Stability of Metronidazole Free-base Oral Suspensions Formulated with *United States Pharmacopeia*-grade Metronidazole Powder and Commercial Metronidazole Tablets

Marian Jarouche, PhD
Martha Ibrahim, BBioTech
Jarryd Pearson, BMedSc
Beatrice Venkataya, MRes
Mitchell Low, PhD
James Rowe, PhD

S STABILITY P PENETRATION F FORMULATIVE C CLINICAL STUDY O OTHER

Abstract

This study reports on the stability of *United States Pharmacopeia*-grade metronidazole powder and commercially available metronidazole tablets in two dye-free oral suspending vehicles, namely Oral Mix and Oral Mix Sugar-Free. Metronidazole at 50 mg/mL was prepared individually in Oral Mix and Oral Mix Sugar-Free suspension vehicles and placed in 50-mL amber polyethylene terephthalate bottles and 3-mL amber plastic syringes and stored at 4°C or 25°C/60% relative humidity for 90 days. The solutions were analyzed at the time of preparation and at 7 days, 14 days, 30 days, 45 days, 60 days, 75 days, and 90 days, with the concentration of metronidazole measured by high-performance liquid chromatography with photodiode array detection. The oral solutions were also monitored for pH, homogeneity, color, and odor. Except for the Oral Mix suspension of metronidazole prepared from the *United States Pharmacopeia*-grade powder and from the commercial tablet, when stored in pre-filled syringes, all the other preparations were stable at 4°C or 25°C/60% relative humidity for 90 days, with the metronidazole remaining within ± 10% of the initial concentration. The pH, color, odor, and resuspendability remained essentially unchanged. Metronidazole in Oral Mix and Oral Mix Sugar-Free oral suspensions, compounded from *United States Pharmacopeia*-grade powder or commercially available tablets, are a suitable alternative as an extemporaneously prepared medication.

Introduction

Metronidazole is a synthetic nitroimidazole antibiotic that can be administered intravenously, orally, and topically.[1-3] Orally, it is available in tablet, capsule, and suspension forms with the suspension favored among those with swallowing difficulties. The bitter and metallic taste of metronidazole free-base can be overcome by using its ester form, metronidazole benzoate, which has a bland taste. However, there is also uncertainty surrounding the bioavability of the ester[3,4] as it does not hydrolyze significantly to the free-base in simulated gastric fluid or in simulated intestinal fluid.[5] A report comparing the pharmacokinetics of a 6.4% metronidazole benzoate oral suspension (400-mg metronidazole equivalent) and 400-mg metronidazole tablet reported distinctly different Tmax, Cmax, and "area under curve," although elimination half-life remained the same.[6] The 6.4% metronidazole benzoate oral suspension used in the study is a commercial product marketed as Flagyl-S 200-mg/5-mL Oral Suspension (SANOFI).[6]

There are limited studies on the stability of the metronidazole free-base in suspension vehicles.[7,8] There is literature on the use of 50-mg/mL suspensions prepared using Ora-Blend, Ora-Plus/Ora-Sweet (1:1), Ora-Plus/Ora-Sweet SF (1:1) (Perrigo

The authors are affiliated with the National Institute of Complementary Medicine, Western Sydney University, Penrith NSW in the following capacities: ***Marian Jarouche,*** *Scientific Consultant;* ***Martha Ibrahim,*** *QC Chemist;* ***Jarryd Pearson****, QC Chemist;* ***Beatrice Venkataya,*** *QC Chemist;* ***Mitchell Low,*** *Postdoctoral Researcher;* ***James Rowe,*** *Biomedical Consultant.*

Company, Dublin, Ireland) suspension vehicles, and Cherry Syrup/Simple Syrup (1:4) (Robinson Laboratory Inc., San Francisco, California) with metronidazole powder.[7] The sources of the drug were powder, capsules, and tablets. Amber plastic bottles were used, as light exposure reportedly promotes metronidazole hydrolysis in aqueous solution and gives rise to darkening of suspensions. All the Ora-type mixtures were reportedly stable for 60 days when stored at either 25°C or 5°C.[7] The Ora-type products are described as having a pinkish appearance, so they presumably contain a dye.

