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STUDY OF RELATED IMPURITIES PROFILE BY HPLC: CASE OF FIVE SAMPLES OF FLUCONAZOLE ACTIVE PHARMACEUTICAL INGREDIENT

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The main objective of this work was to analysis nine drug related impurities (A-I) by High Performance Liquid Chromatography (HPLC) in five samples (F1-F5) of Fluconazole active pharmaceutical ingredient (API), collected from five pharmaceutical industries installed in Algeria. For the organic related-impurities analysis, a liquid chromatography apparatus HPLC-UV device equipped with an automatic injector and UV/Vis detector and a column (C_{18}), deactivated for the bases, post-grafted (5 µm) and dimensions (w: 0.15 m, Ø: 4.6 mm) were used. Each sample of Fluconazole API was processed according to the related substances procedures of the European Pharmacopoeia (EP), 8th edition. The HPLC related-impurities analysis showed that the F1, F3, F4 and F5 samples had an individual content of specified impurities (A, B and C) and unspecified impurities meeting the required standards with a total of all impurities present meeting with the standard. F2 sample had a high content of unspecified impurity 0.126 % compared to the acceptance limit and a total of impurities 0.387 % meeting the standard. This can be explained either by the sample degradation which may be due to poor storage conditions or the batch from which this sample comes wasn't well purified during the synthesis route.

Keywords: *drug related impurities, related substances, unspecified impurities, specified impurities HPLC-UV, Fluconazole.*

INTRODUCTION

The pharmaceutical industry has shown tremendous interest in drug impurity profiling over the past ten years. Even a little amount of these unwanted compounds can have an impact on the safety and effectiveness of medicinal goods. A number of pharmacopoeias, including the United States Pharmacopeia (USP)[1], the Indian Pharmacopoeia (IP)[2], the British Pharmacopoeia (BP)[3], the European Pharmacopoeia (EP)[4], and others, have created monographs to ensure that users are receiving drug substances and products of a minimum acceptable quality. Regulatory authorities are giving the pharmacopoeia's monograph on impurity profiling severe consideration[5& 6].

Impurities are compounds found in a product that are neither Active Pharmaceutical Ingredients (API) themselves nor the excipients used to create it, according to the International Conference on Harmonization (ICH) rules[7]. However, according to IP, an impurity is any ingredient in a drug substance intended for pharmaceutical use or a drug product that is not the chemical entity that characterizes the substance or, in the case of a drug product, is not an excipient in the product[2].

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Any substance that coexists with the original drug, such as beginning material, intermediates, or generated due to any side reactions, is referred to as an impurity. The recognized and unidentified contaminants that are present in drug products are described in the impurity profile[8&9].

The organic related-impurities are defined as organic chemical compounds appear during manufacturing process or storage. They can be the starting products, synthesis intermediates, by-products which form with pharmaceutical raw materials synthesized and the degradation products form mainly due to poor storage conditions[9&10]. Chiral impurities have the same molecular formula but they only differ in the 3D arrangement of their atoms. The differences in pharmacological and toxicological profiles were observed in vivo; this suggests that chiral impurities should be carefully monitored[11].

Fluconazole is a synthetic imidazole that is used to treat and prevent a range of fungal and yeast infections, including cutaneous-mucous candidiasis and mycoses connected to AIDS. Fluconazole is a systemic antifungal medication[13].

The European Pharmacopoeia (Eur Ph) 8th edition describes nine impurities of Fluconazole **(Figure 1)**, some are related to either synthesis or degradation, and others may be common to both processes[14]. The impurities A, B, C, D, H and I are related to synthesis route, the impurity G is the only impurity whose origin is exclusively degradation process, the impurities E and F whose origin can be synthesis route or degradation. The impurities A, B, C are specified, that is means that they are described individually and limited by a specific acceptance criterion. The impurities D, E, F, G, H and I are not specified[15] **(Table 1)**.

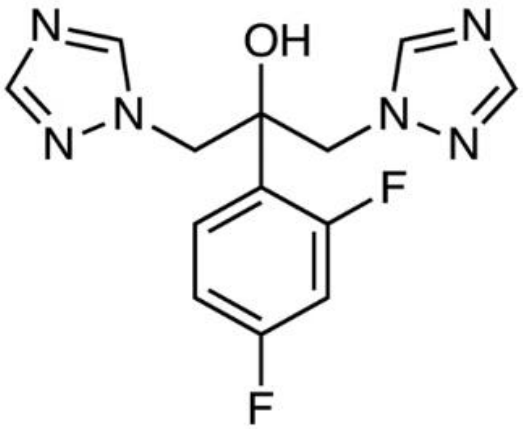


Fig. 1: Chemical structure of Fluconazole[12].

