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In vitro evaluation of Ciprofloxacin Hydrochloride

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Abstract

The in vitro evaluation of the physical characteristics of the pharmaceutical products ensures their quality as well as bioavailability and impart optimum therapeutic activity. Ciprofloxacin HCl, a widely used antibiotic to treat different types of bacterial infections, was chosen for this in vitro comparative study of different pharmaceutical company. The present study compared the content uniformity, weight variation, hardness, friability, thickness, diameter, disintegration and dissolution ability of five brands of ciprofloxacin HCl tablets marketed in Bangladesh to confirm whether they follow USP guidelines. All five brands of ciprofloxacin HCl tested meet the specification of the USP for content uniformity, weight variation, hardness, friability, thickness, diameter, disintegration and dissolution. The amount of active ciprofloxacin HCl varies from 244.46 mg to 248.46 mg among the products. The average hardness and friability of the products varies 73.9 N to 77.6 N and 0.013% to 0.031%, respectively. All the brands had shown disintegration time 5 to 8 minutes while they showed 80 to 95 % release of active ingredient within 30 minutes in dissolution testing. This may confirm the absorption of the drug from gastrointestinal tract for optimum therapeutic effect.

Keywords: Ciprofloxacin HCl; UV visible spectroscopy; Disintegration test; Dissolution test

Introduction

Ciprofloxacin hydrochloride (Fig. 1), a synthetic antibiotic, belongs to the family of fluroquinoloes, widely used as an anti infective agent in the management of respiratory tract infection, urinary tract infections including infection of the bones and joints endocarditis, gastroenteritis, malignant otitis, cellulites and anthrax etc (Neu, 1987). For the optimum therapeutic effect, the drug must be released quickly from the conventional tablet dosage form, dissolved in the aqueous medium and absorbed from the gastrointestinal tract to get proper therapeutic efficacy. Retardation of release of drug from the tablet may lead to sub-therapeutic level of the drug in plasma resulting in the delayed onset of action or short duration of action or no therapeutic action. Moreover, the sub-therapeutic level of antibiotic in the body might be the reason for the development of drug resistance, a major problem of antibiotics (Campoli-Richards *et al.,* 1988; Hyatt *et al.,* 1994).

Product selection of the same active ingredients from several generic products available in the market is very important step during the course of therapy and cause several concerns to a healthcare practitioner. Therapeutic equivalence must be ensured by ascertaining the biopharmaceutical equivalency of such drug products (Olaniyi *et al.,* 2001). To reduce the medicines expenditure burden on a healthcare system, the World Health Organization (WHO) has continuously advocated the use of generic products but this should be supported with sufficient evidence for the substitution of one brand for another. This could not be achieved without proving its efficacy through bioequivalence studies (WHO, 2004). Bioequivalence studies for generic products are essential to ensure the absence of any significant difference in the rate and extent to which the active ingredients become available at the site of drug action administered under similar conditions in an appropriately designed study (US Food and Drug Administration, 2003). Dissolution testing, a surrogate marker for bioequivalence test, is a very practical and economic approach to identify bioavailability problems and assess the need for in vivo bioavailability (Shah, 2001). Therefore, the in vitro dissolution is a vital tool in assessing

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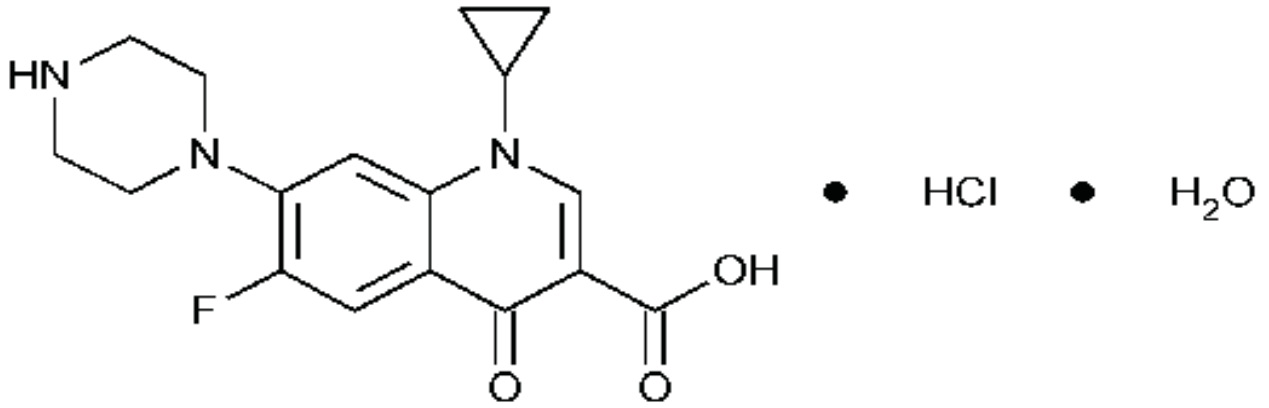

