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QUALITY CONTROL ON FLUCONAZOLE CAPSULS IN TURKISH DRUG MARKET

TÜRKİYE İLAÇ PİYASASINDA BULUNAN FLUKONAZOL KAPSÜLLERİ ÜZERİNDE KALİTE KONTROL CALIŞMALARI

MİNE ÖZYAZICI, ESRA BALOĞLU

Ege Unıversıty Faculty of Pharmacy, Department of Pharmaceutical Technology
35100- Bornova, İzmir Turkey

Fluconazole, a triazole derivative, with the chemical formula 2-(2, 4-difluorophenyl)-1,3-bis (IH, 2, 4-triazol-l-yl)-propan-2-ol, is a white to off-white crystalline powder. with a molecular weight of 306.3 and is soluble in water which allows it an excellent penetration into the cerebrospinal fluid.

The pharmaceutical quality control of fluconazole capsules in the Turkish market were carried out in this study as: Tests for disintegration, weight variation and uniformity of dosage units with special emphasis on dissolution rate. The dissolution tests were carried out by the basket and the paddle methods of USP and varying profiles were obtained therefrom.

Flukonazol, 2-(2, 4-difluorofenil)-1,3-bis (1 H, 2, 4-triazol-1-il)-propan-2-ol kimyasal yapsında bir triazol türevidir. Beyazımsı kristal tozdur ve molekül ağırlığı 306.3 olup suda çözünür ve serebro spinal sıvılara kolaylıkla penetre olur.

Bu çalışmada Türk ilaç piyasasında bulunan flukonazol kapsüllerinin farmasötik kalite kontrolleri yapıldı. Kapsüller dağılma, ağırlık sapması, içerik ve çözünme hızları açısından incelendi. Çözünme hızı deneyleri USP döner sepet ve palet yöntemi olmak üzere iki ayrı yöntemle yapıldı ve farklı profiller elde edildi.

Keywords: *Fluconazole capsules; Quality control; Dissolution; Kinetic evaluation*

Anahtar Kelimeler: *Flukonazol kapsülleri; Kalite kontrol; Dissolüsyon; Kinetik değerlendirme*

Introduction

Fluconazole is a bis-triazole antifungal agent and is widely used in the management of systemic fungal infections. Following oral administration, it is rapidly and almost completely absorbed(1,2) Fluconazole is supplied in capsules of 50, 100 and 150 mg potencies. It is soluble in water and is chemicallv stable in ordinary storage conditions(3). Compared to other antifungal agents the adverse effects caused by fluconazole are relatively rare and benign(4,5)

Pharmaceutical quality control is carried out during the preparation and after the production process by the producer. Previous studies have shown quality differences between chemically equivalent formulations (6-8)

In our work, fluconazole capsules manufactured in Turkey were studied and quality control tests as weight variation, uniformity of dosage units, disintegration and dissolution rates were applied.

Materials

Fluconazole was supplied from Biofarma Pharm. Comp., Turkey. Commercial fluconazole capsules (50, 100 and 150 mg) produced by

twelve different Turkish pharmaceutical manufacturers were tested. They were purchased from different pharmacies. Capsules used in this study were coded as shown in table 1.

Table 1. The codes of the fluconazole capsules used in the study.

Codes	Label dose (mg/capsule)	Serial number	Production date
C1	150	8050874	05/1998
C2	100	8020199	02/1998
C3	150	9010127	01/1999
C4	150	111	10/1997
C5	150	005	07/1997
C6	100	970902	09/1997
C7	150	981002	10/1998
C8	50	990301	03/1999
C9	150	005	04/1997
C10	150	062	01/1998
C11	150	07	05/1998
C12	50	01	03/1998

Instruments were as: Disintegration apparatus (D 69 Z Aymes), dissolution apparatus (Pharma Test PTW II), spectrophotometer (Shimadzu UV-1208), automatic shaker (B.Braun). All chemicals used were of analytical grade.

