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AAA conceived and designed the study. FAM performed the assay test with HPLC, and HMD studied the physical properties and UV experiments. AAN and MMA analyzed data, wrote and revised the paper.

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A Comparative Study to Assess the Quality of Different Marketed Brands of Metformin HCl

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Abstract:

The present work reported quality assessments and stability studies of metformin hydrochloride in various brands with a label claim of 500 mg marketed in the capital Sana'a, Yemen. Physical parameters including thickness, diameter, hardness, friability, weight variation, and disintegration time were evaluated. Assay tests and dissolution rates were carried out using HPLC-UV and spectrophotometric methods respectively. All investigations were done at purchase time and after one month, three months, and six months storage conditions under an accelerated stability environment (40±2°C and 75±5% RH). The results showed that all brands of metformin hydrochloride complied with the official specification for thickness, diameter, hardness, friability, weight variation, disintegration time, dissolution, and assay tests. Assay evaluation results revealed that all tested brands have met the acceptance criteria (95%-105%) with exception of ME1 samples stored for three months whose values (94.29%) were lower than the acceptable limit and ME4 (105.95%) and ME5 (105.66%) stored for one month that was higher than the acceptable range.

INTRODUCTION

Metformin HCl is an oral anti-diabetic drug from the biguanide class in the form of monohydrochloride and it is available in different brand names and different strengths (Papanas and Maltezos, 2009). World Health organization lists metformin HCl as an essential drug for the treatment of overweight and obese patients suffering from type 2 diabetes (WHO, 2019; Chaudhury *et al.,* 2017). Scientific reports conclusively show that metformin HCl minimizes cardiovascular complications of diabetes, helps to reduce LDL cholesterol and triglyceride levels, and limits weight gain in patients during use (Williams and Agbotse, 2013).

Drug stability is an essential parameter that has to be evaluated carefully to ensure drug efficacy and improve safety (Ali *et al.,* 2016; Ali *et al.,* 2017; Madni *et al.,* 2016,17; Tawfik, 2017) because many pharmaceutical drugs are vulnerable to degradation during packing, shipping, and storage (Zothanpuii *et al.,* 2020). The physical and chemical degradations could result in an unwanted alternation of the pharmacological properties of the drugs (Akash, 2020).

Metformin HCl chemically, is N,N-dimethylimidodicarbonimidic diamide and has a molecular formula of $C_4H_{11}N_5$.HCl. Metformin hydrochloride is freely soluble in water and practically insoluble in acetone, and chloroform. The chemical structure of metformin HCl is shown in figure 1 (Gul, 2016).

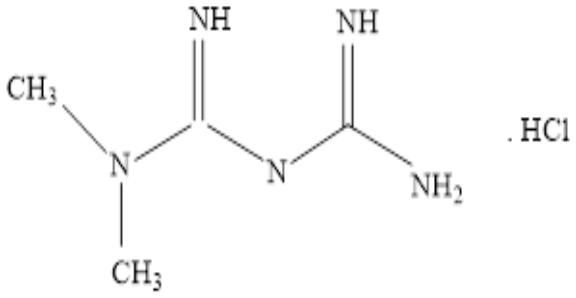

Fig. 1. Chemical structure of metformin HCl.

The stability parameters that affect drug quality and safety include physical properties of the drug such as shape, color, dissolution, and friability. Chemical reactivity under the influence of an acid/base hydrolysis, oxidizing agent, temperature, humidity, and photolysis is another factor that has to be considered (Yasmeen and Sofi, 2019). The physical and chemical properties of the drug product are not only governed by the properties of the active pharmaceutical ingredient (Aashigari *et al*., 2018) API, but also by those of the additives as well as by the manufacturing methods, diffusion of the drug, the nature of packing materials, the environmental conditions and the type of storage containers (Bhagyashree *et al.*, 2015). The evaluation of the drug properties can be performed through in-vivo and in-vitro tests. In vitro evaluations are performed according to the official pharmacopeia (USP 39, 2016) and usually confirm the physical parameters of pharmaceutical products such as diameter, thickness, hardness, friability, weight variation, disintegration time, assay, and dissolution tests (Sultana and Hosen, 2018).

