Stability of Alprazolam, Atropine Sulfate, Glutamine, Levofloxacin, Metoprolol Tartrate, Nitrofurantoin, Ondansetron Hydrochloride, Oxandrolone, Pregabaline, and Riboflavin in SyrSpend SF PH4 Oral Suspensions

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ABSTRACT

The objective of this study was to evaluate the stability of 10 commonly used active pharmaceutical ingredients compounded in oral suspensions using an internationally used suspending vehicle (SyrSpend SF PH4): alprazolam 1.0 mg/mL, atropine sulfate 0.1 mg/mL, glutamine 250.0 mg/mL, levofloxacin 50.0 mg/mL, metoprolol tartrate 10.0 mg/mL, nitrofurantoin 2.0 mg/mL, ondansetron hydrochloride 0.8 mg/mL, oxandrolone 3.0 mg/mL, pregabaline 20.0 mg/mL, riboflavin 10.0 mg/mL. All suspensions were stored at both controlled refrigeration (2°C to 8°C) and controlled room temperature (20°C to 25°C). Stability was assessed by measuring the percent recovery at varying time points throughout a 90-day period. Active pharmaceutical ingredients quantification was performed by high-performance liquid chromatography via a stability-indicating method. Given the percentage of recovery of the active pharmaceutical ingredients within the suspensions, the beyond-use date of the final products (active pharmaceutical ingredients + vehicle) was at least 90 days for all suspensions with regard to both temperatures. This suggests that the vehicle is stable for compounding active pharmaceutical ingredients from different pharmacological classes.

INTRODUCTION

Swallowing is a complex process, involving both the muscles of the throat as well as the lips, tongue and cheeks.[1] A healthy person unconsciously swallows approximately two times per minute.[2] Nevertheless, dysphagia or swallowing difficulty is common among various types of patients. Studies have shown that 25% to 45% of the pediatric patients, 50% to 75% of the elderly, and almost 23% of the general population suffer from dysphagia.[3-5] Dysphagia may be caused by physical changes of the mouth, throat, and/or larynx. In addition, with age, due to medication side effects or local nerve damage, problems may also arise in the control of the muscles. Dysphagia may subsequently lead to malnutrition, exsiccosis, aspiration pneumonia, and respiratory failure.[6]

In practice, dysphagia is infrequently acknowledged and considered when prescribing medication. An important factor is that patients or their caretakers do not address the problem or are not aware of it. Dysphagia, however, has a great impact on medication intake. Common solutions to allow patients to take their medication are the crushing of tablets, the filling of capsules, or, if possible, the abandonment of medication. These modifications will affect both safety, efficacy, and quality of life.[7] Crushing enteric-coated or controlled-release tablets might result in degradation of the active or dose dumping, respectively, which can result in decreased efficacy or an increased risk of side effects.[8]

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For patients with dysphagia, oral liquids are often a more convenient, better adhered, and safer alternative. Because the majority of medicines are not readily available as a liquid, pharmacists frequently need to compound the oral medication. In order to obtain sufficient physical, chemical, and microbiological stability as well as an acceptable taste, suspensions are often a better option than solutions, or even the only possible option.[9]

Since many people suffer from dysphagia, it is important to determine the feasibility of using SyrSpend SF for the compounding of many different active pharmaceutical ingredients (APIs), so it can be a better alternative to crushed tablets or capsules. During this study, we investigated the stability of 10 APIs representing different pharmacological classes, including alprazolam, atropine sulfate, glutamine, levofloxacin, metoprolol tartrate, nitrofurantoin, ondansetron hydrochloride (HCl), oxandrolone, pregabaline, and riboflavin. SyrSpend SF is designed to help optimize the compounding of suspensions. The patented "Active Suspending Technology" assists in administering the right dose throughout the therapy. The use of starch instead of methylcellulose makes SyrSpend SF highly compatible with a wide range of APIs.[10-25] A single concentration of the APIs (Table 1) was selected based on commonly prescribed medications, and the suspensions were stored both at refrigerated and at room temperature throughout the study.

TABLE 1. CONCENTRATIONS OF THE SUSPENSIONS USED IN THE STUDY.

