IJPC PEER REVIEWED

Stability of Metronidazole Benzoate in SyrSpend SF One-Step Suspension System

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ABSTRACT

The objective of this study was to determine the stability of metronidazole benzoate suspension in SyrSpend SF One-Step Suspension System. The studied samples were packaged in 60-mL amber plastic prescription bottles, which were stored protected from light under controlled environmental conditions for a period of 360 days. Stability of metronidazole benzoate suspension in SyrSpend SF was assessed based on retention of initial color or appearance, pH of suspension, and recovery of metronidazole benzoate from the packaged product. Duplicate samples were evaluated at each predefined time interval. An assay method by high performance liquid chromatography was validated for its specificity and stability-indicating characteristics through a forced-degradation study, and was used in metronidazole benzoate assay. Metronidazole benzoate in SyrSpend SF retained its normal appearance of an opaque suspension, with acceptable pH values ranging from 4.43 to 4.53 (range 4.45 ± 0.5). Recovery of metronidazole benzoate at subsequent time points was within 90% to 110% of initial concentration for samples stored at refrigerated temperature (2°C to 8°C), and ambient condition (25°C/60% relative humidity), with no detectable changes in chromatographic profile for most tested samples. The rates of change in potency for metronidazole benzoate were determined under the assumptions of first-order kinetics, and the time to reach 90% to 110% initial concentration was determined to be 366 days for samples in ambient storage, or 716 days for samples stored at refrigerated temperature. Metronidazole benzoate in SyrSpend SF, which was packaged in amber plastic prescription bottles, is stable for at least 1 year when stored protected from light at ambient condition (25°C/60% relative humidity). The shelf life for this product may be extended to 2 years when stored at refrigerated temperature.

INTRODUCTION

Metronidazole belongs to the nitroimidazole group of antibiotics whose antimicrobial properties are thought to derive from the formation of toxic-free radicals by intracellular reduction. Metronidazole activity is partially inhibited by the presence of oxygen, thus it is commonly used in anaerobic infections, although it is also effective in the treatment of trichomoniasis.[1] Additionally, metronidazole is the agent of choice in patients with antibiotic-associated colitis due to *Clostridium difficile*.[2]

Both parenteral and enteral routes have been used to administer metronidazole. Nevertheless, the need for additional dosage forms has been warranted for patients who require a different dosage form than what is commercially available (e.g., patients who are incapable of swallowing tablets or capsules, or pediatric patients who are incapable of swallowing the available dosage forms).[3] Recently, oral dosage forms of metronidazole were extemporaneously prepared using a 1:1 mixture of Ora-Sweet and Ora-Plus, a 1:1 mixture of Ora-Sweet SF and Ora-Plus, or cherry syrup. These mixtures, through stability testing, have shown to retain up to 93% of the initial drug activity at 60 days.[4] Similarly, metronidazole benzoate is often used in oral liquid dosage forms due to its non-bitter taste. The solubility for metronidazole benzoate, an ester derivative of metronidazole, was estimated to be 0.1 mg/mL in water.[5] Compounding liquid dosage forms with metronidazole benzoate, therefore, requires the use of suspending agents.

SyrSpend SF (Gallipot, St. Paul, Minnesota) is a starch-based and sugar-free suspension system with characteristics of low osmolality (<50 mOsmol).[6] Its use is associated with low gas production and fewer laxative effects due to the absence of methylcellulose and sorbitol. These outstanding advantages of SyrSpend SF lend itself well as a formulation vehicle, and its use as a suspending base is currently a consideration in the formulation of metronidazole benzoate for an oral liquid dosage form.

The objective of this study was to determine the stability of metronidazole benzoate suspension in SyrSpend SF packaged in 60-mL amber plastic prescription bottles. Assessment of stability was based on maintenance of initial physical characteristics, and recovery of metronidazole benzoate from the packaged product stored under controlled environmental conditions for 90 to 360 days.

TABLE 1. Stability Data for Metronidazole Benzoate in SyrSpend SF at Refrigerated Condition (2°C to 8°C) for 360 days.

