USP Emerging Standards: Methods for the Analysis of Ketoconazole Foam

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1. Introduction

To jump-start the standard development process and have earlier stakeholder engagement, USP is piloting a new approach for developing procedures and sharing information with our stakeholders. Through a collaboration between USP's Small Molecules Department and Global Analytical Development Laboratory, methods are being developed and validated for drug substances and drug products for which no monographs are currently available. The Emerging Standards are intended to improve USP's official standards elaboration process by increasing transparency and allowing for broader stakeholder participation by publishing on the USP website prior to formal notice and comment through publication in the Pharmacopeial Forum.

Ketoconazole Foam has been evaluated and shown to be a suitable candidate for development under this new program. The methods in this document are being published to help analyze Ketoconazole Foam. Additional method development and validation information is provided to justify the use of method parameters.

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This document is not a USP compendial standard and is intended to serve as a resource for informational purposes only. It does not reflect USP or USP's Expert Body opinions of future revisions to the official text of the *USP-NF*. Parties relying on the information in this document bear independent responsibility for awareness of, and compliance with, any applicable federal, state, or local laws and requirements.

2. Available Resources

USP Reference Standard:

- Ketoconazole (200 mg)

3. Background

Ketoconazole is in a class of antifungals called imidazoles. It works by slowing the growth of fungi that cause infection. Ketoconazole is used to treat fungal infections when other medications are not available or cannot be tolerated[1]. Ketoconazole is the active ingredient in Ketoconazole Foam.

The *USP-NF* contains a monograph for Ketoconazole drug substance[2] and several monographs for drug products including Ketoconazole Tablets[3] and Ketoconazole Compounded Oral Suspension[4]. The EP contains a monograph for Ketoconazole drug substance[5]. The BP contains monographs for Ketoconazole

drug substance[6], cream[7] and shampoo[8]. However, there is no monograph for Ketoconazole Foam. As part of the Emerging Standards initiative, it was decided to develop methods for Ketoconazole Foam.

The recently published USP General Chapter <1220>[9] provides a framework for the implementation of the analytical procedure life cycle approach that is consistent with the quality by design (QbD) concepts described in the ICH guidelines. Stage 1 of the life cycle includes systematic procedure development experiments that result in an understanding of the effect of procedure parameters on procedure performance. Design of Experiment (DOE) which includes statistical multi-variate analysis and modeling is an important tool in Stage 1. The knowledge acquired through DOE studies also enables the determination of robust operation regions for procedure parameters and, if desired, a method operable design region (MODR).

This document summarizes the robustness studies used by the Design Expert software and forced degradation study results. It also describes final procedures that may be suitable for identification, and strength and purity determination of ketoconazole in the presence of various impurities and excipients in Ketoconazole Foam. Summary of validation data and representative chromatographic results are included.

4. Materials

4.1. Ketoconazole and Impurities Standards

USP Ketoconazole RS was used. Ketoconazole related impurities didehydroketoconazole (EP Impurity-A), ketoconazole diaryl analog (EP Impurity-B), *trans*-ketoconazole (EP Impurity-C), deacetyl ketoconazole (EP Impurity-D), ketoconazole tosyl analog (EP Impurity-E), bromomethyl analog, and ketoconazole N-oxide were procured from different impurity suppliers. Chemical structures of ketoconazole and related impurities are shown in **Figure 1** and **Figure 2** .

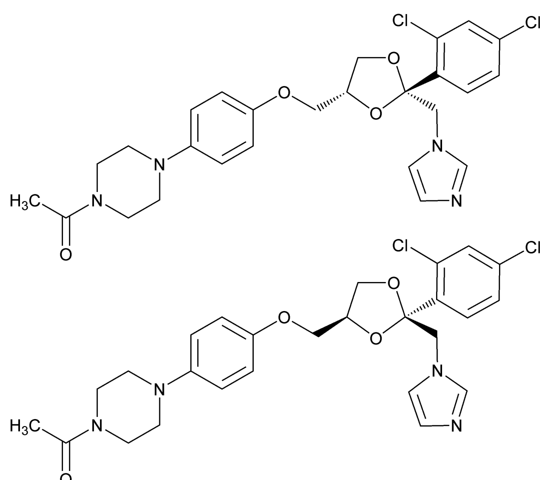

Figure 1. Ketoconazole

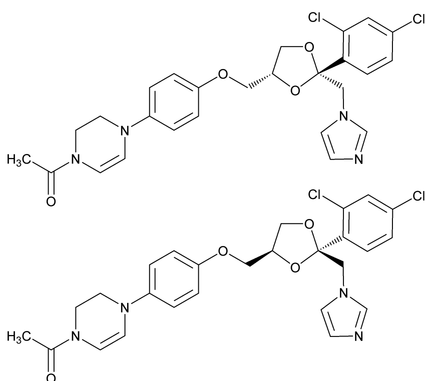

Figure 2a. Didehydroketoconazole (EP Impurity-A)

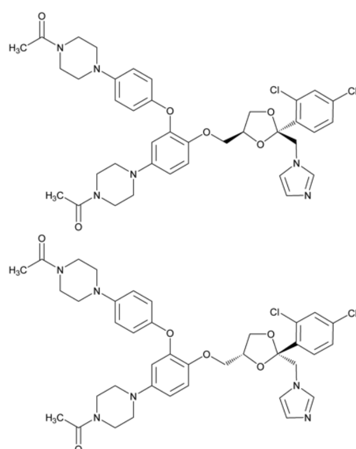

Figure 2b. Ketoconazole diaryl analog (EP Impurity-B)

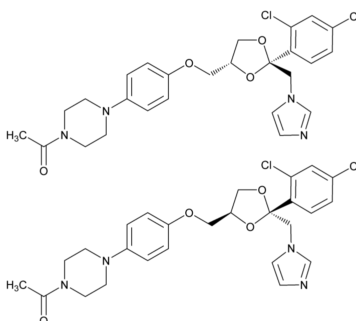

Figure 2c. *trans*-Ketoconazole (EP Impurity-C)

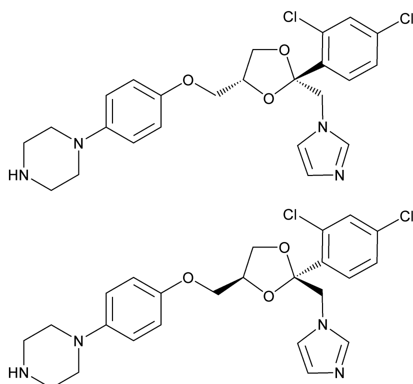

Figure 2d. Deacetyl ketoconazole (EP Impurity-D)