In-vitro stability studies on metformin HCl under different environmental conditions have been carried out on different brands and in different countries such Syria (Mansour *et al.*, 2018, Mexico (Alemón-Medina *et al.*, 2014) and Addis Ababa. Bangladesh (Kassahun *et al.*, 2019). These reports reveal that the stability and quality of metformin HCl vary depending on its brands and storage conditions under which this investigation was performed.

Yemen is a low-income country with critical health challenges, including a high incidence of both communicable and non-communicable diseases and the lack of a systematic plan to monitor adverse drug reactions and drug-related problems (Yousuf *et al.*, 2019). Yemen exhibits a higher prevalence of lifestyle risk factors due to the civil war that has been taking place since 2014 which deteriorates further the already weak health system. As a result, the public is faced with many health challenges related to drug smuggling, counterfeit drugs, importation of unnecessary drugs, irrational use of medicines, medical errors, and other drug-related problems.

Some studies indicated that that about 60% of all imported medicines in Yemen come through illegal channels (Alshami and Azm, 2014), which results in a serious threat to the health of the public. The drug safety challenges in Yemen should be faced with cooperative efforts from the drug authorities in the country, local industries, and the scientific community. Thus, the present study came in this context and shed some light on the stability of the anti-diabetic drug, metformin HCl (500 mg tablets) from different brands available in the Yemeni market. Furthermore, and to the best of our knowledge, the literature survey did not show any related studies on the stability of metformin HCl marketed in Yemen and stored under accelerated storage conditions.

MATERIALS AND METHODS

Ethical approval

The protocol of this work was approved by the Ethics Committee of the Sana'a University.

Drug

Metformin HCl Standard was purchased from Exemed, India.

Dosage form

Six brands of metformin HCl tablets with a label claim of 500 mg were purchased from local pharmacies in Sana'a city-Yemen.

Chemicals

All chemicals were of analytical grade. Monobasic ammonium phosphate was purchased from Safc Pharm, USA. Phosphoric acid, monobasic potassium phosphate, and sodium hydroxide were obtained from Scharlau, Spain. Deionized water was prepared in-house using Millipore Mill-Q water system (Watford UK).

Equipment

HPLC Waters 2695 (Waters, USA) equipped with an autosampler and PDA detector, UV/ visible Spectrophotometer (Varian, cary 50 Cocc USA), Stability Cabinet (Lab Tech, Korea), Analytical Balance (Mettler Toledo, USA), Semi microbalance 0.01mg (Mettler Toledo, USA), pH-meter (Jenway, Britain), Ultra Sonic bath (Sapeen, China), Hardness apparatus (Pharm Test, Germany), Friability apparatus (Pharm Test, Germany), Disintegration apparatus (Pharm Test, Germany) were used.

Chromatographic Conditions

The chromatographic assay of metformin HCl was achieved on a Chromolith (150 mm - 4.6 mm i.d. 5 µm Particle size) (Thermos Scientific, Germany) Scx biobasic column. Orthophosphoric acid adjusted to pH 3 was used as a mobile phase and was pumped at a rate of 1 mL/min. at room temperature. The chromatogram was recorded by measuring the UV absorbance of the eluted analyte by a diode array detector at 218 nm. Diluted concentrations of working standard solutions and sample solutions were transferred into vials and placed into the auto-sampler. The injection volume of the auto-sampler was set at 20 µl for investigation.

Visual examination

The shape and color of the different brands of Metformin tablets were examined visually at the time of purchase, one month, three months, and six months storage time under accelerated conditions (40 ± 2 °C and 75 ± 5% RH).