Elapsed Time (day)	Appearance	pH	Recovery (%)
T0	Opaque suspension Normal appearance	4.43	100.0[a]
15	Opaque suspension Normal appearance	4.44	100.7
30	Opaque suspension Normal appearance	4.43	101.3
45	Opaque suspension Normal appearance	4.48	101.6
54	Opaque suspension Normal appearance	4.46	100.0
75	Opaque suspension Normal appearance	4.47	104.4
90	Opaque suspension Normal appearance	4.50	102.6
120	Opaque suspension Normal appearance	4.37	99.3
180	Opaque suspension Normal appearance	4.43	104.8
270	Opaque suspension Normal appearance	4.49	105.3
360	Opaque suspension Normal appearance	4.44	104.3
Limits	Opaque suspension Normal appearance	4.45 ± 0.5	90-110

[a]Initial concentration was 69.77 mg/mL.
Initial time (T0) results for metronidazole benzoate were established as target values. The assay results for subsequent time points were expressed as percentage of initial value. Average data were reported for duplicate samples.

TABLE 2. Stability Data for Metronidazole Benzoate in SyrSpend SF at Ambient Condition (25°C/60% RH) for 360 days.

Elapsed Time (day)	Appearance	pH	Recovery (%)
T0	Opaque suspension Normal appearance	4.43	100.0[a]
15	Opaque suspension Normal appearance	4.44	102.4
30	Opaque suspension Normal appearance	4.42	103.1
45	Opaque suspension Normal appearance	4.48	102.8
54	Opaque suspension Normal appearance	4.45	101.9
75	Opaque suspension Normal appearance	4.46	105.8
90	Opaque suspension Normal appearance	4.50	102.0
120	Opaque suspension Normal appearance	4.35	103.9
180	Opaque suspension Normal appearance	4.43	103.8
270	Opaque suspension Normal appearance	4.50	107.0
360	Opaque suspension Normal appearance	4.44	111.7
Limits	Opaque suspension Normal appearance	4.45 ± 0.5	90-110

[a]Initial concentration was 69.77 mg/mL.
Initial time (T0) results for metronidazole benzoate were established as target values. The assay results for subsequent time points were expressed as percentage of initial value. Average data were reported for duplicate samples.

MATERIALS AND METHODS

Chemicals and Reagents

Chemicals and reagents used in this study were *United States Pharmacopeia–National Formulary*, *British Pharmacopeia* (BP), or American Chemical Society grade, and were used as supplied. The reference material was Metronidazole Benzoate, BP 100.0% pure, which was obtained from Spectrum (Lot SX0972; Gardena, California). Acetonitrile was obtained in chromatographic grade from Pharmco (Lot PL00063SACN, Fort Worth, Texas). Purified water Type I ASTM analytical grade (purity 18 MΩ-cm) was generated in-house (Barnstead NANOPure Water Purification System; Dubupue, Iowa).

Equipment and Chromatographic Conditions

The high-performance liquid chromatography (HPLC) instrument was the Hewlett-Packard (HP) Series 1100 (Agilent Technologies, Santa Clara, California), which was operated using HP ChemStation software (Windows version A.10.02). The instrument is equipped with a diode array detector, an auto-sampler, a programmable injector, and a solvent delivery system that consists of a quaternary gradient pump, and a solvent module with online vacuum degasser. The mobile phase had a flow rate of 1.0 mL/min, which was a 50:50:0.05 mixture of acetonitrile, water, and glacial acetic acid, respectively. Chromatographic separation was performed using a Gemini C18 5-mcm analytical column with dimensions 4.6-mm × 150-mm (Phenomenex, Torrance, California). The mobile phase was used as a solvent in the preparation of standard and assay preparations, and the reference standard used for metronidazole benzoate assay was a solution of 0.4 mg/mL Metronidazole Benzoate, BP (Lot SX9072; Spectrum) in mobile phase. Sample and standard preparations were evaluated at 314 nm by 10-mcL injection volume. The pH of samples was measured using Corning pH/Ion analyzer 350 and Acumet electrode (13620183, Fisher Scientific, Pittsburgh, Pennsylvania).

TABLE 3. Stability Data for Metronidazole Benzoate in SyrSpend SF at Accelerated Condition (40°C/75% RH) for 90 days.