Table 1: Organic related-impurities of Fluconazole[15].

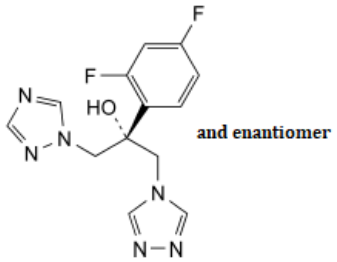
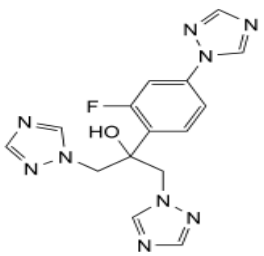
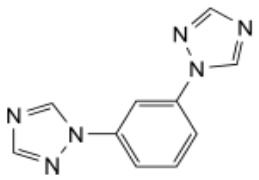
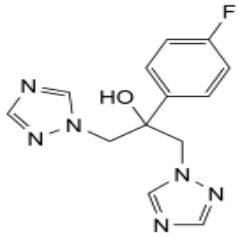
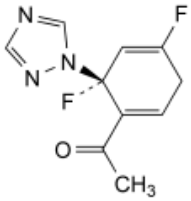
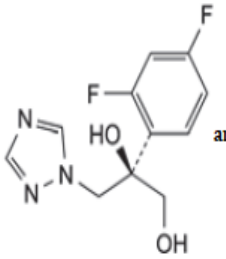
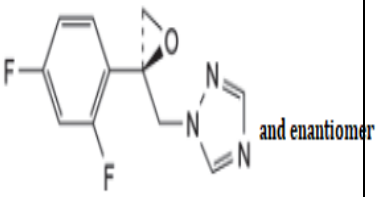
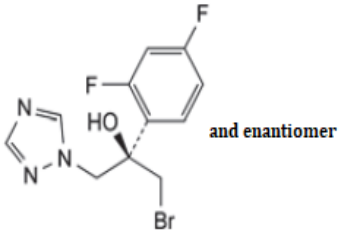
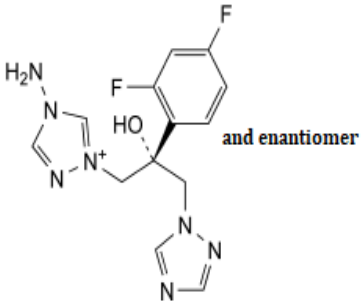
Impurity	Structure	Source	Specification	Minimum Accepted Limits (%)
Impurity A		Synthesis only	Specified	0,4
Impurity B		Synthesis only	Specified	0,3

Table 1: Continued.

Impurity C		Synthesis only	Specified	0,1
Impurity D		Synthesis only	Non-Specified	0,1
Impurity E	 and enantiomer	Synthesis or Degradation	Non-Specified	0,1
Impurity F	 and enantiomer	Synthesis or Degradation	Non-Specified	0,1
Impurity G	 and enantiomer	Degradation only	Non-Specified	0,1
Impurity H	 and enantiomer	Synthesis only	Non-Specified	0,1
Impurity I	 and enantiomer	Synthesis only	Non-Specified	0,1

Fluconazole is made in Algeria by about 13 different pharmaceutical companies[16]. In Dongrea V. and al study, four impurities in Fluconazole API sample obtained from a recently proposed synthetic process were detected by HPLC. One of the impurities was unknown having not been reported previously. This less polar unknown impurity was isolated from the crude sample of fluconazole bulk drug using semi-preparative HPLC. Structure of impurity was elucidated as 2-(2-(dimethylamino)-4-fluorophenyl)-1,3-di(3*H*-1,2,4-triazol-1-yl)propan-2-ol by using NMR spectroscopy(^{1}H, ^{13}C, ^{19}F, ^{1}H–^{1}H, ^{1}H–^{13}C, HMBC and nOe) and mass spectrometry. The formation and synthesis of the impurity was discussed[17]. In the study realized by Bouriachi. H and al. entitled Solid-state characterization and impurities determination of fluconazol generic products marketed in Morocco[14], a solid-state characterization of the three samples was realized with different physicochemical methods as: X-ray powder diffraction, Fourier-transformation infrared spectroscopy, differential scanning calorimetry. High performance liquid chromatography was used to quantify the impurities in the different samples[14].The primary goal of this research was to use High Performance Liquid Chromatography (HPLC) to analyze nine drug-related contaminants in five samples of Fluconazole active pharmaceutical ingredient (API) that were gathered from five pharmaceutical companies with facilities in Algeria.