A study[8] on the use of metronidazole *United States Pharmacopeia (USP)*-grade powder in Simple Syrup and Ora-Blend suspensions at a concentration of 50 mg/mL, stored in amber plastic bottles, at 5°C and 23°C reported that metronidazole was stable for 93 days. The blend suspension is not suitable for oral consumption, as the Simple Syrup has no masking for the highly bitter taste of metronidazole.

It has been reported that drug degradation in suspension formulations is primarily due to interactions between the drug substance with formulation components rather than by standard routes such as oxidation, hydrolysis, photolysis, or thermolysis.[9] As such, when considering the safety and efficacy of the drug prepared extemporaneously, the stability of the complete formulation should be considered rather than the drug on its own. Storage in sealed, amber containers and refrigeration help reduce oxidation, photolysis, and thermolysis.[10]

This study aimed to examine the 90-day stability of metronidazole free-base in Oral Mix (OM) and in Oral Mix Sugar-Free (OMSF) suspending vehicles (both by Medisca Australia, NSW Australia). The components of OM are sucrose, cellulose, and glycerine, and, for OMSF, sodium saccharin replaces sucrose. Both vehicles are cherry flavored with a pH of 4 to 5 and are dye free. OMSF has about a third the calories of OM, as well as a third lower osmolality, slightly reducing the risk of stomach upset. Omitting the dye is believed to alleviate concerns that some in the pediatric population may have sensitivities to food colorings. This study reports on metronidazole sourced as the *USP*-grade raw powder, as well as the commercially available tablet, as it is the more readily available form to the compounding chemist.

Four different formulations, stored at two environmental conditions (4°C and 25°C, both at 60% relative humidity [RH]) in two packaging types (amber polyethylene terephthalate [PET] bottles and amber plastic oral syringes) were studied. Chemical stability was measured over 90 days by a modified *USP* monograph assay.[11] While there is a current *USP* monograph available for oral suspensions prepared with metronidazole benzoate *USP*-grade powder in Ora-Blend,[12] there is not one available for alternative suspending vehicles or from alternative sources of metronidazole, such as tablets, therefore one had to be developed and validated for this study.

Materials and Method

CHEMICALS AND REAGENTS

USP-grade metronidazole raw powder for preparing the test suspensions was supplied by Medisca Inc., NSW, Australia (Lot 112833/D). *USP*-grade metronidazole reference material was also supplied by Medisca Inc., NSW, Australia (Lot 119893/E). Metrogyl 400-mg metronidazole tablets were from Alpha Pharm Pty. Ltd., QLD, Australia (Lot 8035620). OM and OMSF were supplied by Medisca Inc., Quebec, Canada (Lot 00121M/A and Lot 00171M/A for OM and OMSF, respectively). Liquid chromatography (LC)-grade methanol was purchased from Chem Supply, SA, Australia. Purified water with resistivity greater than 18 MΩ.cm was obtained from an ELGA PURELAB ultrapure water purification system from Thermo Fisher Scientific, NSW, Australia.

EQUIPMENT AND CHROMATOGRAPHIC CONDITIONS

A Shimadzu Prominence high-performance liquid chromatographic (HPLC) system comprising of a LC-20AD pump, DGU-20A5 solvent degasser, SIL-20AC auto-sampler, CTO-20AC column oven, and a SPD-M20A photodiode array (PDA) detector (Shimadzu Corp., Kyoto, Japan) was used. The detector was set to acquire data from 254-300 nm. Separation was achieved on a Kinetex EVO C18 column (250 × 4.6-mm, 5 µm particle size, 100 Å pore size) (Phenomenex, Australia). The HPLC was operated using Shimadzu's LabSolutions software (Windows version 5.57 SP1).

The mobile phase of aqueous methanol (1:4 [methanol:water]) was run isocratically at a flow rate of 0.8 mL/min. The injection volume was 30 µL and run time 10 minutes. The column oven temperature was set at 30°C. The mobile phase was used as a solvent for the preparation of standard and sample preparations. Chromatograms were visualised at 316 nm.

The pH of samples was measured with a Schott Lab 850 pH meter (Schott Laboratories, SI Analytics, Mainz, Germany).