Elapsed Time (day)	Appearance	pH	Recovery (%)
T0	Opaque suspension Normal appearance	4.43	100.0[a]
15	Opaque suspension Normal appearance	4.44	101.3
30	Opaque suspension Normal appearance	4.43	102.1
45	Opaque suspension Normal appearance	4.49	99.3
54	Opaque suspension Normal appearance	4.46	103.1
75	Opaque suspension Normal appearance	4.47	106.6
90	Opaque suspension Normal appearance	4.50	104.8
Limits	Opaque suspension Normal appearance	4.45 ± 0.5	90-110

[a]Initial concentration was 69.77 mg/mL.
Initial time (T0) results for metronidazole benzoate were established as target values. The assay results for subsequent time points were expressed as percentage of initial value. Average data were reported for duplicate samples.

TABLE 4. Stability Data for Metronidazole Benzoate in SyrSpend SF at Accelerated Condition (55°C) for 90 days.

Elapsed Time (day)	Appearance	pH	Recovery (%)
T0	Opaque suspension Normal appearance	4.43	100.0[a]
15	Opaque suspension Normal appearance	4.44	104.8
30	Opaque suspension Normal appearance	4.44	107.1
45	Opaque suspension Normal appearance	4.50	111.9
54	Opaque suspension Normal appearance	4.47	112.3
75	Opaque suspension Normal appearance	4.47	130.2
90	Opaque suspension Normal appearance	4.53	126.6
Limits	Opaque suspension Normal appearance	4.45 ± 0.5	90-110

[a]Initial concentration was 69.77 mg/mL.
Initial time (T0) results for metronidazole benzoate were established as target values. The assay results for subsequent time points were expressed as percentage of initial value. Average data were reported for duplicate samples.

Validation for Stability-Indicating Characteristics of the HPLC Method

Stress studies were conducted to ensure that the HPLC method employed had the ability to monitor and detect low level of degradants and impurities. Thus, test samples of metronidazole benzoate containing approximately 80-mg/mL suspension in SyrSpend SF were diluted to 0.4 mg/mL in mobile phase for exposure to heat (80°C) and ultraviolet (254nm to 400 nm), or diluted with solutions of acid (1 N HCl), base (1 N NaOH), and hydrogen peroxide (3% H2O2). Assay and chromatographic profiles for metronidazole benzoate under the effects of stressors were obtained after 72 hours of exposure, or for a time period where metronidazole benzoate content was reduced to about 90% compared to the control sample. Additional peaks representing decomposition products of metronidazole benzoate or formulation components in these samples were then identified by relative retention time (rRT), and were separated from the main metronidazole benzoate peak.

Preparation of Metronidazole Suspension Samples[7]

Metronidazole benzoate in SyrSpend SF 70 mg/mL sample was compounded by placing the Metronidazole Benzoate, BP (Lot MB/60110; Medisca, Plattsburg, New York) in a suitable mortar. The powder was triturated with 1.25 g of Propylene Glycol, NF (Lot STCOK; Professional Compounding Centers of America, Houston, Texas) to a smooth paste, then increasing the amount of SyrSpend SF that was added and mixed until the suspension was pourable. The liquid suspension was transferred to a suitable graduated container and the mortar was rinsed with three small aliquots of SyrSpend SF, which were added to the suspension. Additional SyrSpend SF was used to bring the suspension to the final volume of 750 mL. The well-mixed suspension was then packaged in 60-mL amber plastic prescription bottle for stability study.

Stability Study

Samples submitted for stability study were supplied as metronidazole benzoate 80-mg/mL suspension in SyrSpend SF One-Step Suspension System (Lot DBAF:73; Gallipot), which were packaged in 60-mL amber plastic prescription bottles. A total of 33 samples each containing 20-mL suspension were allocated for storage protected from light, at controlled temperatures and relative humidities (RH). Stability was investigated for samples, which were stored at 2°C to 8°C, with the use of a temperature controlled refrigerator (Model 13-986-272GR, Lot 1556060242164; Fisher Scientific, Pittsburgh, Pennsylvania), and two environmental chambers (Model 9010L, Lot 0600102; and Lot 05021205; VWR International, Inc., West Chester, Pennsylvania), which were set at 25°C/60% RH and 40°C/75% RH, respectively. In addition, an incubator (Model 1545; Lot 1100293; VWR International, Inc.) were employed in accelerated testing and set at 55°C. Sampling occurred at 15-day intervals for the first 75 days, and subsequently, at 90-, 120-, 180-, 270-, and 360-day periods. The evaluation parameters were appearance, pH, and assay. Appearance of each sample was evaluated by visual inspection of the suspension and the integrity of its container. The acceptance criterion for sample appearance was the retention of the original opaque suspension with intact container and closure. Sample pH was determined for duplicate preparations at each time point, and the limits for pH stability were 4.5 ± 0.5. Chemical sta-

TABLE 5. Estimated Stability Parameters for Metronidazole Benzoate in SyrSpend SF.