MATERIALS AND METHODS

Collection of samples

By using the Algerian drug nomenclature on the 31st of December 2014[16], five samples of Fluconazole API were gathered from five pharmaceutical companies situated in Algeria. The samples are gathered between April 1st, 2015, and December 31st, 2016. Along with the API, the compendium also includes the following crucial details: origin, supplier or manufacturer, expiration date, analytical certificate, synthesis route, Drug Master File, etc.)[18,19,20&21] **(Table 2).** The samples were not past their expiration dates, and we called them F1, F2, F3, F4, and F5. They were examined just before their expiration date while being kept at ambient temperature, shielded from light and humidity. We didn't get all the necessary information for certain samples.

Table 2: Collection of Fluconazole API from local producers[18,19,20&21].

Sample	Local Producer	Batch number	Expiration Date	Manufacturer-Supplier
F1	Saidal-Medea	FLP 0270313	03/2017	Synergene Active Ingredients (P) LTD (India)
F2	Inpha-Medis	FLU_1411026	11/2019	Granules India Limited (India)
F3	Mérinal	FL0A 4005	04/2019	Quimica Sintetica (Chemo) (Spain)
F4	CPCM Pharma	FLP 1021012	09/2017	Synergene Active Ingredients PVT LTD (India)
F5	Hikma Pharmaceuticals	20021067	05/2018	Mylan Laboratories Limited (India)

Equipments

(Thermo Scientific Dionex UltiMate 3000 Rapid Separation LC systems, Germany) liquid chromatography equipment HPLC-UV device with an automated injector and UV/Vis detector was utilized for the analysis of organic related-impurities. Column (C_{18}), post-grafted (5 µm), deactivated for the bases, and measurements (w: 0.15 m, Ø: 4.6 mm).

A pH meter (Mettler Toledo, USA) was used to measure the pH of solutions, an ultrasonic bath (Elmasonic S 130 H, Germany) was used to dissolve the samples, and an analytical balance (Kern ALS-200-4N, Germany) was used to weigh the materials.

Chemicals and reagents

The reference standards " Fluconazole for peaks identification containing Impurity A", "Impurity B of Fluconazole " and " Impurity C of Fluconazole " used for the identification of impurities A, B and C peaks were provided by the EDQM laboratories (Strasbourg, France). Acetonitrile HPLC grade (99.9 %) and Ammonium formate (99 %) were procured from Sigma-Aldrich, France.

Preparation of test and standard solutions

Mobile phase: 86 volumes of ammonium formate solution were combined with 14 volumes of acetonitrile at a concentration of 0.63 g/L[15].

Each sample taken underwent the following processing:

Test solution: 100 mg of Fluconazole was dissolved in 10 mL of mobile phase[15].

Control solution (a): 5 mL of test solution was taken and made up to 100 mL with the mobile phase. 1 mL of this solution was taken and made up to 10 mL with the mobile phase[15].

The impurities standards A, B and C were prepared as follows:

Control solution (b): To identify peaks, 5 mg of Fluconazole with impurity A was dissolved in the mobile phase, sonicated as needed, and diluted to a final volume of 10 mL using the same solvent[15&22].

Control solution (c): The same solvent was used to sonicate 3 mg of Fluconazole impurity B in the mobile phase before emulsifying it to a volume of 100 mL[15&23].

Control solution (d): 2 mg of impurity C of Fluconazole was dissolved in 20 mL of the mobile phase. 1 mL of this solution was taken and added to 1 mL of test solution and made up to 10 mL with the mobile phase[15&24].

Control solution (d): 20 mL of the mobile phase was used to dissolve 2 mg of Fluconazole impurity C. The mobile phase[15&24] was used to make up 10 mL from 1 mL of this solution plus 1 mL of test solution.

