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Original Article

Conformity Studies of Ciprofloxacin Commercial Brands (Yemeni and Importation)

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Abstract

Four different products of 500 mg ciprofloxacin tablets were selected and purchased from Yemeni pharmacies in Sana'a zone as follows:
Two importation products one termed A (with price of 1650 Y.R/10 tablets), the second was termed B (with price of 200 Y.R/10 tablets)Two Yemeni products one termed C (with price of 350 Y.R/10 tablets), the other termed D (with price of 300 Y.R/10 tablets).In-vitro pharmaceutical comparatively conformity studies of the four above mentioned ciprofloxacin tablets products, included weight variations, drug dissolution, drug contents (assay by U.V and HPLC), disintegration time, hardness resistance, and friability were done according to the USP pharmacopoeia. The results of the study revealed that the Yemeni ciprofloxacin product tablet is comparable to that of the importation marketed brands of ciprofloxacin; irrespective of the general psychology of population that the quality of Yemeni pharmaceutical formulation is poor.
Key Words: Lead, Cadmium, Alhakimi, Dughish, Yemen

1-Introduction:

Drugs have the potential to reduce morbidity and mortality from illness for millions of people. The main pillars of the essential drug concepts are establish safety and efficacy, proven quality, constant availability and rational use, studies have been reported in the area of rational drug use1, but not much information available concerning the quality of the essential drugs in the Yemeni market2. Ciprofloxacin is approved for use in U.T.I, lower respiratory infection, typhoid fever, urethral & cervical gonococcal infection, sinusitis, bone and joints3. Ciprofloxacin tablets, are synthetic broad spectrum antimicrobia

agents for oral administration. Ciprofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms4. Ciprofloxacin hydrochloride, a fluoroquinolone derivative, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid5. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8, it is practically insoluble in water6. Its structural formula is C17H18FN3O3 . HCl . H2O 5,7. Ciprofloxacin film-coated tablets are available in 250 mg, 500 mg and 750 mg (ciprofloxacin equivalent) strengths8. Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the GIT. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin 6,8.

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The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF). Low levels of the drug have been detected in the aqueous and vitreous humors of the eye6.

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged, dosage adjustments may be required 4.

There are so many antibiotics available in the Yemeni market from different companies and different countries, and with high differences in their prices, the price difference may reach up to eight times between one product and other product, this price difference may leading to confuse the consumer and the physician in case of choosing the suitable product, that is the best quality of drug in high price? Or the best quality in the manufacture's country? And irrespective of the general psychology of the Yemeni population that the quality of Yemeni pharmaceutical formulation is poor. Therefore, the purpose of this study was to carry out the comparative pharmaceutical conformity studies of ciprofloxacin one of the famous, wide spread used antibiotics and present in different prices in Yemen.

2- Materials and equipments:

2.1- Materials

1-Ciprofloxacin powder standard gift from Modern Pharma (Sana'a, Yemen).

2-Two importation commercial 500 mg ciprofloxacin products purchased from the Yemeni market termed A and B.

3-Two Yemeni commercial 500 mg ciprofloxacin products purchased from the Yemeni market termed C and D.

4- Acetonitrile and Methanol HPLC grades.

5-Hydrochloric acid , Acetic acid , phosphoric acid all of pharmaceutical grades.

2.2- Equipments:

Dissolution apparatus, friability apparatus, disintegration apparatus, hardness resistance apparatus were from (Erweka, Germany) , HPLC apparatus (Kontron Instruments, Switzerland), sonicator (Cole-Parmer Instrument Company ,Chicago, USA), spectrophotometer apparatus (Shimadzu Corporation, Japan), shaker water bath (Julabo, Japan), and Digital PH meter (JENCO U.S.A).

3-Methodology (7):

3.1- Wight variations:

Weight variation was carried out according to the method described in USP, by random selection of 20 tablets.

Results are shown in table 1

3.2. DISSOLUTION STUDY :

The experimental conditions are, medium is 0.01 N HCL , the temperature is kept constant 37+ 0.5º C. Dissolution test was carried out using 900 ml of 0.01 N HCL as a dissolution medium at a paddle speed of 50 rpm for 30 min. The samples of three ml were taken at each 10 min interval, filtered and diluted suitably; it was replaced by same amount of the fresh medium each time. Absorbance of the resulting solution was measured spectrophotometerically at about 276 nm against 0.01 N

HCL as a blank. The amount of dissolved drug was calculated using standard calibration curve results

3.3. ASSAY :

The percentage content of ciprofloxacin in tablets were determined by using:

A- U.V Spectrophotometer:

Standard preparation:

Dissolve an accurately weighed quantity of ciprofloxacin hydrochloride reference standard in 0.01 N hydrochloric acid to obtain a solution having known concentration of about 0.005 mg per ml of ciprofloxacin.

