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Original Article

A COMPARATIVE QUALITY CONTROL STUDY OF CETIRIZINE HYDROCHLORIDE 10MG TABLETS ON THE ALBANIAN PHARMACEUTICAL MARKET

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ABSTRACT

Objective: The aim of this study was to carry out a quality control test on a range of different production of cetirizine hydrochloride 10mg tablets and to compare the generic productions with the reference one in order to evaluate if there are any outstanding differences in terms of quality and price.

Methods: Various pharmacopeias tests were carried out: weight variation test, disintegration test, dissolution test, as well as other tests such as: setting the diameter, thickness, tensile strength, friability and hardness test. The pharmaceutical equivalents were compared to the reference product in terms of similar dissolution factor (f_2) of dissolution profiles and the evaluation of dissolution efficiency (DE). Tablet dissolution was carried out in a multi bath (n=6) dissolution test system (Varian Dissolution Apparatus 2) (50rpm, 37.0±0.5 ºC, bi distillated water 900 ml, pH 7.0). An UV-Vis spectrophotometer (Cary 100, Varian) was used to determine cetirizine concentration at wavelength 230.1 nm. Varian Hardness VK200, Guoming CS-2 friability apparatus and Guoming BJ-2 disintegration apparatus are used for the specific tests.

Results: The study showed that all the products met with the standards of pharmacopoeia and that dissolution profiles were significantly the same but, however, there is also a remarkable difference in price.

Conclusion: All the productions met the requirements and are within the limits of pharmacopoeia for the presented tests. Cetirizine reference product still sells well on the open pharmaceutical market even though it costs more and regardless of the fact that other generics have practically the same qualities.

Keywords: Cetirizine hydrochloride, Quality control, Pharmaceutical equivalents.

INTRODUCTION

According to Food and Drug Administration (FDA), when we say 'quality control' we mean the total number of procedures carried out to ensure the identity and purity of a particular pharmaceutical product. Such procedures may range from the results of some simple chemical experiments to determine the identity, screening to uncover the presence of particular pharmaceutical substances and the more so the complicated requirements of pharmacopoeia monographs. A generic drug should be the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. The FDA (Food and Drug Administration), in order to issue approval for a generic drug product, has laid down quite a few strict, mandatory regulations on tests and procedures to guarantee that the generic drug can actually be a substitute for the brand name drug. The FDA bases its approval for substitution, on the "therapeutic equivalence," of generic drugs through specific scientific evaluations. By law, a generic drug product must contain identical amounts of the same active principal (s) as the brand name product. Drug products considered "therapeutically equivalent" have to have exactly the same effect as the brand name product [1].

In the framework of tablet quality control on the Albanian pharmaceutical market, the reference product (A) and two generic tablets (B,C) of cetirizine hydrochloride 10mg were subject to this study. Cetirizine is an antihistaminic-H_1 and comes under class I in the range of active principles according to Biopharmaceutical Classification System (BCS) [2]. Cetirizine is also included in the fundamental drug list drawn up by the World Health Organization (WHO) which goes to explain the importance of this medicine on the pharmaceutical market.

MATERIALS AND METHODS

The materials used in this study included the reference product cetirizine hydrochloride tablet 10mg (A) and two generic ones (B, C) purchased on the pharmaceutical market in Tirana, Albania along with their respective prices (Table 1).

Weight variation

20 tablets from each product of cetirizine hydrochloride were weighed one by one through an analytical scale and the average weight was calculated together with the standard deviations and relative standard deviations (RSD).

Hardness

10 tablets of each brand were measured using Varian VK 200 for hardness. The mean value was calculated with standard deviation (SD).

Diameter and thickness

Caliber WT was used to measure the diameter and thickness of 10 different tablets of each brand. The average diameter and thickness was evaluated along with the respective standard deviation (SD).

Friability

10 tablets were first weighed $(W)_1$. The friability apparatus Guoming CS-2 was set at 25rpm for 4 min. The tablets were then accurately weighed (W_2). Formula (1) calculated the friability of the tablets.

$$(1)\ \text{friability} = \frac{W1-W2}{W1} * 100$$

Disintegration

6 tablets of different brands were subjected to a disintegration test with a Guoming BJ-2 disintegration apparatus set at 29-32 cycles per minute at a temperature of 37°C with 1L medium of distilled water.