Chromatographic conditions

- 40 °C is the temperature.
- 1 mL per minute of flow.
- 20 L for injection.
- UV/Vis spectrophotometer set to 260 nm for detection.

Column (C_{18}): octadecylsilyl silica gel for chromatography (5 µm) and dimensions (l: 0.15 m, Ø: 4.6 mm)[15].

Compliance of system

Control solution (d): the resolution was at least 3.0 between the peaks due to Fluconazole and impurity C[15].

RESULTS AND DISCUSSION

Compliance of system

The **figures 2, 3 and 4** represent respectively the obtained chromatograms of the control solution (d), (c) and (b). The **figure 5** represents the typical chromatogram supplied with the Fluconazole for peaks identification containing impurity A.

The main peak of Fluconazole and the impurities A, B, C peaks were identified. The retention time obtained for Fluconazole was 13.672 min **(Figure 2)**, value close to that required by the EP which must be around 11 min[15]. The retention time obtained for each impurity B, A and C was respectively 6.308 min, 6.735 min and 11.757 min **(Figure 2, 3, 4)**. All these values were close respectively to those provided in the typical chromatogram or calculated from RRT (5.468 min, 6.836 min and 10.937 min)[15].

The resolution between the peaks due to impurity C and Fluconazole was 3.15 **(figure 2)**, value complies the required standard which was at least 3[15]. The symmetry factors of Fluconazole and impurity C peaks were 1.04 and 1.02 **(figure 2)**, values in accordance with the EP standards which were between 0.8 and 1.5.

In conclusion, the system is compliant.

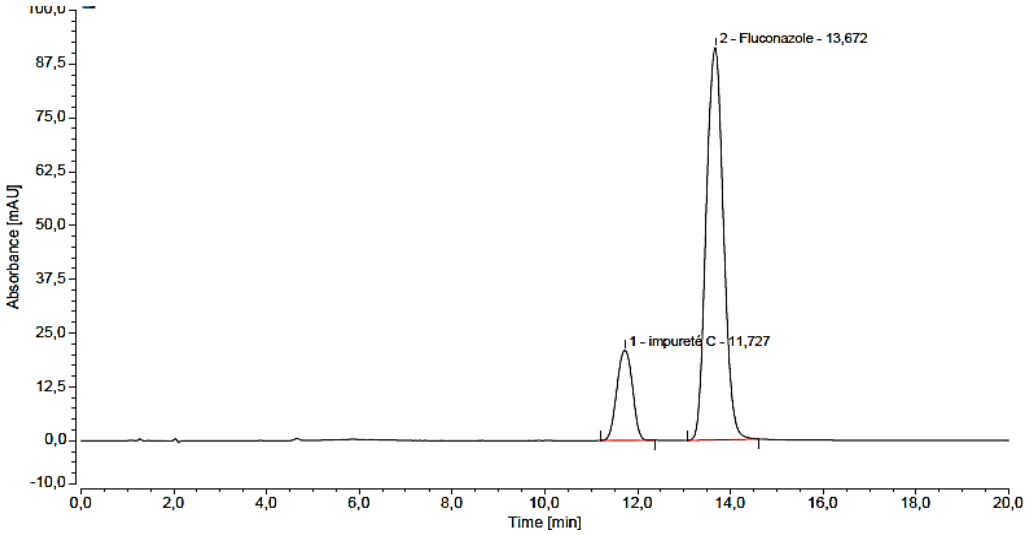


Fig. 2: Chromatogram of the control solution (d).

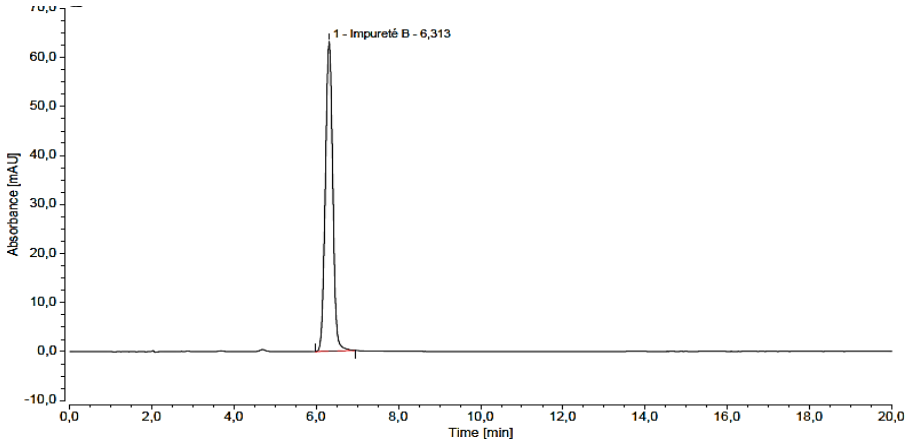


Fig. 3: Chromatogram of the control solution (*c*).

