Malaysian Journal of Pharmaceutical Sciences
Vol. 19, No. 2, 73–86 (2021)

IN VITRO BIOPHARMACEUTICAL AND PHYSICOCHEMICAL EVALUATION OF DIFFERENT BRANDS OF CIPROFLOXACIN MARKETED IN ADEN-YEMEN

WAFA F BADULLA*, DUA'A H AL-MAQDI AND EBTESAM S BAMAHMOOD
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Aden University, Aden, Yemen

Published online: 23 November 2021
To cite this article: WAFA F BADULLA, DUA'A H AL-MAQDI & EBTESAM S BAMAHMOOD (2021) *In vitro* biopharmaceutical and physicochemical evaluation of different brands of ciprofloxacin marketed in Aden-Yemen, *Malaysian Journal of Pharmaceutical Sciences*, 19(2): 73–86. https://doi.org/10.21315/mjps2021.19.2.5
To link to this article: https://doi.org/10.21315/mjps2021.19.2.5

ABSTRACT

The current study conducted to evaluate the biopharmaceutical and physicochemical equivalence of the three available pharmaceutical dosage forms of ciprofloxacin (CIP) in the local markets (tablets, infusion and eye drops). Three brands for each dosage form were selected and coded as Tablets I, II, III; CIP infusion (Infusion I, II, III) and CIP eye drops (Eye drops I, II, III). Different in vitro quality control tests, physiochemical and determination of active ingredients contents were performed. All brands of tablets have a satisfactory result that complies with the pharmacopeia specification except the hardness of the tablets was more than the recommended value, and the salinity of Infusion II and III was lower than 0.9, the viscosity of the eye drops was lower than the specified value. Post-marketing surveillance is an essential issue to distinguish poor-quality medicines and must be routinely performed to weed out substandard and counterfeit medicine.

Keywords: Ciprofloxacin, Biopharmaceutical, Quality control tests, Physicochemical, Pharmacopeia

INTRODUCTION

Ciprofloxacin (CIP) is a synthetic antibacterial of the fluoroquinolones' group. It has a concentration-dependent bactericidal effect (Hamam 2014). It is effective for urinary, respiratory and gastrointestinal tracts, soft tissue, and sexual infections (Rao and Nagaraju 2004; Lode and Allewelt 2002; Bedor *et al*. 2007). It is one of the most prescribed antibiotics by physicians in Yemen.

*Corresponding author: aden.wf.77@gmail.com

There are many brands of CIP circulating in the Aden-market. The quality of the pharmaceuticals' is an essential part to ensure that the drugs are safe, efficient, suitable for their intended use, conform with the condition of the marketing authorisation and not harm to the consumers. Like many developing countries some of the marketed drugs in this city are substandard, falsified or counterfeits. Many reasons contributed to the entrance of low-quality drugs such as market forces, getting medicines at affordable prices due to low-income of most people, and inadequate resources for regulating and controlling the quality of pharmaceutics on the market. However, low-quality medicines pose many hazards to public health and many of them are sold without control particularly in developing countries (Pecoul *et al*.1999; WHO 2005).

The World Health Organization (WHO) stated guidelines for worldwide standard and specification for the registration, assessment, marketing, authorisation and quality control of generic medicinal products (WHO 2005; 1996). As reported in a previous study carried out in Aden city, 40% were fake or of low quality and 80% of medications pass into the country through illegal routes (Sallami *et al.* 2017). Also, storage conditions play an important role in drug stability. Due to the continuous shortage of electricity in this city, high temperature and humidity may lead to the decomposition of the active ingredients. Consequently, the aforementioned problems lead to deny the patients safe and effective therapy, expose patients to noxious impurities, participate in microorganism resistance, increased mortality and morbidity (Cockburn *et al*. 2005; Johnston and Holt 2014).

The primary physicochemical evaluation of medications has a significant indication of the quality of drug products. The bioavailability and bioequivalence of oral solid dosage forms *in vivo* can be estimated by *in vitro* dissolution testing (Itiola and Pilpel 1996).

The literature on the post-marketing surveillance of CIP in Yemen shows the presence of a study carried out in Sana'a City only for tablet dosage forms. The study indicated that all tested brands confirmed the pharmacopeia's specifications (Alyahawi and Alsaifi 2018). The current study conducted to evaluate the biopharmaceutical and physicochemical equivalence of the three available pharmaceutical dosage forms in the local markets (tablets, infusion and eye drops).

