dx.doi.org/10.14227/DT240217P22

Stability and In Vitro Dissolution Studies of Metronidazole Tablets and Infusions

Fadilah S. Aleanizy[1,*], Huda Al-Eid[2], Eram El Tahir[1], Fulwah Alqahtani[1], and Omaimah Al-Gohary[1]
[1]*College of Pharmacy, Department of Pharmaceutics, King Saud University, Riyadh, Saudi Arabia*
[2]*College of Pharmacy, Department of Pharmaceutics, Dammam University, Dammam, Saudi Arabia*

e-mail: faleanizy@ksu.edu.sa

ABSTRACT

The aim of this study was to compare metronidazole tablets (500 mg) and infusions (500 mg/100 mL) obtained from Saudi and Egyptian suppliers. Evaluation of the tablets included weight variation, hardness, friability, drug content, disintegration time, and dissolution profiles. Stability of the tablets in their original packages after 3-month storage at various temperatures (75% relative humidity) was evaluated, and degradation kinetics was determined. The infusion solutions underwent accelerated stability testing. The Q_{10} method was used to estimate the shelf life of metronidazole infusions at room temperatures (75% relative humidity) of various climates. Results revealed that all tablets complied with *USP* specifications, and degradation was slowest at room temperature (20 °C). The mechanism of drug release for all tablets at all temperatures conformed to the Korsmeyer–Peppas model. Metronidazole intravenous infusion solutions stored at 40 °C or 50 °C for 90 days exhibited good stability. The studied Saudi infusion brand is more stable than Egyptian one. The metronidazole tablets and infusion solutions complied with *USP* specifications and showed similar results in quality control testing. Standard quality control measures should be maintained to ensure safety and efficacy of drug products, especially in climates with extreme temperatures.

KEYWORDS: Metronidazole; Riazole; Amrizole; stability study; expiry date; infusion; quality control; dissolution.

INTRODUCTION

Metronidazole is classified as an antiamoebic, antigiardiasis, amoebicidal, antiprotozoal, and antibacterial drug in the World Health Organization's Essential Medicines List (*1*). Metronidazole is commonly used in combination with other antibiotics and either bismuth compounds or proton pump inhibitors to treat peptic ulcer disease caused by *Helicobacter pylori*. Metronidazole is also used to treat periodontal disease caused by *Gardnerella vaginalis* and infections caused by anaerobic bacteria including intra-abdominal infections, skin and skin structure infections, gynecological infections, bacterial septicemia, bone and joint infections, central nervous system infections, lower respiratory tract infections, and endocarditis (*2–4*). Metronidazole is rapidly absorbed, with a bioavailability approaching 100% (*5, 6*). The solubility of metronidazole in water at room temperature is 64.8 mg/mL at pH 1.2 and approximately 10 mg/mL at pH 2.5–8.0 (*7*).

The stability of a drug is a primary concern in climates with extreme temperatures. Previous studies (*8, 9*) have reported the stability and other quality control parameters of various brands of metronidazole tablets. In a study testing metronidazole tablets marketed in Zaria, Nigeria, only 60% of the tested metronidazole drugs passed the quality control test (*10, 11*). Another study testing the bioavailability of 10 brands of metronidazole tablets from different manufacturers reported wide variations in hardness, weight uniformity, friability, disintegration time, absolute drug content, and dissolution efficiency. Only some of the brands showed acceptable tablet characteristics. These results are clinically important because drugs are expected to conform to label claims and exhibit satisfactory bioavailability (*12–14*).

In this study, we evaluated the effect of temperature on the stability of two brands of metronidazole tablets and intravenous infusion solutions manufactured in Saudi Arabia and Egypt.

METHODS AND MATERIALS

Materials

Metronidazole tablets (Riazole 500 mg and Amrizole 500 mg) were kindly provided by Riyadh Pharma (Riyadh, Saudi Arabia) and Amriya Pharmaceutical Industries (Alexandria, Egypt), respectively. Metronidazole intravenous infusion solutions (500 mg/100 mL; sterile, nonpyrogenic) were kindly provided by Pharmaceutical

*Correspondence author

Solution Industry (Jeddah, Saudi Arabia) and Amriya Pharmaceutical Industries (Alexandria, Egypt). Distilled water was used to reconstitute metronidazole.

