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A Comperative Study of A New Formula of Ciprofloxacin With Five Marketed Brands

Ahmed M. A.Masaad[1*], Majed Al robaian[2] Mohammed E. A. Shayoub[3a], and Badraddin M. H. Al-hadiya[4]

[1*]*Department of Pharmaceutics, College of Pharmacy,Taif University, KSA, Department of Clinical Pharmcy, College of Pharmacy,Taif University, KSA,*[3]*Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Sudan*

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, Taif University, KSA*

Abstract:- This study aimed to formulate ciprofloxacin hydrochloride as effervescent tablets and comparing them with five local marketed ciprofloxacin hydrochloride coated tablets. The samples were selected by different batches numbers randomly and the physicochemical experiments were done according to monographs and microbiological sensitivity test also was done on microorganisms (*Escherichia coli, Salmonella typhi, Salmonellapara typhi and Staphylococcus aureus).* The new formula give more phrmacological effect than marketed brands due to improvement of physicochemical properties.

Keywords:- quality control tests, ciprofloxacin, dissolution, weight variation, hardness, friability and disintegration

I. INTRODUCTION

Importance of comparative study

Five brands of ciprofloxacin HCl 500 mg (figure 1and figure 2) were randomly w collected and quality control tests of uniformity of weight, hardness, friability, assay, disintegration and dissolution tests were carried out with the aim to assess its physicochemical properties and their quality. The results obtained have been discussed in some details using monographs, the results were also subjected to statistical analysis. Also the formulation of the ciprofloxacin as effervescent tablets was carried out by two methods and comparison between two methods was done with fundamental tests. (2)

Post-market surveillance or monitoring involves all activities undertaken to obtain more data and information about a product after it had been granted marketing authorization and made available could be employed for product improvement, development of standards and regulations.

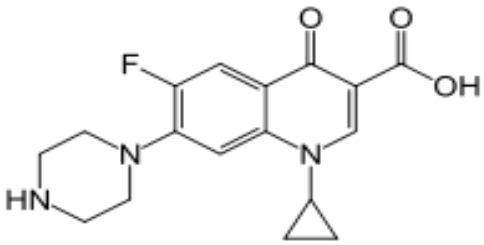

Figure 1: Structure of Ciprofloxacin

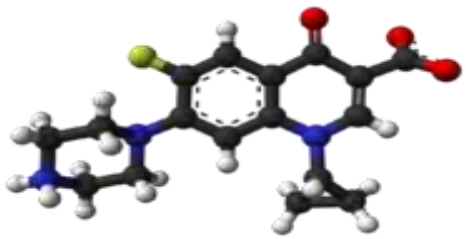

Figure 2:3D Structure of Ciprofloxacin

Regulatory agencies rely on limited information obtained during clinical trails and to some extent scientific literature as guides to granting marketing authorization of medicines for public use. It is therefore imperative to conduct post-market surveillance to assess the quality. Post-market monitoring ought not to be one event rather it should be a continuous event throughout the life of a drug have been identified to include: review of product's condition of approved study; evaluation and investigation of reported drug complaints; inspection of manufacturer's processes and procedures for production and complaint handling; market surveys of technical and clinical documentation; review of product claims/labeling; public access to information taken and reported to the regulatory agency (ies); and in vitro testing to products for compliance to standards. In vitro testing or quality control of drug is a set of studies or experiments undertaken during production (in process) and occasionally ought to be undertaken post-production by regulatory testing of drugs in the market is crucial to protect public health especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. In Sudan, several attempts have been made to combat counterfeit and substandard drugs from the Indian sub-continent. Counterfeit and substandard medicines are a

major cause of morbidity, mortality and loss of public confidence in drugs and health structures [(3)]. India happens to be one of the largest exporters for the fake and substandard drugs to Sudan other countries are Egypt, Jordan, Pakistan, China and Syria [(20)]. China and India are known as the leading countries in counterfeit drugs production and also the bulk active ingredients they produce are used for counterfeiting worldwide [(4)].