ACTIVE PHARMACEUTICAL INGREDIENTS	CONCENTRATION IN SUSPENSION	ACTION AND USE
Alprazolam	1.0 mg/mL	Benzodiazepine
Atropine sulfate	0.1 mg/mL	Anticholinergic
Glutamine	250.0 mg/mL	Aminoacid
Levofloxacin	50.0 mg/mL	Antibacterial
Metoprolol tartrate	10.0 mg/mL	Beta-adrenoceptor agonist
Nitrofurantoin	2.0 mg/mL	Antibacterial
Ondansetron hydrochloride	0.8 mg/mL	Serotonin $5HT_3$ antagonist
Oxandrolone	3.0 mg/mL	Anabolic steroid
Pregabaline	20.0 mg/mL	Antiepileptic
Riboflavin	10.0 mg/mL	Vitamin B_2

MATERIALS AND METHODS

REAGENTS, REFERENCE STANDARDS, AND MATERIALS

All API raw materials and SyrSpend SF PH4 (liquid) (Lot 14F02-U59-019404) were obtained from Fagron (St. Paul, Minnesota). High-performance liquid chromatography (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 and <10 ppb total organic carbon) was used throughout the experiments. The reference standards used were all work standards obtained using primary *United States Pharmacopeia (USP)* (Rockville, Maryland) 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 analytical balances used were calibrated.

EQUIPMENT

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

VALIDATION OF THE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

The validation protocol and the acceptance criteria were established based upon *USP* (2015) and International Conference on Harmonization (ICH) (2005) guidelines.[26,27]

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 {[(standard area – sample area)/standard area] × 100} between the peak areas of less than 2%. 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.

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]) 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

TABLE 2. CHROMATOGRAPHIC CONDITIONS USED IN THE COMPATIBILITY STUDY.

ACTIVE PHARMACEUTICAL INGREDIENT	MOBILE PHASE COMPOSITION	WORK CONCENTRATION (µG/ML)*	COLUMN	FLOW (ML/MIN)	UV DETECTION WAVELENGTH (NM)
Alprazolam	Acetonitrile and water (75:25), with pH adjusted to 2.75 with hydrochloric acid	20.0; 20 µL injection	L1, 4.6-mm × 25-cm; at 25°C[1]	1.0	254
Atropine sulfate	5.1 g of tetrabutylammonium hydrogen sulfate with 50 mL of acetonitrile and qs of buffer (4.1 g of sodium acetate and 2.9 mL of glacial acetic acid in 1 L of water) to 1 L. This solution was adjusted with 5 N sodium hydroxide to a pH of 5.5.	80.0; 20 µL injection	L1, 3.9-mm × 30-cm; at 25°C[2]	2.0	254
Glutamine	Acetonitrile and ammonium hydroxide buffer pH 7.5 (75:25)	500.0, in a mixture of acetonitrile and water (75:25); 20 µL injection	L8, 4.6-mm × 15-cm; at 35°C[3]	1.0	195
Levofloxacin	Acetonitrile and water (18:82), containing 1 mL of trifluoroacetic acid in each 1000 mL of solution	15, in a mixture of acetonitrile and water (18:82); 20 µL injection	L11, 4.6-mm × 15-cm; at 30°C[4]	1.5	294
Metoprolol tartrate	961 mg of 1-pentanesulfonic acid sodium salt (monohydrate) and 82 mg of anhydrous sodium acetate in a mixture of 550 mL of methanol and 470 mL of water, with 0.57 mL of glacial acetic acid	100.0; 20 µL injection	L1, 4.6-mm × 25-cm; at 25°C[5]	1.0	254
Nitrofurantoin	5 mM potassium phosphate and acetonitrile (80:20), with pH adjusted to 3.0 with phosphoric acid	2,500.0 in acetonitrile; 20 µL injection	L1, 4.6-mm × 15-cm; at 30°C[6]	1.0	370
Ondansetron hydrochloride	43 mM monobasic potassium phosphate buffer adjusted with a mixture of 1 N sodium hydroxide and acetonitrile (85:15) to a pH of 5.4	4.0; 50 µL injection	L10, 4.6-mm × 25-cm; at 30°C[7]	1.5	216
Oxandrolone	Water and acetonitrile (50:50)	1,200.0, in acetonitrile; 20 µL injection	L1, 4.6-mm × 25-cm; at 25°C[8]	1.0	210
Pregabaline	0.05 M phosphate buffer pH 6.9 and acetonitrile (35:5)	800.0; 20 µL injection	L1, 4.6-mm × 25-cm; at 25°C[9]	1.0	200
Riboflavin	Methanol, glacial acetic acid, and water (27:1:73), containing 1.40 mg/mL of sodium 1-hexanesulfonate	10.0; 20 µL injection	L1, 4.6-mm × 15-cm; at 25°C[10]	1.0	280

*Diluted with mobile phase, unless specified otherwise.