Storage of Metronidazole Tablets at Different Temperatures

All of the tested samples were within their shelf life and expiry dates. The tablets were stored at different temperatures (4, 20, and 40 °C) at 75% relative humidity (RH) for 3 months and then tested as follows.

Dissolution Test

Dissolution testing was conducted according to *USP 32* (*15*). Dissolution rates of metronidazole tablets were determined in 900 mL of HCl (0.1 M) at 37 ± 0.5 °C using an Erweka dissolution apparatus (Automated Dissolution Testing Apparatus Type I, Germany) at a rotational speed of 100 rpm. Triplicate samples (5 mL) were removed at 5-min intervals over 60 min and replaced immediately with an equal volume of 0.1 M HCl to maintain sink conditions. Three experimental runs were performed, and the results were averaged. The amount of metronidazole that dissolved over 60 min was determined by measuring absorbance at 277 nm using a UV–vis spectrophotometer (Spectro UV–VIS Auto Scanning UV–2602).

Hardness Test (Crushing Strength)

Tablet hardness was evaluated using an Erweka hardness tester. The average force required to break 10 randomly selected tablets of each metronidazole brand was calculated. *USP 32* states that a crushing strength of 4–8 kg is acceptable for uncoated, non-sustained-release tablets.

Disintegration Test

Six tablets from each metronidazole batch were placed in the six tubes of the apparatus and immersed in distilled water at 37 ± 0.5 °C. The time required for all six tablets to break into particles and pass into the disintegration medium was recorded. As specified by *USP 32*, if one tablet failed to disintegrate within 30 min, the disintegration test was repeated on 12 additional tablets. Sixteen of the 18 tablets tested disintegrated completely within 30 min.

Drug Content Test

All samples examined were within their shelf life and expiry dates. After storage at 4 °C (refrigerator), 20 °C (room temperature), or 40 °C (oven) at 75% RH for 1 week, 1 month, 2 months, or 3 months, the tablets were subjected to a drug content test ($n = 3$ for each condition). One tablet was transferred to a 250-mL volumetric flask with 100 mL diluted hydrochloric acid (1:100) and shaken for 30 min, according to *USP 32* specifications. The filtrate (100 mL) was transferred to a 100-mL volumetric flask, diluted to volume with 0.1 M HCl pH 1.2 (1:100), and mixed to obtain a solution that was approximately 0.2 mg/mL. The absorbance of this test solution and a standard solution of USP Metronidazole RS (approx. 20 µg/mL) in a 1-cm matched cell was determined concomitantly at 277 nm using a UV–vis spectrophotometer. Diluted hydrochloric acid (1:100) was used as a blank, and the mean of at least three absorbance readings was calculated. The quantity of metronidazole (mg) in the tablets was calculated using the following equation:

$$(TC/D)(A_u/A_s) \quad (1)$$

where T is the label quantity (mg), C is the concentration (µg/mL) of USP Metronidazole RS in the standard solution, D is the concentration (µg/mL) of the test solution, A_u is the absorbance of the test solution, and A_s is the absorbance of the standard solution. Acceptable values are 90–110% of the labeled amount.

Stability of Metronidazole Intravenous Infusion Solutions

The stability of the metronidazole intravenous infusion solutions was evaluated under accelerated storage conditions of 40 °C and 50 °C (75% RH) for 7, 30, 60, and 90 days. The shelf life under recommended storage conditions may be estimated by storing the product under extreme conditions (e.g., temperature, humidity, light, and radiation). Temperature is the most common acceleration factor for chemical, pharmaceutical, and biological products because its relationship with the degradation rate is characterized by the Arrhenius equation (eq 2).