METHODS

Drugs and Chemicals

The standard of CIP-hydrochloride (HCl) was given as a gift from the Modern pharma-Yemen. Three commercially available brands of CIP for each dosage form were purchased from local community pharmacies in Aden. The most widely prescribed brands were selected, information related to them is summarised in Table 1. The brands were coded as I, II, III. Other chemicals were of analytical grads.

Table 1: Different brands of CIP dosage forms.

Brand code	Made in	Strength	Manufacture (Mfg) & expire (Exp) dates
Brands of CIP tablets			
Tablet-I	Germany	500 mg	Mfg. Aug. 2018 Exp. Jul. 2021
Tablet-II	India	500 mg	Mfg. Mar. 2018 Exp. Feb. 2021
Tablet-III	Yemen	500 mg	Mfg. Apr. 2017 Exp. Apr. 2020
Brands of CIP infusion			
Infusion-I	India	2mg/mL	Mfg. Jul. 2017 Exp. Jun. 2020
Infusion-II	India	2 mg/mL	Mfg. Apr. 2018 Exp. Mar. 2021
Infusion-III	India	2 mg/mL	Mfg. Nov. 2018 Exp. Oct. 2021
Brands of CIP eye drop			
Eye drop-I	Turkey	0.3%	Mfg. Feb. 2019 Exp. Feb. 2021
Eye drop-II	Saudi Arabia	0.3%	Mfg. May. 2018 Exp. May. 2020
Eye drop-III	India	0.3%	Mfg. Sep. 2018 Exp. Aug. 2021

Instruments

The information related to the instruments used in this study is listed in Table 2.

Table 2: List of instruments.

No.	Instrument	Made in	No.	Instrument	Made in
1	Conductometer	Inolabcond level 2, Germany	10	Electronic shaker	Patterson Scientific LTD, Germany, KS130
2	Disintegration tester	Pharma-Test-PTZ-Germany	11	Friability tester	THERMONIK, Campbell Electronics, Mumbai, India
3	Dissolution tester	ERWEKA, Germany	12	Hardness tester	PTB 311F, Germany
4	Electronic balance	A&D company LTD, Japan, HR-250	13	Thickness and diameter tester	PTB 311F, Germany
5	Electrical oven	VACIOTEM-T SELECTA, Spin	14	UV-visible spectroscopy	Lasany® advanced microprocessor UV-VIS-L1-295
6	pH meter	Inolab WTW, Germany	15	Ultrasonic	ROHS, China, 031

Methodology for Tablets

Weight variation test

The test conducted as stated in the United States Pharmacopeia-National Formulary (USP-NF) weight variation test. Twenty tablets from each brand were weighed individually by using an analytical balance. The average weight for each brand, as well as percentage deviations, were calculated by using the following formula.

$$Weight\ \ variation = \frac{A_w\ x\%}{100} \quad (1)$$

where
A_w = Average weight of the tablet
Upper limit = A_w + Weight variation
Lower limit = A_w – Weight variation

The tablet complies with the test if not more than two of the individual weights deviate from the average weight by more than 5%.

Furthermore, calculate the upper and lower limits at double the % difference allowed:

Upper limit = A_w + [(2x%/100) (W)]
Lower limit = A_w – [(2x%/100) (W)]

After that, the individual weights of tablets were compared to the upper and lower limits calculated at the % difference allowed and at double that percentage (Uddin *et al*., 2015; Uduma *et al*. 2011).

Diameter and thickness test

Tablet diameters and thickness were determined with a micrometre. Twenty tablets are dusted then individually placed between the calipers of the micrometre using forceps. The instrument gave a visual reading of tablet thickness. The allowed limit of thickness variation is ±5% of the size of the tablet.

Friability test

The evaluation of friability was carried out by Roche friabilator. It was performed by weighing 20 tablets (w_1) by placing them in the apparatus. The apparatus was rotated at a speed of 25 rpm per minute for 4 min. The tablets are exposed to rolling and operated shocks resulting from free falls within the apparatus. The tablets were dedusted and reweighed (w_2). The weight difference and percentage friability were calculated. According to USP-NF, weight loss should not be more than 1% (Swarbrick 2007; British Pharmacopeia 2016).

Percentage friability was calculated as:

$$Percentage\,friability = \frac{W_1 - W_2}{W_1}\ X\ 100 \quad (2)$$

Hardness test

To perform this test, a tablet was placed in electrically-operated hardness tester and the crushing strength that just causes the tablet to break is recorded. The procedure was repeated for 20 tablets. The acceptable limit for this test is 6 ± 2 kg/cm^2.

