic factors detailed in table 2 were assessed to carry the greatest risk to method performance and so were the subject of a Design of Experiments investigation to determine impact on method system suitability based on allowable changes within Appendix III D – Chromatographic Separation Techniques, published in the British Pharmacopoeia.

Table 2: System suitability results from DoE runs. Note that runs highlighted in the last column failed the resolution requirement of NLT 5.0 and that run times are also significantly affected in some other runs.

		Mobile Phase Factors					Atorvastatin			Related compound F			
	Run	Tetrahydrofuran (%)	Acetonitrile (%)	Buffer (%)	Buffer conc (%w/v)	Buffer pH	RT	Asymmetry	Efficiency	RT	Asymmetry	Efficiency	Resolution
DoE 2 - Chromatographic	1	26	35	39	0.866	3.8	2.65	1.12	6689	2.99	1.13	8308	2.67
	2	14	19	67	0.866	3.8	62.67	1.05	11822	83.47	1.04	13055	7.98
	3a	20	27	53	0.962	4	6.57	1.06	8431	8.61	1.06	10589	6.61
	3b	20	27	53	0.962	4	6.49	1.07	8420	8.54	1.06	10569	6.67
	3c	20	27	53	0.962	4	6.54	1.06	8400	8.61	1.05	10608	6.69
	3d	20	27	53	0.962	4	6.61	1.08	8454	8.7	1.07	10614	6.69
	3e	20	27	53	0.962	4	6.61	1.08	8436	8.71	1.07	10615	6.71
	4	26	19	53	1.058	3.8	6.61	1.06	8139	7.83	1.08	9654	4
	5	14	19	53	1.058	4.2	57.09	1.06	11797	86.22	1.03	12704	11.32
	6	26	19	55	0.866	4.2	6.84	1.1	7965	8.89	1.08	9916	6.2
	7	14	35	39	0.866	4.2	5.89	1.09	8376	8.55	1.08	11280	9.21
	8	14	35	39	1.058	3.8	6.25	1.06	8847	8.33	1.06	11266	7.19
	9	26	35	39	1.058	4.2	2.51	1.17	6511	2.97	1.08	8223	3.61
DoE 3 - Chromatographic Refinement	1	20	27	53	0.962	4	6.51	1.1	8276	8.36	1.09	10399	6.03
	2	20	21.4	58.6	0.962	4	11.99	1.1	9436	15.58	1.07	11072	6.64
	3	20	27	53	0.962	4	6.55	1.12	8309	8.43	1.07	10375	6.07
	4	23	31	46	0.962	4	3.69	1.17	7036	4.47	1.16	8860	4.31
	5	20	32.6	47.4	0.962	4	4.21	1.11	7461	5.27	1.13	9549	5.18
	6	17	31	52	0.962	4	6.35	1.09	8491	8.41	1.11	10524	6.84
	7	17	23	60	0.962	4	15.74	1.07	10132	21.25	1.07	12111	7.9
	8	24.2	27	48.8	0.962	4	4.34	1.12	7421	5.29	1.07	9100	4.49
	9	20	27	53	0.962	4	6.57	1.09	8214	8.43	1.06	10494	6.05
	10	15.8	27	57.2	0.962	4	11.27	1.08	9919	15.43	1.09	11827	8.16
	11	20	27	53	0.962	4	6.55	1.1	8399	8.43	1.08	10159	6.05
	12	20	27	53	0.962	4	6.57	1.1	8414	8.45	1.05	10641	6.14
	13	23	23	54	0.962	4	6.73	1.11	7979	8.41	1.1	10001	5.3

It was noted that lower percentages of tetrahydrofuran and acetonitrile in the mobile phase were optimal for all system suitability criteria but also resulted in extremely long run times. Increasing the percentages of tetrahydrofuran and acetonitrile in the mobile phase led to the resolution failing the system suitability criterion of not less than 5, although baseline resolution was achieved in all cases. Resolution was also found to be optimal at higher pH values.

The impact of changing organic composition in the mobile phase on the retention time of related compound F is illustrated in Figure 1, where longer retention times are indicated by the grey area and shorter retention times are indicated by the white area.

Data from the DoE 2 is plotted in blue (box plot) while data from DoE 3 is plotted in red (star shaped central composite). The centre points represent the Normal Operating Conditions and have been averaged, the bracketed average being from DoE 3.