Sample Preparation:

5 tablets of 0.5 gm of ciprofloxacin were transferred to 1000 ml volumetric flask , add about 900 ml of 0.01 N hydrochloric acid and sonicate for about 20 minutes to dissolve, dilute with 0.01 N hydrochloric acid to volume , filter the solution and discard the first 20 ml of filtrate solution.

Transfer 1 ml from the filtrate into 500 ml volumetric flask, dilute to volume with 0.01 N hydrochloric acid, and mix well. Absorbance of resulting solution was measured at 276 nm spectrophotometerically.

The percentage of drug content was calculated according to the following equation:

$$\%\ \text{of drug content} = \frac{\text{Abs. of test solution}}{\text{Abs. of stand. solution}} x \frac{\text{Conc. of stand. solution}}{\text{Conc. of sample solution}} x100$$

Results are shown in tables 2 and 3

Tolerance N.L.T 80%.

B- HPLC method:

The retention time of the major peak in the chromatogram of the sample preparation correspond to the standard preparation as obtained in the assay.

Mobile phase:

Prepare a filtered and degassed mixture of 0.025M phosphoric acid, previously adjusted (with triethylamine) to a pH of 3.0, and acetonitrile (80:20). Make adjustments if necessary.

Test condition:

25cm x 4mm stainless steel column (contains C18, 5 um packing material, flow rate of 1.5 ml/min, wave length at 278 nm, sample size 20 µL .

Standard preparation:

Dissolve an accurately weighed quantity of USP ciprofloxacin hydrochloride Reference Standard quantitatively in water to obtain a solution having a known concentration of about 0.25 mg per ml of ciprofloxacin.

Test preparation

5 tablets of 0.5 gm of ciprofloxacin were transferred to 500 ml volumetric flask , add about 400 ml of water and sonicate for about 20 minutes to dissolve dilute with water to volume , filter the solution and discard the first 20 ml of filtrate solution.

Transfer 5 ml from the filtrate into 100 ml volumetric flask dilute it to volume with water, and mix well.

Procedure :

Separately inject equal volumes (about 20 µL) of the standard preparation and the test preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

The percentage of drug content calculated according to the following equation:

$$\%\ \text{of drug content} = \frac{\text{AUC of sample solution}}{\text{AUC of standar solution}} x \frac{\text{Conc. of stand. solution}}{\text{Conc. of sample solution}} x \textit{Assay of standard}$$

Results are shown in table 4

Conformity (90.0% - 110.0% of ciprofloxacin).

3.4. DISINTEGRATION STUDY:

The experimental conditions are, medium is distilled water, speed is 30 cycles/min, temperature is 37+ 0.5º C .

One tablet was added in to each of the six tubes. Assembly was suspended in beaker containing water and time required to disintegrate each tablet was noted, from this average disintegration time was determined

Results are shown in table 5.

3.5. HARDNESS :

Hardness was carried out according to the method described in USP.

Results are shown in table 6.

3.6. FRIABILITY :

Friability test was carried out according to the method described in USP, random sample of ten intact tablets were accurately weighed and placed in drum and drum was rotated for 100 times, tablets were removed and weighed again accurately. Percent friability was calculated by using the following equation:

$$\frac{\text{wieght of sample before test - wieght of sample after test}}{\text{wieght of sample before test}} x100$$

4-Results:

Table 1: Weight variations of different products of ciprofloxacin tablets ± SD:

20 tablets weighed	Weight in grams of different commercial products			
	A	B	C	D
X	0.816± 0.017	0.815± 0.006	0.826 ±0.005	0.872± 0.003
Min	0.789	0.801	0.819	0.871
Max	0.839	0.821	0.834	0.879

X= Average weight Min= Minimum weight Max = Maximum weight Limit (average weight ± 5%)

Table 2: Rate of Dissolution (In-vitro) of different products of ciprofloxacin tablets spectrophotometrically:

Sl. No.	**Medium**	**Time in min**	Cumulative % Drug Release*				
			Standard	A	B	C	D
1	0.01 N HCL	10	99.1	70	58	70.2	78
2	0.01 N HCL	20	99.1	83	70	86	85
3	0.01 N HCL	30	99.1	97	91	100	98.3

* Results are the mean of five replicates

Table 3: Percentage of ciprofloxacin content in different products of ciprofloxacin tablets at λ max 276 nm by using spectrophotometer method after 30 minutes.