To reduce the cost of medicines especially for the low income groups of developing countries, the world health organization (WHO) has continuously advocated the use of generic brands [(5)]. But this approach has not provided sufficient evidence for the substitution of one brand for another. The difference in cost between a brand and generic medicine may be as high as 90%. [(6)]

Generic substitution could be considered when a generic copy of a reference drug contains identical amounts of the same active .

Ingredient in the same dose formulation and route of administration as well as meet standards for strength, purity quality, and identity. [(7)]

However evidences over the years indicate that marketed products with the same amount of active ingredient exhibit marked differences in their therapeutic responses. [(8)]

In this study was taken to evaluate the efficacy and justification of generic substitution of ciprofloxacin five brands in the Sudan market and formulation of effervescent ciprofloxacin tablet. Ciprofloxacin is an anti bacterial agent of the class fluoroquinolones.

It was first sold by Bayer pharmaceuticals. In the 1990s there were just a few brands in Sudan market but recently many brands of ciprofloxacin have flooded the market. The prices range from Sudan local currency equivalent of $1.25to$12.50.There is a growing concern about this situation. How can a patient know if buying a cheaper brand would be cost effective or not? The price of the cheapest is ten times lower than the most expensive. The increase in the number of generics of ciprofloxacin can be attributed to increased prescription of ciprofloxacin. It would appear that for most infections, empirically and sometimes after laboratories investigations. Physicians prescribe ciprofloxacin as the first drug of choice. This has resulted in higher demand and the need to increase supply has led to more importation while some indigenous pharmaceutical industries began to produce their own brands of ciprofloxacin. For the health care providers to use these brands have to ascertain. This means that there should be continued post marketing surveillance of the drugs. [(9)]

II. MATERIALS AND METHODS

Five different brands of ciprofloxacin as shown in table 1 where purchased from retail pharmacies in Khartoum, Sudan. Pure ciprofloxacin HCl powder was obtained as agift from a research colleague. The reagents utilized include hydrochloric acid (DH, UK) and ferric chloride. The media (Moller Hinton Agar).

Table 1: Brands of Ciprofloxacin

Code	Brand name	Dosage form	Country of origin
A	Bactiflox	Tablet	Switzerland
B	Amiciprox	Tablet	Sudan
C	Ciproquin	Tablet	India
D	Safloxin	Tablet	Sudan
E	Epoflox	Tablet	Sudan

III. FORMULATION OF TABLETS

Tablet was prepared by two methods to achieve the most effective one and then compare between two methods.

In the two methods the ratios of the effervescent ingredients were taken as (1:2:3.4) respectively for citric acid: tartaric acid: sodium bicarbonate according to the following equation.

Citric acid:

$$3NaHCO_3 + C_6H_8O_7 \cdot H_2O \rightarrow 4H_2O_+3CO_{2+}Na_3C_6H_5O_7 \quad (1)$$
$$3 \times 84 \qquad 210$$

One gram of citric acid (mwt=210) reacts with 1.2gm of sodium bicarbonate (mwt=84) as obtained from the following calculations: $\frac{1}{210} = \frac{x}{3} \times 84 \rightarrow 1.2$gm.

Tartaric acid:

$$2NaHCO_3 + C_4H_6O_6 \rightarrow 2H_2O + 2CO_2 + Na_2C_4H_4O_6 \quad (2)$$
$$2 \times 84 \qquad 150$$

Since it desired to use a 1:2 ratio of citric acid to tartaric acid , two grams of tartaric acid (mwt=150) reacts with 2,24gm of sodium bicarbonate according to the following calculations:

$\frac{2}{150} = \frac{x}{2} \times 84$(gm)

$x = 2{,}24$

From the above calculations, 1, 2gm+2, 24 are required to react with 1+2gm of the citric: tartaric acid combination. Since it is desired to leave a small amount of the acid in excess to enhance palatability and taste, 2,24gm +1,2gm = 3,44gm only 3,4gm of sodium bicarbonate was utilized. Therefore, the ratio of effervescent ingredients used was (1:2:3.4) for the citric acid tartaric acid: sodium bicarbonate [(10)].

