Shahnaz Usman. *et al*. / *International Journal of Biopharmaceutics.* 2014; 5(1): 65-72.

e- ISSN 0976 - 1047
Print ISSN 2229 - 7499

International Journal of Biopharmaceutics

Journal homepage: www.ijbonline.com

IJB

EVALUATION OF DISSOLUTION TESTING FOR CIPROFLOXACIN (500MG) TABLETS: POST MARKET SURVEILLANCE OF DIFFERENT BRANDS AVAILABLE IN RAS AL KHAIMAH (UAE)

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ABSTRACT

The objective of the present study was to compare and evaluate the price and quality of different brands of ciprofloxacin tablets against the innovator tablet formulation that are present in the local market of Ras al Khaimah. The comparative biopharmaceutical and chemical analytical study of six brands of ciprofloxacin tablets were performed through the assessment of the uniformity of weight, hardness, disintegration, dissolution, and content assay of the products. All the studied brands complied with the official specifications for uniformity of weight (with SD ± 4.63-18.27), hardness between 8-12 kg, disintegration time laid between 1.18 to 4.2 minutes, whereas content analysis showed that the amount of active ingredient present in all the six brands was in between 98.98 – 103.39%. The present study showed that all six brands dissolved more than 80% in 10 minutes. Statistical calculation such as ANOVA and different Kinetic model were used to explain the dissolution profile of drug products. The drug release data fit well to the first order and Wiebull release model. Prescription drugs in the UAE are significantly more expensive than in other parts of the world. The study should raise health care professionals' and patients' awareness of the need to modify the drug price policy and to monitor marketed branded and generic products regularly and widely for quality and price.

Key words: Ciprofloxacin tablets, comparative study, pharmaceutical quality analysis, dissolution test and Post market surveillance of drug products.

INTRODUCTION

According to recent studies prescription drugs in the UAE are significantly more expensive than in other parts of the world, even when compared with prices in the Middle East. The highest-priced drug in the survey was Ciprofloxacin, which is used to treat severe and life-threatening bacterial infections. The cost of branded version is 121.90 times the international reference price in the private retail pharmacies. Dr John Craig, a primary care physician at the American Hospital Dubai, said a number of his patients had stopped taking drugs because they could not afford to pay for them (Anonymous 1; Anonymous 2Abu Dhabi news dated 11th July 2009; www.thenational.news).

Ciprofloxacin, a fluoroquinolone antimicrobial agent, was approved in 1987 as a broad-spectrum antibiotic (Gebremedhin *et al*., 2011). It acts by interfering with microbial DNA synthesis. It is relatively non-toxic, well tolerated and has proven especially useful for oral therapy of chronic Gram-negative infections such as osteomyelitis and recurrent cholangitis, and for acute exacerbations of Pseudomonas infection in cystic fibrosis.

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Approximately 400 different brands of ciprofloxacin are available world-wide and 40 to 50 countries are engaged in manufacturing of this drug. There are more than 10 to 15 brands of ciprofloxacin, manufactured in different countries that are available in Ras Al Khaimah.

In 2007 Adegbolagun *et al*., suggested a need to analyse and evaluate the generic brands (drugs) available on the market. These drugs should be analysed for their chemical and biopharmaceutical equivalence, strength, quality, purity and releasing profile of active ingredient in comparison to the innovator drug. This is important especially for second and third world countries.

Any substantial variation in the dissolution rate amongst the generic drugs indicates deficiency in the entire drug formulation and the delivery system. Dissolution testing plays an important role as a quality control tool to monitor batch- to- batch consistency of drug release (Awofisayo *et al.*, 2010) and with certain drug products, as predictor of in-vivo bioavailability (Esiomone *et al*., 2008; Osadebe and Akabogu, 2004; Pamula *et al*., 2010).

To this extent, manufacturing methods, coupled with excipients used in the production processes, could contribute to the overall quality and release proficiency of medicament.