Fig. 1. Ciprofloxacin hydrochloride

the in vivo performance and also serves as a tool to identify unacceptable or substandard drug products.

As ciprofloxacin is widely used antibiotic in Bangladesh, the objective of this work is to check whether ciprofloxacin HCl tablet of different brands available in Bangladesh comply the United States Pharmacopoeia (USP) specification of different pharmaceutical parameters such as weight variation, content uniformity, hardness, friability, disintegration and dissolution for the confirmation of proper release of drug in gastrointestinal tract (GIT), absorption from the GIT and optimum therapeutic action of the drug.

Materials and methods

Materials

Five available brands of ciprofloxacin tablets (250 mg) were collected for this study. The samples were named as brand number 1, 2, 3 4, and 5. Sodium phosphate monobasic ($NaH_2PO_4.2H_2O$), sodium phosphate dibasic (Na_2HPO_4), methanol were collected from sigma chemicals. Standard ciprofloxacin HCl was collected from Eskayef Bangladesh Ltd. as a gift.

Methods

Content uniformity test of ciprofloxacin HCl tablets

100 mg of accurately weighed ciprofloxacin HCl was dissolved in a small quantity of phosphate buffer of pH 6.0 and the final volume was made up to 100 ml with the same solvent to get 1mg/ml or 1000 µg/ml concentration of standard stock solution. Various working concentrations (such as 10, 5, 2.5 & 1.25 µg/ml) were made by further dilution with same medium. Then absorbance of each concentration solution was measured at 274 nm by a Shimadzu UV-1650PC spectrophotometer (Japan). Each tablet was crushed into powder and sufficient amount of powder from each crushed tablet was taken so that the amount contains 100 mg of active ciprofloxacin. The total content of active in each tablet was determined from the standard plot and was cross-examined on regression equation (Liu, 1994). The average amounts (mg) of tablet, standard deviations (STDEV), standard error of mean (SEM) were then calculated for 20 tablet of each brand.

Weight variation test

20 tablets for each brand were weighed by using ELB 3000, Shimadzu analytical balance (Japan) and average weight for each brand was calculated and compared the individual tablet weight to the average.

Hardness test

The standard method used for tablet hardness testing was compression testing. For each brand, the hardness of 20 tablets was determined by using the Monsanto hardness tester (Japan). The tablet was placed between two jaws that crush the tablet. The machine measured the force applied to the tablet and detected when it fractures.

Friability test

It was measured by the use of bellstone BHI-PTM-4530 friabilator (Japan). 20 tablets for each brand were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100

revolutions, the tablets were reweighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability.

Diameter and thickness test

The thickness and diameter of 20 tablets for each brand were determined by using Bitsco Slide Calipers (UK) and their respective average values were calculated.

Disintegration test

AVI-PH-4558 LAB 4553 disintegration tester (Germany) was used to test disintegration time. In order to test disintegration time, one tablet was placed in each tube and the basket rack was positioned in a 1L beaker of water at 37±2^{0}C such that the tablet remained 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 30 cycles per minute. Then the disintegration time for each formulation was calculated.