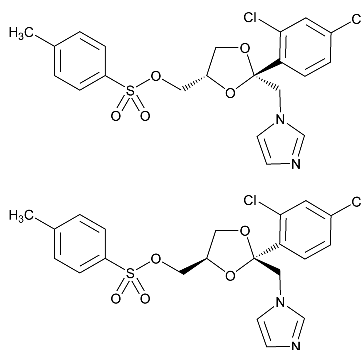

Figure 2e. Ketoconazole tosyl analog (EP Impurity-E)

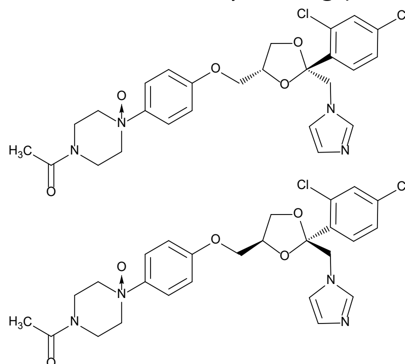

Figure 2f. Ketoconazole N-oxide

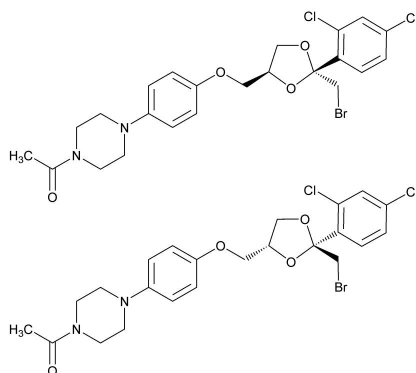

Figure 2g. Ketoconazole bromomethyl analog

Figure 2. Ketoconazole Impurities

4.2. Samples

Two Ketoconazole Foam samples from two different commercial sources were used to evaluate methods described in this document.

4.3. Reagents

Ammonium formate (ACS grade), formic acid (ACS grade), acetonitrile (HPLC grade) and methanol (HPLC grade) were obtained from Qualigens. Ultrapure water was obtained from Sartorius water purification system.

5. Method Development

The goal was to develop a stability-indicating Organic Impurities (OI) method for all known impurities and other potential degradants for Ketoconazole Foam, using the high-performance liquid chromatograph (HPLC) conditions from the OI procedure of the current USP Ketoconazole monograph[2] as the starting point, and Design Expert software for the DOE study to explore the MODR.

5.1. Chromatography Optimization

Some of the official monographs of USP, EP and BP for Ketoconazole drug substances and products[2-8] were evaluated to separate all impurities and observed that few impurities were co-eluted. Based on these observations, it was concluded that the existing monograph methods are not suitable for the separation of all impurities in Ketoconazole Foam. Hence, an isocratic HPLC procedure was developed for the Assay and OI. See the *Assay* section 7 and *Organic Impurity* section 8 for the method conditions.

5.2. Robustness

The Robustness solution, consisting of 0.2 mg/mL of ketoconazole, and 0.03 mg/mL of each of the related impurities in Diluent, was analyzed under the proposed variable LC conditions. Small changes in three variables, including pH of mobile phase, flow rate, and column temperature were studied for the isocratic method. The changes included flow rate ±0.2 mL/min (0.8 mL/min and 1.2 mL/min), column temperature ±3° (42° and 48°), mobile phase pH ± 0.2 (pH 4.8 and pH 5.2). A multifactorial robustness study conducted using Design Expert software is presented in **Table 1**. The software generated 23 runs for the study.

Table 1. Design of Experiments for Robustness

Instrument Methods	Factor-A Flow Rate (mL/min)	Factor-B Column Temp (°)	Factor-C Mobile Phase pH
Method condition	1.0	45	5.0
DOE_1	0.8	48	5.0
DOE_2	1.0	48	5.2
DOE_3	1.0	42	4.8
DOE_4	0.8	42	5.2
DOE_5	1.0	45	4.8
DOE_6	1.0	45	5.0
DOE_7	1.0	48	4.8
DOE_8	1.0	45	5.0
DOE_9	1.0	42	5.0
DOE_10	1.2	42	5.2
DOE_11	1.2	48	5.0
DOE_12	1.2	48	5.0

DOE_13	0.8	48	4.8
DOE_14	1.2	42	4.8
DOE_15	1.0	48	5.2
DOE_16	0.8	45	4.8
DOE_17	1.2	42	4.8
DOE_18	0.8	42	4.8
DOE_19	1.2	42	5.2
DOE_20	1.0	45	5.2
DOE_21	1.2	45	5.2
DOE_22	0.8	42	5.2

The result of the multi-variate study indicated that the method is robust for concomitant but small changes in mobile phase pH, flow rate and column temperature. The resolution criteria of not less than (NLT) 2.0 between ketoconazole and adjacent peaks, and NLT 1.5 between other peaks were met in all conditions studied.

5.3. Forced Degradation

Forced degradation studies were performed by exposing ketoconazole API to acid, base, oxidation, heat, heat/humidity, and light. The stressed samples were analyzed. The chromatograms were processed at 225 nm to detect the degradation impurities of ketoconazole. Photodiode array (PDA) data from 200–400 nm showed homogeneity of the UV spectrum for the ketoconazole peak, indicating absence of coelution. The obtained results for each of the forced degradation conditions are presented in **Table 2**

Table 2. Forced Degradation Results

Condition	Medium	Total Impurities in % Area	Major Degradant in % Area (Name of Impurity/RRT)
Control	Unstressed	NA	NA
Acidic	0.1 N HCl for 3 days	13.6	13.6%- (EP Impurity-D at 0.47)
Basic	0.1 N NaOH for 3 days	5.4	5.4%-(EP Impurity-D at 0.47)
Oxidative	3% H_2O_2 for 4 hours	5.4	5.4%-(Ketoconazole N-oxide at 0.39)
	0.5 mg/mL Azobisisobutyronitrile (AIBN) at 40° for 3 days	5.2	0.3%-(Ketoconazole N-oxide at 0.39) 0.7%- (Unknown at 0.56) 1.7%- (Unknown at 0.59) 0.2%-(EP Impurity-C at 0.75) 0.7%- (Unknown at 0.94) 1.3%- (Unknown at 1.10) 0.1%- (EP Impurity-A at 1.54)
Heat	105° for 3 days	NA	NA
Heat/Humidity	85° and 85% relative humidity for 3 days	NA	NA
Light	NLT 200 watt hours/square meter (for UV light) and NLT 3.6 million lux hours (for visible light)	NA	NA

Under heat, heat/humidity and light exposure conditions, no degradation was detected. EP Impurity-D was observed after acid (13.6%) and base degradation (5.4%). Ketoconazole N-oxide was observed as a major degradation product after oxidative degradation using hydrogen peroxide (5.4%). Under AIBN oxidation, ketoconazole N-oxide, EP Impurity C, EP Impurity A and several unknown degradants were detected. All known and unknown impurity peaks were separated from each other, and no coelution was observed with the main peak.