Therefore, in order to ensure the standard quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product (Chow, 1997). As such, the need to establish pharmaceutical equivalence of generic and branded drugs products cannot be overemphasized (Adegbolagun *et al*., 2007).

Currently about half of all prescriptions written are for drugs that can be substituted with a generic product (Miller, 1990). In 1975, approximately 9% of all prescription drugs dispensed were generic versions. This percentage rose to 20% in 1984, and 40% in 1991. Indeed substitution of generic drugs for branded products is highly controversial and is often met with suspicion by health care providers and patients (Covington, 1992; Meredith, 2003).

The objective of this work was to assess the quality of different brands of ciprofloxacin 500 mg tablets commercially available in the market of Ras Al Khaimah, United Arab Emirates and to compare their quality on the basis of *in-vitro* dissolution profiles with innovator for surety of its pharmaceutical equivalency. There might be chance of presence of some superiors along with sub-standard drugs because currently the UAE imports about 90 per cent of its pharmaceutical products (www.thenational.news). The findings can serve as source of information to manufacturers, prescribers, patients and regulatory agencies.

MATERIALS AND METHODS

Instruments

Shimadzu UV- 1800 spectrophotometer, Analytical balance, Dissolution test apparatus Veego-VD-6D, Disintegration test apparatus.

Materials and reagents

Reference ciprofloxacin was a kind gift sample from Julphar Pharmaceutical. Six different brands of ciprofloxacin were obtained from different retail pharmacies of Ras Al Khaimah, freshly prepared distilled water.

Spectrophotometric condition

Base line was adjusted to zero by using blank solvent. Standard and test sample were analyzed.

Physiochemical parameters

The basic use of medicines as described by WHO is to be prescribed appropriately based on the clinical needs, in doses that meet individual requirements, for an adequate period of time, and at the lowest cost to patients and their community" (WHO, 1985). So it is important to keep eye on the quality and cost of the drugs that are available in the markets. The label information of six different brands of tablets is presented in Table 1.

Uniformity of weight

The tablets were examined for the uniformity in their weight and for tablet- to- tablet variations which should be within the limits of the percentage deviation allowed by USP-27. 20 tablets from each of the 6 brands were weighed individually. The average weights for each brand as well as the percentage deviation from the mean value were obtained.

Uniformity of thickness, Length and diameter

Tests were performed on twenty units of each brand. The limits for thickness and diameter are ±5% and ±3% for 12.5 mm and 15 mm tablets respectively (BP - 2002).

Hardness

Tablets are constantly subjected to mechanical shocks and aberration during the manufacturing, packaging and transportation process. The ability of the tablets to resist breakage under the above mentioned circumstances depends on its hardness. In 1993, Gupta investigated that hardness also depends on the nature and quantity of excipients that used in formulation.

In purposed study six different commercial brands were used for evaluation of minimum and maximum force needed to break the tablet according to BP-2007.

Disintegration

The disintegration test was carried out by using Erweka ZT 3 Disintegrator. A 1000 ml beaker was filled with distilled water (approx. 900ml), equilibrated to 37±0.5ºC. Six tablets from each brand were subjected to the test. Time required for the last tablet to disintegrate was recorded in present study.

Dissolution

The test thus describes the overall rate of the processes involved in release of the drug into a bioavailable form. Dissolution test was carried out by using paddle method (apparatus-2; USP-32) at 50 rpm.

Distilled water (900ml) used as dissolution medium, was poured into the vessel and equilibrated to 37±0.5ºC. Six tablets from each brand were tested.

1. 5ml of aliquot was withdrawn at the intervals of 5, 10, 20, 30, 45 and 60min, and the volumes withdrawn, replaced with fresh dissolution medium.
2. The sample was filtered, using Whatman filter paper and 3ml of filtrate was further diluted as working solution (16.66µg/ml).
3. The absorbance was measured at 276 nm against dissolution medium.

