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Effect of Heat, Time and UV Light on Different Brands of Fluconazole by UV Spectrophotometeric Method

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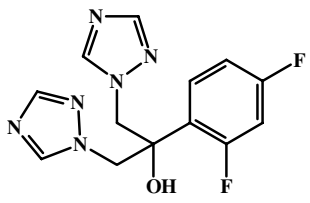
Fluconazole *i.e.*, 2,4-difluoro-α,α′-*bis*(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol belongs to the class of drug antifungal (subclass of synthetic triazole). The purpose of this research is to study the effect of acid and base by using UV spectrophotometry, on different brands of fluconazole under ICH guideline Q1A (R2). According to USP, fluconazole contains calcium not less than 98 % and not more than 102 % of $C_{13}H_{12}N_6OF_2$, calculated on the anhydrous basis. The result of the study concluded that chosen brands of fluconazole *i.e.* hiflucan (A), arsozole (B) and zolanex (C), were used for evaluating the effect of UV light, time and heat. When the three chosen brands of fluconazole; hiflucan (A), arsozole (B) and zolanex (C) were subjected to heat for 0, 30 and 60 min, no degradation was observed in brand A at 30 and 60 min, slight degradation was observed in brand B at 30, 60 min and significant degradation was observed in brand C at 30 and 60 min. When different brands of fluconazole were subjected to UV light, slight degradation were observed in brand A (86.39 %) and significant degradation were observed in B and C (73.61 %) and (69.15 %) respectively. Similarly when 3 different brands of fluconazole were left for a week, no degradation was observed in brand A, slight degradation was observed in brand B and C respectively.

Keywords: Fluconazole, antifungal, UV light.

INTRODUCTION

Fluconazole (FNZ) 2,4-difluoro-α,α′-*bis*(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol [1] belonged to the class of drug antifungal [2] (subclass of synthetic triazole). The empirical formula of fluconazole is $C_{13}H_{12}N_6OF_2$ [3] and molecular weight of fluconazole is 306.3. The structural formula of fluconazole is [4]



Structure of fluconazole

It is slightly soluble in water, saline and soluble in alcohol. Fluconazole is a white crystalline solid. Antifungal can be grouped into three classes based on their mode of action: 'azoles' inhibits the synthesis of ergosterol (the main fungal sterol) [5], 'polyenes' which physicochemically interact with fungal membrane sterols and '5-fluorocytosine' which inhibits macromolecular synthesis. Several mechanisms of action contribute to the development of resistance to antifungals. Mechanisms of fluconazole action are "alteration in drug target and sterol biosynthesis, decreased intercellular concentration of target enzyme and also expression of the antifungal drug targets [6]". Fluconazole is used in the treatment of vaginal candidiasis, tineacapitis, cryptococcal meningitis, Auto-brewery syndrome and coccidioidomycosis [7]. The adverse effect of fluconazole is "rash, headache, dizziness, nausea, vomiting, abdominal pain, fatigue, diarrhea and raised liver enzymes [8]". The elimination half-life of fluconazole follows zero (0) order kinetics and 10 % of elimination is due to metabolism.

Recent studies showed that the gas-liquid chromatographic method detection was developed for the analysis of fluconazole in human plasma, serum, urine. The assay result was linear [9]. A high-performance liquid chromatographic (HPLC) assay with UV-visible detection was developed and validated for the determination of fluconazole in human plasma. This method used solid-phase extraction for sample clean-up. The separation was carried out on a column C_{18} by isocratic elution at 210 nm. Validation was also performed giving to the current references of the USFDA bioanalytical method validation guide line [10].

The purpose of present work is to study the effect of effect of UV light, time and heat by using UV-visible spectrophotometric method, on different brands of fluconazole under given the ICH guideline Q1A (R2), it is most commonly preferred as related to other methods because of less time consuming and maintenance cost.

Parameters in forced degradation: The forced degradation studies were on drug substance which include temperature and UV light.

Thermal/stress testing: Thermal stress testing is applied to force the degradation of a drug substance to its primary degradation products by exposure to thermal/humidity conditions over time.

Degradation by UV light: The well-known problem is UV-instable products which are made up of synthetic and natural polymers as they disintegrate or crack when exposed to continuous exposure to sunlight.

EXPERIMENTAL

Fluconazole: The fluconazole brands used were Hiflucan, arozole and zolanex of 150 mg.

Glass wares: Volumetric flask, funnel, beakers, measuring cylinder, pipette and stirrer were used and washed with chromic acid thorough washing with distill water and finally rinsed with double distilled or deionized water which was newly prepared in the laboratory.

1601 Spectrophometer: PG Instrument (T80 UV/visible spectrometer) along with a pair of (5 cm) quartz; Cuvettes; Weighing balance: Pioneer OHAIUS (Item PA214C); Water Bath: DT; Digital constant temperature tank HH- 4; UV Lamp.

Preparation of fluconazole solution: Separately weigh capsule of each of the brands than empty the capsule and weigh the empty shell. Weigh granules of different brand individually and triturate the granules in mortar pestle. Powder equivalent to 150 mg of active of fluconazole *i.e.* hiflucan, arozole and zolanex accurately weigh for making primary solution of fluconazole Weighed samples were introduced into three different volumetric flasks (100 mL). Hot water of 70 mL was used to dissolve the powdered material and shake well and finally make up the volume to respectively for every sample. Solutions obtained of desired concentration *i.e.* 200 ppm were transferred one by one to cuvette for the determination of absorbance at max 210 nm by using UV spectrophotometer.