Disintegration test

This test was performed by taking six tablets from each brand and placing it in the disintegration apparatus. The time required for tables to break and pass through the sieve was taken as disintegration time. The test performed by placing one tablet in each tube form each brand and the basket rack was sited in a 1000 mL vessel encompassing 900 mL of water reserved at 37 ± 2°C. The basket holding the tablets was moved up and down through a distance of 5–6 cm at a frequency of 28–32 cycles per min. Perforated plastic discs were placed over each tablet to prevent floating. The apparatus was worked for 30 min. To obey the USP-NF standards, the tablets must fragment and all particles must pass via the10-mesh screen within 30 min. The residue remains should have a soft mass with no firm coated (Uduma *et al*. 2011; Swarbrick 2007).

Dissolution test

The dissolution test was carried out according to British Pharmacopeia (BP) (apparatus II [paddle method]). The dissolution medium was 900 mL of water which was maintained at 37± 0.5°C. The rotational speed of the apparatus was adjusted at 50 rpm. After 30 min, a 10 mL sample of the medium was withdrawn. After filtration, 0.5 mL of filtrate was taken and diluted to 50 mL with distilled water and measured the absorbance at the maximum at 278 nm, using dissolution medium in the reference cell. The percentage then calculated by comparing with the absorbance of standard CIP solution in water at the maximum at 278 nm using dissolution medium in the reference cell. The amount of CIP released is not less than 80% of the stated amount (British Pharmacopeia 2016).

Methodology for Infusions and Eye Drops

Measurement of pH

Approximately, 5–10 mL of the infusion and eye drops were put into a beaker. Then the pH of the infusion and eye drops samples was measured using pH meter, having an automatic temperature compensation (ATC) probe. The pH meter was calibrated using standard buffer solutions of pH 4.01, 7.00 and 10.01, before the measurements.

Total dissolved solids (TDS), conductivity and salinity

An increment of infusion and eye drops was taken into a small beaker and then parameters measured using conductometer. The same steps were repeated in measuring the remaining six samples. The measurement was carried in quintuplicate.

Density and specific gravity

The empty density bottle was washed with acetone weighed by using the electrical balance, then filled with water and weighed. After that, the bottle was washed with acetone and filled with infusion and weighed. The density and specific gravity were calculated. Then each of the remaining samples was weighed three times and the average was taken and density and specific gravity were calculated.

$$\text{Density } (\rho) = \frac{w_3 - w_1}{w_2 - w_1} - \text{x } \rho_{st} \quad (3)$$

where
w_1 = weight of the empty bottle
w_2 = weight of bottle with water
w_3 = weight of the bottle with the sample
ρ_{st} = density of water at 25℃ (0.99602 g/mL)

Viscosity

Ostwald was fixed on the holder and the time required for the fluid to pass the Ostwald was measured using the stopwatch. First, it was started with water as a standard solution with known viscosity and repeated three times. Then the same procedure was carried out for samples and calculated individually by the aid of density results which discussed previously.

$$\text{Viscosity } (\eta) = \eta_w \frac{t_{liq}\rho_{liq}}{t_w \rho_w} \quad (4)$$

where
t_{liq} = time of liquid
ρ_{liq} = density of liquid
t_w= time of water
ρ_w= density of water
η_W = viscosity of water

Determination of sodium chloride content in CIP infusion

Transfer 10 mL of sample solution to a suitable container, dilute with water to 150 mL, add 1.5 mL of potassium chromate (10%), and titrate with 0.1 N silver nitrate. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride (NaCl). Acceptance criteria: 85.5–94.5 mg (US Pharmacopeia 2016).

Drug content

A stock standard solution containing 50 µg/mL CIP-HCl was prepared by dissolving 10 mg of standard in water and diluting to the mark in a 200 mL calibrated flask. A series of CIP-HCl (3.5–11.5 µg/mL) were prepared and examined at max absorbance of 278 nm (Naveed and Waheed 2014). The procedure carried for tablet dosage forms, by weighing and then the average weight of ten tables was taken as the correct value. The tablets were

grained into a fine powder. An amount of the powder equivalent to the mean weight of one tablet was dissolved with 100 mL water (milli-Q) and sonicated for 10 min. The stock is further diluted to get the final concentration equal to 7.5 µg/mL, the solution was filtered before measuring the absorbance. A volume of CIP infusion and eye drop was diluted to get the final concentration equal to 6.0 µg/mL. The content was mixed and examined by spectroscopy.

RESULTS

Data of each performed test for each brand was recorded in MS-Excel® sheet and analysed.