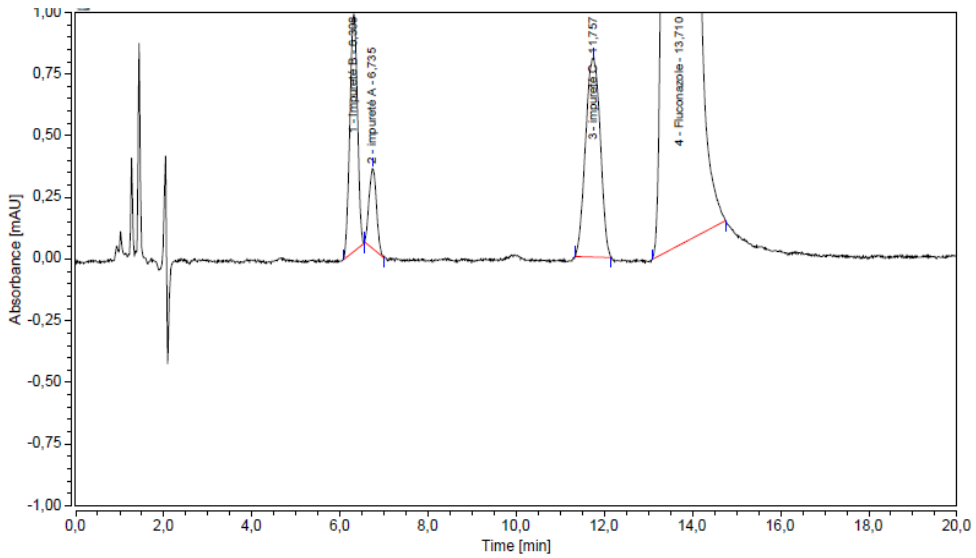


Fig. 4: Chromatogram of the control solution (b).

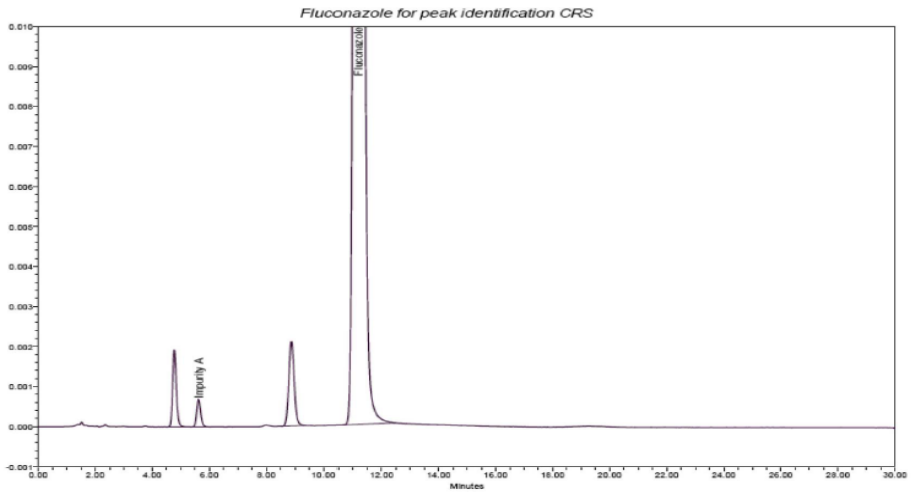


Fig. 5: Typical chromatogram supplied with the Fluconazole for peaks identification containing impurity A[25].

Analysis of samples

The **Figures 6, 7, 8, 9 and 10** show respectively the obtained chromatograms of the test solutions of F1, F2, F3, F4 and F5 samples. The **Table 2** summarizes the results of the individual content of impurities A, B, C, unspecified impurities and the impurities total of the various samples of Fluconazole analyzed as well as the standards required by the EP.