Hardness, thickness, and diameter of the tablets

A pharm test apparatus (PTB 311E) was used to measure the thickness, diameter, and hardness of 10 tablets selected randomly from each brand. The tablets were placed between the jaws of the hardness tester individually as recommended (Elghnimi *et al.*, 2019). The pressure was increased until the tablets were broken. The thickness and diameter of tablets from each brand were also measured by the same apparatus at the same time. All the results were recorded and the mean and the relative standard deviation for hardness, thickness, and diameter were calculated.

Friability Test

A single-drum tablet friability apparatus was used to measure the friability of 10 whole tablets. The initial weight (W_i) of the tablets was recorded to the nearest 0.1 mg, then the tablets were placed in the drum. The drum was set to rotate at 25 rpm for 4 minutes (Chavan *et al.*, 2018). The final tablets' weight (W_f) was recorded accurately after removing the loose dust. The percentage of weight loss (% friability) was calculated using the following equation.

Percentage friability % = $[(W_i-W_f)/W_i]*100$

Where: W_i the initial weight, and W_f the final weight.

Weight variation test

Twenty tablets from a particular brand were randomly selected and weighed collectively to obtain a mean weight (Gupta and Gupta, 2016). The tablets were then weighed individually and the mean and standard deviation of each tablet was then calculated. This method was repeated for all other brands.

Tablet disintegration

Six tablets of each brand were placed in a disintegration apparatus filled with distilled water at 37±0.5°C. The apparatus was set to rotate at 30 rpm. The tablets were considered completely disintegrated when all formed particles passed through the wire10- mesh (Desai *et al.*, 2016). The time taken to break each tablet into small particles to pass through the mesh was recorded and the meantime and standard deviation were calculated.

Dissolution test

The dissolution test was performed using USP apparatus 1 (basket). The dissolution medium was 1000 mL of phosphate buffer (pH 6.8), and the basket speed was set to 100 RPM. One liter of the medium was placed in each vessel of the dissolution apparatus, and then the dissolution medium was equilibrated to 37±0.5°C. One tablet was placed in each vessel of the dissolution apparatus. After 45 min., the sample was withdrawn from each vessel, filtered using 0.45 µm filter paper, and 1 mL of filtrate solution was transferred into a 50 mL volumetric flask. The flask was filled to the mark with phosphate buffer (pH 6.8) to make a final concentration of 0.01 mg/mL. The samples were analyzed spectrophotometrically against blank solution at 233 nm (USP 39, 2016). Then, the concentration of metformin hydrochloride in the samples was calculated.

Calibration Curve

To construct a calibration curve of standard metformin HCl, a stock solution of pure Metformin hydrochloride powder of concentration 0.1% w/v was prepared by dissolving 0.1g of pure metformin hydrochloride powder in 100 mL deionized water. A series of standard solutions with different concentrations (2.5-15 ppm) were prepared. The absorbance of each solution was determined spectrophotometrically at 233 nm against the blank.

Assay test

Twenty tablets of metformin hydrochloride were weighed and crushed to powder. An accurate powder mass equivalent to 50 mg of metformin HCl was weighed and was transferred into a 100 mL volumetric flask containing some buffer solution at pH 3. The content was shaken for 15 min until all solid was dissolved. The volume was brought to the mark by adding more buffer (pH=3). A volume of 1 mL was withdrawn from the prepared solution, filtered, and transferred to a 100 mL volumetric flask. Enough buffer (pH=3) was added to the mark to make a final concentration of 0.005 mg/mL metformin HCl (USP 39, 2016). A volume of 20 µL of 0.005 mg/mL metformin HCl solution was analyzed chromatographically at 218 nm using HPLC with PDA detector at a follow rate of 1 mL/ min of a mobile phase containing buffer solution (pH = 3).

Statistical analysis

The obtained data was analysed using SPSS to determine mean and RSD.