The retention of related compound F is observed to decrease from bottom left to top right of the figure. It is noted that the retention time of related compound F is not significantly impacted by changes to the ratio of Acetonitrile to Tetrahydrofuran.

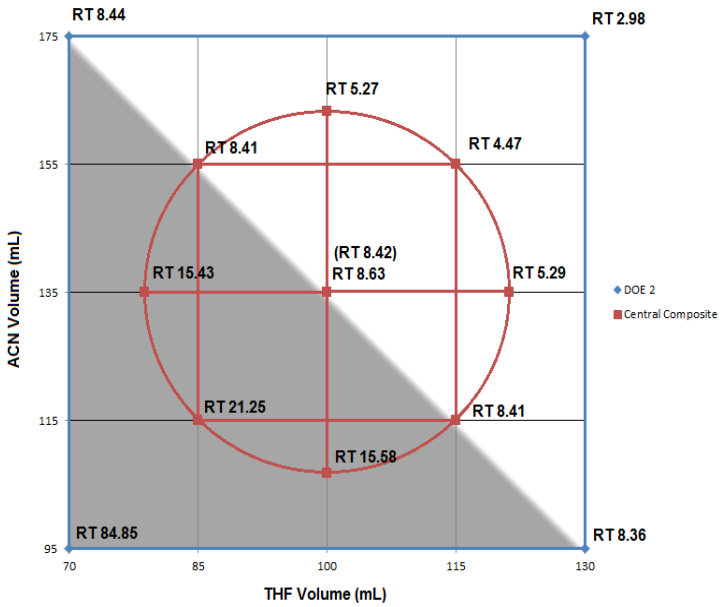


Figure 1: Model of retention time for Related Compound F against the organic content of the mobile phase. The centre point represents normal operating conditions.

Using a statistical software package, a 3D surface response model (figure 2) was generated looking at the impact of changing organic composition of the mobile phase on the method performance. The software package calculated the desirability of the method based on various conditions from the donor method which were set as:

- Minimise the retention time
  - Upper limit of 10 mins for Atorvastatin, 15 mins for RCF
- Maximise the Resolution
  - Lower limit of 5 based on donor method
- Maximise the Efficiency
  - Lower limit of 5000 based on donor method
- Attain a target peak asymmetry of 1.
  - Between 0.8 and 1.5 based on BP Appendix III.

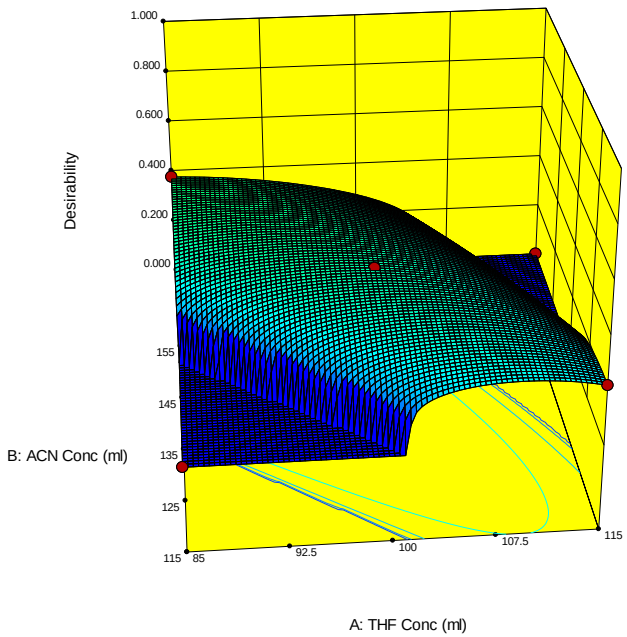


Figure 2: 3D surface model of method desirability against organic composition of the mobile phase

The model demonstrates that the method is stable around the normal operating conditions (central red dot) as evidenced by the teal-coloured plateau representing the stable region for mobile phase composition where slight changes do not have significant effects on the methods desirability.

The near, left hand side, blue corner of the 3D surface model represents low organic content in the mobile phase. In this region, desirability is low because the retention times of Atorvastatin and related compound F exceed the limits of 10 and 15 minutes, respectively. If these limits were removed, the desirability in this area would be greater.

The far, right hand side, blue corner represents high organic content in the mobile phase. In this region system suitability fails because the resolution between Atorvastatin and related compound F was less than the specified limit of 5.