6. Identification

Identification of ketoconazole in Ketoconazole Foam was evaluated using the final HPLC conditions from the *Assay* section, with PDA spectral match and chromatographic retention time match. See the *Assay* section for method conditions and solution preparations.

6.1. PDA Spectral Match

The validation parameters and results are summarized in **Table 3**, and representative UV spectra of ketoconazole from the Standard solution and Sample solution are shown in **Figure 3** and **Figure 4**, respectively.

Table 3. Summary of Validation Parameter, Solutions, and Results for the Identification Test by PDA Spectral Match

Parameter	Solutions	Results
Spectral Agreement	Collect PDA data from 200 to 400 nm for the Standard solution and Sample solution.	The UV spectrum of the ketoconazole peak from the Sample solution matched the spectrum of ketoconazole in the Standard solution and exhibited maxima and minima only at the same wavelengths as the Standard solution.

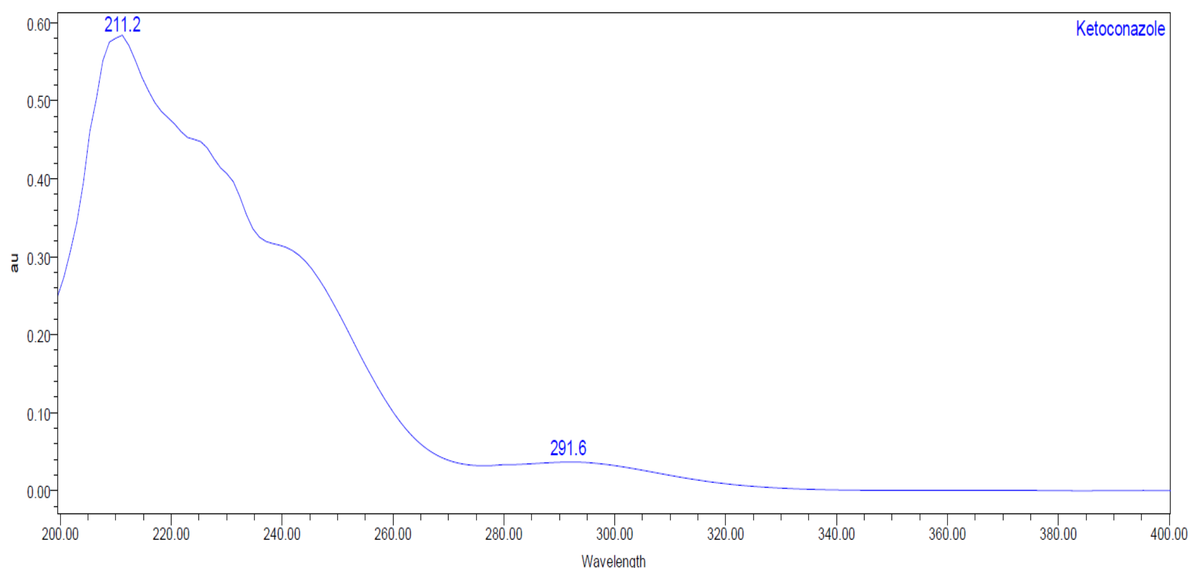

Figure 3. UV spectrum of ketoconazole from the Standard solution

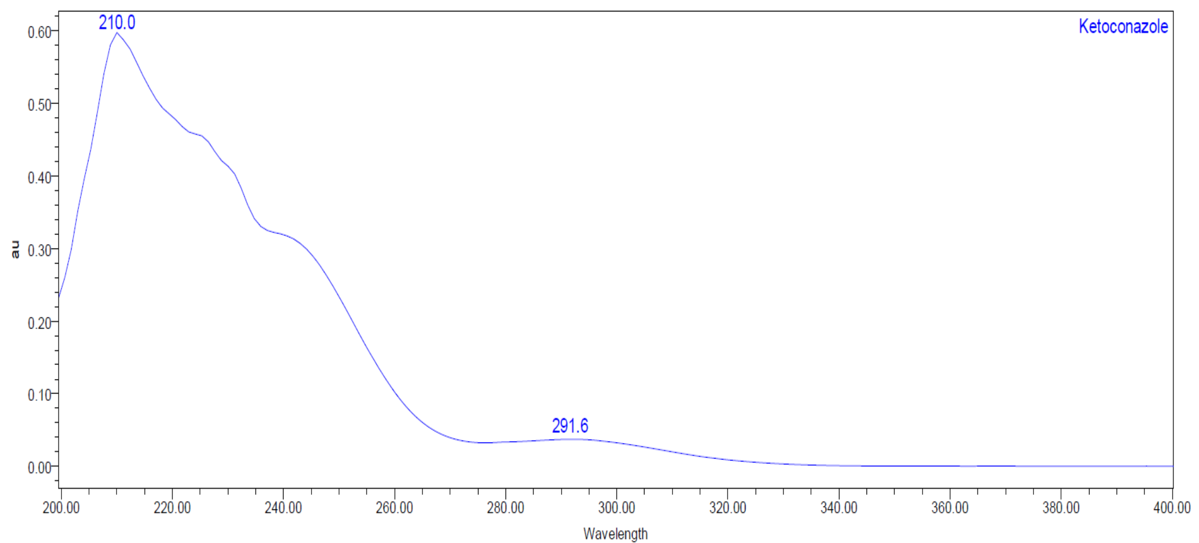

Figure 4. UV spectrum of ketoconazole from the Sample solution

6.2. Retention Time Match

The validation parameters and results are summarized in **Table 4**, and representative chromatograms of the Standard solution and Sample solution are shown in **Figure 5** and **Figure 6**, respectively.

Table 4. Summary of Validation Parameter, Solutions, and Results for the Identification Test by Retention Time Match

Parameter	Solutions	Results
Retention Time Match	Standard solution and Sample solution	The relative standard deviation (RSD) of the ketoconazole peak retention time for all injections of the Standard solution and Sample solution was <1.0%.