Evaluation of Tablet Dosage Forms

The average weight and weight deviation of the different brands of CIP tablets are shown in Table 3. All tablets of all brands were conformed with the specification of USP for uniformity of weight which states that for tablets weighing more than 324 mg, the weight of not more than two tablets should not differ from the average weight by more than 5% (US Pharmacopeia 2007). All tablets length and thickness were within the recommended limits as it is represented in Table 3. The mean values of the friability of the various brands of CIP tablets examined shown in Table 3.

Table 3: Some quality control parameters for CIP tablets.

Brand	Average weight (gm), %RSD	Hardness (kg/cm²)% RSD	Friability (%)	Thickness(mm), %RSD	Length (mm), %RSD
Tablet-I	0.7476 ± 1.91	27.90 ± 0.25	0.013	6.552 ± 2.06	17.220 ± 0.058
Tablet-II	0.8648 ± 0.97	30.48 ± 0.12	0.115	6.192 ± 0.43	19.404 ± 0.182
Tablet-III	0.6909 ± 1.58	30.47 ± 0.15	0.337	5.257 ± 2.33	18.30 ± 0.046

Note: RSD = relative standard deviation

The mean values of the disintegration of the different brands of CIP tablets tested are shown in Table 4. The data of disintegration time (min) of CIP tablets were ranging from 1.20–7.31 min.

The data of the dissolution test are presented in Table 4. The obtained dissolution content at 30 min was within the range stated in pharmacopeias which stated that not less than 80% of the drug must be released. All the brands of the CIP tablets complied with the official specification for content uniformity.

Table 4: Result of dissolution test and disintegration time for CIP tablets.

Brand	Disintegration time, RSD	Dissolution test %, RSD
Tablet-I	1.20 ± 0.12	97.68 ± 0.72
Tablet-II	6.11 ± 0.24	94.48 ± 1.93
Tablet-III	7.31 ± 0.43	86.55 ± 2.47

Note: RSD = relative standard deviation

Evaluation of CIP Infusion and Eye Drops

All examined infusion of CIP was containing NaCl, so to determine its concentration, an aliquot of infusion was titrated by using $AgNO_3$. The result of titration of all infusion brands was within the limit of 95%–105%. The result is shown in Table 5. The result of evaluating the viscosity revealed that all brand has a viscosity less than 1 cp which equal to 1 mPa/s as represented in Table 5.

All examined brands' pH was within the permitted limit. In the case of infusion, the allowed limit according to BP and USP is pH 3.9–4.5 and pH 3.3–3.9. *In vitro* experiments have demonstrated that solution pH values of 2.3 and 11.0 kill venous endothelium cells on contact. The nearer the pH value is to 7.4, the less the damage that occurs. However, all brands showed compatibility with the BP limits. The salinity of infusion should be 0.9 to be isotonic with blood, however, the only brand that showed this value was Infusion-I while the other two brands' values were 0.74 and 0.69 for Infusion-II and Infusion-III. The results are illustrated in Table 5.

Table 5: The physicochemical properties of CIP infusion and eye drops.

Property ± RSD	Infusion-I	Infusion-II	Infusion-III	Eye drop-I	Eye drop-II	Eye drop-III
NaCl%	97.56 ± 0.59	95.90 ± 1.04	95.57 ± 1.21	-	-	-
Density (gm/mL)	1.04 ± 0.002	1.043 ± 0.002	1.054 ± 0.004	1.056 ± 0.093	1.046 ± 0.386	0.955 ± 0.006
Sp. Gr	1.009 ± 0.002	1.009 ± 0.002	1.01 ± 0.002	0.995 ± 0.051	1.003 ± 0.005	1.004 ± 0.002
Viscosity (cP)	0.897 ± 1.91	0.973 ± 1.84	0.963 ± 1.06	0.977 ± 1.81	0.986 ± 0.799	0.860 ± 1.419
pH	4.54 ± 0.127	4.52 ± 0.49	4.57 ± 0.22	4.80 ± 0.72	4.65 ± 0.54	4.45 ± 0.79
Salinity	0.91 ± 0.64	0.74 ± 0.78	0.69 ± 0.00	0.4 ± 0.00	0.01 ± 0.00	0.30 ± 0.00
Conductivity (ms/cm)	2.11 ± 0.98	1480.33 ± 0.04	4.64 ± 1.39	1187 ± 0.47	13.13 ± 0.44	1106 ± 1.00
TDS (mg/mL)	1512 ± 0.07	74166 ± 0.21	916.67 ± 0.70	814.33 ± 0.07	9.00 ± 0.00	761.33 ± 0.15

Note: RSD = relative standard deviation; TDS = total dissolved solids

The result of the determination of CIP content by using UV-spectroscopy revealed that all brands were within the permitted limits. The result is represented in Table 6.

