Stability of Azathioprine, Clonidine Hydrochloride, Clopidogrel Bisulfate, Ethambutol Hydrochloride, Griseofulvin, Hydralazine Hydrochloride, Nitrofurantoin, and Thioguanine Oral Suspensions Compounded with SyrSpend SF PH4

S STABILITY | P PENETRATION | F FORMULATIVE | C CLINICAL STUDY | O OTHER

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Abstract

To allow for tailored dosing and overcome swallowing difficulties, compounded liquid medication is often required in pediatric patients. The objective of this study was to evaluate the stability of oral suspensions compounded with SyrSpend SF PH4 and the commonly used active pharmaceutical ingredients azathioprine (powder) 50 mg/mL, azathioprine (from tablets) 50 mg/mL, clonidine hydrochloride (powder) 0.1 mg/mL, clopidogrel bisulfate (from tablets) 5 mg/mL, ethambutol hydrochloride (powder) 50 mg/mL, ethambutol hydrochloride (from tablets) 50 mg/mL, ethambutol hydrochloride (powder) 100 mg/mL, griseofulvin (powder) 25 mg/mL, hydralazine hydrochloride (powder) 4 mg/mL, nitrofurantoin (powder) 10 mg/mL, and thioguanine (powder) 2.5 mg/mL. Suspensions were compounded at the concentrations listed above and stored at controlled room and refrigerated temperatures. Stability was assessed by measuring the percentage recovery at 0 day (baseline), and at 7 days, 14 days, 30 days, 60 days, and 90 days. Active pharmaceutical ingredients quantification was performed by high-performance liquid chromatography, via a stability-indicating method. The following oral suspensions compounded using SyrSpend SF PH4 as the vehicle showed a beyond-use date of 90 days when stored both at room or refrigerated temperatures: clonidine hydrochloride 0.1 mg/mL, ethambutol hydrochloride 50 mg/mL and 100 mg/mL, griseofulvin 25 mg/mL, nitrofurantoin 10 mg/mL, and thioguanine 2.5 mg/mL, all compounded from the active pharmaceutical ingredients in powder form. Suspensions compounded using the active pharmaceutical ingredients from tablets presented a lower beyond-use date: 30 days for ethambutol hydrochloride 50 mg/mL and hydralazine hydrochloride 4 mg/mL, stored at both temperatures, and for clopidogrel bisulfate 5 mg/mL when stored only at refrigerated temperature. Azathioprine suspensions showed a beyond-use date of 14 days when compounded using active pharmaceutical ingredients in powder form at both temperatures. This suggests that SyrSpend SF PH4 is suitable for compounding active pharmaceutical ingredients from different pharmacological classes.

Introduction

Drug treatment in children can be more challenging than that seen in adults; age-appropriate drug formulations are required because of the wide age range seen in pediatric patients. Additionally, many children have difficulty swallowing tablets and capsules. A suitable liquid alternative with acceptable taste and palatability can help to overcome both hurdles and allow for maximal dosing flexibility over different ages. Although many liquid formulations are commercially available, there is still a broad range of drugs that need to be compounded by the pharmacist. To assure accurate treatment of the compounded medication, the dosing needs to be in accordance to what is defined in the various pharmacopoeias. In the perception of many doctors and pharmacists, compounded capsules offer a safer alternative to suspensions, as they bypass the risk of sedimentation and caking. An earlier study has shown that for many extemporaneously compounded capsules, a routine weight-variation check does not seem to be enough to guarantee the right content. Compounded oral liquids with SyrSpend SF PH4 (liquid) (Fagron, St. Paul, Minnesota) have shown little variation in content for 74 different active pharmaceutical ingredients (APIs), and were all well within the criteria defined by the *United States Pharmacopeia (USP)*, the *European Pharmacopoeia,* and the *British Pharmacopoeia*. Compounding oral liquids were therefore considered to be a valuable alternative when compounding individualized medication for patients.[1]

The purpose of the current study was to determine the stability of different active pharmaceutical ingredients in SyrSpend SF, a vehicle for the compounding of oral liquid dosage forms, providing consistent, individual dosing throughout treatment. This paper focuses on the stability of azathioprine, clonidine hydrochloride (HCl), clopidogrel bisulfate, ethambutol HCl, griseofulvin, hydralazine HCl, nitrofurantoin, and thioguanine oral suspensions compounded with SyrSpend SF PH4.

Methods

REAGENTS, REFERENCE STANDARDS, AND MATERIALS

All API raw powders and SyrSpend SF PH4 (liquid) (Batch number 14F02-U59-019404) were obtained from Fagron. Concentrations and intended use are listed in **TABLE 1**. High-performance liquid chromatographic (HPLC)-grade reagents (Panreac, Barcelona, Spain) were used. Ultrapure water obtained with an AquaMax-Ultra 370 Series (Young Lin, Anyang, Korea) (18.2 MΩ·cm resistivity at 25°C) was used throughout the experiments. The reference standards used were all work standards obtained using primary *USP* (Rockville, MD) reference materials. All the mobile phases and receptor media were filtered through a 0.45-µm filter membrane (RC-45/15 MS; Chromafil, Düren, Germany) and degassed using an ultrasonic apparatus (Model 1600A; Unique, Indaiatuba, Brazil) for 30 minutes immediately before use. All volumetric glassware and the analytical balance used were previously calibrated.