Table 1: It shows the materials used in the study

Brand	Pharmaceutical form	Dose	Expiry data	Price/tabler (€)
Reference A	Uncoated tablet	10mg	Sept 2016	0.26
Generic B	Uncoated tablet	10mg	Aug 2016	0.17
Generic C	Uncoated tablet	10mg	May 2016	0.20

Calibration curve

100mg of cetirizine hydrochloride were dissolved in 50 ml of water, stirred with *"ultrasonic"* for 30 minutes and then filled with up to 100 ml of water. The mother solution with a concentration of 1mg/ml, filtered beforehand, was then used to make up the standard solutions (5, 10, 20, 40 µg/ml). The diluted solutions were then scanned using a Varian Cary UV-Vis spectrophotometer in the range [200-400 nm]. Absorption maximum was obtained at 230.1 nm. A standard curve was plotted to study the linearity of Beer Lambert's Law.

Dissolution

A dissolution test was carried out in line with a USP monograph, with a dissolution apparatus II *Guoming RC-6,* paddle type, 50 rpm at a temperature of 37°C with 900 ml water as medium. Aliquots of 5 ml were taken at intervals of 5, 10, 20, 30, 45 minutes, and then replaced with the same medium (replacement method). The aliquots were properly diluted (1:100) and the respective absorbance was measured with the spectrophotometer at a maximum wavelength of 230.1 nm. The percentage of the drug released was calculated using the regression equation from the calibration curve by extrapolation.

Comparing dissolution profiles

The dissolution performance of each brand was developed according to USP guidelines. In order to characterize the drug release profile, parameters such as, $t_{x\%}$ sampling time (a commonly used parameter of the Pharmacopoeias) and dissolution efficiency (DE) can be used. Data obtained from these parameters, to thoroughly understand the release mechanism, were fairly limited and said parameters should be associated among each other [3]. Dissolution performance was compared through:

1. Extrapolating the $t_{30\ min}$, the percentage of drug released in a time frame of 30 minutes.

2. Calculating similarity (f2) and difference (f1) factors [4] of the formula (3) and (4) first development by Moore and Flanner 1996.

$$(2)\ f1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} * 100$$

$$(3)\ f2 = 50 * \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0,5} * 100$$

Where: R_t dhe T_t were the percentages of drug release of the reference product and generic product in time t

n was the number of points were the samples of both reference and generic were released above 80%.

Values of f1 in the range of [0-15] and f2 in the range of [50-100] suggested that the dissolution profiles were somewhat the same.

3. Calculating the dissolution efficiency from the formula (5). The dissolution efficiency of a pharmaceutical form (Khan and Rhodes 1972; Khan 1975) was defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [4].

$$(4)\ DE_t = \frac{(\sum_0^T y_t * dt)}{y_{100} * T}$$

Where: y is the percentage of drug dissolved in time t

DE estimated the release of the active pharmaceutical principal into the absorptive medium. The determination of DE was to calculate the rhythm of release of the drugs in the simulated media so as to get a clear idea of the amount of drugs absorbable in the GIT. The dissolution efficiency was calculated for every six vessels and a mean value was obtained along with a confidence interval of 95%. A t test p-value was calculated in order to determine any significant difference in the %DE30 min of the generics compared to the reference product (significance difference *p<0,05).

RESULTS AND DISCUSSION

Weight variation

All tablets complied with the standards of USP for weight variation [5], no more than two of the individual weights deviated from the average weight by more than 10%. The results are listed in table 1.

Hardness

The hardness test in a non-official pharmacopeia test indicated whether a tablet was too hard or too soft or friable. The recommended hardness value is 4-10 N [6], but even if the values are beyond this limit, the disintegration test should be carried out before rejecting the whole batch. All the tablets and requirements and are listed in table 1.

Diameter and thickness

The different tablets have the same diameter but differ in thickness. The results are listed in table 1.

Disintegration

All the tablets met with the standards set by USP on disintegration which is not more than 30 minutes [7]. All tablets disintegrated rapidly within 4 to 7 minutes.

Table 2: Results of weight variation test, hardness test, diameter, thickness, friability and disintegration time.