Parameter	Refrigeration (2°C-8°C)	Ambient (25°C/60% RH)	Accelerated (40°C/75% RH)	Accelerated (55°C)
k $(day^{-1})^a$	0.00006	0.00010	0.00026	0.00126
$t_{90\text{-}110\%}$ [b]	716	366	167	37
Shelf-life (month)	23.9	12.2	5.6	1.2

[a] k: First-order rate constant in unit of reciprocal of time (day^{-1})
[b] $t_{90\text{-}110\%}$: Time (days) to reach 90% - 110% concentration for metronidazole benzoate.
Stability data for the submitted Lot DBAF:73 were obtained over a period of 90 to 360 days under controlled storage conditions: Refrigeration (2°C to 8°C), ambient (25°C/60% RH), and accelerated temperatures (40°C/75% RH or 55°C).

TABLE 6. Summary of System Suitability Parameters for the Stability-Indicating High-Performance Liquid Chromatographic Method Used in the Stability Study of Metronidazole Benzoate in SyrSpend SF.

Evaluation Parameters	Results
System Suitability (Determined from metronidazole benzoate peak)	Peak tailing = 1.28 RSD = 0.07% N = 9595
Linear range	0.1 – 0.5 mg/mL R^2 = 0.9998
Precision	RSD: 0.09 – 0.13%
Accuracy	|RE| = 0.8 – 1.8%
Sensitivity	LOQ = 0.12 mcg/mL (0.03% of assay concentration) LOD = 0.05 mcg/mL (0.01% of assay concentration)
Ruggedness (Inter-assay variation)	|RD| = 0.1%
Robustness (10% change in HPLC conditions)	|RD| <5.0%
Specificity	Metronidazole benzoate and impurities (or decomposition products) identified by relative retention time (rRT) Metronidazole benzoate: 1.0 Impurities: 0.3, 0.6, 0.7, and 0.8

LOD = limit of detection; LOQ = limit of quantitation; N = number of equivalent theoretical plates; |RD| = absolute relative deviation; |RE| = absolute relative error; RSD = relative standard deviation; R^2 = regression coefficient of determination

bility was defined in terms of metronidazole benzoate average recovery from duplicate sample preparations using the validated HPLC method, and the assay limits were 90% to 110% of initial drug concentration. Sample preparation for metronidazole benzoate assay was made by diluting 0.5 mL of the suspension in mobile phase.

RESULTS

Stability data of metronidazole benzoate suspension in SyrSpend SF (Lot DBAF:73) are shown in Tables 1 through 5. The assay result for metronidazole benzoate at initial time (T0) was established as target value, which was determined to be 69.77 mg/mL, and results for subsequent time points were expressed relative to concentration at T0. Metronidazole benzoate recovery at subsequent time points was found to be within ± 10% of initial concentration for most studied samples. However, the drug concentration reached 110% limit at ambient storage after 360 days, and after 37 days at 55°C (Figures 1 and 2). Visual inspection of samples and pH measurements were within normal limits for all tested samples. Rates of change in potency for metronidazole benzoate were determined under the assumptions of first-order kinetics, and probable shelf life for the submitted Lot DBAF:73 was estimated to be approximately one year at 25°C/60% RH (Figures 3 and 4).