Shelf life was estimated using the Q_{10} method, where Q_{10} is the factor by which the rate constant increases for a 10 °C rise in temperature. The absorbance of the samples in 0.1 N HCl was determined at 277 nm using a UV–vis spectrophotometer. Equation 17 describes the relationship between temperature and degradation rate, where A is absorbance, R is the rate, and T is temperature (°C).

$$k = A\, e^{(-Ea/RT)} \quad (2)$$

where A is the pre-exponential factor, E_a is activation energy, R is the universal gas constant, and T is temperature in degrees Kelvin.

$$\log k = \log A\text{-}(E_a/2.303\, RT) \quad (3)$$

For k_1 and k_2, we can rearrange in the following manner:

$$\log k_2/k_1 = -Ea/2.303\,R\,(1/T_2 - 1/T_1) \quad (4)$$

or $$\log k_2/k_1 = Ea\,(T_2 - T_1)/2.303\,RT_2T_1 \quad (5)$$

$$Q_{10} = e^{[-Ea/R\,(1/T+10 - 1/T)]} \quad (6)$$

or $$Q_{10} = e^{[Ea.10/R(T+10)T]} \quad (7)$$

For an arbitrary temperature change ΔT,

$$Q_{\Delta T} = e^{[Ea.\,\Delta T/R\,(T+\Delta T)\,T])} \quad (8)$$

Multiplying the exponential term by 10(T+10)/ 10(T+10), gives the following:

$$Q_{\Delta T} = e^{[Ea/R\,\{\Delta T.\,10(T+10)/\,(T+\Delta T)\,T.\,10\,(T+10)\}]} \quad (9)$$

or $$Q_{\Delta T} = e^{[Ea/R\,\{10/(T+10)T \times \Delta T(T+10)/\,(T+\Delta T)10\}} \quad (10)$$

or $$Q_{\Delta T} = e^{\{Ea/R\,\{10/(T+10)\,T\}\,[\Delta T(T+10)/\,(T+\Delta T)10]} \quad (11)$$

or $$Q_{\Delta T} = Q_{10}^{\,[(\Delta T/10)\,(T+10)/\,(T+\Delta T)]} \quad (12)$$

$T \equiv 300K$, $(T+10)/\,(T+\Delta T) \equiv 1$

(For a 10–20 °C interval, it is almost equal to 1.)

Therefore, $$Q_{\Delta T} = k_T + \Delta T\,/k_T = Q_{10}^{\,\Delta T/10} \quad (13)$$

In this way, for a 10–20 °C interval,

$$Q_{\Delta T} = Q_{10}^{\,\Delta T/10}$$

To evaluate the effect of temperature on shelf life, we can correlate the $Q_{\Delta T}$ value with shelf life. Degradation reactions generally follow zero-order, first-order, or pseudo-first-order kinetics. The shelf life in these cases is:

$$t_{90} = 0.1\,[D_0]/k_0 \quad (14)$$

where the degradation process is zero-order, and D_0 is the initial concentration,

$$t_{90} = 0.105/k_1 \quad (15)$$

where the reaction is a first-order process and 0.1, D_0, and 0.105 are the constants.

Therefore, shelf life can be written as $t_{90} = a / kT$.

For T_1 and T_2,

$t_{90}\,(T_1) = a / kT_1$ and $t_{90}\,(T_2) = a / kT_2$

Since, $T_2 = T_1 + \Delta T$,

$$t_{90}\,(T_2) = a / k\,(T_1 + \Delta T) \quad (16)$$

Using $k_{(T+\Delta T)}/k_T = Q_{10}\,\Delta T/10$ of eq 16 in the above equation, we get

$$t_{90}\,(T_2) = a\,/(kT_1.Q_{10}\,\Delta T/10\,)$$

Because $t_{90}\,(T_1) = a / kT_1$:

$$t_{90}\,(T_2) = t_{90}\,(T_1)/Q_{10}^{\,\Delta T/10} \quad (17)$$

The Q_{10} equation (eq 17) is independent of the order of reaction. Q_{10} has low, average, and high estimate values (2, 3, and 4, respectively). A zero- or first-order kinetics reaction occurs at elevated temperatures and at the recommended storage temperature. The same model was used to fit the degradation patterns at each temperature.

Kinetics Study

The in vitro release mechanisms of the drug in tablets and infusions were evaluated using four kinetic models (Table 1).

Table 1: Kinetic Models Used for the Analysis of Metronidazole Release

No.	Model name	Model
1	Zero order	$Q_t = Q_0 + K_0t$
2	First order	$\log Q_t = \log Q_0 + K_1t /2.303$
3	Higuchi	$Q = K_H\,t^{1/2}$
4	Korsmeyer–Peppas	$M_t / M_\infty = Kt^n$

Model parameters were obtained by linear regression. Q and M denote fraction of drug released up to time t, K is the rate constant, and n is the release exponent.