Dissolution test

ERWEKA DT 600 UV dissolution apparatus (Germany) was used for conducting dissolution test. Dissolution test was followed as (USP, 2000): Six tablets were taken for the first phase to study the dissolution pattern of the tablets. 900 ml of 0.1N HCl was used as the dissolution medium. The rpm of the stirrer was maintained at 50 and the temperature of the medium was set at 37 ^{0}C. When the temperature was set each tablet was placed in each basket for 30 min. After the desired time, 20 ml solution was collected and filtered. The filtrate was then analyzed by UV spectrophotometer. For the quantification of the drug, a standard calibration curve was established first.

Results and discussion

Content uniformity test of ciprofloxacin tablet

Content uniformity test of ciprofloxacin HCl in each tablet of the different brands was carried out by measuring the quantity of the drug by UV-spectrophotometric method. The ingredient was extracted after grinding the tablet into powder. For extraction methanol and phosphate buffer (pH 6.0) were used at a ratio of 1:5. The buffer solution is highly effective to solubilize all the drugs in the powder due to high solubility.

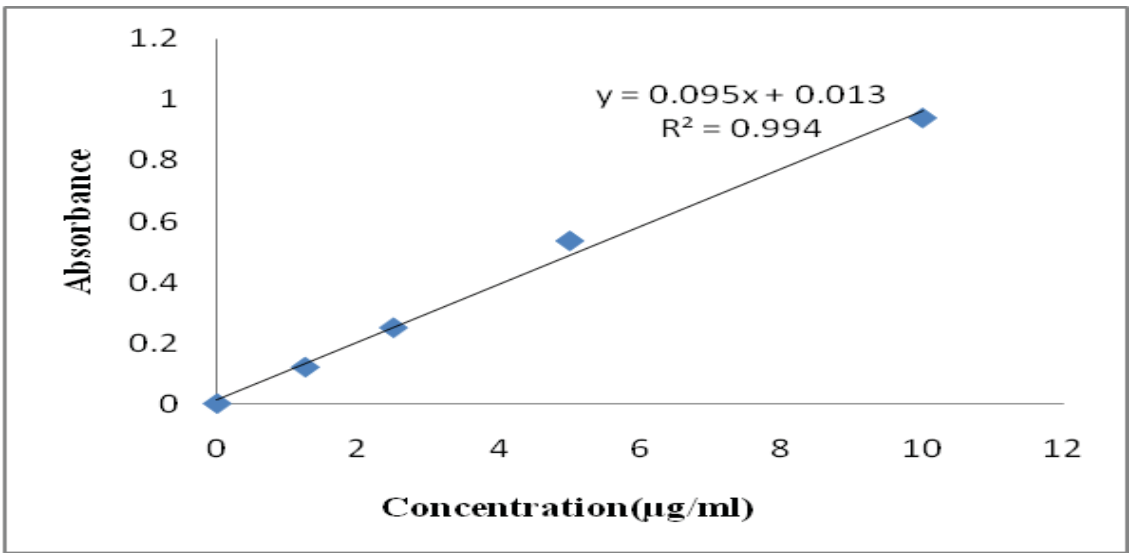

Fig. 2. Calibration curve for Ciprofloxacin HCl.

To remove the insoluble inert excipients the solution was filtered through a filter paper. The filtered solution was diluted and measured the absorbance at 274 nm. The amount of the drug per tablet was then measured using the calibration curve (Fig. 2).

The results as shown in the Table I indicate that all the products contain the amount of ciprofloxacin HCl very close to the claimed value (250 mg). Moreover, standard deviation of the content from the average value is very low (0.67 to

2.22) suggesting the content uniformity of the drugs is very close among the tablets. All these values comply the USP specification indicating the good quality of tablets in terms of content uniformity.

same time must provide satisfactory disintegration and dissolution results. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications. Again, if it is too soft, it may not

Table I. Physicochemical parameters of different brands of Ciprofloxacin HCl tablets