For the identification and the calculation of impurities content and according to the EP standards, the individual impurity A content must be less than or equal to 0.4 %, the individual impurity B content must be less than or equal to 0.3 % and the individual impurity C or unspecified impurity content must be less than or equal to 0.1 %. Any other impurity with an individual content less than or equal to 0.05 % should not be taken into consideration. The total impurities content should not exceed 0.6 %[15].

The F1, F3, F4 and F5 samples had an individual content of specified impurities (A, B and C) and unspecified impurities meeting the required standards with a total of all impurities present meeting with the standard **(Table 3)**.

The F2 sample had a total of 0.387% contaminants that were within the acceptable range and a high level of an unidentified impurity that was 0.126% higher than the acceptability limit. This may be due to sample degradation brought on by poor storage circumstances, or it may be because the batch from which this sample was drawn wasn't properly purified throughout the production process **(Table 2).**

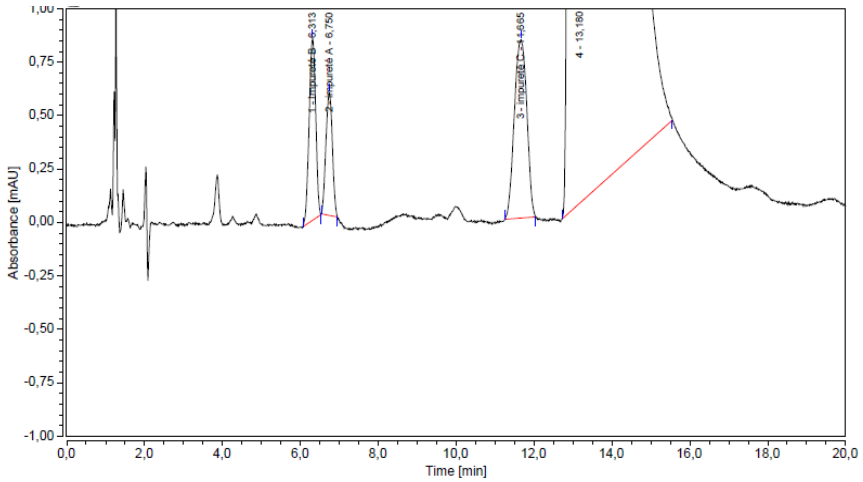


Fig. 6: Chromatogram of the test solution of F1sample.

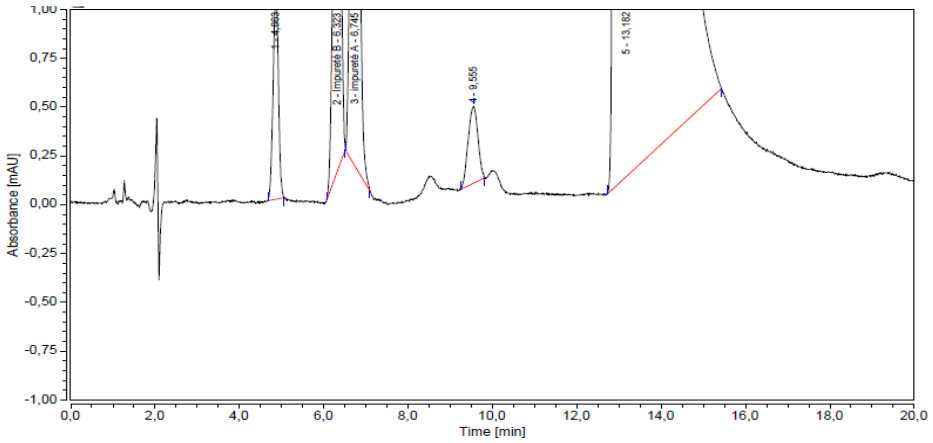


Fig. 7: Chromatogram of the test solution of F2 sample.