EQUIPMENT

HPLC analyses were performed on a qualified and calibrated chromatography system (Young Lin) composed of a quaternary gradient pump (YL 9110), a photodiode array (PDA) detector (YL 9160), a 96-vial programmable autosampler (YL 9150), a column oven compartment (YL 9130), a variable sample loop up to 200 mL, and a software controller (Clarity).

CHROMATOGRAPHIC CONDITIONS

The chromatographic determinations were based upon *USP* methods for the APIs or their final products, with minor modifications when necessary. The exact chromatographic conditions used

TABLE 1.

CONCENTRATIONS OF THE SUSPENSIONS USED IN THE STUDY.

ACTIVE PHARMACEUTICAL INGREDIENTS	CONCENTRATION IN SUSPENSION (MG/ML)	ACTION/INDICATION
Azathioprine	50.0	Immunosuppressant
Clonidine hydrochloride	0.1	Alpha-2-adrenoceptor agonist; treatment of hypertension
Clopidogrel bisulfate	5.0	Inhibitor of adenosine diphosphate-mediated platelet aggregation
Ethambutol hydrochloride	50.0 and 100.0	Antituberculosis drug
Griseofulvin	25.0	Antifungal
Hydralazine hydrochloride	4.0	Vasodilator; treatment of hypertension
Nitrofurantoin	10.0	Antibacterial
Thioguanine	2.5	Treatment of acute myeloid leukemia; acute lymphocytic leukemia; and chronic myeloid leukemia

for each API are stated in **TABLE 2.** The columns were connected with a pre-column with the same packing (4.0 × 3.0 mm, 5 µm) from the same vendor as the columns.

VALIDATION OF THE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

Validation protocol and the acceptance criteria were established based upon *USP* and International Conference for Harmonisation (ICH) guidelines.[2,3] Specificity of the method was determined by running HPLC analyses of a standard solution, a SyrSpend SF PH4 (liquid) blank solution, and a mobile phase/diluents blank solution. The acceptance criterion was defined as a percentage of discrepancy between the peak areas of less than 2% (Eq. 1). In addition, the specificity of the method was obtained through comparison of standard chromatograms with and without the SyrSpend SF PH4 (liquid) matrix. All analyses were run in triplicate.

$$\% \text{ discrepancy} = 100 \left(\frac{\text{standard area - sample area}}{\text{standard area}} \right) \quad \text{Eq. 1}$$

Precision was evaluated as repeatability and intermediate precision. Repeatability was determined by consecutively analyzing six replicates by a single analyst in a single day. Intermediate precision was also performed in six replicates, but over two days, by different analysts. An injection precision of more than 95% (coefficient of variation (CV) <5%) was considered acceptable.

The accuracy of the method was determined through spike-recovery of the SyrSpend SF PH4 (liquid) matrix, diluted within the range used for final sample measurements (to the calibration curves). Percent recovery was calculated from the concentration measured relative to the theoretical concentration spiked.

For linearity, concentrations from 70% to 130% of the working concentration of the API in SyrSpend SF PH4 (liquid) were prepared and analyzed. The data from each experiment was fitted by ordinary least squares method and was evaluated by analysis of variance (ANOVA).

The limit of detection (LOD) and limit of quantification (LOQ) were determined from three standard calibration curves of the APIs in the presence of the SyrSpend SF PH4 (liquid) matrix and were calculated as shown in Eq. 2 and Eq. 3, respectively:

TABLE 2.

CHROMATOGRAPHIC CONDITIONS USED IN THE COMPATIBILITY STUDY.

ACTIVE PHARMACEUTICAL INGREDIENTS	MOBILE PHASE COMPOSITION	WORK CONCENTRATION (µG/ML)*	COLUMN	FLOW (ML/MIN)	ULTRAVIOLET DETECTION WAVELENGTH (NM)
Azathioprine	1.1 g of sodium heptanesulfonate in 700 mL of water and 300 mL of methanol; pH adjusted to 3.5 with hydrochloric acid	100; 20-µL injection	L1, 4.6-mm × 25-cm; at 25°C	2.0	254
Clonidine hydrochloride	Acetonitrile and 1 mL/L triethylamine in water (32:68); pH adjusted to 6.9 with phosphoric acid	50.0; 50-µL injection	L1, 3.9-mm × 30-cm, at 25°C	2.0	220
Clopidogrel bisulfate	Acetonitrile and 1.36 g/L potassium phosphate monobasic in water (25:75)	100.0, in methanol; 10-µL injection	L1, 4.6-mm × 25-cm, at 25°C	1.0	220
Ethambutol hydrochloride	Acetonitrile and 1 mL/L triethylamine in water (50:50); pH adjusted to 7.0 with phosphoric acid	300.0; 50-µL injection	L10, 4.6-mm × 15-cm, at 25°C	1.0	200
Griseofulvin	Acetonitrile, tetrahydrofuran, and water (35:5:60)	125; 20-µL injection	L10, 4.6-mm × 25-cm, at 40°C	1.0	254
Hydralazine hydrochloride	1.44 g of sodium dodecyl sulfate and 0.75 g of tetrabutylammonium bromide in 770 mL water and 230 mL of acetonitrile. pH adjusted to 3.0 with 0.1N sulfuric acid	40.0; 25-µL injection	L10, 4.0-mm × 25-cm, at 25°C	1.0	230
Nitrofurantoin	Acetonitrile and buffer (12:88). Buffer = 6.8 g of potassium phosphate monobasic in 1000 mL of water; pH adjusted to 7.0 with 1N sodium hydroxide	250.0, in water and dimethylformamide (2:8); 15-µL injection	L1, 3.9-mm × 30-cm; at 40°C	1.2	254
Thioguanine	6 g of sodium phosphate monobasic in 1 L of water; pH adjusted to 3.0 with phosphoric acid	40.0, in 0.01M sodium hydroxide; 10-µL injection	L1, 4.6-mm × 5-cm, at 25°C	2.0	248

*Diluted with mobile phase, unless specified otherwise

$$LOD = s\frac{3}{a} \qquad \text{Eq. 2}$$

$$LOQ = s\frac{10}{a} \qquad \text{Eq. 3}$$

where a is the slope of the calibration curve, and s is the standard deviation of the y-intercept. The LOD and LOQ were confirmed by the analysis of chromatograms generated by injecting solutions in their respective limit concentrations.