Methods

Standard curve: A calibration curve was obtained using a $1 mgml^{-1}$ (w/v) solution of fluconazole in distilled water. Ten samples from this solution (0.5-5.0 ml consecutive) were each adjusted to 10 ml with water and the absorbences were measured spectrophotometrically at 260 nm against blank.

Weight variation studies of twenty capsules for each batch were carried out according to the T.F. 1974(9).

Disintegration time tests were performed in distilled water (37 ± 2^0C) according to T.F. 1974(9). The mean of six determinations was calculated.

Determination of the active ingredient: For this purpose, fluconazole contents of the capsules were determined spectrophotometrically at 260 nm content uniformity studies were examined in triplicates for ten capsules of each batch.

Dissolution rates: The capsules were examined using Apparatus I and II of USP XXII at 100 rpm and 50 rpm respectively(10). Distilled water was used as the dissolution medium. Six samples from each batch were assayed spectrophotometrically at 260 nm and the means were calculated for plotting.

Result and Discussion

Therapeutic differences can be found between capsules containing the same ingredients depending on their physicochemical properties varying from one formulation to another or from production to administration.

In the present work, twelve different fluconazole capsules produced by different manufacturers were tested. The weight variation, content uniformity and disintegration time results were shown in table 2.

All the capsules were acceptable with regards to weight variation, fluconazole content and disintegration time.

In the literature there are various studies for gelatine capsules comparing the effect of two different dissolution methods(8). In this study we investigated the dissolution profiles of fluconazole from the hard gelatine capsules and the effect of the two different dissolution methods on the release rate of fluconazole. Paddle method usually resulted with a higher release rate than the basket method in most of the previous works. We found that the dissolution of fluconazole was faster with basket method rather than the paddle method. It was most probably due to the difference of rpm between the two methods as the pharmacopea points out.

Table 2. Weight variation, content uniformity and disintegration time results of fluconazole capsules.

Codes	Weight variation (g)			Content Uniformity (g)			Disintegration time (min)		
	x	SD (±)	CV	x	SD (±)	CV	x	SD (±)	CV
C1	0.323	0.007	2.2	0.155	0.002	1.29	11.7	1.1	9.6
C2	0.234	0.019	8.3	0.102	0.001	0.98	7.9	0.9	11.6
C3	0.352	0.023	6.6	0.146	0.003	2.05	8.5	1.7	20.4
C4	0.344	0.007	2.1	0.145	0.002	1.37	8.1	0.6	7.6
C5	0.375	0.022	5.8	0.154	0.001	0.64	9.4	0.7	7.7
C6	0.236	0.011	4.8	0.101	0.002	1.98	4.6	0.5	11.7
C7	0.349	0.006	1.8	0.145	0.002	1.37	9.4	0.5	5.1
C8	0.118	0.002	1.9	0.052	0.001	1.92	5.8	0.4	7.1
C9	0.358	0.020	5.5	0.142	0.003	2.11	10.5	1.8	16.8
C10	0.345	0.002	0.7	0.152	0.001	0.65	9.3	0.7	7.1
C11	0.347	0.007	0.2	0.148	0.001	0.67	8.2	0.8	9.3
C12	0.115	0.008	7.1	0.052	0.002	3.84	9.6	2.2	22.3

x: mean, SD: Standart deviation CV: Coefficient of variation (%)

The dissolution results of fluconazole capsules obtained with rotating basket and paddle method were shown in figs 1 and 2, respectively.

As depicted on Fig. 1, the fastest release of fluconazole was observed for C1 and C10 as ten minutes while the slowest rate of dissolution was obtained for C5. Meanwhile, C10 provided the fastest release while C11 showed the slowest release of fluconazole with rotating paddle method. The AUC values of the dissolution profiles were shown in table 3.