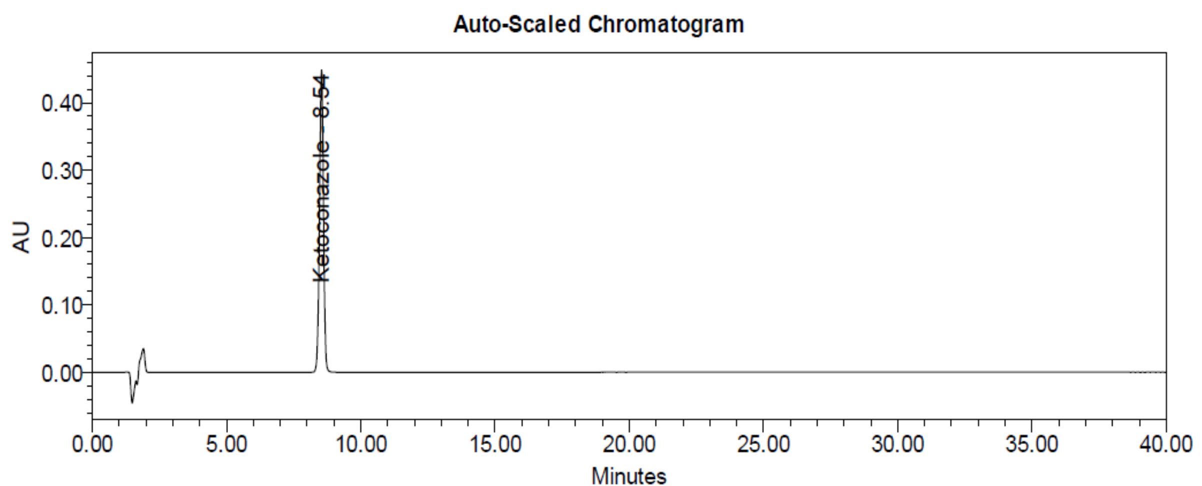

Figure 5. Chromatogram of Standard solution using the HPLC assay procedure

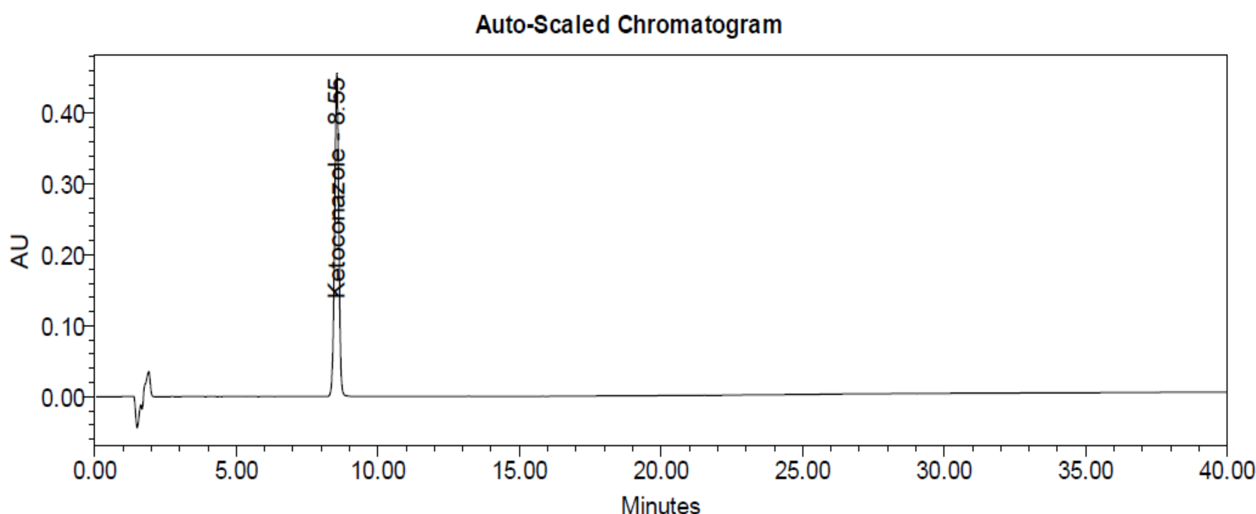

Figure 6. Chromatogram of Sample solution using the HPLC assay procedure

7. Assay

Validation of the assay procedure for Ketoconazole Foam, using the criteria described in USP General Chapter <1225>, *Validation of Compendial Procedure*[10], found the method to be specific, linear, accurate, and precise for the samples evaluated.

7.1. Instruments and Method

The analysis of Ketoconazole Foam was performed using Waters Alliance 2695 and Agilent 1260 instruments with PDA detectors. The Waters Xbridge BEH C8, 4.6-mm x 15.0-cm, 3.5 µm column was used. The analysis was performed at 45° column temperature, with a flow rate of 1.0 mL/min and 10 µL as the injection volume. The autosampler temperature was kept at 15°. The PDA detector was set at 200-400 nm and the detection of chromatogram was at 225 nm. The separation was achieved in an isocratic elution mode with run time of 40 minutes. The results were processed using Empower (Waters software).

7.2. Solutions

Buffer (50 mM ammonium formate): Weighed and transferred about 3.15 g of ammonium formate into 1000 mL of water and adjusted the pH to 5.0 with 1.0 % formic acid.

Mobile Phase: Mixed 400 mL of acetonitrile and 600 mL of Buffer (40:60, v/v).

Diluent: Mixed 900 mL of methanol and 100 mL of water (90:10, v/v).

Preparation of Standard solution (0.2 mg/mL of ketoconazole): Weighed and transferred about 10 mg of ketoconazole standard into 50 mL volumetric flask, added 20 mL of Diluent, sonicated to dissolve, and diluted to volume with Diluent.

Preparation of Sample stock solution (1.0 mg/mL of ketoconazole): A solution with nominal 1.0 mg/mL of ketoconazole from Ketoconazole Foam in Diluent was prepared as follows. Prepared a composite by mixing not less than 2 containers of Ketoconazole Foam and pouring the sample into a suitable container.

Transferred and weighed about 1 g of the Ketoconazole Foam composite (equivalent to 20 mg of ketoconazole), into 50 mL centrifuge tube, added 15 mL of Diluent, mixed well and transferred this solution into a 20 mL volumetric flask and diluted to volume with Diluent.

Preparation of Sample solution (0.2 mg/mL of ketoconazole): Transferred 5.0 mL of sample stock solution into 25 mL volumetric flask and diluted to volume with Diluent.

7.3. Validation Parameters and Results

The system suitability parameters and results are summarized in **Table 5**. The validation parameters and results are summarized in **Table 6**. Representative chromatograms of the Standard solution and Sample solution are shown in **Figure 5,** and **Figure 6** respectively.