Table 6: Results of assay of pharmaceutical dosage forms by the UV-method.

Brand	Content ± SD
Tablet-I	102.0 ± 0.77
Tablet-II	101.6 ± 0.89

(continued on next page)

Table 6: (*continued*)

Brand	Content ± SD
Tablet-III	100.3 ± 1.250
Infusion-I	101.9 ± 0.57
Infusion-II	101.6 ± 0.41
Infusion-III	101.9 ± 0.55
Eye drop-I	102.4 ± 0.72
Eye drop-II	103.6 ± 0.61
Eye drop-III	102.1 ± 1.03

DISCUSSION

Evaluation of Tablet Dosage Forms

Any medicine, to be effective and safe, must possess all the characteristics of high quality that are compatible with the international pharmacopeias. According to the Pharmaceutical Manufacturers Association of U.S., "quality is the sum of all the factors which contribute directly or indirectly to the safety, effectiveness, and acceptability of the product" (Verpoorte and Mukherjee 2003). The percentage, quality and pureness of chemically and biopharmaceutical equivalent medicines should be identical. The content uniformity, disintegration and dissolution rates must be comparable (Dressman *et al.* 1998).

The uniformity of the weight of the tablet is a sign of good manufacturing practice (GMP) as well as the quantity of active pharmaceutical ingredients. Weight difference may result in an erratic therapeutic response (Gennaro 2000). The results from this study are similar to the previous study carried out by Alyahawi and Alsaifi (2018), where uniformity of weight was between 679.3 mg ± 2.63% and 842.7 mg ± 3.58%, indicated that all examined brands complied with the compendial specification for uniformity of weight.

The hardness test of the tablets is stated as a non-compendial test. It is a significant standard for tablets to resist fragmentation, abrasion or cracking under conditions of storage, transport and handling before storage (Rawlins 1977). It may also influence other characteristics such as friability and disintegration and dissolution release rate (Lachman, Liberman and Kanig 1986). Tablet hardness can be related to the difference in the criteria of excipients involved in the production formula of the different brands. Hardness values did not relate to friability values (Merchant *et al.* 2006). The limit range of hardness is between 4 and 10 kg/cm^2 (US Pharmacopeia 2007). The mean values of the hardness of the various brands of CIP tablets are illustrated in Table 3. Average hardness was found in the range of 27.90 kg/cm^2 to 30.48 kg/cm^2. The results indicated that all brands of CIP tablets were not in the limit. However, the current result is parallel with the previous study in Yemen which was between 20.03 kg/cm^2 and 31.535 kg/cm^2 (Alyahawi and Alsaifi 2018). Tablet hardness is not a definitive indicator of the tablet strength because the power of tablets when pressed to very hard tablets, may lose their crown part. Therefore, another parameter of the tablet strength, its friability is required. The loss due to abrasion is a measure of the tablet friability. The pharmacopeia states that the friability value of tablets should be not more than 1% and as such, all the brands of CIP were passed this friability specification (US Pharmacopeia

2007). The Tablet-I had a low value that means the highest resistance to abrasion. The result is similar to the previous study in Yemen with the friability range between 0.01% and 0.37%.

Tablet disintegration time is one of the very important physicochemical characteristics in solid dosage forms. The disintegration test measures the time required for tablets to disintegrate into particles. This is a significant condition for dissolution could be the rate-determining step in the drug absorption step. Disintegration must be directly correlated to the dissolution and consequently with the bioavailability of the drug (Niazi 2007). All brands of the CIP tablets compliment the pharmacopeia requirements which specify a disintegration time of not more than 15 min for uncoated tablets, while the USP requirement for disintegration is 30 min both for uncoated and film-coated tablets. All the brands complied with both BP and USP stipulations.

The dissolution test is also vital parameters that specified the release of medicine from the dosage form and be accessible for subsequent gastrointestinal tract (GIT) absorption at a specific time. This test is considered a sensitive test for distinguishing between formulations of the same medicine (Hsu and Ayres 1989; Bruntion 1991). The proposed therapeutic effect would not be obtained if the medicine has a poor dissolution profile (Giri *et al.* 2012). Dissolution testing, a surrogate marker for bioequivalence test, is a very practical and economic approach to identify bioavailability problems and evaluate the need for in vivo bioavailability (Shah 2001). Consequently, the *in vitro* dissolution is a vital tool in measuring the *in vivo* performance and also helps to recognise unacceptable or sub-standard drug products. Delay of the release of drugs from the tablet may lead to the sub-therapeutic level of the drug in plasma resulting in the retardation in the onset of action or short duration of action or no therapeutic action. Furthermore, the sub-therapeutic level of antibiotic in the body could be a cause for the development of drug resistance, a major problem of antibiotics (Campoli-Richards *et al.*1988; Hyatt, Nix and Schentag 1994).