Statistical Analysis

Stability of the intravenous infusion solutions over time was analyzed using regression analysis.

RESULTS AND DISSCUSION

Characterization of Metronidazole Tablets

Figure 1 shows dissolution profiles of the 500-mg metronidazole tablets, demonstrating that dissolution was within *USP* limits (i.e., not less than 85% of the labeled amount of metronidazole dissolved in 60 min). However, dissolution fluctuated in tablets that were stored at 40 °C, because the dissolution medium pH was 1.5.

Table 2 shows the remaining drug (log percent) over time in tablets stored at 4 °C, 20 °C, or 40 °C (75% RH) for 3 months. The highest concentration of metronidazole in the tested tablets was 482 mg per tablet after storage at 20 °C for 7 days, and the lowest concentration was 339 mg per tablet after storage at 40 °C for 90 days. The drug content was highest when the tablets were stored

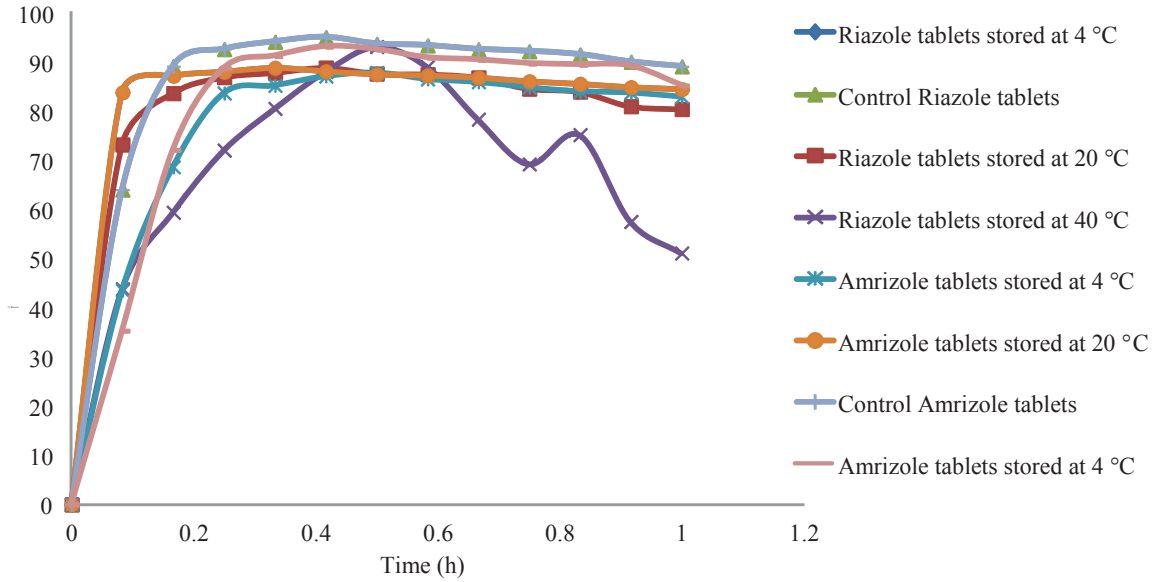

Figure 1. Dissolution profile of Riazole and Amrizole tablets after storage at 4 °C, 20 °C, or 40 °C and 75% RH for 3 months (n = 3).

Table 2. Drug Content of Two Brands of Metronidazole Tablets Stored at Accelerated Conditions[a] for Three Months

Drug remaining (%)														
	7 days		15 days		30 days		45 days		60 days		75 days		90 days	
Temp. (°C)	S	E	S	E	S	E	S	E	S	E	S	E	S	E
4	89	94.24	88	94.24	87	94.11	86.8	93.72	86	86.27	84	81.96	81	73.72
20	90	96.33	89	95.94	88	95.55	86	93.85	85	91.50	83	81.96	82	73.72
40	92	95.81	92	94.24	92	92.81	86	92.41	81	89.52	79	78.69	77	67.84

[a] 4, 20, or 40 °C and 75% RH
S = Riazole 500-mg tablet (manufactured in Saudi Arabia).
E = Amrizole 500-mg tablet (manufactured in Egypt).