RESULTS AND DISCUSSION

The stability of selected tablets of metformin HCl was tested according to the International Conference on Harmonization guidelines ICH guidelines (ICH, 2003). The tablets were stored at accelerated temperature (40°C ± 2 and relative humidity (RH)75% ± 5%) for one, three, and six months.

Visual examination

The tablets looked good and non-sticky. The color and the shape of tablets were analyzed with the naked eye. The observation results showed that, no defects in the uniformity of color or shape within a single tablet, from tablet to tablet, or from batch to batch for all selected brands at all periods. The observation results were reported in (Table 1).

Table 1. Visual parameters for metformin HCl tablets at accelerated temperature (40 °C±2 and RH 75%±5%).

Code	Time	Color	Shape
ME1	zero time, one, three, and six months	White	Round
ME2	zero time, one, three, and six months	White	Round
ME3	zero time, one, three, and six months	White	Round
ME4	zero time, one, three, and six months	White	Round
ME5	zero time, one, three, and six months	White	Round
ME6	zero time, one, three, and six months	White	Capsule-shaped

Physical properties

The results of the physical properties of all tested metformin HCl brands were shown in (Table 2).

Thickness and diameter:

The thickness values of all brands were within the specification (±5%) variation of the standards (Zuheir *et al.*, 2017; Prithi *et al.,* 2018). Controlling thickness is essential. Thickness must be controlled to facilitate packaging (Uddin *et al*., 2016).

The USP specification of acceptable diameter is ≤ 13 mm (Al-Madhagi *et al*., 2016). Two of the tested brands (ME4 and ME6) had exceeded the acceptable limit, while the rest of the bands were within this specification at all accelerated conditions.

Hardness test:

The hardness of the metformin HCl tablet brands as presented in (Table 2) increased while the friability decreased generally with time across the accelerated conditions in which they were exposed. The lowest mean tablet hardness (117.56 N) for the ME4 sample at zero time was observed and the highest value (330.37 N) was recorded for ME6 at six months. Conventional compressed tablets that have crushing strength greater than 40 N are generally considered acceptable (Kassahun *et al.*, 2019).

Friability Test

Friability assessment is essential and reveals whether the tablets have good mechanical strength or not (Alam *et al.*, 2017). The values of friability in the present work were calculated for 10 tablets from each different brand. The data summarized in (Table 2) indicated that all brands at all storage conditions have met the acceptable friability criteria (< 1%) indicating the availability of good mechanical strength. Even though ME2 and ME5 samples at 6 months had shown minimum friability of 0.01% and ME1 had a maximum friability of 0.49% but all were still within the limit of specification (USP 39, 2016).

Weight variation Test

The results of weight variation tests shown in (Table 2) revealed that the average weight of all brands was> 324 mg and the calculated % deviation did not exceed the acceptable limit (<± 5%) indicating that all brands successfully passed the weight variation tests and comply with USP specification for weight uniformity (Chavan *et al.*, 2018; USP 39, 2016; Uddin *et al.*, 2016).

Disintegration Test

The summary of mean disintegration times of the different brands of metformin hydrochloride tablets was also shown in (Table 2). The observed disintegration times for all brands of Metformin hydrochloride investigated were less than the 30 min limit prescribed by the official pharmacopeia (Kassahun *et al.,*, 2019; Uddin *et al.*, 2016). All tablets of the different brands passed the disintegration tests. The fastest disintegrated tablets were the ME6 samples while the slowest times were observed for ME1 samples.

Calibration Curve

The calibration curve was constructed between the absorbance at 233 nm and concentrations of metformin HCl standard solutions (0-15 ppm). The data shown in Figure 2 revealed high linearity with R^2= 0.9999 over the tested range.

Dissolution test of metformin HCl by using UV-spectrophotometry

Dissolution rate signifies the amount of drug released over a specified time.