All the brands of the CIP tablets complied with the official specification for content uniformity. Of note, the Tablets-I and -II were completely dissolved while in the case of Tablet-III, the tablets were not completely dissolved a small palpable part remained after 30 min. The result from the previous study carried in Yemen was more than 80% drug release after 30 min.

Evaluation of CIP Infusion and Eye Drops

The content of NaCl was determined as part of the quality control of the IV dosage form. Usually, NaCl is added to the IV solution to preserve its osmolarity. NaCl 0.9% solution is iso-osmotic with blood and the venous endothelium; the solution leads to no movement of water into or out of endothelial cells. Cellular damage does not occur when endothelial cells contact an iso-osmotic solution. The result of titration of all infusion brands was within the limit of 95%–105%.

In the preparation of ophthalmic solutions, an appropriate thickening agent is often added to increase the viscosity. Although they lessen surface tension significantly, their main advantage is to rise the ocular contact time, thus reducing the drainage rate and increasing drug bioavailability and control the rate at which the drop flows out of the container (and thus enhance ease of application). The other advantage of most of the thickening agents is a lubricating effect. For instance, it has been revealed that the holding of an aqueous solution within the precorneal region is short (frequently less than 1 min); but, if the viscosity is increased, the retention may be enhanced. The optimal viscosity for ophthalmic solutions is in the range of 15–25 centipoises (cp) (Allen, Popovich and Ansel 2005; Gibson 2007). The corneal contact time of topical ophthalmic solutions increases

with the viscosity of the formulations up to 20 cp. Additional increases lead to reflex tearing and blinking to recover the original viscosity of the lacrimal fluid (1.05–5.97 cp). The result from this study showed that all brand has a viscosity less than one cp which equal to one mPa/s, that means all brands viscosity is below the allowed limit maybe because viscosity is formulation dependent, it is not part of an official monograph for ophthalmic products but it is part of the manufacturer's specification of the drug product.

The pH scale is a measurement of the concentration of hydrogen ions (H^+) in a solution. The normal physiological pH of the ocular surface in humans is noted to be 7.11 ± 1.5. Control of pH by the addition of buffers is essential not only for comfort but also for drug stability and solubility. Because the buffering capacity of tear fluid is very low, ophthalmic formulations contain excipients that maintain a pH range of 4.75 to 7.40. The recommended pH value for the CIP eye drops form BP and USP is 3.9–4.5 and 3.5–5.5, respectively (British Pharmacopeia 2016; US Pharmacopeia 2016). However, all brands showed compatibility with the BP limits.

Generally, a range of 0.5% to 2% saline tonicity is well-tolerated. Irritating hypertonic solutions can induce tearing, which increases tear outflow and decreases the concentration and efficacy of the drug in the tears, while hypotonic solutions are often used effectively in tear substitutes to compensate for the high tonicity in the tears of dry-eye subjects (WHO 2018). The salinity of infusion should be 0.9 to be isotonic with blood, however, the only brand that showed this value was Infusion-I while the other two brands' values were 0.74 and 0.69 for Infusion-II and Infusion-III. There are no literature limits for the TDS and conductivity for eye drops and infusion. The results of these parameters are illustrated in Table 5.

As stated in the USP, CIP content should contain not less than 90 % and not more than 110% and according to BP, the allowed range is 95%–105%. The result revealed that all brands were within the permitted limits.

CONCLUSION

The objective of the present study was the evaluation of the quality control characteristics of the different pharmaceutical dosage forms of CIP present in Aden-Yemen markets. All the dosage forms displayed homogeneity in terms of the active ingredient, and other *in vitro* quality control tests. However, all tablets showed the hardness value that exceeds the recommended specification. The value of the salinity of two infusion dosage forms was lower than 0.9, as well as, the viscosity of the eye drops was lower than one. The in confirmation of these parameters may be due to the effect of the formulation ingredients which have a significant influence on the quality parameters and physicochemical properties (Ofori-Kwakye, Osei-Yeboah and Kipo 2010). Post-marketing surveillance is a must to weed out substandard and counterfeit medicine from the local markets.