VALIDATION OF HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYTICAL METHOD

The analytical method was tested to determine if it was suitable for determining metronidazole in the matrices of interest. This was achieved by checking if the metronidazole peak is resolved from the suspension vehicle components and forced-degradation product peaks produced by exposing the OM and OMSF samples (blank and containing 100 µg/mL of metronidazole) to heat, acidic, basic, and oxidizing chemical conditions (70°C, 1 M hydrochloric acid, 1 M sodium hydroxide, and 30% v/v hydrogen peroxide, respectively; 1 mL each added to a 1-mL sample) for 30 minutes. The acidified and basified samples were neutralized with sodium hydroxide and hydrochloric acid, respectively, prior to analysis. Prior to analysis, the metronidazole concentration was adjusted to approximately 50 µg/mL with LC mobile phase. Calibration curve linearity was determined over the 5.0-µg/mL to a 100.0-µg/mL range using 5 metronidazole standards. The working standards were prepared by diluting a 100-µg/mL metronidazole standard stock. All standards were prepared in LC mobile phase on day of use. To determine metronidazole peak area and retention time precision, a 50-µg/mL standard solution was injected 6 times. The relative

standard deviation (RSD) of both the peak areas and retention times were determined and deemed acceptable if the RSD was ≤2.0%. A plot is made of metronidazole peak area versus concentration and a standard curve produced by linear regression. The calibration curve is deemed acceptable if the coefficient of determination, r^2 is ≥0.999. Blank injections of suspension vehicles were made to check for interfering peaks. Overlay of the ultraviolet spectrum of the metronidazole peak obtained from the standard and sample solutions was performed to check for peak purity.

SAMPLE PREPARATION

Oral suspensions of metronidazole (50 mg/mL) were prepared from the *USP*-grade powder and, separately, from ground Metrogyl 400-mg metronidazole tablets. The raw drug powder was used directly, while the tablet was ground to a fine powder in a domestic herb grinder prior to use. The suspension was prepared by triturating the powder with small amounts of OM or OMSF in a mortar, and the mixture quantitatively transferred to a 1-L container and made up to volume with the suspension base. The preparation was homogenized with a Silverson mixer homogenizer (Silverson Machines Ltd., England, United Kingdom), and, with the mixer running, aliquots of the suspension were sampled and packaged in 60-mL PET amber bottles and 3-mL PreciseDose dispenser amber polypropylene syringes with tip cap (filling volume 3 mL), both from Medisca Inc., Quebec, Canada (Lot 46499 and Lot 605080/B for the bottles and syringes, respectively).

Twelve bottles and twenty four syringes of each metronidazole suspension was stored in a temperature-controlled refrigerator (Model TLR-1150-3-SD; Thermoline Scientific, NSW, Australia) set at 4°C ± 2°C and 60 ± 5% RH. A duplicate bottle and syringe set was stored in a stability oven (Model TRH-850-GD; Thermoline Scientific) set at 25°C ± 2°C and 60 ± 5% RH.

At the time of preparation and at 7 days, 14 days, 30 days, 45 days, 60 days, 75 days, and 90 days, aliquots of preparation from the bottles and syringes stored at the two temperatures were sampled in triplicate. After 1:1000 dilution with LC mobile phase to an expected concentration of 50 µg/mL, the samples were analyzed in triplicate by HPLC-PDA. The bottles were shaken vigorously by hand for about 30 seconds prior to sampling by use of a glass pipette. The syringes were mixed by vigorous hand agitation and inversion for about 30 seconds, and the entire content weighed into a volumetric flask. The contents were inspected for color, odor, and homogeneity and the pH determined with a Schott Lab 850 pH meter (Schott Laboratories). Suspensions packaged in syringes were transferred to clear 15-mL centrifuge tubes and similarly inspected.

The prepared metronidazole samples prepared in bottles and syringes stored at 4°C and 25°C (both 60% RH) were analyzed at the eight indicated time points. The acceptance criteria are for the analyte to remain within 90% to 110% of the initial concentration, the pH to change by less than 0.5 units, and negligible change in visual appearance, color, and odor.

Intraday variability of the method was determined using metronidazole suspensions prepared from metronidazole raw powder in OM, and in OMSF to a concentration of 50 mg/mL. Six samples of each preparation were diluted (1:1000) in mobile phase and injected in duplicate. For interday variability, metronidazole preparations of each suspension were assayed under identical conditions but on subsequent days.