	Weight Variation					
	(g) (mean) (%RSD)	Hardness (N) (mean±S. D)	Diameter (mm) (mean±S. D)	Thckness (mm) (mean±S. D)	Friability (%)	Disintegration
Reference A	0,1215 (1,10)	10,03±1.8	6.563±0,86	1,38±0,22	0,06%	4
Generic B	0,1747 (0,77)	9,28±0.68	7,316±0,55	3,91±0,49	0,21%	7
Generic C	0,1776 (1,85)	7,06±0.81	5,570±1,04	5,35±1,09	0,01%	5

Dissolution

The final results of the dissolution test on each tablet production are listed in table 2. The dissolution profiles can be seen in chart 2.

All tablets dissolved within USP limits (more than 80% should be released in 30 minutes). It is obvious that the tablet dissolves very fast, within the first 5 minutes, on average more than 50% of the drug is released.

Table 3: Results of dissolution tests of different cetirizine hydrochloride tablets expressed in percentage drug release within certain time intervals

	%drug release (avg)		
Time (min)	**Reference A**	**Generic B**	**Generic C**
5	63%	57%	67%
10	82%	84%	73%
20	94%	93%	88%
30	100%	103%	100%
45	103%	107%	101%

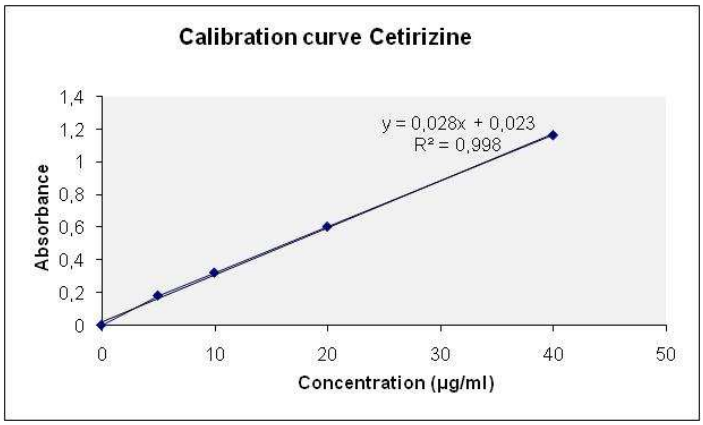

Fig. 1: Calibration curve of cetirizine hydrochloride in distilled water

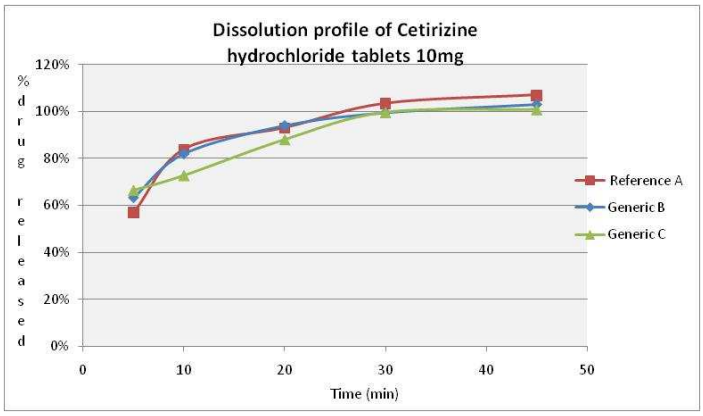

Fig. 2: Dissolution profile of cetirizine hydrochloride tablets 10mg (Reference A, Generic B, Generic C)

Table 4: Comparison and characterization of dissolution profiles by $t_{30\ min}$, dissolution efficiencies with 95% confidence intervals, and similarity/difference factors (f2 and f1)

	$t_{30\ min}$	**%DE 30 min (CI)**	**Similarity Factor f2**	**Difference Factor f1**
Reference A	100%		-	-
Generic B	103%		4	69
Generic C	100%		5	61

Comparison of dissolution profiles

The dissolution profiles are characterized and compared through different parameters: first, $t_{30\ min}$ sampling time (the % of drug release within 30 minutes from the beginning of the test), then the evaluation of $\%DE_{30\ min}$ (dissolution efficiency at 30 minutes mean value of six vessels every 30 minutes with confidence intervals CI 95%) as well as similarity and difference factors (f_2 and f_1). The results are shown in the table 3.