PREPARATION OF ACTIVE PHARMACEUTICAL INGREDIENTS SUSPENSION SAMPLES

The suspensions compounded with raw powders were prepared using the following general protocol:

1. The required quantity of each ingredient for the total amount to be prepared was calculated.
2. Each ingredient was accurately weighed.
3. The API was placed in a mortar and triturated until a fine powder was obtained.
4. A small amount of the SyrSpend SF PH4 (liquid) was added to the powder and mixed to form a uniform paste.
5. The SyrSpend SF PH4 (liquid) was further added in approximately geometric portions almost to volume, mixing thoroughly after each addition.
6. Sufficient SyrSpend SF PH4 (liquid) was added to bring the volume to 300 mL, and then mixed well.
7. The final product was packaged in low-actinic, light-resistant prescription bottles and labeled.
8. The suspensions were then immediately assayed at T = 0.
9. The suspensions were then separated into two different 150-mL bottles: one sample was stored at controlled refrigerated (2°C to 8°C) and the other at room temperature (20°C to 25°C), for the duration of the study.
10. Temperature and humidity were checked in real-time throughout the duration of the experiment, using a calibrated, digital thermohygrometer (Incoterm).

The suspensions compounded with tablets were prepared using the following general protocol:

1. The required quantity of tablets for the total amount to be prepared was calculated.
2. The tablets were crushed using a mortar and pestle until a fine powder was obtained.
3. The exact quantity of powder needed to prepare the suspension was accurately weighed.
4. A small amount of the SyrSpend SF PH4 (liquid) was added to the powder and mixed to form a uniform paste.
5. The SyrSpend SF PH4 (liquid) was further added in approximately geometric portions almost to volume, mixing thoroughly after each addition.
6. Sufficient SyrSpend SF PH4 (liquid) was added to bring the volume to 100 mL, and then mixed well.
7. The final product was packaged in low-actinic, light-resistant prescription bottles and labeled.
8. The suspensions were then immediately assayed at T = 0.
9. The suspensions were then separated into two different 150-mL bottles: one sample was stored at controlled refrigerated (2°C to 8°C) and the other at room temperature (20°C to 25°C), for the duration of the study.
10. Temperature and humidity were checked in real time throughout the duration of the experiment, using a calibrated, digital thermohygrometer (Incoterm).

FORCED-DEGRADATION STUDIES: STABILITY-INDICATING CHARACTERISTICS

API samples were subjected to the following stressing conditions for 24 hours to determine the capacity of the HPLC method and to detect any possible degradation products that may arise during storage of the oral suspension:

1. Dilution in acid (0.1M HCl, at 25°C);
2. Dilution in base (0.1M NaOH, at 25°C);
3. Exposure to ultraviolet (UV) light at 365 nm (at 25°C);
4. Heating to 70°C; and
5. Dilution in H_2O_2 35% (v/v) (at 25°C).

These solutions were prepared for each API at its respective work concentration by means of serial dilution from a stock-solution and using suitable diluents (see **TABLE 2**). The stock solutions were sonically dispersed by 10 minutes, and the final solutions were filtered (15-mm regenerated cellulose syringe filters, with 0.45-µm pore size) before injection onto the HPLC system. Any extraneous peaks found in the chromatograms were labeled. A resolution of 1.5 between the peaks of the degradation products and the API was considered full separation. Also, a discrepancy greater than 2% between the stressed sample peak and the standard, non-stressed sample peak was considered indicative of API decomposition.

STABILITY STUDY

The API samples were assayed by HPLC at pre-determined time points to verify the stability of the API in SyrSpend SF PH4 (liquid). Before analyses, the bottles were shaken until the API was uniformly dispersed by visual inspection. Aliquots for quantification (variable for each API) were withdrawn from the middle of the bottles, without contact with the inner surface of the bottle, and diluted in order to obtain work solutions in the concentra-

TABLE 3.

SUMMARY OF VALIDATION RESULTS OF THE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHODS.