Table 5. Summary of System Suitability Parameters, Solutions, and Results for the Assay Test

Parameter	Solutions	Results
Retention time	Standard solution	About 8.5 min
Tailing factor	Standard solution	1.0
System Precision (%RSD of 5 replicate injections)	Standard solution	0.2

Table 6. Summary of Validation Parameters, Solutions, and Results for the Assay Test

Parameter	Solutions	Results
Specificity (Chromatographic Separation) **Peak Purity Analysis (Spectral Homogeneity)**	Diluent, Standard solution, and Sample solution	Any peak adjacent to the ketoconazole peak was separated from the peak by a resolution ≥2.0. The PDA data showed spectral homogeneity for ketoconazole and no coelution between 200 – 400 nm.
Linearity	Linearity solutions from 50% to 150% of the nominal concentration (0.10, 0.15, 0.20, 0.25, 0.30 mg/mL of ketoconazole)	The correlation coefficient was ≥ 0.999. The bias of the linearity curve due to the intercept not being zero was within ±2.0%.
Accuracy	Accuracy solutions with 110-130% of the nominal concentration: 110% (0.22 mg/mL), n=3 120% (0.24 mg/mL), n=3 130% (0.26 mg/mL), n=3	The average recovery at each spiked level was within 100 ± 3.0%.

Repeatability	Repeatability solutions*:* 6 *Sample solutions*	The %RSD of assay results was ≤ 2.0 (n=6).
Intermediate Precision	6 *Sample solutions* prepared and analyzed by two analysts on a different day, using a different instrument and different column serial number	The %RSD of assay results was ≤ 2.0 for the second analyst (n=6). The %RSD of assay results was ≤ 3.0 for the combined data of the first and second analysts (n =12).
Solution Stability	Standard solution and Sample solution	Stable for 32 hours at 15° autosampler temperature.
Sample Assay Test	Sample solution	100.3%, 99.0%, for the two sources of drug product tested.

8. Organic Impurities

OI Procedure:

Validation of the OI procedure for Ketoconazole Foam, using the criteria described in USP General Chapter <1225>, *Validation of Compendial Procedure*[10], found the method to be specific, linear, accurate, precise, and free from interference for the samples evaluated.

8.1. Instruments and Method

The analysis of Ketoconazole Foam was performed using the same instruments and method as described in the Assay section.

8.2. Solutions

Prepare Buffer, Mobile phase and Diluent as per the Assay procedure.

Preparation of Individual stock solutions: Individual stock solutions consisting of 3 mg/mL ketoconazole, 0.3 mg/mL of each EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, ketoconazole N-oxide, and ketoconazole bromomethyl analog were separately prepared by dissolving appropriate amounts of each standard in Diluent.

Preparation of System Suitability Solution (3.0 mg/mL of ketoconazole and 0.03 mg/mL of EP Impurity-B):
A solution consisting of 3.0 mg/mL of ketoconazole and 0.03 mg/mL of EP Impurity-B was prepared in Diluent.

Preparation of Standard solution (0.006 mg/mL of each Ketoconazole, EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, Ketoconazole N-oxide, and Ketoconazole bromomethyl analog [0.2% of sample concentration]):
A solution consisting of 0.006 mg/mL of each ketoconazole, EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, ketoconazole N-oxide, and ketoconazole bromomethyl analog was prepared in Diluent.

Preparation of Sensitivity solution (0.0015 mg/mL of each Ketoconazole, EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, Ketoconazole N-oxide, and Ketoconazole bromomethyl analog , [0.05% of sample concentration]):A solution consisting of 0.0015 mg/mL of each Ketoconazole, EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, ketoconazole N-oxide, and ketoconazole bromomethyl analog was prepared in Diluent.

Preparation of Sample solution: (3.0 mg/mL of ketoconazole): A solution with nominal 3.0 mg/mL of ketoconazole from Ketoconazole Foam in Diluent was prepared as follows. Prepared a composite by mixing not less than 2 containers of Ketoconazole Foam and pouring the sample into a suitable container. Transferred and weighed about 3 g of the Ketoconazole Foam composite solution (equivalent to 60 mg of ketoconazole), into 50 mL centrifuge tube, added 15 mL of Diluent, mixed well, and transferred this solution into a 20 mL volumetric flask and diluted to volume with Diluent.
Preparation of Robustness solution: A solution consisting of 0.2 mg/mL of ketoconazole and 0.03 mg/mL of each of EP Impurity-A, EP Impurity-B, EP Impurity-C, EP Impurity-D, EP Impurity-E, ketoconazole N-oxide, and ketoconazole bromomethyl analog was prepared by combining appropriate volumes of Individual stock solutions in Diluent.

8.3. Validation Parameters and Results

The system suitability parameters and results are summarized in **Table 7**. The validation parameters and results are summarized in **Table 8** and the RRF values captured in **Table 9**. Representative chromatograms of Diluent, System suitability solution, Sensitivity solution, Standard solution, Sample solution, and Sample solution spiked with impurities at recovery lower level (RLL), are presented in **Figure 7** to **Figure 12** respectively**.** Linearity was established for ketoconazole and related impurities, whereas accuracy and repeatability were established for ketoconazole related impurities.

The sensitivity solution concentration was established at 0.05% level with respect to the sample concentration of 3.0 mg/mL.

Table 7. Summary of System Suitability Parameters, Solutions, and Results for the Organic Impurities Procedure

Parameter	Solution	Results
Resolution Resolution between Ketoconazole and EP Impurity B	System suitability solution	4.6 (See **Figure 8**)
Retention time (mins) Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Sensitivity solution (0.05%)	3.1 4.0 5.7 8.4 10.2 12.9 19.5 32.4 (See **Figure 9**)
Relative retention time Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog		0.37 0.48 0.68 1.00 1.22 1.55 2.33 3.88 (See **Figure 9**)
System Precision (% RSD of 6 replicate injections) Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog		0.57 0.38 0.10 0.23 0.30 0.52 0.16 0.48
USP Signal-to-Noise ratio Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A		458 561 1646 1278 483 87

EP Impurity-E Bromomethyl analog		502 221

Table 8. Summary of Validation Parameters, Solutions, and Results for the Organic Impurities Procedure