DISCUSSION

The HPLC method was demonstrated to be stability indicating through forced degradation studies and was suitable for testing stability samples of metronidazole benzoate suspension in SyrSpend SF. An example chromatographic profile of a stressed sample in the combined presence of oxidative agent and heat (3% hydrogen peroxide and 80°C) is presented in Figure 5, which shows metronidazole benzoate was separated from other components in the sample with acceptable resolution (R ≥1.5). Additionally, parameters that demonstrated system suitability for the validated HPLC method are shown in Table 6, with all chromatographic parameters meeting acceptance criteria for metronidazole benzoate assay.[7]

Refrigerated Samples (at 2°C to 8°C)

Table 1 shows stability data for samples from Lot DBAF:73 in refrigerated storage over the testing period of 360 days. The average assay results for metronidazole benzoate at latter time points varied from 99.3% to 105.3% of initial value (Figure 1), and the pH values for these samples were 4.45 ± 0.05, which was within ± 10% when compared to the initial pH value 4.43. All samples maintained normal appearance of an opaque suspension, and the chromatographic profile for this lot over the testing period was consistent with sample profile at T0 with no detectable signs of decomposition. Plots of log metronidazole benzoate concentrations were regressed on time, which yielded rate of change $k_{2\text{-}8°C}$ = -0.00006·day^{-1} for metronidazole benzoate (Figure 3). The time to reach 90% concentration was estimated at about 2 years ($CI_{95\%}$ = 1.3-7.6 years). Thus, based on 360-day stability data, the shelf life for this product was estimated to be 2 years at refrigerated temperature (Table 5).

Samples Stored at Ambient Condition (25°C/60% RH)

The average assay recovery of metronidazole benzoate from samples stored at 25°C/60% RH is presented in

Table 2. Thus, except for the final time point, all assay values were within ± 10% of the initial concentration (Figure 1). The average pH values for these samples were 4.46 ± 0.05, and all samples maintained normal appearance of an opaque suspension. The chromatographic profile for this lot over the testing period was consistent with sample profile at T0 (Figure 6) with no detectable signs of decomposition. Plots of log metronidazole benzoate concentrations were regressed on time, which yielded rate of change $k_{25°C/60\%RH}$ = -0.00010·day^{-1} for metronidazole benzoate (Figure 4). The time to reach 90% concentration was estimated at about 1.02 years ($CI_{95\%}$ = 0.8 to 1.4 years). Thus, based on 360-day stability data, the shelf life for this product was estimated to be at least 1 year at ambient condition (Table 5).

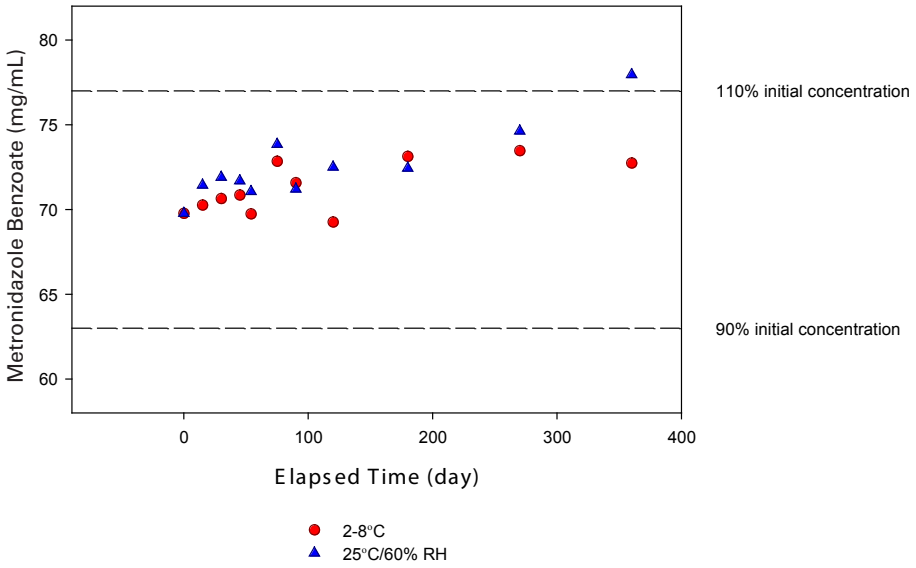
Samples Stored at 40°C/75% RH

The average assay recovery of metronidazole benzoate from samples stored at 40°C/75% RH is presented in Table 3. Thus, all assayed values were within ± 10% of the initial concentration (Figure 2). The average pH values for these samples were 4.46 ± 0.02, and all samples maintained normal appearance of an opaque suspension. The chromatographic profiles for this lot were consistent with the sample profile at T0, although there was one decomposition product detected at less than 0.01% of total sample response. The rate of change for metronidazole benzoate $k_{40°C/75\%RH}$ = -0.00026·day^{-1}, and the time to reach 90% concentration was estimated at about 0.5 year ($CI_{95\%}$ ≥0.3 year). Thus, based on 90-day stability data, the shelf life for this product was projected to be not more than 6 months at 40°C/75% RH storage condition (Table 5).