API	LINEARITY						SPECIFICITY	PRECISION		ACCURACY
	RANGE (µG/ML)	ANALYTICAL CURVE	R^2	ANOVA'S SIGNIFICANCE OF REGRESSION (F)	LOD (µG/ML)	LOQ (µG/ML)	DISCREPANCY (%)	REPEATABILITY (CV, %)	INTERMEDIATE PRECISION (CV, %)	RECOVERY (%)
Azathioprine	70.84 – 131.56	y = 47.40x – 50.92	0.9988	10964.58	1.85	6.16	|0.89|	0.12	0.71	100.11
Clonidine HCl	7.35 – 13.65	y = 664.80x + 40.27	0.9993	18826.39	66.73	222.44	|1.67|	0.03	0.45	99.76
Clopidogrel bisulfate	140.00 – 260.00	y = 2.14x - 26.49	0.9931	1888.93	21.52	71.72	|1.02|	0.73	3.76	100.02
Ethambutol HCl	174.86 – 324.74	y = 233.04x – 926.95	0.9988	10552.86	4.72	15.74	|1.76|	0.31	0.51	99.94
Griseofulvin	87.71 – 162.89	y = 39.20x – 89.57	0.9957	3053.82	9.15	30.49	|0.44|	0.10	1.11	99.41
Hydralazine HCl	75.00 – 130.00	y = 513.98x – 6598.25	0.9909	1426.33	7.60	25.32	|0.67|	0.06	2.17	99.41
Nitrofurantoin	350.14 – 650.26	y = 71.24x + 1374.98	0.9964	3568.05	0.005	0.02	|1.97|	0.35	0.64	99.39
Thioguanine	28.00 – 52.00	y = 6.19x + 29.12	0.9941	1095.34	0.06	0.19	|0.95|	3.44	3.39	100.25

Acceptance criteria were: R^2 >0.99; F (significance of regression) >>4.67; discrepancy <2%; repeatability and intermediate precision <5%; and recovery = 100% ± 2%. All analytical ranges (µg/mL) were adequate to quantify the APIs in the concentrations used in the suspensions (mg/mL).
API = active pharmaceutical ingredient; CV = Coefficient of Variation; HCl = hydrochloride; LOD = Limit of Detection; LOQ = Limit of Quantification (20-µL injections).

tion described in TABLE 1. Sampling times were: 0 days (T = 0), 7 days (T = 7), 14 days (T = 14), 30 days (T = 30), 60 days (T = 60), and 90 days (T = 90).

All suspensions were assayed six times, and the results expressed as the mean from six independent measurements. For that purpose, samples were diluted, sonicated for 10 minutes, and then filtered in 15-mm regenerated cellulose syringe filters, with 0.45-µm pore size before injection onto the HPLC system. The evaluation parameter was the percent recovery with respect to T = 0, using the HPLC method (results given as percentage ± standard deviation).

Results and Discussion

Validation studies of all methods of analysis were performed and all results (TABLE 3) met the respective acceptance criteria, confirming the suitability of the methods for the objectives of this work. Stability-indicating studies were also conducted to determine if the used methods were fully validated and adequate to identify decomposition of the APIs by chromatographic analysis. The decomposition profile of the APIs notably varied for different stressing conditions. Acidic stress affected all APIs tested; alkaline stress also affected all APIs except for clonidine HCl; UV-light exposure and heat exposure decomposed clonidine HCl, clopidogrel bisulfate, griseofulvin, and thioguanine; and oxidative stress impacted all but azathioprine and griseofulvin. Once the forced-degradation profiles of the APIs were determined, the stability of the APIs in SyrSpend

TABLE 4.

SUMMARY OF THE STABILITY-INDICATING STUDY FOR THE ACTIVE PHARMACEUTICAL INGREDIENTS.

ACTIVE PHARMACEUTICAL INGREDIENTS	HCL	NAOH	UV	HEAT	H_2O_2
	%D*	%D*	%D*	%D*	%D*
Azathioprin	**6.81**	**-34.31**	-0.51	0.58	-1.97
Clonidine HCl	**-94.38**	1.29	**-9.78**	**10.84**	**-17.53**
Clopidogrel bisulfate	**38.03**	**ND**	**30.15**	**11.75**	**-27.14**
Ethambutol HCl	**-37.94**	**ND**	-1.81	0.35	**-9.43**
Griseofulvin	**-34.18**	**-2.90**	**0.34**	**-0.67**	-10.04
Hydralazine HCl	**3.79**	**ND**	2.14	-1.11	**-2.79**
Nitrofurantoin	**-73.55**	**ND**	1.01	0.82	**-9.54**
Thioguanine	**37.52**	**63.44**	**76.89**	**80.14**	**ND**

Results are presented as the average of 3 replicates, at the work concentration.
*%d = percentage of discrepancy between the active pharmaceutical ingredient peak without submission to stressing factors (negative control) and the peak of a sample subjected to one of the cited accelerated-degradation factors.
Areas given as mV. Maximum acceptable = 2% (values higher than this are in bold and they represent significant resuts).
HCl = hydrochloride; NaOH = sodium hydroxide solution; ND = non-detected; UV = ultraviolet

SF PH4 (liquid) was assessed. Results are summarized in TABLE 4.

At each sampling time, the visual appearance of the suspensions was also evaluated to verify their homogeneity and physical stability (data not shown). Throughout the whole study, no phenomena such as precipitation, turbidity, macroscopically visible crystal growth, odor generation, phase separation, flocculation, or caking were observed when the drug content was within specifications.

The chemical stability results are shown in TABLE 5 and are expressed as relative percent of recovery (initial sampling time = 100%). For the suspensions to be considered stable, the relative percentage recovery should lie within 90% to 110%.[4]

AZATHIOPRINE

In our study, a beyond-use date (BUD) of 14 days was observed when the suspensions were compounded from powder and stored at both room and refrigerated temperatures. The suspensions compounded from tablets showed a BUD of 7 days at room temperature.

Azathioprine suspensions compounded from tablets were also studied by Dressman and Poust (1983)[5] and Allen and Erickson (1996).[4] In the first study, little or no loss occurred in 56 days at room temperature or in 84 days at 5°C, but assay was performed using UV spectrophotometry, which is low sensitive to detect degradation products. By their turn, Allen and Erickson detected losses lower than 4% through HPLC analysis after 60 days of storage at room or refrigerated temperature, when compounded using Ora-Sweet and Ora-Plus.