Specific amount of ciprofloxacin and saccharine were weighted and were divided into two dishes in equal amount and well mixed to each one of dishes effervescent base was added Citric and Tartaric acid in one and sodium bicarbonate in another one to avoid reaction then the binder combination (Guar and PVP) was added slightly slow after dissolving in a very few amount of water and then the mixture was blended continuously well till become granules and then was put in oven for drying damp mass for twenty hours then the damp mass was passed through mesh ten for granulation and resizing and through mesh fourteen for enhancing uniformity of distribution of mixing.The MCC was added before resizing to avoid sticking and work further as disintegrated agent, lubricant and glident, after this talc powder and Mg stearate were added as lubricant and glident in combination. Granules were compressed into two types one tablet 250 mg (0.25 gm) by punch 20 and 125 mg (0.125 gm) by punch 13 as divided dose. [(11)] The tablets were prepared by wet granulation method and then compared with five brands.

Determination of uniformity of weight

20 tablets from each brand and effervescent tablet was weighed individually with an analytical weighing balance. The average weights for each effervescent tablet and the
percentage deviation from the mean value were obtained. [(12)]

Assay

A solution of 1% w/v ferric chloride was freshly prepared, as well as 100 mcg/ml of pure ciprofloxacin (HCl). Five tablets from each brand were crushed and 100 mg of the powdered samples were weighed. Dissolved in 100 ml 0,1N hydrochloric acid (HCl) and further dilution was made to obtain 100mcg/ml for each brand. To five ml of each brand and the pure sample, 1 ml of ferric chloride was added and made up to 50 ml with 0,1N HCl. The absorbance of each sample was taken at 438λ(nm) against the blank reagent (1ml ferric chloride solution made up to 50 ml with 0,1NHCl)with an ultraviolet spectrophotometer (Jenway, UK).The percentage content was calculated for each brand by using calibration curve already prepared according to monograph. [(13)]

Hardness test

The crushing strength was determined with a tablet hardness tester (Monsant, U.K). Four tablets were randomly selected from each brand with effervescent tablet and then the pressure at which each tablet crushed was recorded and the hardness value obtained. [(14)]

Friability test

Ten tablets from each brand with effervescent ciprofloxacin HCl were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev-min for four minutes. The tablets were then weighed and compared with their initial weights and percentage friability was obtained. [(14)]

Disintegration test

Six tablets from each brand were employed for the test in a freshly prepared medium, 0.1 NHCl at 37 C using educational sciences disintegration apparatus (Es Eagle Scientific limited, Nottingham, UK). The disintegration time was taken to be the time no particle remained in the basket of the system. Effervescent tablet no need for this test and this point of advantages in compare to other brands. [(14)]

Dissolution test

The effervescent tablets were dissolved in sink condition and the time of dissolution of effervescent tablet was recorded by stop watch**.[(15)]** In other brands the dissolution test was undertaken using (USP apparatus1) (basket method) in six replicates (six tablets for each brand). The dissolution medium was 900ml 0.1NHCl which was maintained at 37 ± 0.5 C^o. In all the experiments, 5ml of dissolution sample was withdrawn at 35 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by ultra violet spectrophotometer at 277λ (nm) and compared to standard. The concentration of each sample was determined from a calibration curve obtained from pure samples of ciprofloxacin according to the monograph. [(13) - (15)]

Microbiological sensitivity test

Microbiological test was carried out for new formula and in five brands in four species to inhibit and ensure the effectiveness of the antibiotics and compare between them, those species are *Salmonella typhi, Staph. aureus, Escherechia col* using disc diffusion Kirby-Bauer*i.* (Figure 3 table 3). [15]

IV. RESULTS AND DISCUSSION

Table 2: compression of quality control test between five brands of ciprofloxacin with effervescent tablets
Table 3: Effectiveness of Formula to other brands by inhibition zone in (mm)

Code	Assay%	Average hardness (Kg/cm^2)	Friability (%)	Deviation%	Average disintegrate time(min)
A	100	10.3	0.37	1.379	**9.30**
B	97	12.1	0.20	1.645	**16.92**
C	90	12.87	0.40	1.169	**7.90**
D	96	11.12	0.13	0.762	**16.31**
E	95	11.38	0.24	0.901	**1.47**
F	**98**	**8.5**	**1.90**	**1.220**	**0.17**