At the initial and predetermined time points, metronidazole peak areas were integrated for each injection and averaged for each sample. Results were determined as the mean and standard deviation (SD) for each oral solution packaged in bottles or syringes, stored at 4°C or 25°C (both 60% RH). The reported stability of metronidazole raw USP powder and commercial tablets in dye-free OM and dye-free OMSF suspending vehicles packaged in amber bottles or amber syringes and stored at the two temperatures was determined by calculating the concentration of metronidazole at each time point as a percentage of the initial concentration.

Results

Using the chromatographic conditions described and with the chromatograms visualized at 319 nm, the HPLC-PDA method gave a sharp metronidazole peak (retention time 5.2 minutes), which is well resolved from peaks from the suspension vehicles and degradation products.

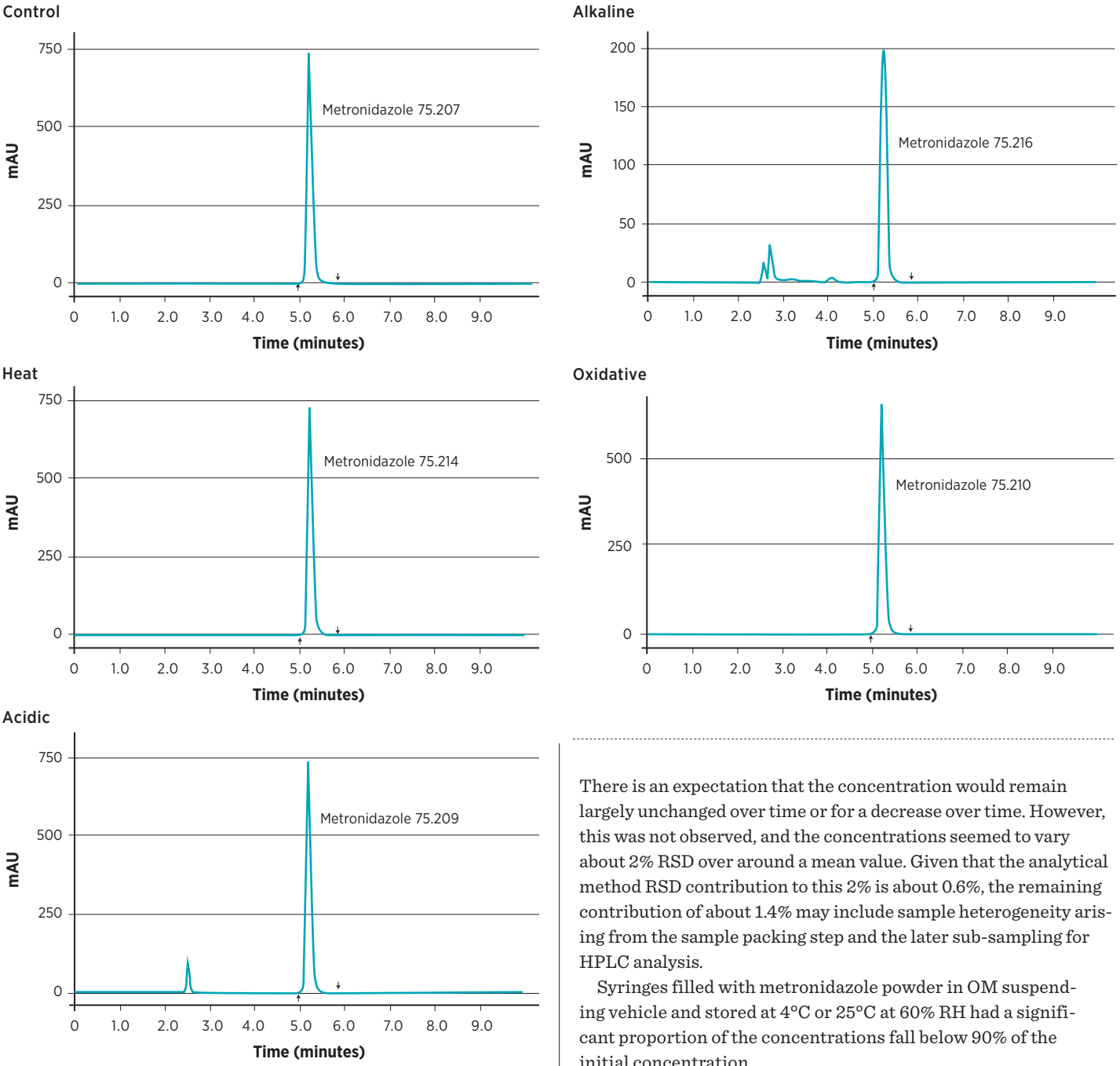
Forced-degradation studies of metronidazole prepared in OM and OMSF suspension vehicles showed little change in concentration for the heat-, acid-, and oxidant-treated samples compared to the untreated control samples. However, for the alkali-treated samples, the decrease in metronidazole peak area is significant with decreases of 70% and 84% for the OM and OMSF preparations, respectively. Degradation product peaks were observed in all treated samples at 2.5 minutes, and in alkaline treated samples, peaks at 2.7 and 4.1 minutes were also observed, but these are well resolved from the metronidazole peak at 5.2 minutes as shown in the **FIGURE** included in this article (chromatogram visualized at 319 nm) for the OM suspension. The OMSF preparation gave essentially the same chromatograms. The metronidazole peaks in the samples and standard chromatograms overlayed very closely, indicating good peak purity in the samples.