For UV light: To study the degradative effect of UV light, 5 mL of 100 ppm solution of fluconazole *i.e.* hiflucan, arozole and zolanex were taken in three different test tubes then 5 mL water is added in each test tube and placed these solutions in UV light and absorbance of the solutions at wavelength of 210 nm.

Heat: To study the degradation effect of heat, 5 mL of 100 ppm solution of fluconazole in three different test tubes were taken and heated for 60 min.

Time: To study the degradative effect of time, take 5 mL of 100 ppm solution of fluconazole *i.e.* hiflucan, arsozole and zolanex in three different test tubes each containing 5 mL of water before addition of primary solution, then place these solutions at room temperature for 7 days then measure the absorbance after 7 days at the similar wavelength *i.e.* 210 nm [11-14].

RESULTS AND DISCUSSION

The research study was based on evaluating the effect of acid and base on three chosen brands of fluconazole (FNZ) [hiflucan (A), arsozole (B) and zolanex (C)] available in Karachi, Pakistan. The absorbance of all the brands of fluconazole after UV light, time and heat treatment is shown in Table-1. The percentage of degradation of three different brands of fluconazole is shown in Table-2. The graphical degradation pattern of different brands of fluconazole after time interval and UV treatment is shown in Fig. 1 and degradation pattern of different brands after heating is shown in Fig. 2. When the three chosen brands of fluconazole; hiflucan (A), arsozole (B) and zolanex (C) were subjected to heat for 0, 30 and 60 min, no changes were observed in brand A at 30 min (94.43 %) and 60 min (87.10 %), changes were observed in brand B at 30 min (74.49 %), 60 min (73.90 %) and significant changes were observed in brand C at 30 min (69.11 %) and 60 min (68.51 %) respectively. When different brands of fluconazole were subjected to UV light, slight changes were observed in brand A (86.39 %) and significant changes were observed in B and C (73.61 %) and (69.15 %) respectively. Similarly when 3 different brands of fluconazole were left for a week, no changes were observed in brand A (113.67 %), slight changes were observed in brand B and C (75.37 %) and (72.25 %), respectively (Table-2).

TABLE-1
ABSORBANCE OF DIFFERENT BRANDS OF FLUCONAZOLE

Parameters	Absorbance		
	Hiflucan	Arsozole	Zolanex
Heat			
0 min	1.705	2.387	2.512
30 min	1.61	1.778	1.736
60 min	1.485	1.764	1.721
UV	1.473	1.757	1.737
Time (1 week)	1.938	1.799	1.815

TABLE-1
DEGRADATION (%) OF DIFFERENT BRANDS OF FLUCONAZOLE

Parameters	Absorbance		
	Hiflucan	Arsozole	Zolanex
Heat			
0 min	100.00	100.00	100.00
30 min	94.43	74.49	69.11
60 min	87.10	73.90	68.51
UV	86.39	73.61	69.15
Time (1 week)	113.67	75.37	72.25

Conclusion

According to USP, fluconazole calcium contains not less than 98.0 % and not more than 102.0 % of $C_{13}H_{12}N_6OF_2$, calculated on the anhydrous basis. The result of the study concluded that chosen brands of fluconazole *i.e.* hiflucan (A), arsozole (B) and zolanex (C), were used for evaluating the effect of UV light, time and heat. When the three chosen brands of fluconazole; hiflucan (A), arsozole (B) and zolanex (C) were subjected to heat for 0, 30 and 60 min, no degradation was observed in brand A at 30 and 60 min, slight degradation was

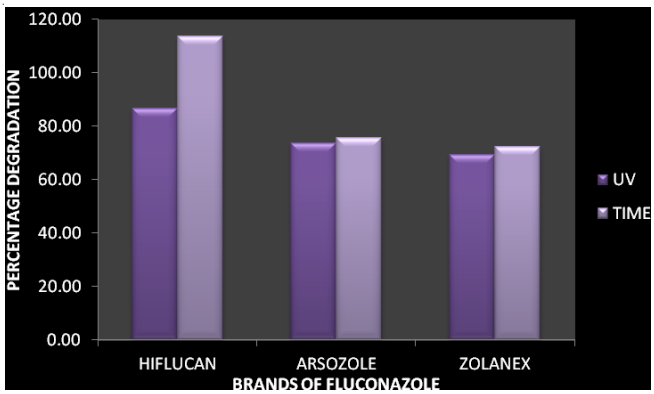


Fig. 1. Degradation pattern after time interval and UV treatment

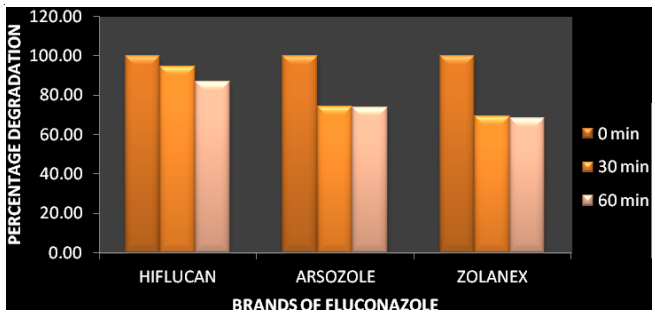


Fig. 2. Degradation pattern of different brands after heating

observed in brand B at 30, 60 min and significant degradation was observed in brand C at 30 and 60 min. When different brands of fluconazole were subjected to UV light, slight degradation were observed in brand A 86.39 and significant degradation were observed in B and C (73.61 %) and (69.15 %) respectively. Similarly when 3 different brands of fluconazole were left for a week, no degradation was observed in brand A, slight degradation was observed in brand B and C, respectively.

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