ACKNOWLEDGEMENTS

The authors acknowledge the help of the Supreme Board of the Drug and Medical Appliances in Aden and its staff and Bachelor graduation students for their contribution to the accomplishment of this study.

REFERENCES

ALLEN, L. V., POPOVICH, N. G. & ANSEL, H. C. (2005) *Ansel's pharmaceutical dosage forms and drug delivery syste*ms, pp. 540–569 (Baltimore: Lippincott Williams & Wilkins).

ALYAHAWI, A. & ALSAIFI, A. (2018) Quality control assessment of different brands of ciprofloxacin 500 mg tablets in Yemen, *Universal Journal Pharmaceutical Research*, 3(4): 31–36.

BEDOR, D. C. G., GONÇALVES, T. M., BASTOS, L. L., SOUSA, C. E. M. D., ABREU, L. R. P. D., OLIVEIRA, E. D. J. et al. (2007) Development and validation of a new method for the quantification of norfloxacin by HPLC-UV and its application to a comparative pharmacokinetic study in human volunteers, *Revista Brasileira de Ciências Farmacêuticas*, 43(2): 231–238. https://doi.org/10.1590/S1516-93322007000200009

BRITISH PHARMACOPEIA (2016) *Ciprofloxacin tablets,* volume III, pp. 327–328 (London: Medicines and Healthcare Products Regulatory Agency).

BRUNTION, L. L. (1991) *The pharmacological basis of therapeutics*, 8th edition, pp. 926–928 (New York: Pergamon Press).

CAMPOLI-RICHARDS, D. M., MONK, J. P., PRICE, A., BENFIELD, P., TODD, P. A. & WARD, A. (1988) Ciprofloxacin: A review of its antibacterial activity, pharmacokinetic properties and therapeutic use, *Drugs*, 35(4): 373–447.

COCKBURN, R., NEWTON, P. N., AGYARKO, E. K., AKUNYILI, D. & WHITE, N. (2005) The global threat of counterfeit drugs: Why industry and governments must communicate the dangers, *PLoS Medicine*, 2: 302–308. https://doi.org/10.1371/journal.pmed.0020100

DRESSMAN, J. B., AMIDON, G. L., REPPAS, C. & SHAH, V. P. (1998) Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms, *Pharmaceutical Research*, 15(1): 11–22. https://doi.org/10.1023/A:1011984216775

GENNARO, A. R. (2000) *Remington: The science and practice of pharmacy*, 20th edition (New York: Lippincott Williams & Wilkins).

GIBSON, M. (2007) Ophthalmic dosage forms, IN: M. Gibson (Ed.) *Pharmaceutical preformulation and formulation*, pp. 459–489 (New York: Informa).

GIRI, T. K., PARVEEN, N., THAKUR, D., ALEXANDER, A., BADWAIK, A. H. & TRIPATHI, D. K. (2012) *In vitro* evaluation of commercially available enteric coated tablet containing diclofenac sodium, *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 3(2): 875–881.

HAMAM, H. A. B. (2014) Comparative *in vitro* evaluation of generic ciprofloxacin hydrochloride tablets, *World Journal of Pharmacy and Pharmaceutical Sciences*, 3(12): 388–390. http://dx.doi.org/10.13040/IJPSR.0975-8232.1(8).51-57

HSU, H. & AYRES, J. W. (1989) Chlorpheniramine dissolution and relative urinary exerction from commercial products, *Journal of Pharmaceutical Sciences*, 78(10): 844–847. https://doi.org/10.1002/jps.2600781013

HYATT, J. M., NIX, D. E. & SCHENTAG, J. J. (1994) Pharmacokinetic and pharmacodynamic activities of ciprofloxacin against strains of *Streptococcus pneumoniae, Staphylococcus aureus* and *Pseudomonas aeruginosa* for which MICs are similar, *Antimicrobial Agents and Chemotherapy*, 38(12): 2730–2737. http://doi.org/10.1128/AAC.38.12.2730

ITIOLA, O. A. & PILPEL, N. (1996) Effects of interacting variables on the disintegration and dissolution of metronidazole tablets, *Pharmazie*, 51: 987–989.

JOHNSTON, A. & HOLT, D. W. (2014) Substandard drugs: A potential crisis for public health, *British Journal of Clinical Pharmacology*, 78(2): 218–243. https://doi.org/10.1111/bcp.12298

LACHMAN, L., LIBERMAN, H. & KANIG, J. (1986) *The theory and practice of industrial pharmacy*, 3rd edition, pp. 293–373 (Philadelphia: Lea & Febiger).