The calibration curve is linear (r^2>0.9998) between 5 µg/mL to 100 µg/mL. The method precision determined by measuring metronidazole *USP*-grade powder prepared in OM and OMSF suspension vehicles (at approximately 50 mg/mL) were 0.34% RSD and 0.60% RSD, respectively, for intraday and 0.36% RSD and 0.67% RSD, respectively, for interday.

The **TABLE** included in this article presents the mean percentages of metronidazole remaining from the original concentration at the seven predetermined time points for the OM and OMSF preparations made from the metronidazole powder and commercial tablets stored in bottles and syringes at 4°C and 25°C (both 60% RH). The mean percentage for the seven time points is also presented along

FIGURE.

SAMPLE CHROMATOGRAM OF METRONIDAZOLE IN ORAL MIX SUSPENSION VEHICLE, IN CONTROL, HEAT TREATED (70°C), ACID TREATED (1 M HYDROCHLORIC ACID), ALKALI TREATED (1 M SODIUM HYDROXIDE), AND OXIDATIVE TREATED (30% V/V HYDROGEN PEROXIDE).



with the SD. The mean is obtained from triplicate samples that were prepared. There is no consistent trend relating the change in metronidazole concentration as a function of time over the study period.

There is an expectation that the concentration would remain largely unchanged over time or for a decrease over time. However, this was not observed, and the concentrations seemed to vary about 2% RSD over around a mean value. Given that the analytical method RSD contribution to this 2% is about 0.6%, the remaining contribution of about 1.4% may include sample heterogeneity arising from the sample packing step and the later sub-sampling for HPLC analysis.

Syringes filled with metronidazole powder in OM suspending vehicle and stored at 4°C or 25°C at 60% RH had a significant proportion of the concentrations fall below 90% of the initial concentration.

All the other samples had concentrations within the range of 92.8% to 108.0% of the initial concentration and are, therefore, considered stable being within the 90% to 110% range of the initial concentration.

All samples maintained their initial pale-yellow color, slight cherry-like odor, and opaque appearance with no observable evidence of caking. Furthermore, the pH of all metronidazole OM and OMSF suspensions packaged in bottles and syringes remained within a pH of 4.4 to 4.5 under all the storage conditions for the entire study period. All the samples remained easily resuspended with no evidence of caking.

Discussion

With the exception of metronidazole powder in OM suspension packaged in syringes, all the other metronidazole powder and commercial tablet suspensions in OM and OMSF in bottles and syringes at 4°C and 25°C (60% RH) maintained their metronidazole concentration within 90% to 110% of the initial concentration. The pre-filled oral syringe method of drug delivery is more convenient and dose consistent but produced more variable results for the metronidazole powder in OM suspension. Some of the time points had metronidazole concentrations greater than 90% of initial concentration while most were slightly below with no trend to the change. The result is not an artefact of inadequate mixing or non-homogenous sampling, as the entire content of the syringe was assayed at each time point. The result is a sub-sampling artefact when the suspension is withdrawn from the bottle into the syringe. However, the corresponding syringe samples prepared in OMSF suspensions gave metronidazole concentrations greater than 90% of initial concentration. In this study, measurement SDs are comparable with those reported in the Ora-Blend study. Replicate measurement RSDs range from about 1% to 5%, and, across the time points, the range is about 1% to 8%. These RSDs are similar for our study. As with this study, the Simple Syrup/Ora-Blend study also reported some later day time points having metronidazole concentrations slightly higher than the earlier ones. This is probably a result of sampling uncertainty.