Samples Stored at 55°C

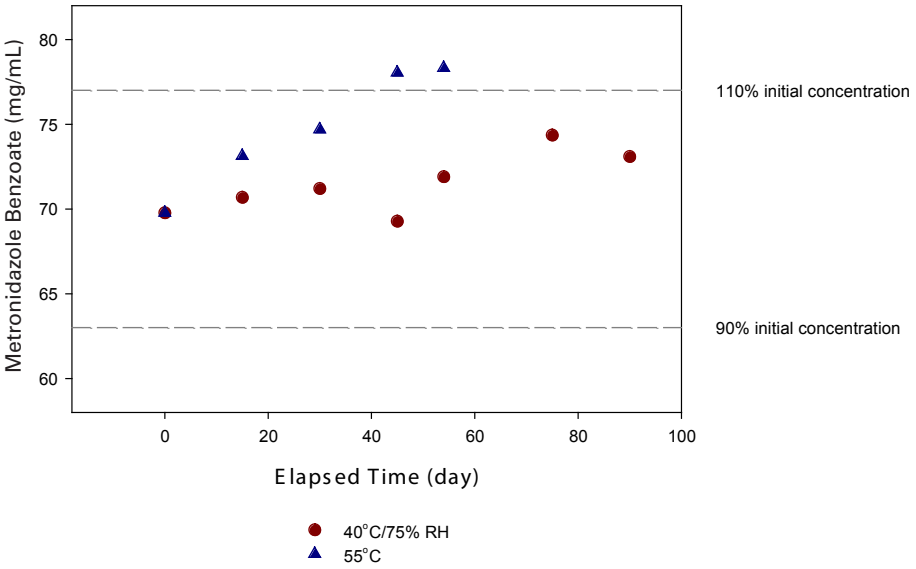
The average assay recovery of metronidazole benzoate from samples stored at 55°C is presented in Table 4. Metronidazole benzoate content exceeded 110% concentration limit after 45 days (Figure 2), and chromatographic profiles of these samples exhibited one decomposition product, which contributed not more than 0.05% of total sample response. The average pH values for these samples were 4.47 ± 0.04, and all samples maintained normal appearance of an opaque suspension. The rate of

FIGURE 1. Plots of metronidazole benzoate concentration (mg/mL) relative to the initial concentration when stored at 2°C to 8°C (refrigeration), and 25°C/60% relative humidity for 360 days.



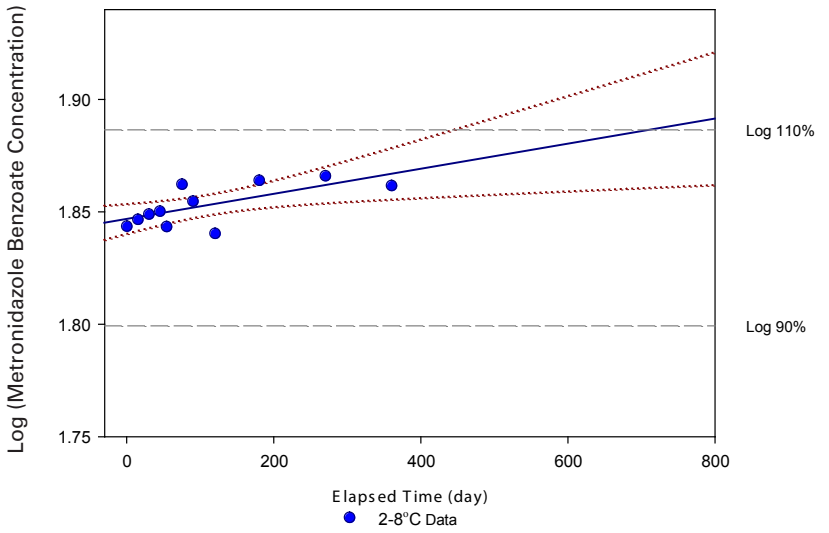
Note: Dotted lines represent lower and upper limits for metronidazole benzoate concentration.