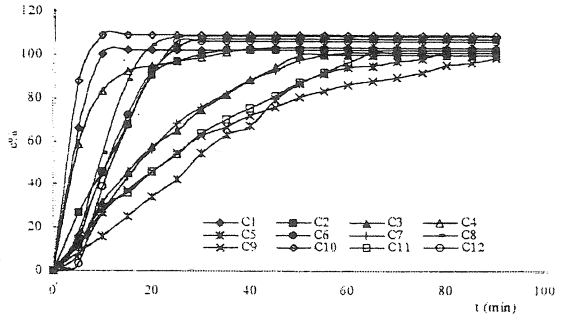

Fig. 1. Dissolution profiles of fluconazole capsules which were obtained by USP XXII rotating basket method.

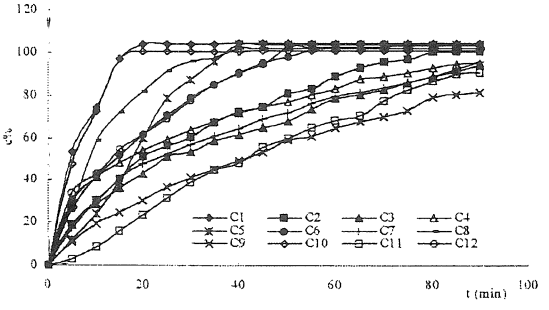

Fig. 2. Dissolution profiles of fluconazole capsules which were obtained by USP XXII rotating basket method.

Table 3. The AUC values of the dissolution profiles

Code	Method	AUC (mg.min)
C1	BM	4394
	PM	4343
C2	BM	4010
	PM	3153
C3	BM	3445
	PM	2781
C4	BM	4281
	PM	3134
C5	BM	3008
	PM	3725
C6	BM	4187
	PM	3668
C7	BM	3487
	PM	2881
C8	BM	4319
	PM	3998
C9	BM	3040
	PM	2245
C10	BM	4743
	PM	4192
C11	BM	3271
	PM	2277
C12	BM	4157
	PM	3713

BM: Basket method, PM: Paddle method

AUC values were calculated by the trapase rule and showed the area under the dissolution profile (8, 11-13). AUC values were normalized by dividing by the real dose values obtained from the uniformity of the dosage studies to eliminate the differences due to the various fluconazole amounts of the capsules. When AUC values were compared, the rank order of the capsules did not change significantly depending on the dissolution method. Usually the paddle method provided lower AUC values than the rotating basket method except for C5 formulation. C5 was the fifth in order according to the paddle method while it was the last by the basket method. During the dissolution studies it was investigated that the capsule bulk of C5 formulation dispersed more slowly by the basket method with respect to the paddle method which could be by virtue of the difference in order.

Table 4. The kinetic assessment of release data for basket method.

Kinetics		Formulations											
		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Zero Order	*kr^0	201.05	150.64	166.16	69.76	108.99	207.49	144.38	125.27	81.82	76.85	125.14	117.37
	r^2	0.835	0.871	0.958	0.618	0.920	0.892	0.903	0.867	0.899	0.878	0.965	0.894
First Order	**kr^1	23.86	12.31	6.44	8.23	4.33	16.12	6.75	20.68	2.42	19.45	4.66	16.42
	r^2	0.978	0.910	0.677	0.982	0.877	0.924	0.835	0.949	0.947	0.966	0.699	0.916
Modified Hixson-Crowell[15]	a	0.812	1.179	1.209	0.545	1.263	1.613	1.347	1.713	0.935	0.435	1.075	2.410
	b	$4.59x10^{-2}$	$2.67x10^{-2}$	$1.54x10^{-2}$	$2.01x10^{-2}$	$1.06x10^{-2}$	$3.38x10^{-2}$	$1.59x10^{-2}$	$4.16x10^{-2}$	$7.83x10^{-3}$	$3.78x10^{-2}$	$1.09x10^{-2}$	$3.71x10^{-2}$
	r^2	0.992	0.984	0.985	0.969	0.995	0.994	0.984	0.987	0.992	0.990	0.983	0.951
RRSBW[16,17]	T(%63.2)	4.97	11.89	21.24	5.54	31.04	12.41	22.39	10.57	31.08	1.00	26.13	14.64
	β	1.353	1.587	1.476	0.882	1.542	2.089	1.669	2.260	1.117	0.561	1.313	2.895
	r^2	0.984	0.969	0.943	0.991	0.975	0.994	0.978	0.997	0.991	0.954	0.935	0.986
Hixson-Crowell[18,19]	***k	9.59	4.35	2.77	4.69	1.92	4.95	2.74	4.82	1.59	10.13	2.15	3.83
	r^2	0.979	0.980	0.927	0.922	0.989	0.990	0.983	0.983	0.991	0.997	0.938	0.990