The forced-degradation studies showed little loss of metronidazole when heated and when exposed to acid and oxidizing condi-

TABLE.

CHEMICAL STABILITY OF METRONIDAZOLE ORAL MIX AND ORAL MIX SUGAR-FREE SUSPENSIONS.

	INITIAL CONCENTRATION	% OF INITIAL CONCENTRATION OF METRONIDAZOLE ± SDA							MEAN ± SD[b]
		DAY 7	DAY 14	DAY 30	DAY 45	DAY 60	DAY 75	DAY 90	
Metronidazole *USP*-grade Powder in Oral Mix Suspension									
Syringe, 4°C	45.8 ± 0.7	90.4 ± 0.3	85.6 ± 0.3	86.7 ± 0.1	91.18 ± 0.02	90.6 ± 0.4	85.22 ± 0.03	91.71 ± 0.02	88.8 ± 2.8
Bottle, 4°C		100.6 ± 10.5	95.0 ± 10.8	97.3 ± 1.4	96.3 ± 3.3	95.6 ± 4.7	99.7 ± 1.7	98.8 ± 3.6	97.6 ± 2.1
Syringe, 25°C		84.2 ± 0.2	89.3 ± 0.5	87.2 ± 0.2	92.3 ± 0.6	90.7 ± 0.3	89.2 ± 0.1	84.9 ± 1.3	88.3 ± 3.0
Bottle, 25°C		98.0 ± 2.7	92.8 ± 6.6	96.9 ± 7.0	106.5 ± 2.3	96.3 ± 3.7	102.5 ± 2.9	101.2 ± 2.3	99.2 ± 4.6
Metronidazole *USP*-grade Powder in Oral Mix Sugar-Free Suspension									
Syringe, 4°C	49.9 ± 0.7	93.1 ± 0.1	96.5 ± 2.5	95.1 ± 0.1	99.3 ± 0.5	97.4 ± 0.1	97.0 ± 0.5	100.4 ± 0.1	97.0 ± 2.5
Bottle, 4°C		102.7 ± 2.7	103.5 ± 1.6	105.3 ± 3.9	104.9 ± 4.4	102.2 ± 4.0	101.2 ± 4.6	107.8 ± 0.7	103.9 ±2.2
Syringe, 25°C		94.9 ± 0.2	96.9 ± 0.1	93.5 ± 0.3	96.7 ± 0.2	93.5 ± 0.3	99.9 ± 0.2	98.5 ± 0.1	96.3 ± 2.4
Bottle, 25°C		102.8 ± 0.8	105.3 ± 2.3	105.5 ± 0.5	104.1 ± 0.7	106.7 ± 2.3	102.2 ± 3.6	108.0 ± 2.8	104.9 ± 2.1
Commercial Metronidazole Tablets in Oral Mix Suspension									
Syringe, 4°C	47.0 ± 0.1	99.5 ± 0.6	98.1 ± 0.3	98.17 ± 0.04	102.6 ± 0.2	99.3 ± 0.4	98.5 ± 0.2	95.7 ± 4.9	98.8 ± 2.1
Bottle, 4°C		99.2 ± 0.5	98.8 ± 1.1	98.4 ± 0.4	100.8 ± 1.1	99.1 ± 0.8	99.8 ± 0.8	96.6 ± 0.5	99.0 ± 1.3
Syringe, 25°C		99.4 ± 0.6	100.5 ± 0.1	97.8 ± 0.2	100.9 ± 0.2	99.4 ± 0.1	97.6 ± 0.2	99.0 ± 0.1	99.2 ± 1.2
Bottle, 25°C		99.8 ± 1.1	99.3 ± 0.4	99.4 ± 0.1	100.9 ± 0.7	98.9 ± 0.7	98.6 ± 0.3	100.4 ± 0.3	99.6 ± 0.8
Commercial Metronidazole Tablets in Oral Mix Sugar-Free Suspension									
Syringe, 4°C	51.1 ± 0.5	95.2 ± 2.3	97.7 ± 0.1	96.0 ± 0.2	99.5 ± 3.8	98.4 ± 0.2	97.8 ± 0.1	100.20 ± 0.02	97.8 ± 1.8
Bottle, 4°C		98.7 ± 0.4	98.3 ± 0.1	98.5 ± 0.7	98.8 ± 0.3	100.4 ± 0.4	99.4 ± 0.7	101.1 ± 1.7	99.3 ± 1.1
Syringe, 25°C		98.0 ± 2.7	97.4 ± 0.1	96.9 ± 0.2	96.7 ± 0.5	98.0 ± 0.1	98.2 ± 0.2	98.4 ± 0.1	97.7 ± 0.7
Bottle, 25°C		98.9 ± 0.2	98.1 ± 1.2	98.1 ± 0.4	99.5 ± 0.6	100.2 ± 0.5	99.2 ± 0.4	100.6 ± 0.9	99.2 ± 1.0