Standard preparation

For the standard solution, 20 mg ciprofloxacin was weighed and dissolved in 50ml of distilled water suitably diluted to produce a 0.016mg/ml (16µg/ml) of final concentration of working solution.

Content assay

Analysis of drug potency in tablets helps to establish the amount of drug in a dosage and it is also an important parameter for the stability study of drug.

Preparation of standard solution

The standard was prepared in the same concentration as for the dissolution testing.

Preparation of sample solution

Sample was prepared by weighing and crushing 20 tablets and transferring amount of drug substance equivalent to 20mg of standard substance of ciprofloxacin in 50ml of volumetric flask dissolved in distilled water.

Portion of solution was filtered and 4ml of filtrate was further diluted upto100ml. The final concentration of working solution was 16µg/ml. The absorbance was measured at 276 nm against dissolution medium

Data Analysis

The uniformity of weight was analyzed with simple statistics – percentage deviation while the dissolution profiles were analyzed using analysis of variance (ANOVA) and model dependent method that included Zero order release, First order release, Higuchi, Hixson-crowell and Weibull release model.

RESULTS

All the brands used in the present study were within their expiry date (Table 1).

Price deviation

The survey shows that in private UAE pharmacies, both the prices of original brands and generics were very high," (WHO report) (www.thenational.news). The percentage price differential of six brands was calculated by using the formula (Akinleye *et al*., 2012):

(Price of innovator – Price of generic) ÷ Price of innovator x 100

A significant variation in the prices of different brands was observed (Figure 1) while no significant variation in physicochemical parameters was found

Physicochemical Parameters

A synopsis of the results of uniformity of weight, hardness, length and thickness, disintegration and assay are shown in Table 3.

Table 1. Label information of six different brands of ciprofloxacin tablets (500 mg)

S.No	Product code	Manufactured by	Batch No.	Mfg. date	Exp. Date	Price/10 units AED	% price differences with innovator
1	cipro–1	Gulf Pharmaceutical	D354A	12/2010	12/2013	41.5	67.45
2	cipro–2	The Jordanian Pharmaceutical	101288	12/2010	12/2013	59	53.73
3	Cipro-3	Neo Pharma	CFB1005	06/2012	06/2015	84	34.12
4	Cipro-4	NP Pharma	2011306	08/2011	08/2014	33.5	73.73
5	Cipro-5	Jamjoom Pharma	NB101	08/2011	08/2014	51	60
6	Cipro-6	Bayer Pharmaceutical (Innovator)	Bxg04z1	8/29/2011	8/29/2016	127.5	Innovator

Table 2. Different Dissolution Model

Model	Equation
Zero-order	$Q_t = Q_0 + K_0t$
First-order	$\ln Q_t = \ln Q_0 - K_1t$
Higuchi	$Q_t = k_H t^{1/2}$
Hixson–Crowell	$W_0^{1/3} - W_t^{1/3} = K_s t$
Weibull	$\log [-\ln (1 - m)] = b \log (t - T_i) - \log a$

Table 3. Physicochemical parameters of six different brands of ciprofloxacin tablets 500mg with its standard deviation

Brand code	wt. variation (mg) ± SD	Av. Length ± SD	Av. Thickness ± SD	Av. Width ± SD	Av. Hardness ± SD	DT	Content Assay
Cipro-1	826.4 ± 10.7	19.1±0.32	5.38± 0.65	9.47± 0.22	11.33± 0.84	2.36±0.02	98.9775±1.9905
Cipro-2	883.46± 5.48	16.73± 0.58	7.49± 0.10	7.49± 0.10	8.11± 0.04	2.57± 0.04	101.31±1.30107
Cipro-3	827.83±6.66	18.1± 3.64	6.37± 0.33	6.37± 0.33	9.58± 0.06	4.2± 0.01	100.385±3.557
Cipro-4	784.46±18.27	18.35± 0.22	6.61± 0.21	6.61± 0.21	12.35± 0.49	2.02± 0.01	103.051±0.048
Cipro-5	680.87±4.63	19.1± 3.55	7.1± 2.66	7.1± 2.66	9.28± 1.21	1.30± 0.03	99.703±0.77357
Cipro-6	766.34± 4.93	18.12± 0.04	5.47± 0.25	5.47± 0.25	9.47± 0.40	1.18± 0.01	99.744±1.930