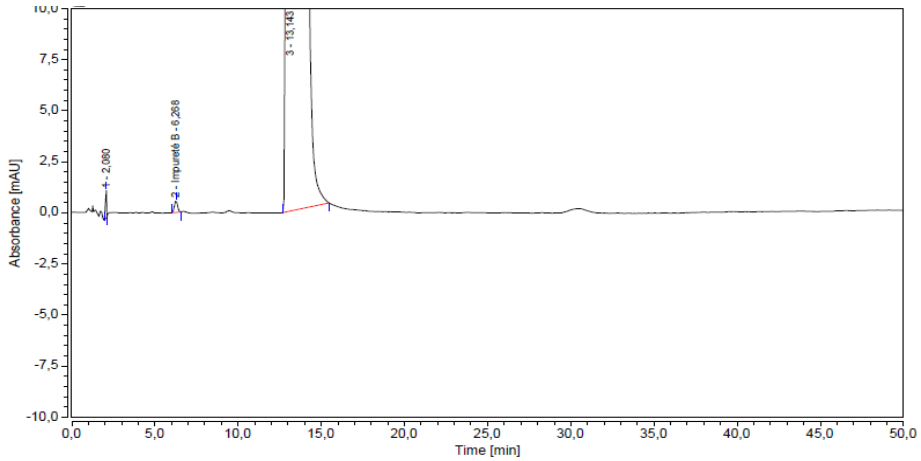


Fig. 8: Chromatogram of the test solution of F3 sample.

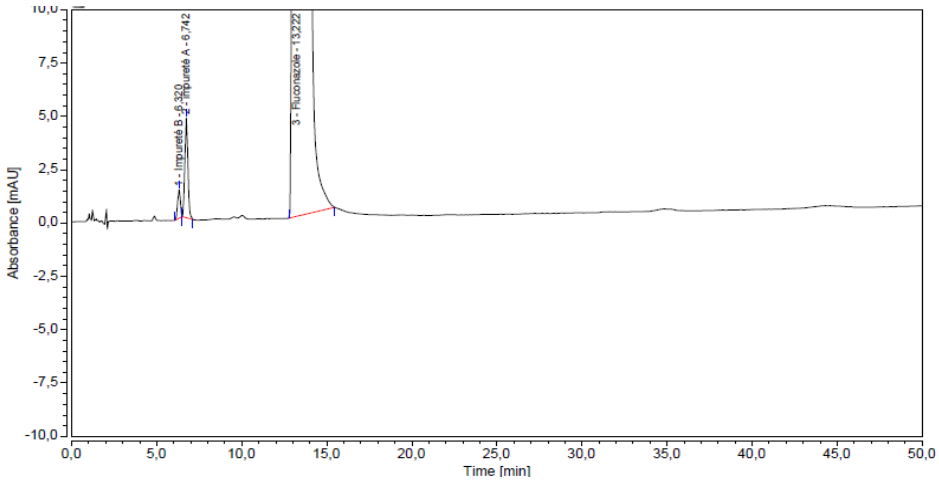


Fig. 9: Chromatogram of the test solution of F4 sample.

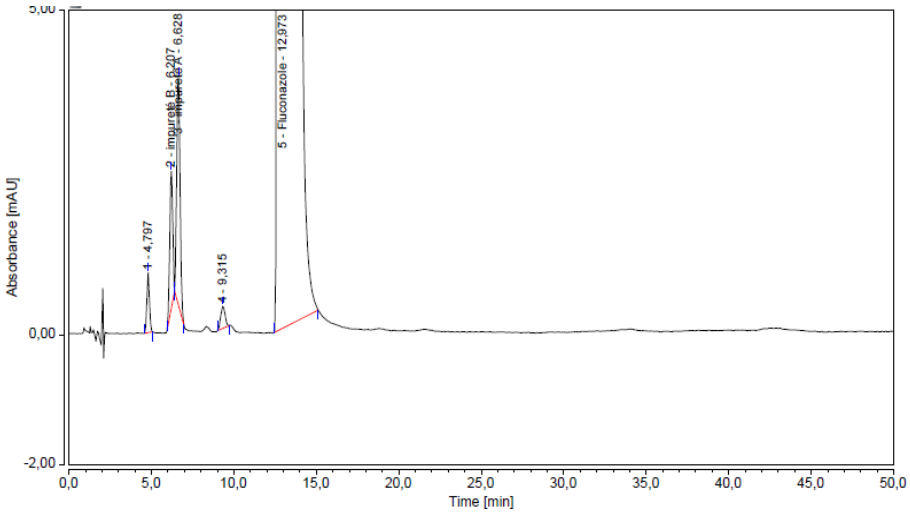


Fig. 10: Chromatogram of the test solution of F5 sample.