CLONIDINE HYDROCHLORIDE

The clonidine suspensions prepared with SyrSpend SF PH4 in this work presented a BUD of 90 days when stored both at refrigerated and at room temperatures. This is a higher stability than the one reported by Levinson and Johnson (1992),[6] which evaluated clonidine suspension prepared from tablets and with simple syrup: their BUD was reported as 28 days, when stored at 4°C in the dark.

CLOPIDOGREL BISULFATE

Clopidogrel bisulfate 5-mg/mL suspensions compounded from tablets and using SyrSpend SF PH4 as the vehicle showed stability for 30 days when stored under refrigeration, and the storage at room temperature is not recommended due to instability.

Skillman et al[7] evaluated suspensions with the same API, in the same concentration, and in the same storage conditions, but, in that study, the suspensions were prepared with Ora-Plus and Ora-Sweet and using Plavix tablets as the raw material. They found that the suspensions remained stable for 60 days in both storage conditions, although the bitter aftertaste of the product intensified between 28 days and 60 days. Tynes et al[8] complemented the study of Skillman et al and verified that during this period the oral suspension of clopidogrel retained at least 98% of the active S-enantiomer for 60 days (more chiral inversion was noted in the clopidogrel suspension stored at room temperature).

ETHAMBUTOL HYDROCHLORIDE

Three ethambutol suspensions were evaluated in the present study, all compounded using SyrSpend SF PH4 as the vehicle, with 50 mg/mL and 100 mg/mL prepared from the API as powder and 50 mg/mL prepared from tablets (Combutol 800). The suspensions prepared from the powder remained stable for the 90-day period of study, with no physical or chemical intercurrences. The suspensions prepared from the tablets remained stable for 30 days, indicating a possible reaction between the vehicle and the excipients of this particular tablet used.

According to the *USP*,[9] a 100-mg/mL suspension compounded with equal parts of Ora-Plus and Ora-Sweet SF has a BUD of 90 days, but no specific stability study was found in the literature.

GRISEOFULVIN

Griseofulvin 25-mg/mL suspensions compounded with SyrSpend SF PH4 presented a BUD of at least 90 days when stored at refrigerated or room temperatures. Losses of less than 2% were found throughout the study, and no physical change was detected. No other report from literature was found for a parameter for comparison.

HYDRALAZINE HYDROCHLORIDE

Hydralazine HCl 4-mg/mL oral suspensions compounded using SyrSpend SF PH4 as the vehicle presented a BUD of at least 30 days when stored both at refrigerated and at room temperatures.

Hydralazine HCl oral suspensions were extensively studied. Alexander et al[10] evaluated various potential adjuvants for compounding the suspension with syrup and tablets, but HPLC analyses calculated a shelf life of only 5.13 days at room temperature and 14 days at 5°C, and they have found that hydralazine HCl was incompatible with sodium edetate and sodium bisulfite. Gupta et al[11] investigated the stability of 1% hydralazine HCl with various aqueous agents, and they verified losses of 30% to 70% in 24 hours when stored at 24°C. In the same study, they evaluated the 1% API in 85% sucrose solution, and losses of 10% occurred in about 7 days at 24°C; in 0.28 mM mannitol, no loss occurred after 21 days of storage at 24°C. Allen and Erickson[12] evaluated the API at 4 mg/mL in Ora-Sweet and Ora-Sweet SF, but losses of 22% and 13% were observed in 1 day for Ora-Sweet and Ora-Sweet SF, respectively; at refrigerated temperature, losses lower than 10% were observed in 1 day for Ora-Sweet and 2 days for Ora-Sweet SF.

NITROFURANTOIN

Nitrofurantoin 10-mg/mL oral suspensions compounded using SyrSpend SF PH4 as the vehicle presented less than 1% of loss in the API amount during the duration of the study, which accounts for a BUD of 90 days. A previous study from Ferreira et al[13] observed the same BUD, but for a 2-mg/mL suspension in the same vehicle

TABLE 5.

STABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 (LIQUID).