Table 3. Testing Results and Estimated n Values[a] for Two Brands of Metronidazole Tablets Stored at 4, 20, or 40 °C (75% RH)

Sample	k (per day)		% Remaining		Half-life (days)		Mean disintegration (min)		Mean hardness (kg)		Estimated n value	
	S	E	S	E	S	E	S	E	S	E	S	E
Control	-	-	-	-	-	-	3.2	3	12.9	12.5	0.0206	0.0199
4 °C	0.0003	0.00088	89	94.24	947.091	343.501	4.6	3.7	15	14.2	0.0031	0.0030
20 °C	0.0005	0.00089	90	96.33	599.684	342.760	3.7	3	13	12.2	0.0269	0.0257
40 °C	0.0014	0.00103	92	95.81	275.700	293.119	2.5	2.7	10.9	11.9	0.1048	0.1026

S = Riazole 500-mg tablet (manufactured in Saudi Arabia).
E = Amrizole 500-mg tablet (manufactured in Egypt).
[a] according to the Korsmeyer–Peppas equation

at room temperature. As shown in Table 3, the hardness values of the tablets exceeded 4–8 kg, meeting *USP 32* specifications. Tablets stored at 4 °C had the highest hardness values (>14 kg). Disintegration times were longest for tablets stored at 4 °C (4.6 and 3.7 min for Amrizole and Riazole 500 mg, respectively) and shortest for tablets stored at 40 °C (2.5 and 2.7 min for Amrizole and Riazole 500 mg, respectively).

Kinetic Modeling of Metronidazole Release from Tablets

We tested zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetics models of metronidazole release from tablets using dissolution data and release data. The best-fit model with the highest correlation coefficient (R^2) was the Korsmeyer–Peppas model. The *n* values for all metronidazole tablets (stored at 4 °C, 20 °C, or 40 °C for

3 months) were less than 0.45, which indicates that the drug release mechanism was Fickian diffusion (i.e., net flux from regions of high concentration to regions of low concentration).

In the present study, dissolution tests of Riazole and Amrizole tablets met *USP* requirements at all storage temperatures (4 °C, 20 °C, and 40 °C, 75% RH) with few differences, indicating that metronidazole tablets are stable over a wide temperature range. However, the ideal storage temperature is 20 °C, and the tablets should not be stored in the refrigerator. These results are in accordance with the results of previous studies (*9, 16*).

Degradation Kinetics of Metronidazole Infusion Solution

In addition, the stability of Egyptian and Saudi metronidazole infusions (500 mg/100 mL) was studied at 37 and 50 °C (75% RH) over 7, 30, 60, and 90 days. The linear relationship between the logarithm of percent drug remaining and time indicates that degradation of metronidazole infusion solution follows pseudo-first-order kinetics (Figure 2).

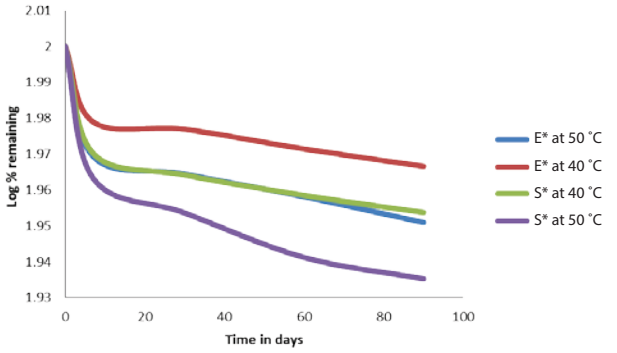

Figure 2. Pseudo-first-order degradation kinetics of metronidazole infusion solutions (S) manufactured in Saudi Arabia and (E) manufactured in Egypt stored at 40 °C or 50 °C.