Table 3: The individual content of impurities A, B, C, unspecified impurities and the impurities total of the various samples of Fluconazole analyzed.

Fluconazole Sample	Impurity	Impurity Area (mAU.min)	Control (a), (c) and (d) Area (mAU.min)	Individual Content of Impurity (%)	Impurties Total (%)	Norms (%)
F1	Imp A	0,110	1,863	0,030	**0,038**	Imp A ≤ 0,4 Imp B ≤ 0,3 Imp C ≤ 0,1 Unsp Imp ≤ 0,1 impurities Total ≤ 0,6 Exclusion Limit : 0.05
	Imp B	0,165	13,183	0,004		
	Imp C	0,310	8,151	0,004		
F2	Imp A	0,879	1,980	0,223	**0,387**	
	Imp B	0,512	13,183	0,011		
	Imp C	ND	8,151	ND		
	Unspf Imp 1	0,498	1,980	**0,126**		
	Unspf Imp 2	0,105	1,980	0,027		
F3	Imp A	ND	1,908	ND	**0,031**	
	Imp B	0,127	13,183	0,003		
	Imp C	ND	8,151	ND		
	Unspf Imp 1	0,106	1,908	0,028		
F4	Imp A	0,975	1,899	0,257	**0,263**	
	Imp B	0,249	13,183	0,006		
	Imp C	ND	8,151	ND		
F5	Imp A	0,814	2,010	0,203	**0,280**	
	Imp B	0,443	13,183	0,010		
	Imp C	ND	8,151	ND		
	Unspf Imp 1	0,165	2,010	0,041		
	Unspf Imp 2	0,104	2,010	0,026		

Imp: impurity, Unspf: unspecified and ND: Not detected.

Conclusion

Nine drug related impurities were analyzed in five samples of Fluconazole API by HPLC. The impurities A, B, C and the unspecified impurities were precisely determined in the different samples of Fluconazole analyzed. The F1, F3, F4 and F5 samples had an individual content of specified impurities (A, B and C) and unspecified impurities meeting the required standards with

a total of all impurities present meeting with the standard. The F2 sample had a total of 0.387% contaminants that were within the acceptable range and a high level of an unidentified impurity that was 0.126% higher than the acceptability limit. This can be explained by either sample deterioration, which may have occurred due to poor storage conditions, or by inadequate batch purification during the synthesis route.

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Conflict of Interest

There is no conflict of interest, according to the authors. The paper's content and writing are solely the authors' responsibility.

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دراسة ملف تعريف الشوائب ذات الصلة بواسطة HPLC: حالة خمس عينات من FLUCONAZOLE API

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كان الهدف الرئيسي من هذا العمل هو تحليل تسعة شوائب متعلقة بالأدوية بواسطة كروماتوغرافيا سائلة عالية الأداء (HPLC) في خمس عينات من Fluconazole API ، تم جمعها من خمس مصانع دوائية في الجزائر. لتحليل الشوائب العضوية ،تم إستعمال جهاز كروماتوغرافيا سائل HPLC-UV مجهز بحاقن أوتوماتيكي وكاشف UV / Vis وعمود (C18)، معطل للقواعد ، بعد التطعيم (٥ ميكرومتر) والأبعاد (ث: ٠,١٥ م ، القطر: ٤,٦ مم). تمت معالجة كل عينة من Fluconazole API وفقًا لإجراءات المواد ذات الصلة في دستور الأدوية الأوروبي (EP)، الإصدار الثامن. أظهر تحليل الشوائب المرتبطة بـــ HPLC أن عينات F1 و F3 و F4 و F5 تحتوي على محتوى فردي من الشوائب المحددة (A و B و C) والشوائب غير المحددة التي تلبي المعايير المطلوبة مع إجمالي جميع الشوائب الحالية التي تتوافق مع المعيار. عينة F2 احتوت على نسبة عالية من الشوائب غير المحددة ٠,١٢٦٪ مقارنة بحد القبول ومجموع الشوائب ٠,٣٨٧٪ المطابقة للمواصفة. يمكن تفسير ذلك إما من خلال تدهور العينة الذي قد يكون بسبب ظروف التخزين السيئة أو أن الدُفعة التي تأتي منها هذه العينة لم يتم تنقيتها جيدًا أثناء مسار التوليف.