* mg/hour, ** $hours^{-1}$, *** $mg/hour/cm^2$, r^2: determination coefficient, k: rate constant, β: shape factor

Although the release amounts were different with both dissolution methods, similar dissolution profiles and rank orders according to the AUC values were obtained for fluconazole capsules.

The kinetic evaluation of the dissolution profiles were studied using Dissol. 406 kinetic programme (14-19) and the results are given in tables 4 and 5. C9 formulation provided the longest

time for releasing 63.2% of the active ingredient according to both dissolution methods. It was found that the release of fluconazole from the marketed gelatine capsules fitted RRSBW and Modified Hixson-Crowell Kinetics.

As a result, the weight variation, content uniformity and disintegration results of the gelatine capsules of fluconazole met the USP limits but the dissolution profiles, which are important criteria for the bioavailability, exhibited the greatest variations. There was no *in vitro* similarity between the brands having the same fluconazole content. When the dissolution methods were compared there was no obvious difference between rotating basket and paddle method.

Table 5. The kinetic assessment of release data for basket method.

Kinetics		Formulations											
		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Zero	*kr^0	294.65	60.78	76.01	63.82	243.20	86.69	72.86	56.21	72.14	327.56	94.49	44.43
Order	r^2	0.926	0.954	0.965	0.942	0.967	0.948	0.945	0.833	0.979	0.920	0.983	0.984
First	**kr^1	24.74	3.57	1.69	1.83	9.62	6.27	1.75	9.58	1.09	25.15	1.64	6.31
Order	r^2	0.914	0.726	0.964	0.982	0.758	0.794	0.944	0.865	0.983	0.917	0.951	0.683
Modified	a	1.034	0.868	0.775	0.609	1.483	0.902	0.758	1.004	0.833	1.141	1.334	0.799
Hixson-	b	$4.37x10^{-2}$	$8.06x10^{-3}$	$5.05x10^{-3}$	$4.69x10^{-3}$	$2.11x10^{-2}$	$1.32x10^{-2}$	$5.28x10^{-3}$	$2.22x10^{-2}$	$3.82x10^{-3}$	$4.49x10^{-2}$	$7.33x10^{-3}$	$1.17x10^{-2}$
Crowell[15]	r^2	0.969	0.979	0.991	0.987	0.986	0.981	0.991	0.988	0.995	0.980	0.993	0.933
	T(%63.2)	6.67	26.94	37.18	25.61	18.63	17.43	34.16	12.04	56.84	7.14	51.67	16.50
RRSBW[16,17]	β	1.584	1.085	0.905	0.749	1.819	1.182	0.892	1.351	0.920	1.703	1.460	1.055
	r^2	0.935	0.923	0.977	0.969	0.949	0.923	0.979	0.975	0.990	0.951	0.995	0.847
Hixson-	***k	8.69	1.60	1.31	1.50	3.57	2.51	1.36	2.99	0.96	8.59	1.11	2.02
Crowell[18,19]	r^2	0.979	0.952	0.993	0.996	0.955	0.974	0.985	0.991	0.993	0.982	0.985	0.921

* mg/hour, ** $hours^{-1}$, *** $mg/hour/cm^2$, r^2: determination coefficient, k: rate constant,β: shape factor

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