Effect of Temperature on Shelf Life of Metronidazole Intravenous Infusion Solution

The effect of higher temperatures on the degradation of the two metronidazole intravenous infusion solutions was evaluated; degradation was more rapid at 50 °C than at 40 °C (Table 4). The shelf life at 40 °C was estimated at 1.9 years based on the rate constant at this temperature from eq 14, and the shelf life at 25 °C was calculated using eq 17. There are three estimates for shelf life at 25 °C because Q_{10} has three values to represent low, average, and high estimates. However, the activation energy indicated a lower estimate value. Using the Q_{10} value of 2 in eq 17, expiry dates for the Saudi brand (usually 6 months shorter than shelf life) were estimated at 4.15 years at 25 °C, 5.8 years at 20 °C, and 2.4 years at 33 °C, while the Egyptian brand showed different expiry dates that were 3.4 years at 25 °C, 4.8 years at 20 °C, and 1.9 years at 33 °C, where these represent room temperatures in the Asian subcontinent, winter zone, and tropical zone, respectively. Metronidazole intravenous infusion solutions stored at 40 °C or 50 °C over 90 days exhibited good stability. The rate constant values (Table 4) were used in modified Arrhenius equations to identify activation energy (E_a), which was 8.7 kcal/mole for this preparation throughout the accelerated stability studies. The infusion solution was clear, and the pH was within the *USP* range at 40 °C (6.11, 6.10, 6.11, 6.12, and 6.13) and 50 °C (6.11, 6.10, 6.08, 6.09, and 6.1) for 0, 7, 30, 60, and 90 days, respectively.

The degradation rate constants of the Saudi brand, determined from the slopes of the plots, were 19.5289 × 10^{-5} day^{s-1} and 34.5217 × 10^{-5} $days^{-1}$ for 40 °C and 50 °C, respectively. The Egyptian brand showed rate constants of 28.194 × 10-5 day-1and 41.225 × 10-5 day-1 for 40 °C and 50 °C, respectively, and the R^2 values of both regression lines were approximately 1.

Metronidazole intravenous infusion solution (500 mg/100 mL) exhibited good stability when stored at 40 °C or 50 °C (75% RH) for up to 90 days. Degradation followed pseudo-first-order kinetics. A previous study (*11*) reported degradation rate constants of 14.1604 × 10^{-5} and 30.1 × 10 5 day^{-1} for 40 °C and 50 °C, respectively.

CONCLUSION

The four commercially available metronidazole products manufactured in the Middle East were physically and chemically equivalent with few exceptions. The quality control methods used in this study are useful for monitoring batch-to-batch consistency of drug release. The therapeutic equivalence of the drugs must also be investigated by comparing their dissolution profiles.

ACKNOWLEDGMENTS

The authors thank Riyadh Pharma for their generous gift of metronidazole powder and tablets. The authors are grateful to the Research Centre of Science and Medical Studies Departments at King Saud University for their financial support.

CONFLICT OF INTEREST

The authors report no conflict of interest.

Table 4. Results of Accelerated Stability Tests and Calculated Half-Life of Metronidazole Intravenous Infusion Solution (100 mL) Stored at 40 °C and 50 °C

Time		50 °C			40 °C		
		Drug % mean	Conc. Mean	Abs. Mean	Drug % mean	Conc. mean	Abs. Mean
Control	S	0.674	500	100	0.674	500	100
	E	0.674	500	100	0.674	500	100
7 days	S	0.629	466.864	93.372	0.6193	459.446	91.880
	E	0.642	476.261	95.252	0.628	465.875	93.175
30 days	S	0.620	460.435	92.087	0.605	449.307	89.861
	E	0.639	474.035	94.807	0.621	460.682	92.136
60 days	S	0.612	454.500	90.901	0.588	436.696	87.339
	E	0.631	468.101	93.620	0.612	454.006	90.801
90 days	S	0.606	449.555	89.911	0.580	430.761	86.152
	E	0.624	462.908	92.581	0.602	446.587	89.317
		50 °C			40 °C		
K	S	19.5×10^{-5} days^{-1}			34.5×10^{-5} days^{-1}		
	E	28.2×10^{-5} days^{-1}			$41.23 \times 1^{0-5}$ days^{-1}		
t_{90}	S	1.0203 y			0.833 y		
	E	1.47365 y			0.697 y		

S = Riazole 500-mg tablet (manufactured in Saudi Arabia).
E = Amrizole 500-mg tablet (manufactured in Egypt).