Table 4. Rate of % dissolution (Mean ± SD) of six brands of ciprofloxacin tablets 500mg

Time (Min)	Cipro-1	Cipro-2	Cipro-3	Cipro-4	Cipro-5	Cipro-6
5	61.04± 8.08	83.22± 13.74	57.87± 24.61	62.34± 12.17	82.19± 7.27	52.2± 11.77
10	93.11± 4.78	98.35± 5.39	86.88± 17.30	89.40± 11.10	90.21± 3.70	80.56± 9.52
20	94.11± 3.89	103.38± 7.33	94.21± 10.05	99.45± 2.82	93.67± 2.99	89.59± 6.82
30	100.21± 2.47	104.27± 2.28	97.14± 9.50	102.81± 2.30	96.71± 3.69	94.68± 2.50
45	101.64± 1.31	103.92± 1.61	98.39± 7.14	104.37± 1.29	99.21± 4.14	98.77± 2.02
60	102± 1.27	103.66± 6.92	102.36± 4.81	105.09± 3.28	100.63± 3.96	101.27± 1.33

Table 5. Results of ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	521.8768	5	104.3754	0.074837	0.995667	2.477169
Within Groups	50209.28	36	1394.702			
Total	50731.16	41				

Table 6. Comparison of parameters and determination coefficient of the ciprofloxacin release from six different brands

Dissolution Model	Cipro-1	Cipro-2	Cipro-3	Cipro-4	Cipro-5	Cipro-6
zero order						
K	2.386	2.481	2.344	2.344	2.451	2.301
R^2	0.685	0.59	0.713	0.713	0.704	0.756
First Order						
K_1	0.207	0.362	0.181	0.205	0.318	0.148
R^2	0.996	0.999	0.998	0.998	0.996	0.997
Higuchi						
K_H	16.897	17.827	16.532	17.318	16.839	16.104
R^2	0.863	0.794	0.883	0.879	0.807	0.912
Hixson-Crowell						
K_{HC}	0.026	0.027	0.026	0.0265	0.026	0.025
R^2	0.915	0.845	0.935	0.93	0.847	0.956
Weibull						
R^2	0.999	0.999	0.999	0.999	0.999	0.999
β	0.352	1.216	0.407	1.206	0.402	0.455
Ti	4.693	-0.0011	4.27	-0.003	1.64E-06	3.861
α	0.699	3.969	1.017	7.138	1.108	1.434
T_{50}	4.821	2.297	4.694	3.764	0.519	4.848

Fig 1. Price fluctuation among different brands of ciprofloxacin tablets

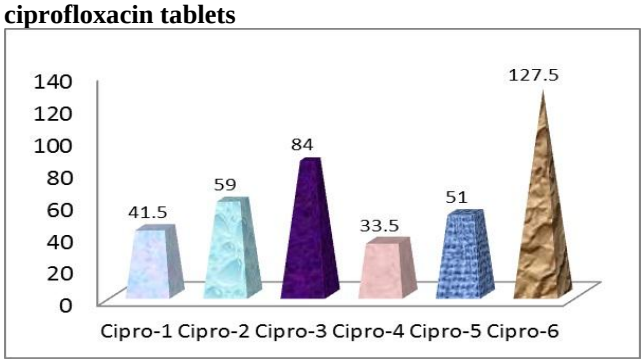


Fig 2. Comparison of weight deviation among different brands of ciprofloxacin tablets