[1]Zorbax Eclipse XDB 5µ (Agilent); [2]Zorbax Eclipse XDB 5µ (Agilent); [3]Microsorb-MV 100-5 (Varian); [4]Zorbax Eclipse XDB 5µ (Agilent); [5]Zorbax Eclipse XDB 5µ (Agilent); [6]Zorbax Eclipse XDB 5µ (Agilent); [7]Kromasil 60 (Kromasil); [8]Zorbax Eclipse XDB 5µ (Agilent); [9]Luna 5µ 100A (Phenomenex); [10]Zorbax Eclipse XDB 5µ (Agilent)

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 equations (1) and (2), respectively:

$$LOD = s\frac{3}{a} \qquad (1)$$

$$LOQ = s\frac{10}{a} \qquad (2)$$

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 API suspensions 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.

The final concentrations in the bottles are summarized in Table 1.

The suspensions were then immediately assayed at T = 0, and then separated into two different 150-mL bottles: one sample was stored at controlled refrigerated (2°C to 8°C) and the other sample at room temperature (20°C to 25°C), for the duration of the study (temperature and humidity were checked in real time throughout the whole experiment, using a calibrated, digital thermo-hygrometer [Incoterm]).

FORCED-DEGRADATION STUDIES: STABILITY-INDICATING CHARACTERISTICS

API samples were subjected to the following stressing conditions to determine the capacity of the HPLC method 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 at 70°C
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 for 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 concentration described in Table 2. Sampling times were:

- Initial (T = 0)
- 7 days (T = 7)
- 14 days (T = 14)
- 30 days (T = 30)
- 60 days (T = 60)
- 90 days (T = 90)

All suspensions were immediately assayed six times (6 aliquots) at each time point (samples were diluted, sonicated for 10 minutes, and then filtered in 15-mm regenerated cellulose syringe filters with a 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 average percentage from six independent measurements ± standard deviation).

TABLE 3. SUMMARY OF LINEARITY'S STUDY FOR THE VALIDATION OF THE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD.

API	LINEARITY							SPECIFICITY	PRECISION		ACCURACY
	Range (µg/mL)	Analytical Curve	R^2	ANOVA's Significance of Regression (F)	ANOVA's Lack of Fit (F)	LOD (µg/mL)	LOQ (µg/mL)	Discrepancy (%)	Repeatability (CV, %)	Intermediate Precision (CV, %)	Recovery (%)
Alprazolam	14.28 – 26.52	y = 130.78x – 95.91	0.9993	18409.20	2.26	0.07	0.25	|1.61|	1.00	0.67	100.15
Atropine sulfate	56.07– 104.13	y = 1.24x + 6.61	0.9951	2621.65	2.53	0.01	0.04	|1.79|	0.39	1.06	99.95
Glutamine	351.96 – 653.64	y = 14.02x + 22.87	0.9991	14178.93	0.98	5.07	16.89	|0.07|	0.41	0.54	100.06
Levofloxacin	84.14 – 156.26	y = 62.63x – 172.63	0.9987	10386.85	0.94	0.004	0.02	|1.50|	0.22	0.49	99.79
Metoprolol tartrate	70.07 – 120.12	y = 1.09x – 0.81	0.9952	2687.89	3.26	0.02	0.08	|0.16|	0.58	3.70	99.46
Nitrofurantoin	350.14 – 650.26	y = 71.14x + 1443.85	0.9961	3336.62	3.26	0.004	0.01	|1.97|	0.35	0.64	99.33
Ondansetron HCl	2.88 – 5.35	y = 140.34x + 27.45	0.9976	5480.33	2.05	0.30	1.00	|0.08|	0.48	1.08	100.13
Oxandrolone	840.56 –1561.04	y = 0.19x – 8.16	0.9908	1399.47	0.36	0.005	0.02	|1.90|	0.99	0.85	100.15
Pregabaline	701.68 –1303.12	y = 1.57x – 57.68	0.9993	1939.78	3.70	0.003	0.01	|1.62|	0.82	1.17	100.73
Riboflavin	7.14 – 13.26	y = 44.95x – 1.65	0.9970	4313.08	1.75	0.33	1.10	|1.48|	0.56	0.92	99.36

Acceptance criteria were: R^2 >0.99; F (significance of regression) >>4.67; F (lack of fit) <3.71; discrepancy <2%; repeatability and intermediate precision <5%; 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; LOD = Limit of Detection; LOQ = Limit of Quantification (20 µL injections); CV = coefficient of variation

TABLE 4. SUMMARY OF THE STABILITY-INDICATING STUDY FOR THE ACTIVE PHARMACEUTICAL INGREDIENTS.