Parameter	**Solutions**	**Results**
Specificity	Blank (Diluent), system suitability solution, sensitivity solution, sample solutions and spiked sample solutions	No interference with peaks of interest. Any peak ≥0.1% total area was separated from the main peak by a resolution of ≥2.0, and from adjacent related impurity peaks by a resolution of ≥1.5.
Linearity Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Linearity solutions From 0.05% to 1.5% of the sample concentration of ketoconazole	The correlation coefficient of the linear curves for ketoconazole and its impurities were not less than 0.99
Relative Response Factor (RRF) Values	RRF values of the impurities were calculated with respect to ketoconazole. The values were obtained by dividing the slope of the linearity curve for the impurity by the slope of the linearity curve for the ketoconazole.	See **Table 9**
Accuracy Ketoconazole N-Oxide EP Impurity-D EP Impurity-C EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Accuracy solutions: Impurities spiked in sample solution at 3 levels; Recovery lower level (RLL) (0.05%): n=6 Recovery middle level (RML) (0.5%): n=3 Recovery upper level (RUL) (1.0%): n=3	The average recovery for each specified impurity at each level were observed within: RLL: 100 ± 20.0%. RML: 100 ±10.0%. RUL: 100 ± 5.0%
Repeatability Ketoconazole N-Oxide EP Impurity-D EP Impurity-C EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Repeatability Solutions: 6 spiked sample solutions at the RLL level.	The RSD of the recovery RLL level was ≤ 10.0% (n=6)

Intermediate Precision Ketoconazole N-Oxide EP Impurity-D EP Impurity-C EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Repeatability Solutions: 6 spiked sample solutions at the RLL level. Prepared and evaluated by a different analyst, on a different day by using different instrument and a different serial number of the column.	The average recovery at RLL level was within 100 ± 20.0%. RSD of the 6 results at RLL was ≤ 10.0%. RSD of the 12 results (for the first and second analysts) at RLL was ≤15.0%.
Sample OI Test	Two replicate sample preparations from each sample material.	About 0.11% w/w of EP Impurity-A, and about 0.17% w/w of an uknown impurity at RRT 0.58 was observed in one of the two samples (Sample-2), and no other impurity was observed in any of the two samples above 0.1% w/w . (See **Figure 11**, **Figure 12**)
Solution Stability Ketoconazole N-Oxide EP Impurity-D EP Impurity-C Ketoconazole EP Impurity-B EP Impurity-A EP Impurity-E Bromomethyl analog	Mix solution (ketoconazole and impurities) at 0.1% level and Spiked sample solution at 0.1% level, freshly prepared and analyzed periodically over 48 hours at 15° of sample cooler temperature.	Observed changes in the peak area from both solutions for each specified impurity and ketoconazole were within ± 10% of the initial time point values up to 48 hours.

Table 9. Relative Response Factor

	Compound Name	**RRF**
1	Ketoconazole	1.00
2	Ketoconazole N-oxide	1.19
3	EP Impurity-D	0.97
4	EP Impurity-C	0.86
5	EP Impurity-B	1.13
6	EP Impurity-A	0.62
7	EP Impurity-E	1.28
8	Ketoconazole bromomethyl analog	0.92

RRF values of the impurities were calculated by dividing the slope of the linearity curve for each impurity by the slope of the linearity curve for ketoconazole.

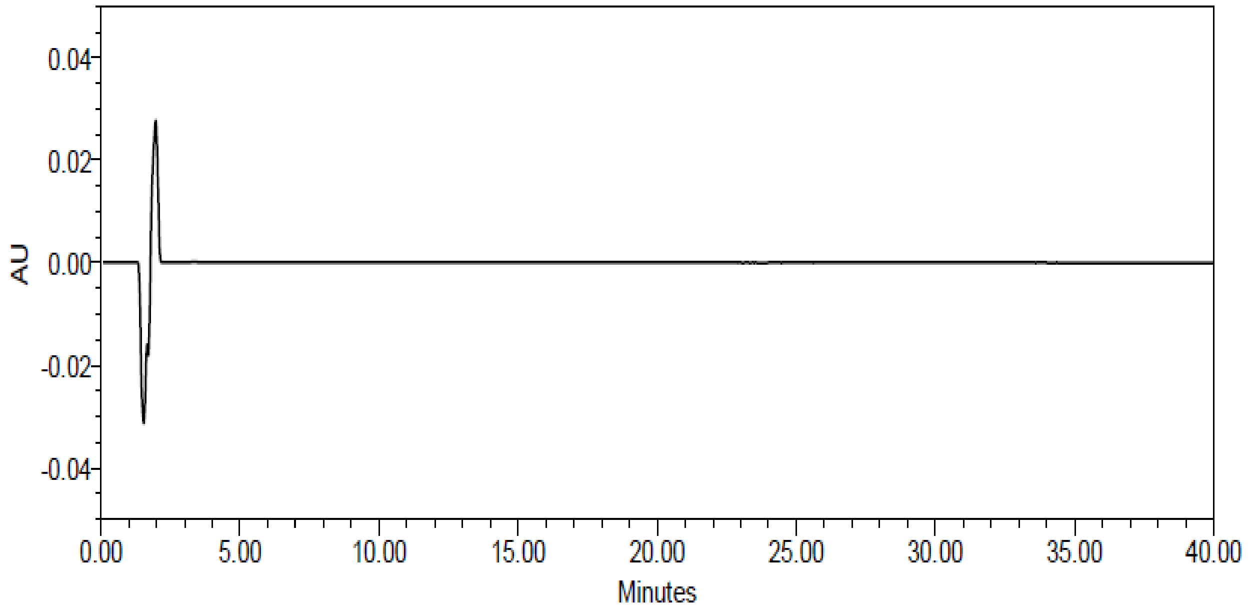

Figure 7. Chromatogram of Diluent (blank)