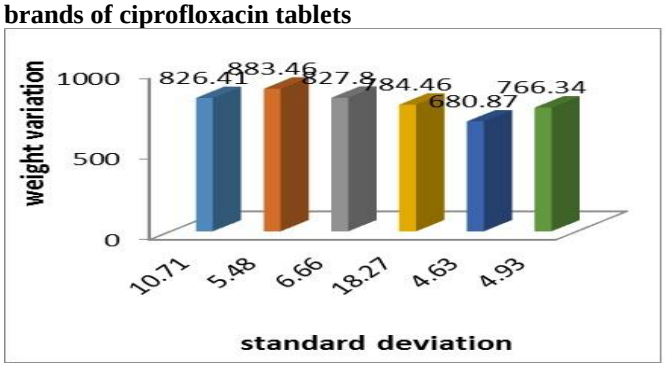


Fig 2a. Disintegration time differences among different brands of ciprofloxacin tablets

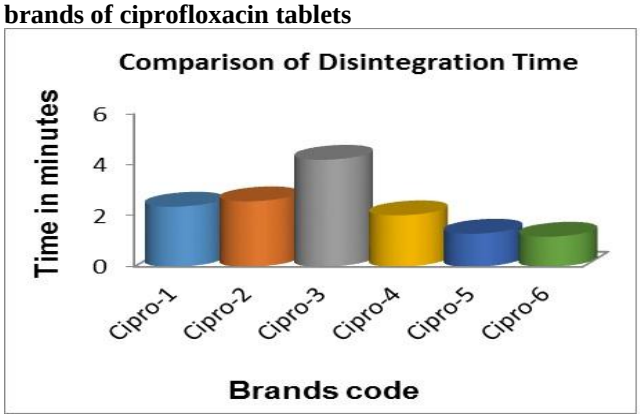
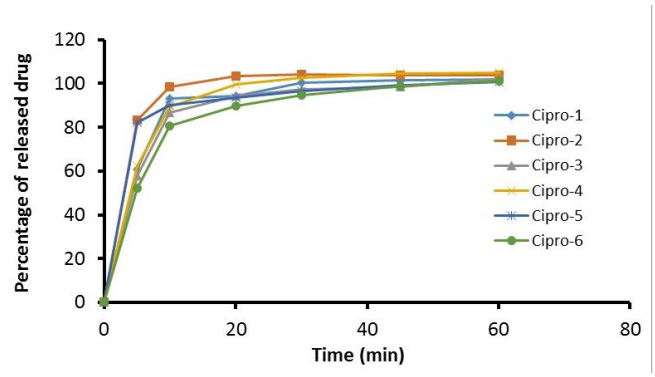
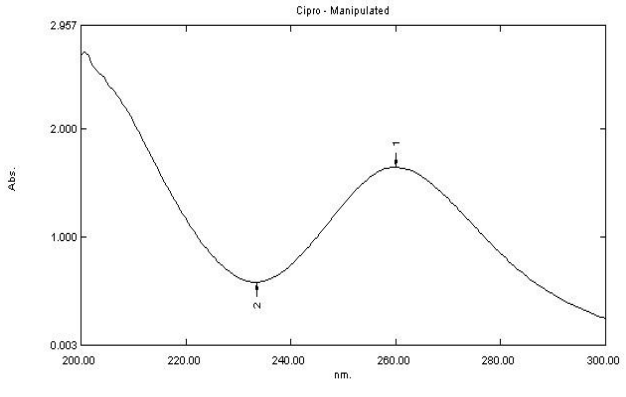