Inhibition zone of different brands and formula in (mm)

Name of Brand	E.Coli Inhibition Zone(mm)	Staph aureus Inhibition Zone(mm)	Salmonella sp Inhibition Zone(mm)
A	16.2	14.5	14
B	15	13.4	13.2
C	16	14.4	14
D	15.4	14	13.8
E	14.5	12.8	13
F	17	15	14.8

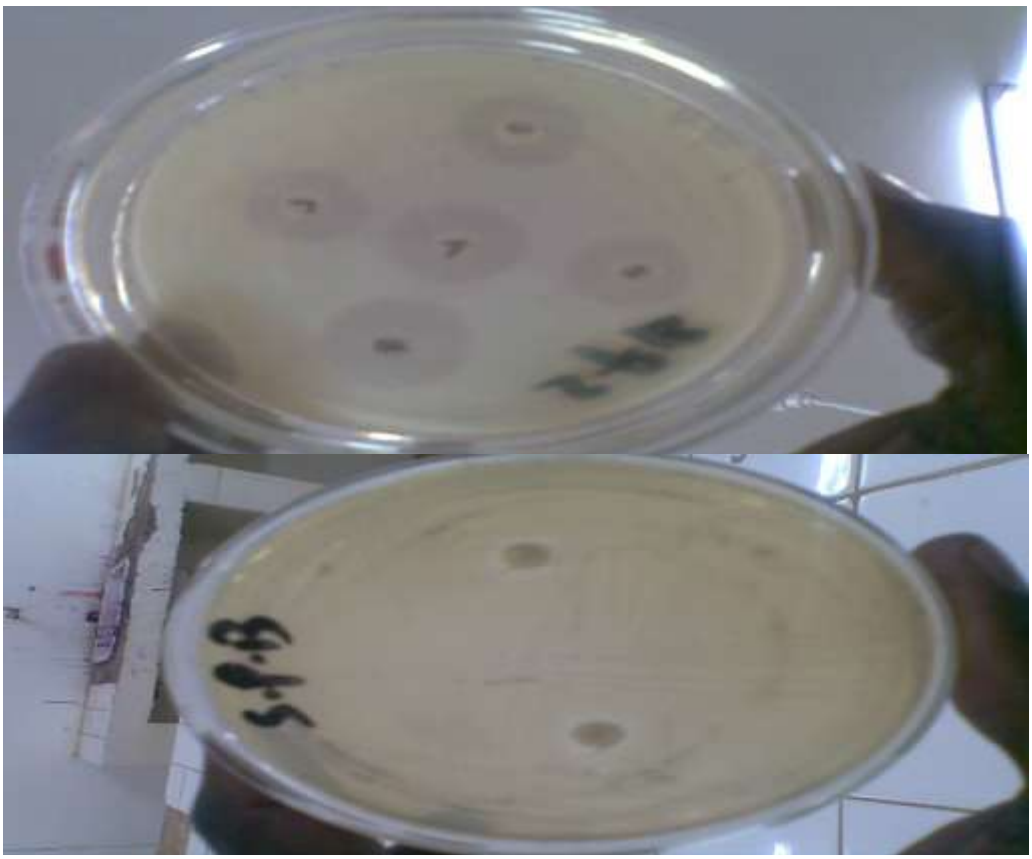

Figure 3: Indicates Inhibition Zone of Different Culture to Different Brands of Ciprofloxacin and Prepared Formula

IV. FROM THE RESULT

A summary of the results of uniformity of weight, assay, hardness test, friability and disintegration are as shown in table 2.Uniformity of weight, assay, disintegration and dissolution are compendia standards to assess the quality of tablets while hardness and friability are referred to as non-compendia standards although friability is now included in united states pharmacopeia.[13]