We have carried out dissolution tests on one tablet from each brand for 45 min under controlled conditions. Spectra were acquired at 233 nm. The dissolution rate (as %) was calculated using the following equation:

Result % = (r_u/r_s) X (C_s/L) X (V/D) X100

Where:

$\mathbf{r_u}$: Peak response from the sample solution.

$\mathbf{r_s}$: Peak response from the standard solution.

$\mathbf{C_s}$: Concentration of the standard solution in µg/ml.

L : label clam (mg/tablet)

V: Volume of medium (1000ml)

D: dilution factor of the sample solution

The obtained data were constructed in Figure 3. From these data, it could be concluded that the release of metformin hydrochloride from all brands tablet was immediate release and the percent of drug released at 45 minutes was more than 70%. Dissolution test results for all brands were in the range (97.65% - 105.27%) which indicated that all brands had met the pharmacopeia specification (> 70%) for dissolutions criteria (USP 39, 2016).

Assay test of metformin HCl by using HPLC:

HPLC is one of the most common methods used to analyze metformin HCl in biological fluids in addition to pharmaceutical products (Gul, 2016). In the present work, we have used HPLC for metformin HCl assay tests. The assay calculations were done using the following equation:

Assay % = (A_u/A_s) X (C_s/C_u) X100

Where:

$\mathbf{A_u}$: Absorbance of the sample solution.

$\mathbf{A_s}$: Absorbance of the standard solution.

$\mathbf{C_s}$: Concentration of standard solution in µg/ml.

$\mathbf{C_u}$: Concentration of standard solution in µg/ml.

The obtained assay data was summarized in Figure 4. It could be concluded from these data that all tested brands of metformin hydrochloride tablets showed values within the monograph specification 95% to 105% except ME1 sample after three months (94.29%), ME4 after one month (105.95%), and ME5 samples stored for one month (105.66%) were out the specified

limit. For comparison purposes, chromatograms of standard metformin HCl solution and ME1 solutions stored for 0, one month, 3 months, and 6 months were acquired and shown in Figure 5. The RSD for the peak areas of the standard solution (n=3) was 0.38 while for ME1 samples did not exceed 0.74% indicating high precession of the analytical procedure used for assay test.

Table 2. Comparative evaluation of physical parameters for all metformin HCl brands at accelerated (40°C±2 and RH75%±5%).