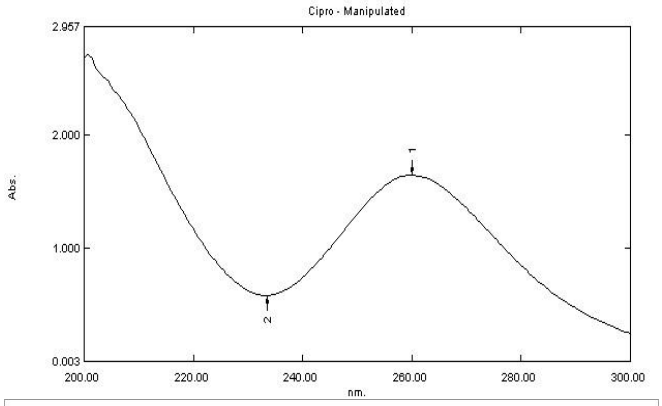
Fig 3. Comparison of dissolution profile of 6 brands

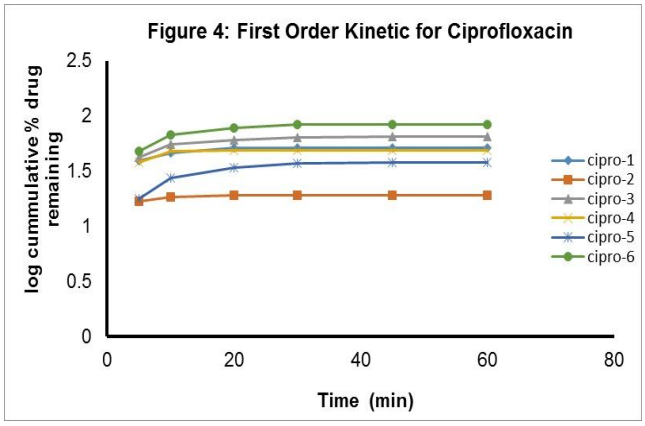


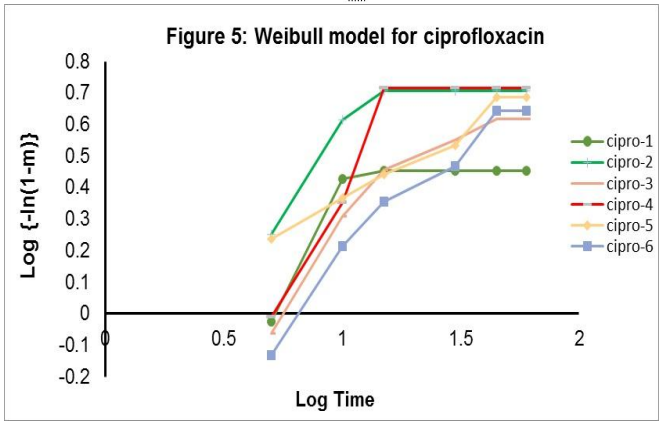
Spectrum of Standard Solution



Spectrum of Sample Solution







DISSOLUTION

The present study shows that almost all the 6 brands dissolved 80 to 98% in 10 minutes. Table 4 indicates that the drug release from innovator brands was 80.56% in 10 minutes whereas from the test brands release was from 86.88 to 98.35% which is higher than innovator.

Data analysis

The statistical evaluation (ANOVA) of dissolution test was also performed that showed that there was no significant variation found between and within different brands of ciprofloxacin tablets (Table 5).

Moreover different mathematical models dependent approaches (Table 2) were used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models (Table 6). The model that gives high 'r' value is considered as the best fit of the release data.

DISCUSSION

In present study a multiple point dissolution test study was performed and the solubility and release profile of drug was calculated. The study was done under the neutral pH condition as most of the drug dissolve and absorb in intestine that has a pH of 6.8-7.4, similar to the neutral (Table 4).

To compare the quality of all the six brands used in the study ANOVA was performed (results for all the six brands are present in Table 5). Results indicate that there are no significant differences in the release pattern of different brands at P = 0.05 level, the calculated F value (0.075) that is lower than tabulated F value (2.48).

There are number of kinetic models (Table 2), which describe the overall release of drug from the dosage forms because qualitative and quantitative changes in a formulation may vary drug release and in vivo availability. These tools are used to explain the correlation between *in-vitro* and *in-vivo* performance and are used to reduce the need of bio-studies (Table 6).