- Uniformity of weight does serve as a pointer to good manufacturing practices (GMP) as well as amount of the active pharmaceutical ingredient (API).ciprofloxacin hydrochloride contained in the formulation. All the brands complied with the compendia specification for uniformity of weight which states that for tablets weighting more than 324 mg, weight of not more than two tablets should not differ from the average weight by more than 5%.From the all result brand A then brand B then brand D then E then C and effervescent tablet are all comply with monograph requirement. In European pharmacopeia tablet must not be above 115% or below 85% of the average weight and from (table 2), the deviation percent is more indication for content uniformity and all brands comply content uniformity and effervescent tablet too.
- All the brands complied with the USP specification for assay. The USP specification is that the content of ciprofloxacin hydrochloride should not be less than 110% while BP specifies that the content should not be less than 95% and not more than 105%, however the result ascertains the presence and compendia quantity of ciprofloxacin hydrochloride in all the brands and so could not be judged as counterfeits without APIs.We found the result of assay that the new formula and brand A same content active ingredient then B then E then D then C.
- The hardness or crushing strength shows the ability of tablets to withstand handling without fracturing or chipping. It can also influence friability and disintegration, the hardness of tablet, the less friable ones and the more time it takes to disintegration. Brand E required the least pressure before fracture while brands A, C, D could not break at 5 kg/cm^2 with Monsanto Hardness tester .A force about 4kg is the minimum requirement for satisfactory tablet [16]. Hence, all brands not yet satisfactory for hardness that might be for bad storage and humidity. The hardness of Brand F (new formula) is better than all brands which comply with European monograph [17].
- The compendia specification for friability is 1% friability for all the brands was below 1%. Due to all the brands are coated hence the friability test is not used for them and used only to evaluate the tablet resistance to abrasion for effervescent tablets although the value of friability is 1.9 but it could be applicable for effervescent tablets and its comply with monograph. [17] - [18]
- Disintegration could be directly related to dissolution and subsequent bioavailability of a drug .A drug in corroborated in a tablet is released rapidly as the tablet disintegrates a critical step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine .All the brands complied with compendia specifications for disintegration. The BP specification is that un coated tablets should disintegrate within 15 min and film coated tablets should disintegrate within 30min while USP specifies that un coated and film coated tablets should disintegrate within30min. Brand E then C then A then B then D it was from this results the best one is the effervescent which overcome all brands in the disintegration test. Due to the presents of carbon dioxide which is work as full disintegrate.
- The USP and BP specifies that the amount of drug released (dissolution should not be less than 80% of the labeled amount at 30min. All brands complied and passed the dissolution test [13].According to the FDA guidance for GMP of drug guidance for the industry, in the dissolution testing of immediate release solid oral dosage forms. The BCS suggests that for class 1 and in some cases class111 drugs 85% dissolution in 0.1 in HCL in 15 min insures that the bioavailability is comply with requirement of monograph [19].
- From microbiological results zone of inhibition of brand A then brand C then brand D then brand B then brand E. (Table 3 and figure 3)In contrast with what was expected the effectiveness of the effervescent tablet (new formula) compared to five brand of ciprofloxacin by using microbiological test as new method to evaluate the effectiveness by using McFarland turbidity standards after preparation of standard in columns suspension and incubation we found diameter of each inhibition zone after measuring using ruler and calibers there was a complete inhibition of the growth of the effervescent tablet that indicate it was more effective than other brands from the

figure 3 it is clear that arrangement of inhibition zone of effervescent came over brand A then C then D then B then E, that emphases the improvement of physicochemical prosperities of the drug.

V. CONCLUSION

- The monitoring and quality control test of medicines in pharmacies randomly to ensure the good storaging conditions and to ensure drug's effectiveness and patient confidence.
- The effervescent formulae are needed and sometimes it is a most to enhance palatability of certain drugs

- The correlation can be made between dissolution rate of effervescent tablets as an indication for it is effectiveness without in vivo studies and that by microbiological inhibition zone assay.
- Effervescent tablet from ciprofloxacin might reduce the microbial resistance, and increase patient compliance
- Post –market monitoring is very crucial for effective clinical medicine and this study has emphasized that chemical equivalence does not indicate same effectiveness.
- Interestingly from this study, it was understood that price may not necessarily indicate the authenticity and effectiveness of drug product. Brand E is sold at Sudan equivalent 3$ but it might be has the same effectiveness to brand A (from inhibition zone) which is sold at 12.50$.
- The study also managed to improve the palatability of the drug solution, via the utilization of saccharin sodium and vanillin flavor and using effervescent formula.

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