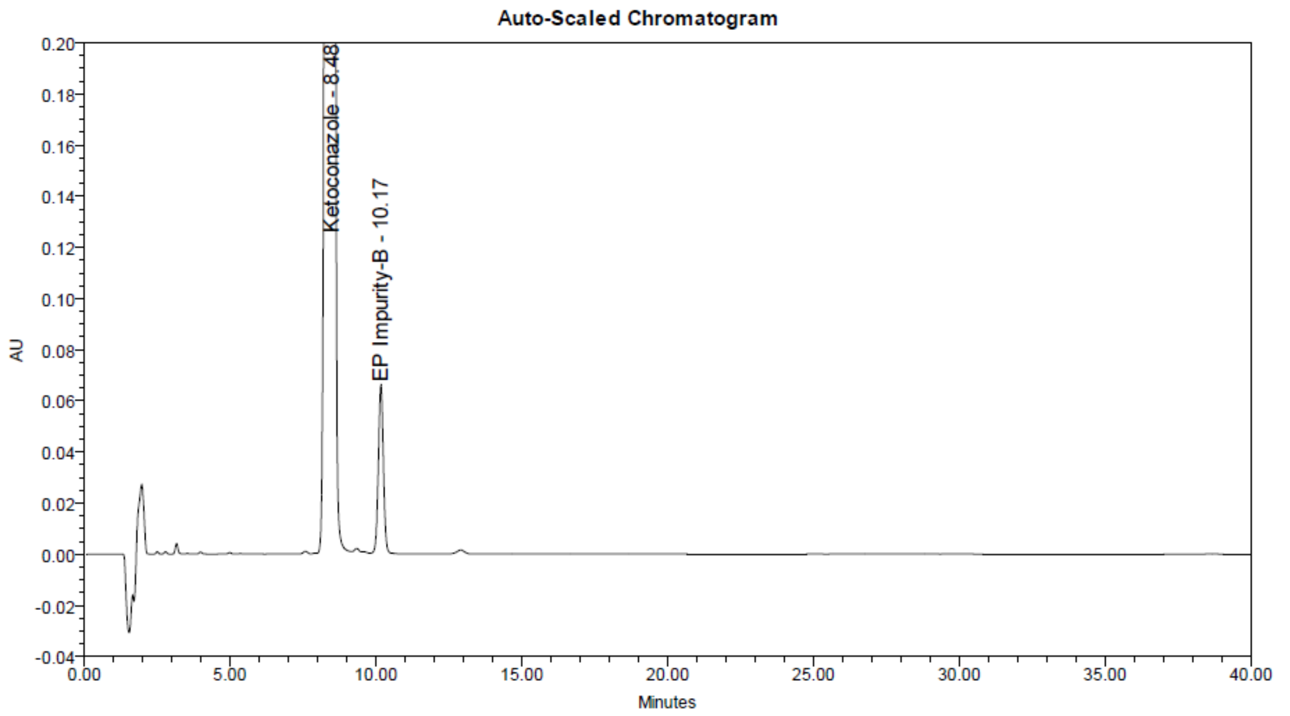

Figure 8. Chromatogram of System suitability solution

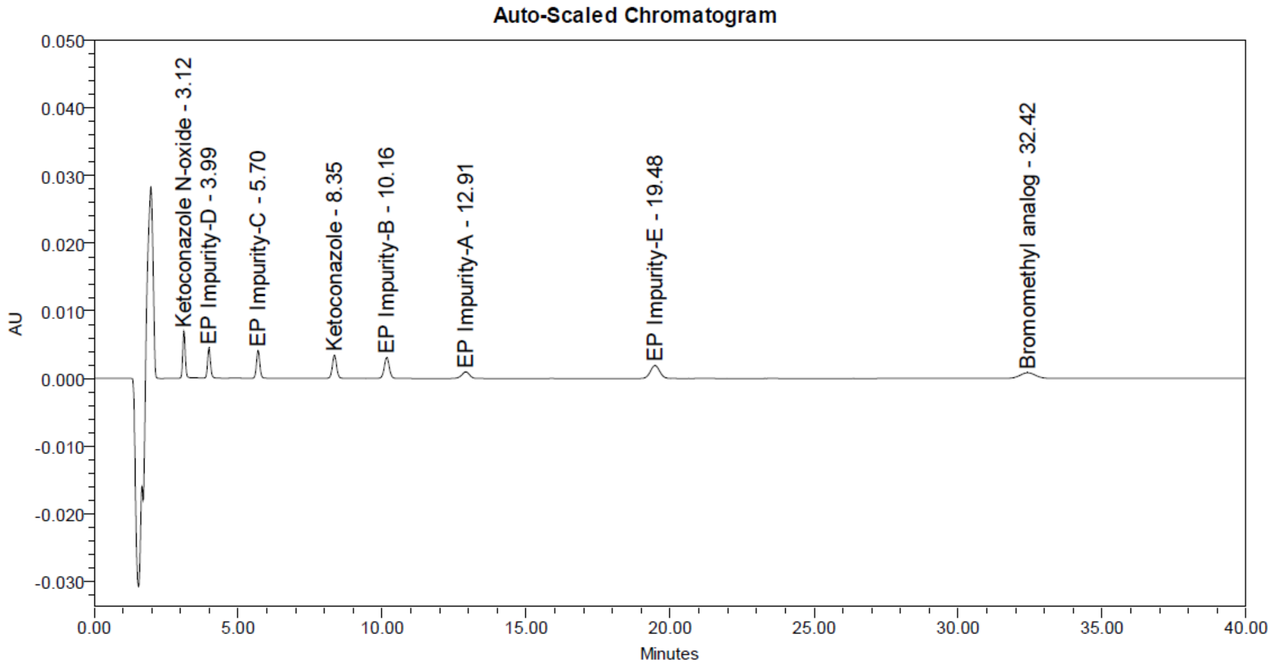

Figure 9. Chromatogram of Sensitivity solution

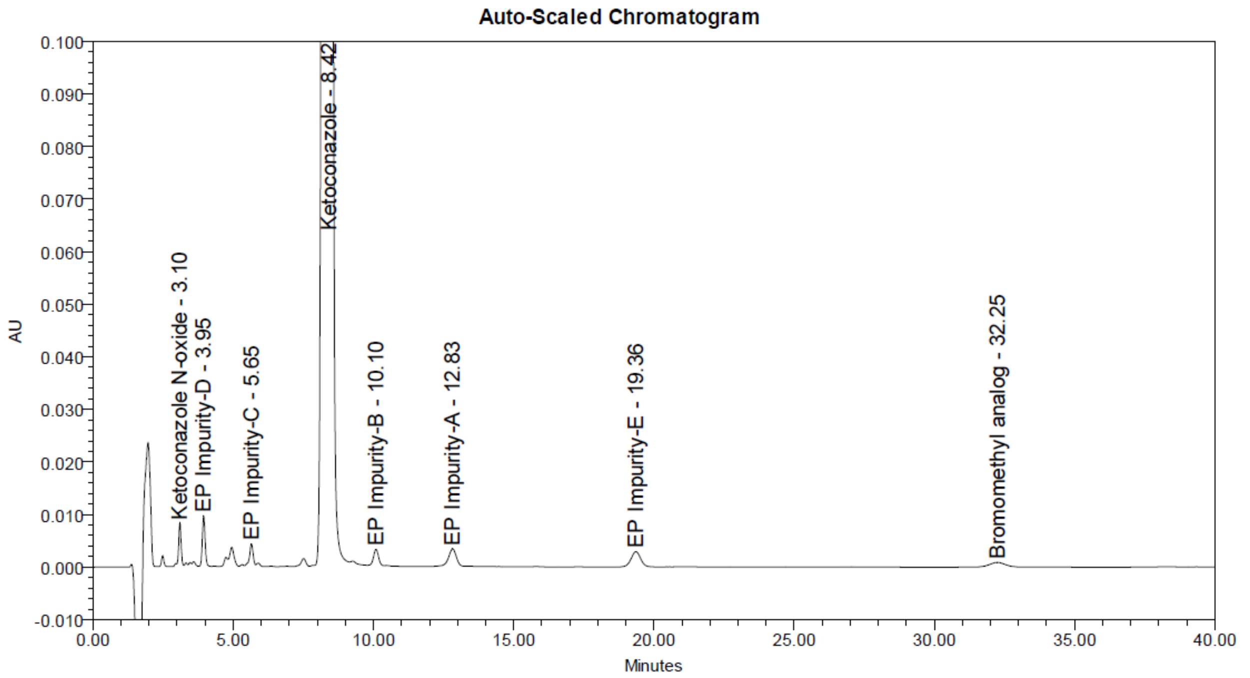

Figure 10. Chromatogram (at expanded scale) of Sample solution (Sample-1) spiked with impurities at the RLL level (0.05%)