Differences found in six different brands were analyzed by projecting the dissolution profile of the drug in linear form (Table 2). Table: 6 shows the different kinetic models that were used to plots various parameters for considering the determination of coefficients (R^2). It shows that the zero-order failed to fit all batches. The Higuchi model fit only cipro-6 but not all other. The Hixson-crowell model fit four brands (cipro-1, 3, 4 and 6) and two brands (cipro-2 and 5) failed to fit this model. Whereas the first-order and Weibull models described the drug dissolution with coefficient r^2 approximately 1 (one) for all the six brands (Table 6). According to Costa, 2001 and Niebergall *et al*., 1963, the geometric shape of the tablet diminishes proportionally over time. It is assumed that the release rate is limited by the dissolution rate of drug particles.

The analysis performed by the first order (Figure 4) and Weibull model (Figure 5) suggested that ciprofloxacin was released from formulations in a linear relationship which was then evaluated by correlation coefficient (r^2) and was found in the range of 0.996 - 0.999. Among the studied models, Weibull is considered a better model as it possesses the parameters that are sensitive to the ranges of dissolution profiles. The shape of Weibull curve depends on the β value. If *b* has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas the shape of the curve with *b* lower than 1 would show a steeper increase than the one with *b* = 1(Figure 5). From the results of the model-dependent (First order and Weibull), it was indicated that there were no differences in the dissolution profile of six brands. So in this regards all the six brands are pharmaceutically equivalent.

Moreover a number of research articles are available that indicate the post-market evaluation and comparison of different drugs substance that is obligatory for the accomplishment of a stable and effective drug product (Samar and Shaimaa, 2012; Gauhar et al., 2011; Anand and Amareshwar, 2012; Akinleye *et al*., 2012; Pamula *et al*., 2010; Shefaat U *et al*., 2011; Ashour *et al*., 2005; Alvarez-Lerma *et al*., 2004; Bundrick *et al*., 2003).

The comparison and evaluation of therapeutic activity of two medicinal products (innovator and any essentially similar drug product) that contain the same active ingredient could be calculated by the pharmacokinetics data to establish the bioequivalence. But the bioequivalence study is very costly as well as time consuming.

All the brands included in this study complied with the compendial specification for uniformity of weight, hardness, disintegration and content assay are shown in Table 3. All the brands are within their expiry dates but there is significant difference in price that varies between 3.35 to 12.75 AED per unit (Table 1). The concerns of the healthcare providers heighten due to the price fluctuation, as it might bring the patient's compliance at stake.

According to the World Health Organisation's World Health Statistics 2009 survey, the prices of selected generic medicines sold in pharmacies are 13.8 times the international reference price. This is the average procurement price at which the generic versions of drugs are offered to developing countries on a not-for-profit basis. The survey also shows that branded drugs in private UAE pharmacies cost on an average 23.52 times the reference price (www.thenational.news). This makes the choice of appropriate medication difficult for the physician. This problem may also be solved by producing more drugs locally.

CONCLUSION

Effective and appropriate clinical outcome is based on appropriate dosing of medication and patient compliance. The patient compliance is majority of time poor because of economical constrain. The post-market monitoring provides a very important and crucial assessment regarding the chemical and pharmaceutical equivalence that do not indicate the bioequivalence but give a clear picture on releasing pattern of drug in-vitro condition that might help in prediction of *in-vivo* absorption.

The price of brands is one of the big issues that affect indirectly the therapeutic effectiveness. Cipro-1 (innovator) price is 12.75 AED / tablet whereas the cipro-4 has 3.35 AED / tablet but both compiled USP/ BP specification for physicochemical properties and are similar in percentage release of drug from its formulations (Table 4 and 6). In this situation all the six brands are pharmaceutical equivalent to innovator and can be substituted for each other in their prescription and use.

ACKNOWLEDGEMENT

The authors would like to thank RAK college of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, UAE

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