FIGURE 2. Plots of metronidazole benzoate concentration (mg/mL) relative to the initial concentration when samples were stored at 40°C/75% RH, and 55°C for 90 days.



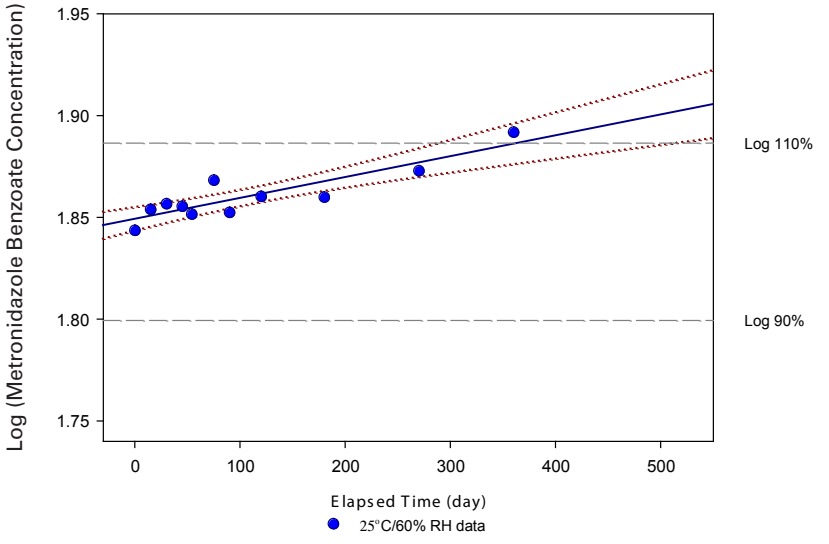
Note: Dotted lines represent lower and upper limits for metronidazole benzoate concentration.

FIGURE 3. Plot depicts rate of change ($k_{2\text{-}8°C}$) for metronidazole benzoate concentration in refrigerated storage (2°C-8°C). Time to reach concentration limits was estimated at approximately 2 years (or 716 days).



Note: Red dotted lines represent 95% confidence interval ($CI_{95\%}$) of prediction; dash lines represent log metronidazole benzoate concentration at 90% to 110% of initial concentration.

FIGURE 4. Plot depicts rate of change ($k_{25°C/60\%RH}$) for metronidazole benzoate concentration in ambient storage (25°C/60% RH). Time to reach concentration limits was estimated at ~ 1 year (or 366 days).



Note: Red dotted lines represent 95% confidence interval ($CI_{95\%}$) of prediction; dash lines represent log metronidazole benzoate concentration at 90% to 110% of initial concentration.

change for metronidazole benzoate $k_{55°C}$ = -0.00126·day^{-1} and the time to reach 90% concentration was estimated at about 37 days ($CI_{95\%}$ ≥26 - 47 days). Thus, based on 90-day stability data, the shelf life for this product was projected to be about one month at 55°C storage condition (Table 5).

CONCLUSION

As previously discussed, the 60-day stability of extemporaneous formulations of metronidazole has been well established with previous results lending support to the present study.[4] This report has demonstrated that except for the accelerated conditions (55°C), all samples were found to be within acceptable ranges for assay recovery. In addition, sample appearance and pH were determined to be within normal limits for all tested samples. Thus, real-time chemical and physical data for metronidazole benzoate suspension in SyrSpend SF (Lot DBAF:73) have indicated that the described formulation is stable for at least 1 year in ambient storage. Better preservation of the sample was observed at refrigerated condition, and, therefore, is the recommended storage temperature for this preparation. The most significant effect in storage was determined to be a result of solvent loss due to evaporation and/or permeation, which was accelerated at higher temperatures and in drier environments such as the storage conditions at 40°C to 55°C. Alternatively, impervious glass containers may be used for packaging of liquid formulations to reduce solvent loss and to further extend the shelf life of these products.