Code	Time	Thickness (mm)		Diameter (mm)		Hardness (N)		Friability (%)	Weight variation (mg)		Disintegration time (min)	
		Mean (n=10)	RSD %	Mean (n=10)	RSD%	Mean (n=10)	RSD %		Mean n=20	RSD%	Mean n=6	RSD %
ME1	zero time	5.61	1.25	12.20	0.36	199.17	6.26	0.49%	649.66	0.78	12.60	1.78
	1 month	5.65	0.88	12.29	1.83	261.22	1.50	0.26%	650.78	0.73	16.16	1.00
	3 months	5.78	0.73	12.23	0.26	270.93	0.52	0.08%	650 .37	0.67	18.44	2.05
	6 months	5.84	0.43	12.35	0.84	281.32	2.03	0.04%	648.50	0.77	20.87	3.27
ME2	zero time	4.68	2.99	12.18	0.62	140.09	21.07	0.03%	531.71	0.59	8.81	4.11
	1 month	4.67	0.91	12.21	0.12	157.27	9.02	0.02%	531.29	0.73	9.49	0.17
	3 months	4.67	0.27	12.20	0.11	157.30	8.13	0.02%	532.87	0.69	8.31	0.84
	6 months	4.67	2.18	12.31	1.82	158.26	10.09	0.01%	529.97	0.63	8.53	0.25
ME3	zero time	4.16	0.28	12.26	0.13	193.19	9.93	0.15%	554.30	1.20	10.34	0.79
	1 month	4.15	1.30	12.21	0.36	208.55	5.64	0.07%	557.63	0.84	10.50	0.88
	3 months	4.17	0.29	12.20	0.21	225.03	3.86	0.06%	557.05	0.68	8.20	1.34
	6 months	4.16	1.43	12.22	0.77	240.61	7.55	0.03%	557.41	0.59	8.44	0.90
ME4	zero time	4.66	0.69	13.34	0.23	117.56	6.72	0.07%	658.77	1.51	8.56	2.52
	1 month	4.82	1.23	13.39	0.24	247.27	8.99	0.06%	658.55	1.51	8.63	2.65
	3 months	4.86	1.85	13.35	0.56	268.27	5.42	0.06%	669.50	1.72	13.50	10.98
	6 months	4.90	0.69	13.38	0.45	286.13	2.98	0.05%	656.37	1.82	13.88	14.24
ME5	zero time	5.13	0.55	12.27	0.13	175.19	8.19	0.10%	554.62	1.69	7.45	0.47
	1 month	5.11	0.69	12.22	0.25	289.73	3.26	0.07%	556.02	1.80	8.30	1.35
	3 months	5.09	0.77	12.17	0.16	312.54	2.75	0.06%	558.53	1.59	10.50	2.09
	6 months	5.11	0.26	12.17	0.10	330.37	2.35	0.05%	554.40	1.98	12.09	3.47
ME6	zero time	5.43	1.41	18.89	1.29	177.30	2.36	0.41%	916.85	0.66	2.38	2.38
	1 month	5.44	1.37	19.11	0.85	183.10	3.92	0.24%	914.27	0.73	0.71	4.03
	3 months	5.63	0.60	19.45	1.11	236.52	8.88	0.07%	931.05	1.38	0.50	5.53
	6 months	5.67	1.85	19.54	0.87	272.68	3.94	0.04%	909.21	0.49	0.41	1.88
Acceptance value		± 5 % variation of a standard (Prithi *et al.*, 2018; Zuheir *et al.,* 2017)		less than 13 mm (Al-Madhagi *et al.*, 2016)		Greater than 40N (Kassahun *et al.,*, 2019)		less than 1% (USP, 2016)	±5% weight variation for weights >324 mg (USP 39, 2016)		less than the 30min (Kassahun *et al.,*, 2019)	