ELAPSED TIME (DAYS)	% RECOVERY	
	REFRIGERATED TEMPERATURE (2°C TO 8°C)	CONTROLLED ROOM TEMPERATURE (20°C TO 25°C)
AZATHIOPRINE (FROM POWDER) 50.0 MG/ML		
T = 0	100 ± 1.69	100 ± 1.69
T = 7	99.35 ± 0.60	99.94 ± 0.51
T = 14	100.81 ± 0.66	100.64 ± 0.61
T = 30	82.33 ± 0.81	77.83 ± 1.61
T = 60	NP	NP
T = 90	NP	NP
AZATHIOPRINE (FROM TABLETS) 50.0 MG/ML		
T = 0	100 ± 0.38	100 ± 0.38
T = 7	77.90 ± 0;39	100.29 ± 0.22
T = 14	ND	82.96 ± 0.34
T = 30	NP	ND
T = 60	NP	NP
T = 90	NP	NP
CLONIDINE HYDROCHLORIDE (FROM POWDER) 0.1 MG/ML		
T = 0	100 ± 0.27	100 ± 0.27
T = 7	95.20 ± 0.10	94.52 ± 0.76
T = 14	95.75 ± 0.98	96.17 ± 1.14
T = 30	96.82 ± 0.83	95.56 ± 0.71
T = 60	96.34 ± 0.55	95.88 ± 0.60
T = 90	95.99 ± 0.47	98.23 ± 0.45
CLOPIDOGREL BISULFATE (FROM TABLETS) 5 MG/ML		
T = 0	100 ± 0.90	100 ± 0.90
T = 7	103.02 ± 0.81	ND
T = 14	96.18 ± 0.45	NP
T = 30	101.14 ± 0.72	NP
T = 60	ND	NP
T = 90	NP	NP
ETHAMBUTOL HYDROCHLORIDE (FROM POWDER) 50 MG/ML		
T = 0	100 ± 0.35	100 ± 0.35
T = 7	101.54 ± 0.79	97.53 ± 1.92
T = 14	98.58 ± 0.27	99.61 ± 2.52
T = 30	98.66 ± 0.20	98.82 ± 0.31
T = 60	99.69 ± 0.42	95.45 ± 0.53
T = 90	99.14 ± 0.23	98.09 ± 0.40
ETHAMBUTOL HYDROCHLORIDE (FROM TABLETS) 50 MG/ML		
T = 0	100 ± 0.77	100 ± 0.77
T = 7	94.03 ± 0.16	93.45 ± 0.20
T = 14	93.09 ± 1.10	91.69 ± 0.60
T = 30	96.54 ± 0.32	94.37 ± 0.36
T = 60	70.88 ± 0.21	80.15 ± 0.14
T = 90	NP	NP

TABLE 5 CONTINUED.

STABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 (LIQUID).

ELAPSED TIME (DAYS)	% RECOVERY	
	REFRIGERATED TEMPERATURE (2°C TO 8°C)	CONTROLLED ROOM TEMPERATURE (20°C TO 25°C)
ETHAMBUTOL HYDROCHLORIDE (FROM POWDER) 100 MG/ML		
T = 0	100 ± 0.26	100 ± 0.26
T = 7	94.84 ± 0.38	97.78 ± 0.59
T = 14	94.99 ± 0.19	96.66 ± 0.23
T = 30	94.31 ± 0.78	98.23 ± 0.55
T = 60	94.96 ± 0.46	98.89 ± 0.56
T = 90	94.91 ± 0.63	97.91 ± 0.75
GRISEOFULVIN (FROM POWDER) 25 MG/ML		
T = 0	100 ± 0.17	100 ± 0.17
T = 7	100.03 ± 0.23	101.20 ± 0.20
T = 14	98.51 ± 0.18	101.48 ± 0.19
T = 30	99.28 ± 0.25	101.87 ± 0.34
T = 60	98.81 ± 0.10	101.68 ± 0.16
T = 90	98.42 ± 0.29	100.83 ± 0.25
HYDRALAZINE HYDROCHLORIDE (FROM POWDER) 4 MG/ML		
T = 0	100 ± 0.57	100 ± 0.57
T = 7	100.25 ± 0.26	101.75 ± 0.50
T = 14	102.32 ± 0.40	97.10 ± 0.41
T = 30	101.90 ± 0.21	98.05 ± 0.45
T = 60	67.32 ± 0.53	65.02 ± 2.02
T = 90	NP	NP
NITROFURANTOIN (POWDER) 10 MG/ML		
T = 0	100 ± 0.34	100 ± 0.34
T = 7	96.77 ± 0.82	100.26 ± 0.89
T = 14	98.59 ± 0.58	99.32 ± 0.29
T = 30	100.12 ± 0.65	100.07 ± 0.40
T = 60	99.67 ± 0.26	100.11 ± 0.38
T = 90	99.89 ± 0.39	99.88 ± 0.45
THIOGUANINE (FROM POWDER) 2.5 MG/ML		
T = 0	100 ± 1.03	100 ± 1.03
T = 7	101.05 ± 0.24	100.43 ± 0.13
T = 14	101.76 ± 0.38	102.04 ± 0.24
T = 30	101.79 ± 0.31	101.59 ± 0.11
T = 60	100.88 ± 2.33	99.15 ± 1.68
T = 90	101.37± 0.37	100.03 ± 1.06

ND = not detected; NP = not performed

(losses of less than 1.5%), which indicates that this API has a good stability in SyrSpend SF PH4. No other report using other vehicles was found in available literature.

THIOGUANINE

Thioguanine suspensions (2.5 mg/mL) compounded with SyrSpend SF PH4 and stored at room or refrigerated temperatures showed no significant loss of API during the period of 90 days of evaluation. Dressman and Poust[5] previously evaluated the stability of thioguanine 40 mg/mL in a suspension prepared from tablets and Cologel (Lilly) and a 2:1 mixture of simple and cherry syrups. Their suspension was stored in amber glass bottles at 5°C and at ambient temperature, and remained stable for 84 days.

A plot of the APIs in SyrSpend SF PH4 throughout the compatibility study is represented in **FIGURE 1**.

Conclusion

The following oral suspensions compounded using SyrSpend SF PH4 as the vehicle and compounded from the API in powder form showed a BUD of 90 days when stored both at room or refrigerated temperatures: clonidine HCl 0.1 mg/mL, ethambutol HCl 50 mg/mL and 100 mg/mL, griseofulvin 25 mg/mL, nitrofurantoin 10 mg/mL, and thioguanine 2.5 mg/mL. Suspensions compounded using the API from tablets presented a lower BUD: 30 days for ethambutol HCl 50 mg/mL and hydralazine HCl 4 mg/mL, stored at both temperatures, and for clopidogrel bisulfate 5 mg/mL when stored only at refrigerated temperature. Azathioprine suspensions showed a BUD of 14 days when compounded using API in powder form, at both temperatures. In an earlier publication with SyrSpend SF PH4 liquid, no influence of excipients of tablets and capsules on the BUD of several APIs was found.[1] This new publication suggests that raw pharmaceutical materials can be the preferred source for certain APIs. Considering this new result and the previous ones from literature,[13-39] it is noteworthy that SyrSpend SF is one the most studied oral vehicles worldwide, with over 100 different API compatibility combinations studied.