Medium	Ciprofloxacin product				
0.01 N HCL	**Standard**	A	B	C	D
% Drug Content*	99.1% w/w	97% w/w	91% w/w	100% w/w	98.3% w/w

Limit: N.L.T 80%. * Results are the mean of five replicates

Table 4: Percentage of ciprofloxacin content in different products of ciprofloxacin tablets by using HPLC method after 30 minutes.

Parameters	Ciprofloxacin product				
	Standard	A	B	C	D
AUC± SD	29069524± 173707	27648334± 312972	27038921± 83448	30011400 ± 91925	28446042± 328692
% Drug Content*	99.1 % w/w	95.11% w/w	93% w/w	103% w/w	97.8% w/w

* Results are the mean of three replicates

Table 5: Disintegration of different products of ciprofloxacin tablets in distilled water.

Drug	A	B	C	D
Disintegration time (min)	5	5	12	7

Limit (not more than 15 min)

Table 6: Hardness resistance of different products of ciprofloxacin tablets:

10 tablets	Hardness resistance in kg			
	A	B	C	D
Max	18.6	21.6	32.3	22.6
Min	18.00	19.2	24.0	20.2
X	18.44	20.52	27.5	21.26

X= Average hardness Min= Minimum hardness Max = Maximum hardness
Limit (0.00- 50.0Kg)

Table 7: Percentage of friability test of different products of ciprofloxacin tablets:

Test	**Weight of tablets in grams**			
Drug	A	B	C	D
Weight before	8.1336	8.1930	8.2733	8.7250
Weight after	8.1303	8.1838	8.2667	8.7100
% of friability	0.041	0.11	0.08	0.0.17

Limit (Not more than 1%)

Discussion:

All the products were confirm with the USP for friability, hardness, weight variation, disintegration, dissolution and assay, the dissolution pattern was found to be varying for each product, but within the prescribed limit. From the results obtained it is clear that, the overall quality of different ciprofloxacin commercial product tablets were within the standard limit.

Even most of the professionals think that the quality of Yemeni medicines is poor, but this experimental study will help to change the view of people towards the Yemeni supplied drugs.

Table 1 showed the weight variations of the four brands, in which product D showed slightly heavier than the other brands, all the investigated brands were within the normal weight variations, and all conform.

The amount of drug content as a percentage after their in vitro dissolution method for 30 minutes which assayed by using spectrophotometer method at λ max 276nm was showed in table 3 , and by using HPLC was showed in table 4 ,the results showed that all of the drug content in the four investigated ciprofloxacin products tablets were conform.

Table 5 showed the disintegration time of the four brands, in which product C showed the highest time 12 min to

disintegrate, while product A and product B showed the lowest time 5 minutes for each one to disintegrate, this is may be attributed to the presence of thick coating in the product C, and low disintegrating agents as component of the tablets in products A and B ,in comparison to the other brands, all the investigated brands were within the normal disintegration time, and all conform.

Table 6 showed the hardness resistance of the investigated tablets to crushing, in which product C showed the highest hardness resistance to crush, and this is in a good reason for their high disintegration time, in comparison to the other brands, all the investigated brands were within the normal hardness resistance, and all conform.

Conclusion:

The results showed that all the pharmaceutical conformity tests done for the four drug products were conform and there is no reason for the high differences of prices between those products.

Recommendations:

1- Bioavailability or bioequivalence study must be done for those products and other products to ensure the accuracy of results.

2- The price of the any product must not to depend on the country of the manufactory, but must the quality of the drug.

3- We must to encourage our national products.

4- The local manufactories must to improve and developing their products by:

a- Establishing a pharmaceutical research center in each local manufactory.

b- The continuous education & qualification for the pharmacist working in the local manufactories.

c- The continuous cooperation between the local manufactories and the faculties of pharmacy .

d- References:

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