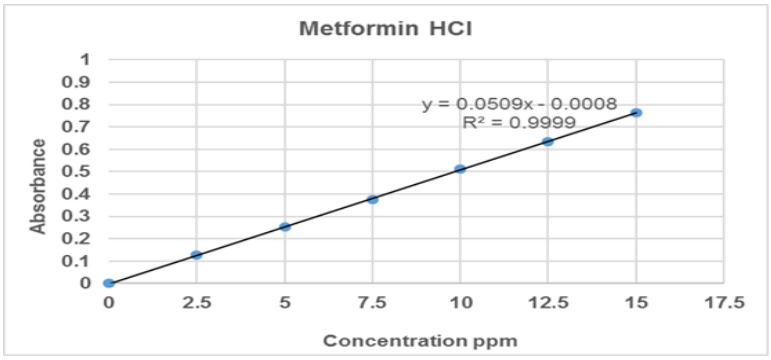

Fig. 2. Standard Calibration Curve of Metformin HCl

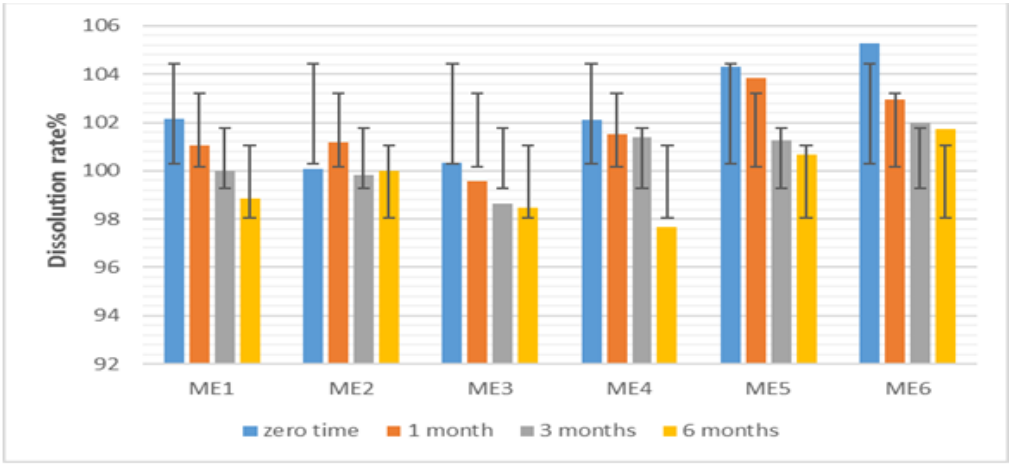

Fig. 3. Percentage of dissolution tests of different brands of metformin HCl before and after storage at stability conditions (40± 2°C and 75±5% RH).

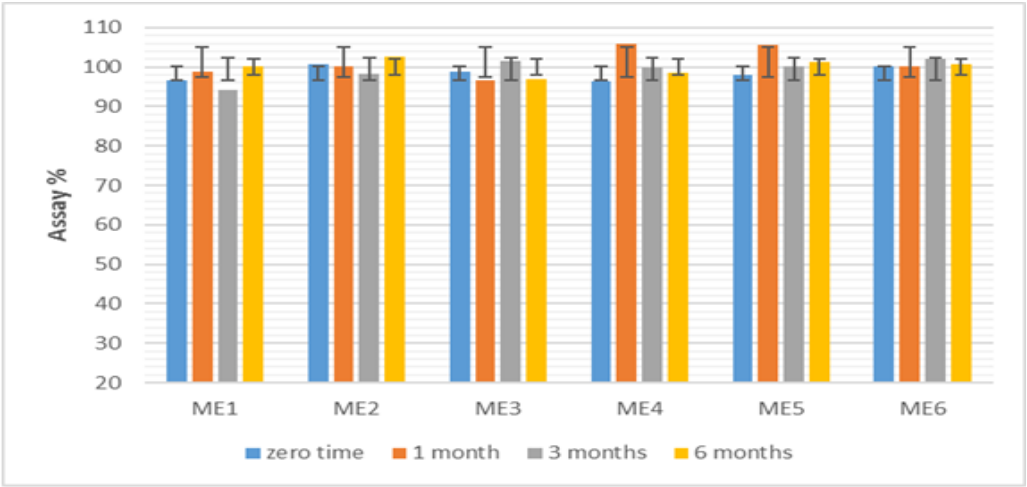

Fig. 4. Percentage of assay test of different brands of Metformin HCl. Data were acquired using HPLC. Conditions: Chromolith (150 mm-4.6 mm i.d, 5 µm particle size, flow rate 1 mL/min, buffer (pH =3) at room temperature, absorbance was recorded at 218 nm, injection volume was 20µL of 5 µg/mL (n =3).