LODE, H. & ALLEWELT, M. (2002) Role of newer fluoroquinolones in lower respiratory tract infections, *Journal of Antimicrobial Chemotherapy*, 49(5): 709–712. https://doi.org/10.1093/jac/dkf133

MERCHANT, H. A., SHOIAB, H. M., TAZEEN, J. & YOUSUF, R. I. (2006) Once-daily tablet formulation and *in vitro* release evaluation of cepfodoxime using hydroxypropyl methylcellulose: A technical note, *Journal of American Association of Pharmaceutical Scientists*, 7(3): E178–E183. https://doi.org/10.1208/pt070378

NAVEED, S. & WAHEED, N. (2014) Simple UV spectrophotometric assay of ciprofloxacin, *Mintage Journal of Pharmaceutical and Medical Science*, 3(4): 10–13.

NIAZI, S. K. (2007) *Handbook of bioequivalence testing*, 1st edition (New York: Informa Healthcare).

OFORI-KWAKYE, K., OSEI-YEBOAH, F. & KIPO, S. L. (2010) Formulation and quality evaluation of two conventional release tablet formulations, *International Journal of Pharmaceutical Sciences Review and Research*, 4(1): 94–99.

PECOUL, B., CHIRAC, P., TROUILLER, P. & PINEL, J. (1999) Access to essential drugs in poor countries: A lost battle? *American Medical Association*, 281: 361–367.

RAO, N. R. & NAGARAJU, V. (2004) Separation and determination of synthetic impurities of norfloxacin by reversed-phase high performance liquid chromatography, *Journal of Pharmaceutical and Biomedical Analysis*, 34(5): 1049–1056. https://doi.org/10.1016/j.jpba.2003.11.009

RAWLINS, E. A. (1977) *Bentley's text book of pharmaceutics*, 8th edition, pp. 289–290 (London: Bailliere Tindal Publisher).

SALLAMI, Z., KASSIM, Y., SELVARAJ, J., PARRY, E. & WINTER, G. (2017) Impact of the armed conflict of 2015–2016 in Aden on health services and the availability of medicines, *Health*, 9: 685–696. http://creativecommons.org/licenses/by/4.0/

SHAH, V. (2001) Dissolution: A quality control test vs a bioequivalent test, *Dissolution Technologies*, 8(4): 1–2. http://doi.org/10.14227/DT080401P6

SWARBRICK, J. (2007) Encyclopedia of pharmaceutical technology, 3rd edition (New York: Informa Healthcare).

THE UNITED STATES PHARMACOPEIA (2007) *National formulary, Vol. 4, Uniformity of dosage units (905)*, p. 736 (Rockville (MD): United States Pharmacopeial Convention).

THE UNITED STATES PHARMACOPEIA (2016) *National formulary, Vol. 2, Ciprofloxacin*, p. 3164. (Rockville (MD): United States Pharmacopeial Convention).

UDDIN, M. S., MAMUN, A. A., TASNU, T. & ASADUZZAMAN, M. (2015) In-process and finished products quality control tests for pharmaceutical tablets according to pharmacopoeias, *Journal of Chemical and Pharmaceutical Research*, 7(9): 180–185. https://doi.org/10.9734/BJPR/2016/22044

UDUMA, E. O., AYODEJI, A. A., ROSEMARY, C. A., OKORIE, O. & CHRISTIAN, C. O. (2011) Bioequivalence studies on some selected brands of ciprofloxacin hydrochloride tablets in the Nigerian market with ciproflox ® as innovator brand, *Journal of Applied Pharmaceutical Sciences*, 1(6): 81–83.

VERPOORTE, R. & MUKHERJEE, P. K. (2003) *GMP for botanicals: Regulatory and quality issues on phytomedicines*, pp. 383–383 (New Delhi: Business Horizons).

WORLD HEALTH ORGANIZATION (WHO) (2018) High levels of antibiotic resistance found worldwide, new data shows. https://www.who.int/mediacentre/news/releases/2018/antibiotic-resistance-found/en/ (14 July 2020).

WORLD HEALTH ORGANIZATION (WHO) (2005) *Regional strategy for improving access to essential medicines in the Western Pacific Region 2005–2010* (Geneva: World Health Organization).

WORLD HEALTH ORGANIZATION (WHO) (1996) *Technical report series 863. Expert committee on specifications for pharmaceutical preparations: 34th report* (Geneva: World Health Organization).