Brand No.	Content Uniformity (mg) Amount±SD	Weight Variation (mg) Mean±SD	Hardness (N) Mean±SD	Friability (%)	Diameter (mm) Mean±SD	Thickness (mm) Mean±SD	Disintegration time (min) Mean±SD	% Dissolved in 30 min. Mean±SD
1.	244.46±2.22	546.25±2.09	77.6±1.31	0.013	11.52±0.007	4.56±0.008	5.85±0.671	89.74±4.50
2.	245.46±1.82	586.35±8.15	75.95±1.40	0.031	8.15±0.005	6.15±0.010	6.90±0.778	93.57±6.32
3.	246.46±1.42	546.5±1.82	75.85±9.06	0.020	5.72±0.005	5.28±0.015	6.20±0.834	80.82±3.13
4.	247.46±1.02	442.6±2.68	74.15±2.50	0.022	11.62±0.005	6.51±0.029	7.75±0.639	87.09±4.88
5.	248.46±0.67	442.9±2.59	73.9±2.17	0.015	8.87±0.0056	6.15±0.015	7.15±0.745	95.76±3.59

Weight variation test

In order to ensure good manufacturing practices (GMP), appropriate size of the tablets and the content uniformity of the formulation weight variation test was carried out according to the procedure discussed in the experimental section. The United States Pharmacopoeia (USP) provides criteria for tablet weight variation of intact dosage units. As can be noted in the Table 1 all brands complied with the specification for uniformity of weight which states that, weights of not more than 2 tablets should not differ from the average weight by more than 10% and none deviates by more than twice that percentage. All five brands of ciprofloxacin HCl tested conform the USP weight variation test showing a standard deviation 1.82 to 8.15 (Table 1).

Hardness test

Hardness tests helps to measure whether a tablet inherits adequate hardness to withstand consumer handling, at the be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations.

From the Table 1 it can be shown that all brands of ciprofloxacin HCl showed the standard deviation within the compendia range. The study shows the mean values of hardness are 73.9 to 77.6 N and standard deviation from the mean values are 1.31 to 9.06 which suggests that the hardness is very close among the tablets. All these values comply the USP specification indicating the good quality of tablets in terms of hardness.

Friability test

The United State Pharmacopoeia states that the friability value of tablets should be less than 1% (USP, 2007) and as such all the brands of ciprofloxacin HCl tablets passed this friability specification. Friability test can be performed in order to monitor the resistance of tablets to stresses like mechanical shocks and abrasion during the manufacturing,

packing and transportation processes. Such stresses can lead to capping, chipping, abrasion or even breakage of the tablets. It is therefore important that the tablet is formulated to withstand such stress without damage. Weight loss values are presented in the Table I. All the brands of ciprofloxacin HCl were coated. They showed 0.013 to 0.031 % (Table 1) loss of weight after the friability test.

Diameter test

In order to investigate the size uniformity and shape, diameters of tablets of various formulations were measured using bitsco slide calipers. The results are shown in the Table I. From the Table it can be mentioned here that the average diameter is 5.72 to11.62 mm. Deviation from mean value is 0.005 to 0.007.

Thickness Test

Thickness of tablet was measured to maintain uniform size and shape among the tablets of various formulations. The results are shown in the Table 1. The measurement shows the average value of thickness is 4.56 to 6.51 mm. Deviation from mean value is 0.008 to 0.029.

Disintegration test

In order to evaluate the disintegration capability of tablets the test was performed as per procedure described in the experimental section. The results are shown in the Table 1. From the Table it can be seen that the average disintegration time for each formulation is less than 8 minutes. Standard deviation of the disintegration time from the average value is very low 0.639 to 0.834 suggesting the disintegration time of the drugs is very close among the tablets. All the values comply the USP specification indicating the good quality (oral absorption) of tablets in terms of disintegration time.

Dissolution test

Tablet dissolution is a standardized method for measuring the rate of drug release from a dosage form. From the results as shown in the Table I it is obvious that all brands of ciprofloxacin HCl tablets show more than 80% release in the specific medium within 30 minutes that comply USP specification. The result indicates good dissolution of the drug and suggests the proper absorption of the drug from GIT.

Conclusion

All the tablets displayed uniformity in terms of active ingredient, hardness, thickness, diameter and weight variation and met USP standards for friability. They also met USP standards in disintegration and dissolution test. Therefore it can be concluded that all the brands of the ciprifloxacin HCl tested have uniform weight and also sufficient physical stability to maintain physical integrity over time and they will also be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing. Disintegration and dissolution test suggest that the product might sufficiently release in the GIT followed by proper absorption from the GIT and thus provide desired therapeutic activity to the patient.

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