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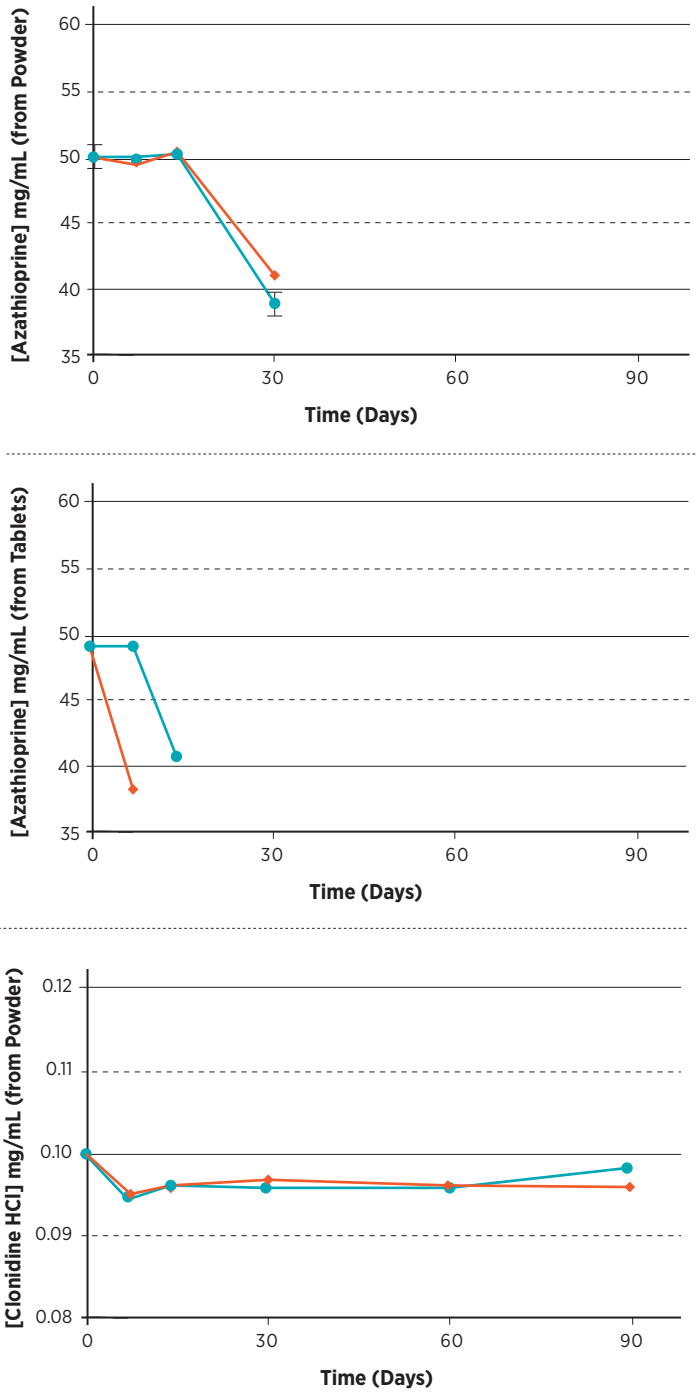
FIGURE 1.