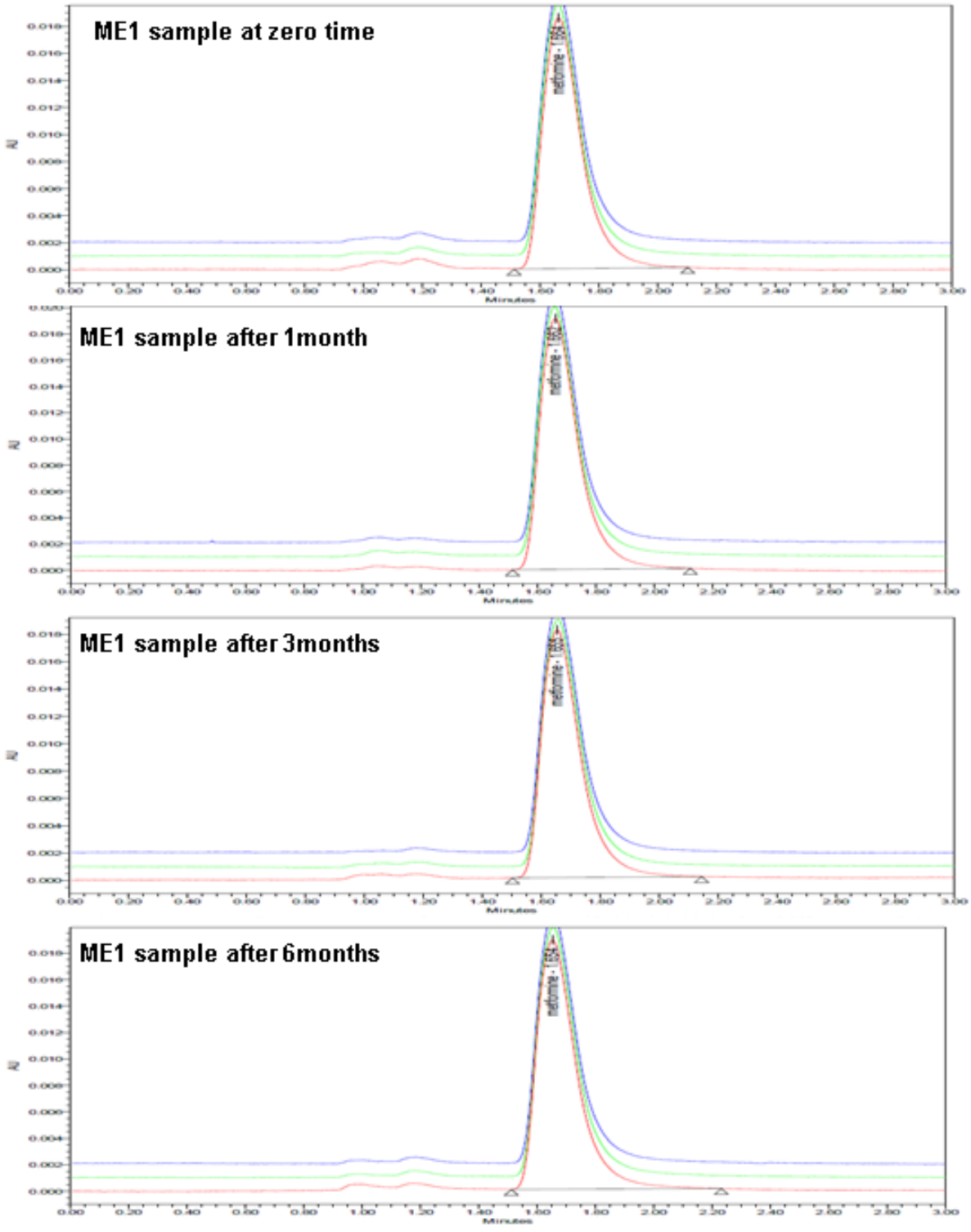

Fig. 5. Chromatograms of metformin hydrochloride standard solution, ME1 sample at zero time, one, three, and six months. Chromatographic Conditions: Chromolith (150 mm-4.6 mm i.d, 5 µm particle size, flow rate 1 mL/min, buffer (pH =3) at room temperature, absorbance was recorded at 218 nm, injection volume was 20 µL of 5 µg/mL.

CONCLUSION

The physicochemical evaluations at storage accelerated conditions of six different brands of metformin HCl tablets that were available in Yemen's market were assessed in this study. The physicochemical evaluation values were compared with the pharmacopeia standards and it was found that all brands of 500 mg metformin HCl tablet meet the pharmacopeia specification of different parameters. The results of various parameters for tablets like thickness, diameter, hardness, weight variation, friability disintegration time, drug assay, and dissolution studies were generally within the pharmacopeia limits.

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CONFLICT OF INTEREST

There is no conflict of interest.

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