[a]Mean concentration of metronidazole ± SD (*n* =3 from triplicate sample preparations with each sample preparation injected 3 times)
[b]Mean % of initial metronidazole concentration calculated from the mean % of the 7 time points; SD calculated from these 7 values.
SD = standard deviation; *USP = United States Pharmacopeia*

tions, but only about 20% remained when exposed to base. This observation is in harmony with the study of metronidazole stability in Simple Syrup and Ora-Blend[8] exposed to base where most of the metronidazole was also lost. That study also reported that losses under oxidative and acidic conditions were much less by comparison, which is, again, in agreement with observations in this study. A direct comparison of the percentage of degradation with this study is not possible as different experimental conditions were employed.

Conclusion

This study provides stability data for the formulation of metronidazole at 50 mg/mL, sourced as the *USP*-grade powder or as commercially available tablets, prepared in OM and OMSF suspension vehicles, packaged in 50-mL amber PET bottles and 3-mL amber plastic syringes, and bottles and stored at 4°C or 25°C/60% RH for 90 days. With the exception of the pre-filled syringes containing OM suspensions of metronidazole *USP*-grade powder, as well as metronidazole tablets, all the other preparations were stable at 4°C or 25°C/60% RH for 90 days, with the metronidazole remaining within ± 10% of the initial concentration. The pH, color, odor, and resuspendability remain essentially unchanged. Thus metronidazole OM and OMSF oral suspensions, compounded from *USP*-grade powder or commercially available tablets present a suitable alternative as an extemporaneously prepared medication.

References

1. Lamp KC, Freeman CD, Klutman NE et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet.* 1999; 36(5): 353–373.
2. Upfal J. *Australian Drug Guide: The Plain Language Guide to Drugs and Medicines of All Kinds.* 8th ed. Carlton, VIC: Black Inc.; 2016.
3. McEvoy GK and American Society of Health-System Pharmacists, eds. *AHFS drug information®* (2016). Bethesda, MD: American Society of Health-System Pharmacists; 2016.
4. Mathew M, Das Gupta V, Bethea C. Stability of metronidazole in solutions and suspensions. *J Clin Pharm Ther.* 1994; 19(1): 27–29.
5. Matthew M, Das Gupta V, Bethea C. Stability of metronidazole benzoate in suspensions. *J Clin Pharm Ther*. 1994; 19(1): 31–34.
6. Irish Pharmaceutical Healthcare Association. Flagyl-S 200-mg/5-mL Oral Suspension. [medicines.ie Website.] Available at: www.medicines.ie/medicine/4179/SPC. Accessed June 20, 2018.
7. Allen LV Jr, Erickson MA 3rd. Stability of ketoconazole metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. *Am J Health Syst Pharm*. 1996; 53(17): 2073–2078.
8. Donnelly RF, Ying J. Stability of metronidazole suspensions. *IJPC*. 2015; 19(3): 248–251.
9. Glass BD, Haywood A. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *J Pharm Pharm Sci*. 2006; 9(3): 398–426.
10. Wang DP, Yeh MK. Degradation kinetics of metronidazole in solution. *J Pharm Sci*. 1993; 82(1): 95–98.
11. United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary.* Metronidazole. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2016: 4862.
12. United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary.* Metronidazole Benzoate Compounded Oral Suspension. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2016: 4864.

Address correspondence to Dr. Mitchell Low, National Institute of Complementary Medicine, Western Sidney University, Locked Bag 1797, Penrith NSW 2751. E-mail: Mitchell.Low@westernsydney.edu.au