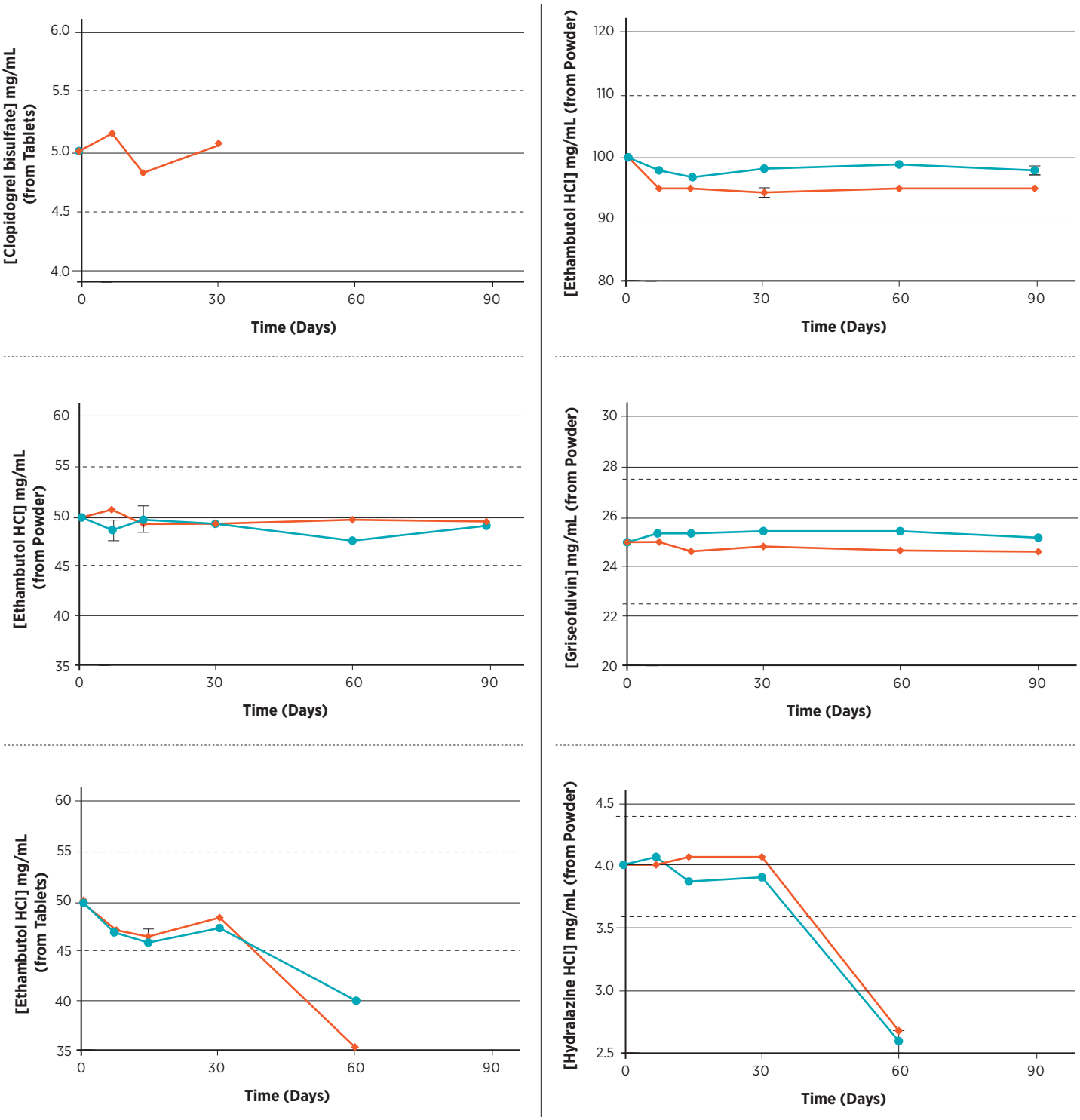
PLOT OF ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 THROUGHOUT THE COMPATIBILITY STUDY.



Dashed lines represent the lower and upper limits, corresponding to 90% and 100% of labeled concentration; blue lines represent results from storage at controlled refrigerated temperature (2°C to 8°C); orange lines correspond to storage at controlled room temperature (20°C to 25°C). Values represent the relative average recovery, as mg/mL (*n*=6).

FIGURE 1 CONTINUED.

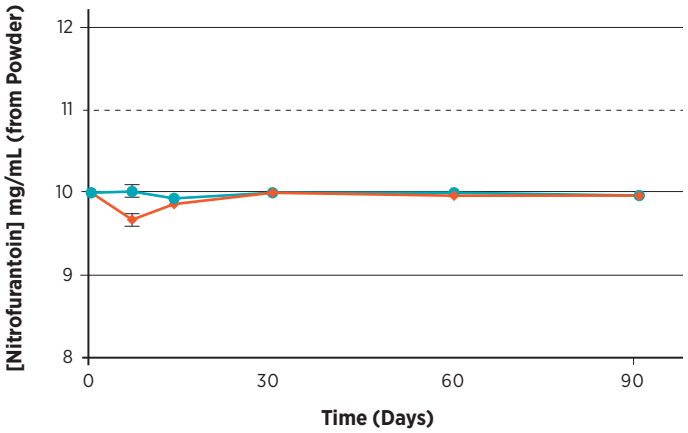
PLOT OF ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 THROUGHOUT THE COMPATIBILITY STUDY.

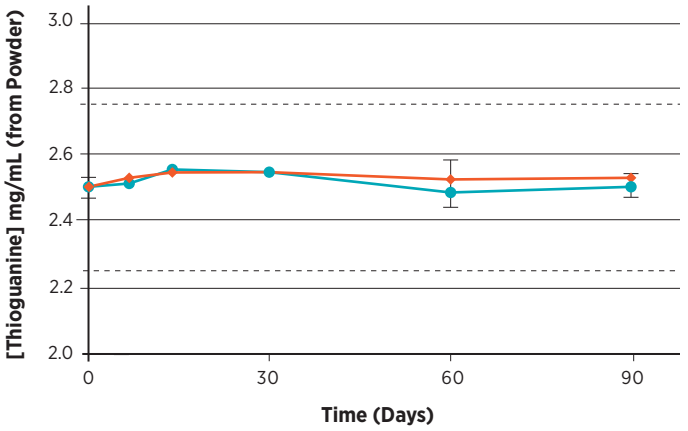


Dashed lines represent the lower and upper limits, corresponding to 90% and 100% of labeled concentration; blue lines represent results from storage at controlled refrigerated temperature (2°C to 8°C); orange lines correspond to storage at controlled room temperature (20°C to 25°C). Values represent the relative average recovery, as mg/mL (*n*=6).

FIGURE 1 CONTINUED.

PLOT OF ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 THROUGHOUT THE COMPATIBILITY STUDY.





Dashed lines represent the lower and upper limits, corresponding to 90% and 100% of labeled concentration; blue lines represent results from storage at controlled refrigerated temperature (2°C to 8°C); orange lines correspond to storage at controlled room temperature (20°C to 25°C). Values represent the relative average recovery, as mg/mL (n=6).

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