REFERENCES

1. *WHO Model List of Essential Medicines*, 16th ed.; World Health Organization: Geneva, Switzerland, 2009. http://apps.who.int/iris/bitstream/10665/70642/1/a95055_eng.pdf (accessed Mar 8, 2017).
2. Robinson, S.; Meeks, T. W.; Geniza, C. Which Agents Work Best: FDA Approved and Off-Label Medications Help Patients Achieve Abstinence and Maintain Sobriety. *Curr. Psychiatry* **2014**, *13* (1), 22–32.
3. Wenisch, C.; Parschalk, B.; Hasenhündl, M.; Hirschl, A. M.; Graninger, W. Comparison of Vancomycin, Teicoplanin, Metronidazole, and Fusidic Acid for the Treatment of *Clostridium difficile*-Associated Diarrhea. *Clin. Infect. Dis.* **1996**, *22* (5), 813–818. DOI: 10.1093/clinids/22.5.813.
4. Zar, F. A.; Bakkanagari, S. R.; Moorthi, K. M. L. S. T.; Davis, M. B. A Comparison of Vancomycin and Metronidazole for the Treatment of *Clostridium difficile*-Associated Diarrhea, Stratified by Disease Severity. *Clin. Infect. Dis.* **2007**, *45* (3), 302–307. DOI: 10.1086/519265.
5. Lamp, K. C.; Freeman, C. D.; Klutman, N. E.; Lacy, M. K. Pharmacokinetics and Pharmacodynamics of the Nitroimidazole Antimicrobials. *Clin. Pharmacokinet.* **1999**, *36* (5), 353–373. DOI: 10.2165/00003088-199936050-00004.
6. *Remington: The Science and Practice of Pharmacy*, 21st ed.; Remington, J. P., Troy, D. B., Beringer, P., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2006.
7. Lachman, L.; Lieberman, H. A.; Kanig, J. L. *The Theory and Practice of Industrial Pharmacy*, 3rd ed.; Lea & Febiger: Philadelphia, 1986.
8. Musa, H.; Sule, Y. Z.; Gwarzo, M. S. Assessment of physicochemical properties of metronidazole tablets marketed in Zaria, Nigeria. *Int. J. Pharm. Pharm. Sci.* **2011**, *3* (Suppl. 3), 27–29.
9. Wu, Y.; Fassihi, R. Stability of metronidazole, tetracycline HCl and famotidine alone and in combination. *Int. J. Pharm.* **2005**, *290* (1–2), 1–13. DOI: 10.1016/j.ijpharm.2004.10.015.
10. Ibezim, E. C.; Attama, A. A.; Obitte, N. C.; Onyishi, I.; Brown, S. A. In vitro prediction of in vivo bioavailability and bioequivalence of brands of metronidazole tablets in Eastern Nigerian drug market. *Sci. Res. Essays* **2008**, *3* (11), 552–558. DOI: 1992-2248.
11. Shaheen, S. M. Accelerated Stability Study of Metronidazole Infusion 100 ml. *J. Teach. Assoc.* **2005**, *18* (2), 118–121.
12. Gad, S. C. *Drug Safety Evaluation*, 2nd ed.; John Wiley & Sons: New York, 2009.
13. Derendorf, H.; Lesko, L. J.; Chaikin, P.; Colburn, W. A.; Lee, P.; Miller, R.; Powell, R.; Rhodes, G.; Stanski, D.; Venitz, J. Pharmacokinetic/Pharmacodynamic Modeling in Drug Research and Development. *J. Clin. Pharmacol.* **2000**, *40* (12), 1399–1418. DOI: 10.1177/009127000004001211.
14. Lockwood, G. B. The quality of commercially available nutraceutical supplements and food sources. *J. Pharm. Pharmacol.* **2011**, *63* (1), 3–10. DOI: 10.1111/j.2042-7158.2010.01159.x.
15. *The United States Pharmacopeia and National Formulary USP 32–NF 27*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2009.
16. *Modern Pharmaceutics*, 4th ed.; Banker, G. S.; Siepmann, J.; Rhodes, C., Eds.; Drugs and the Pharmaceutical Sciences, Vol.121; CRC Press: Boca Raton, FL, 2002.