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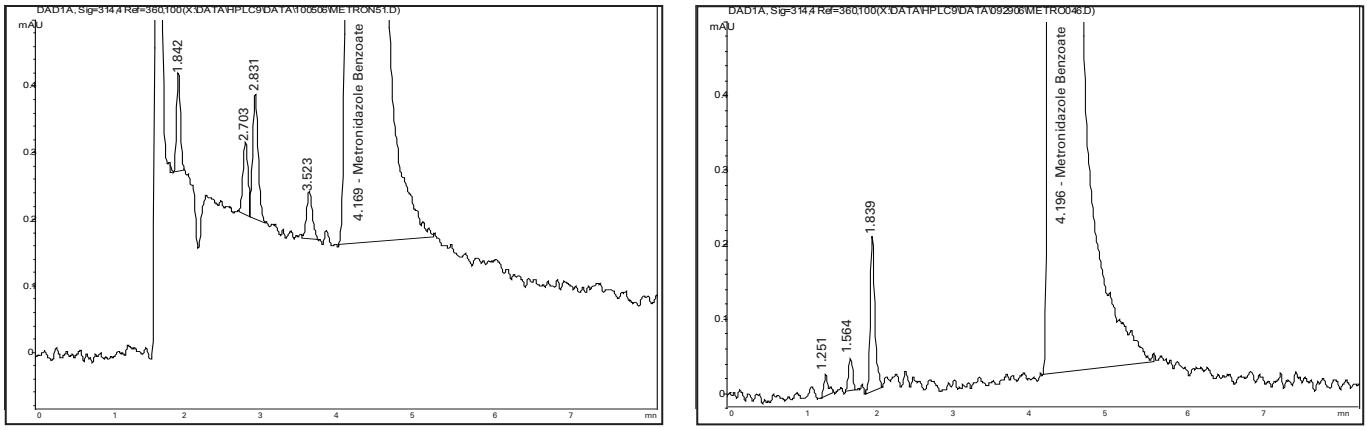
5. Mathew M, Das Gupta V, Bethea C. Sta-

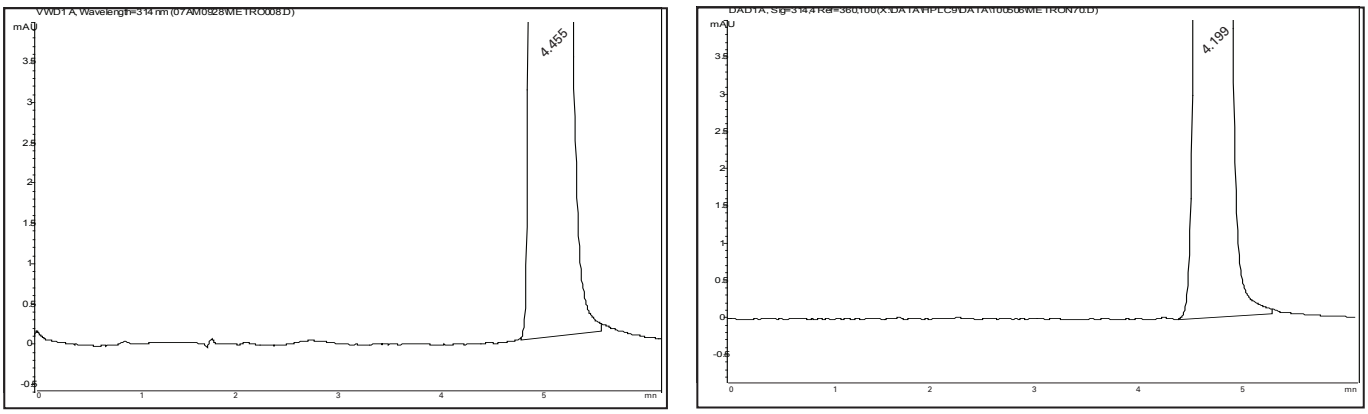
FIGURE 5. Chromatograms of metronidazole benzoate in SyrSpend SF following exposure to 3% hydrogen peroxide and heat at 80°C.



A.) **B.)**

Note: Metronidazole benzoate contributed 99.95% of total detected area (%TDA); degradant peaks identified at retention time 1.84 (0.01%), 2.70 (0.01%), 2.83 (0.02%), and 3.52 (0.01%). Blank artifact peaks were not included in TDA calculation. Sample profiles are shown for stressed sample (a) and control sample (b).

FIGURE 6. Typical chromatographic profiles for metronidazole benzoate in SyrSpend SF sample stored at ambient condition (25°C/60% RH).



A.) **B.)**

Note: Sample profiles were obtained (a) initially (T-0), and (b) at the end of the 360 days (T-360). HPLC profiles were obtained on two different instruments.

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