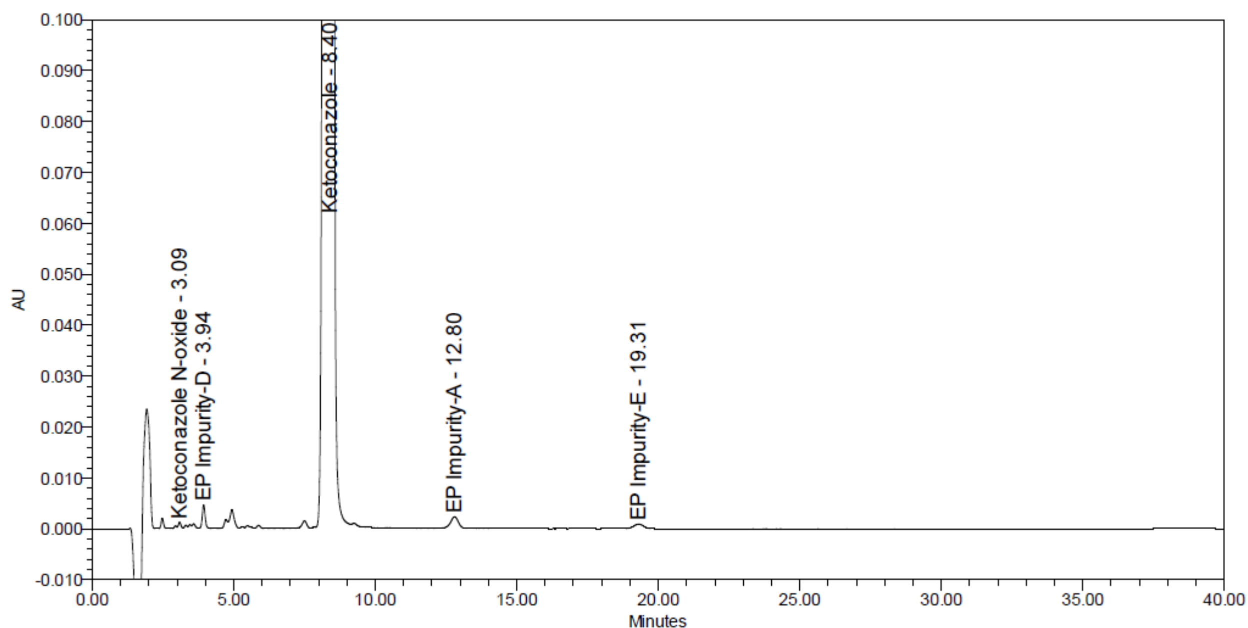

Figure 11. Chromatogram (at expanded scale) of Sample solution (Sample-1)

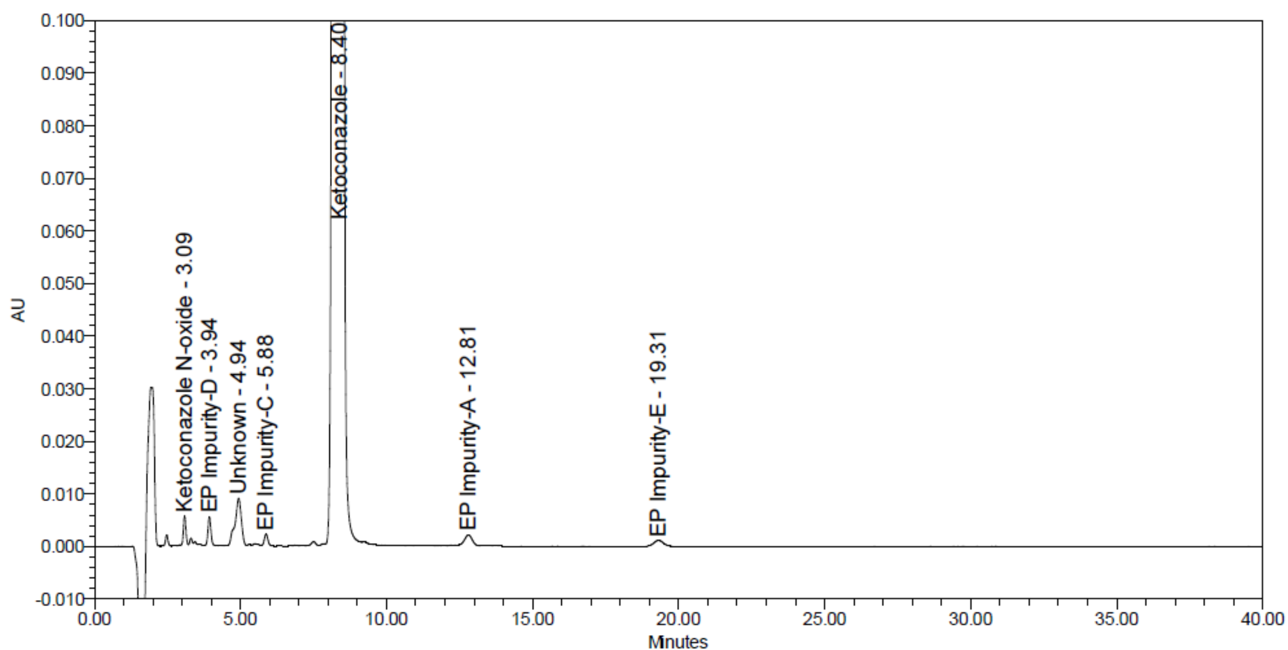

Figure 12. Chromatogram (at expanded scale) of Sample solution (Sample-2)

9. References

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9. <1220> Analytical Procedure Life Cycle

   DOI: https://doi.org/10.31003/USPNF_M10975_02_01

10. <1225> Validation of Compendial Procedures

    DOI: https://doi.org/10.31003/USPNF_M99945_04_01