As shown in table 3, the $t_{30\ min}$ values of the generics are similar to the reference (p=0, 16 for generic B and p=0, 46 for generic C) (*p<0,05), signaled for similarity in the dissolution process. Dissolution efficiency ($\%DE_{30\ min}$) values of the methods used in this study show no significant statistical difference between the reference product and the generic one (p=0, 22 for generic B and p=0, 19 for generic C) (*p<0,05). The factors of similarity and difference demonstrate similarity since the f1 values are within the range [0-15] and f2 values are within [50-100]. The factors f1 and f2 offer straightforward calculation and a simple measure of similarity between pairs of dissolution profiles. This is well suited to the qualitative determination of `similarity' as required by the FDA's SUPAC Guide. Because D. E. has a simple physical meaning, it is easier to interpret D. E. data than the corresponding f1 and f2 results [8]. The quality control test results

showed us that there is no obvious difference between the different generics and the reference product of cetirizine hydrochloride in terms of the parameters in weight variation test, disintegration test, dissolution test. Even other studies (Costa, 2001) shows that the quality control tests, especially the dissolution test, may serve as tools for comparing the generics with the reference product through similarity factor and dissolution efficiency [9].

CONCLUSION

The different quality test results of cetirizine hydrochloride tablets 10mg met with the requirements of pharmacopoeia. Weight variation tests showed that all tablets have a %RSD < 10%. Also the hardness test results were below the limit recommended. A difference between the tablets was seen in the diameter and thickness values which is most likely due to the different choices in production. Friability results were under the recommended limit of 1%. Even the disintegration test results fell within the set limits of pharmacopoeia of not more than 30 minutes. The disintegration time was 4 min for the reference product Cetirizine and 7 min and 5 min for generic B and C respectively. The rapid dissolution rate at the onset can be explained by the high solubility of the active pharmaceutical ingredient, Cetirizine (Class I according to BSC). It was demonstrated that the $t_{30\ min}$ of the products conformed to pharmacopoeia standards ($t_{30\ min}$>80%). The comparison between products was carried out through the comparison of different parameters of the dissolution profile. All proved that there are no significant differences between the products. The factors f_1 and f_2 offer an easy calculation and a simple measure of similarity between pairs of dissolution profiles. This is well suited to the qualitative determination of `similarity' as required by the FDA's SUPAC (Scale-Up and Post Approval Changes) Guide. Because D. E. has a simple physical meaning, it is easier to interpret D. E. data than the corresponding f_1 and f_2 results [9].

The basic difference lies in the price of the products sold on the Albanian pharmaceutical market. The brand Cetirizine tablet has a higher price compared to the other generics. The percentage gap, in terms of price between the reference product and the generic B and C, varies from 34% to 23%. So to sum up, the Cetirizine reference product is still competitive on the open pharmacy. eutical market even though it costs more than the other generics which have practically the same quality.

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ABBREVIATIONS

FDA (Food and Drug Administration), Biopharmaceutical Classification System (BCS), World Health Organization (WHO), Relative standard deviations (RSD), standard deviation (SD), United States Pharmacopoeia (USP), dissolution efficiency (DE), the percentage of drug released in a time frame of 30 minutes $t_{30\ min}$,, similar dissolution factor (f_2), difference factor (f_1), dissolution efficiency at 30 minutes (%DE $_{30\ min}$), Scale-Up and Post Approval Changes (SUPAC)

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. U S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System; Guidance for Industry, U. S. Government Printing Office: Washington, DC, August; 2000.
2. P Costa, JM souse Lobo. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.
3. Prior P Frutos, CP Correa. Comparison of dissolution profiles: current guidelines Zaki. Int J Drug Delivery 2013;5(1):99-109.
4. The United States Pharmacopeial Convention, Uniformity of Dosage Units, Bulletin Official; 2011.
5. Bettiol F. Manuale delle preparazioni galeniche, terza edizione; 2010. p. 239.
6. The United States Pharmacopeial Convention, Disintegration, Revision Bulletin Official; 2008
7. Anderson NH1. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. J Pharm Biomed Anal 1998;17(4-5):811-22.
8. Costa P1, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13(2):123-33.