API	HCl		NaOH		UV		HEAT		H_2O_2	
	Area	%d*	Area	%d*	Area	%d*	Area	%d*	Area	%d*
Alprazolam	171.29	**|-93.09|**	2481.95	|0.18|	2553.00	**|3.05|**	2473.66	|-0.15|	2417.72	**|-2.41|**
Atropine sulfate	27.40	**|-73.68|**	0.00	**|-100.00|**	108.69	**|4.41|**	105.77	|1.61|	103.98	|-0.11|
Glutamine	0.00	**|-100.00|**	16989.88	**|93.52|**	10031.24	**|14.26|**	8830.02	|0.58|	0.00	**|-100.00|**
Levofloxacin	7389.23	|0.47|	7171.50	**|-2.49|**	7217.75	|-1.86|	7127.73	**|-3.09|**	7162.61	**|-2.61|**
Metoprolol tartrate	108.84	**|6.35|**	109.19	**|6.70|**	105.95	**|3.53|**	104.76	**|-2.38|**	107.50	**|5.05|**
Nitrofurantoin	9658.69	**|-73.56|**	0.00	**|-100.00|**	36895.64	|1.02|	36824.46	|0.82|	33041.45	**|-9.54|**
Ondansetron HCl	558.17	**|4.65|**	279.62	**|-47.57|**	561.78	**|5.33|**	587.55	**|10.16|**	546.76	**|2.51|**
Oxandrolone	0.00	**|-100.00|**	213.00	**|2.38|**	215.67	|-1.15|	213.12	**|-2.32|**	207.25	**|-5.01|**
Pregabaline	1504.91	**|-4.88|**	1530.00	**|-3.30|**	1574.19	|-0.50|	1531.12	**|-3.23|**	1369.27	**|-13.46|**
Riboflavin	415.66	**|-5.03|**	19567.98	**|4371.43|**	376.44	**|-13.99|**	421.18	**|-3.76|**	66.37	**|-84.83|**

Note: The results are presented as the average of 3 replicates, at the work concentration.
*%d = Percentage of discrepancy between the API 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).
API = active pharmaceutical ingredient; HCl = hydrochloride; UV = ultraviolet

RESULTS AND DISCUSSION

Validation studies of all methods of analysis (see the chromatographic conditions described in Table 2) 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, and the results are summarized in Table 4. These types of studies are important to determine if the used methods are 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 except for levofloxacin; alkaline stress affected all APIs but alprazolam; UV-light exposure did not decompose levofloxacin, nitrofurantoin, oxandrolone, and pregabaline; heat exposure did not lead to decomposition of alprazolam, atropine, glutamine, and nitrofurantoin; and oxidative stress did not affect atropine sulfate. Once the forced-degradation profiles of the APIs were determined, the stability of the APIs in SyrSpend SF PH4 (liquid) was assessed.

For the stability study, the suspensions were first visually inspected at each sampling time to verify their physical homogeneity and stability. Color, odor, and pH did not change appreciably. None of the following phenomena were observed throughout the study:

TABLE 5. STABILITY OF THE ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 (LIQUID).

Elapsed Time (Days)	% RECOVERY		Elapsed Time (Days)	% RECOVERY	
	Refrigerated Temperature (2°C to 8°C)	Controlled Room Temperature (20°C to 25°C)		Refrigerated Temperature (2°C to 8°C)	Controlled Room Temperature (20°C to 25°C)
ALPRAZOLAM 1.0 MG/ML			**NITROFURANTOIN 2 MG/ML**		
T = 0	100 ± 0.16	100 ± 0.16	T = 0	100 ± 0.19	100 ± 0.19
T = 7	97.15 ± 0.56	97.42 ± 0.54	T = 7	99.04 ± 0.28	99.82 ± 0.42
T = 14	98.30 ± 0.48	98.35 ± 0.47	T = 14	100.18 ± 0.18	99.95 ± 0.25
T = 30	97.35 ± 0.68	99.12 ± 0.51	T = 30	100.32 ± 0.55	100.34 ± 0.65
T = 60	95.83 ± 0.43	97.74 ± 0.79	T = 60	99.72 ± 0.65	99.78 ± 0.36
T = 90	96.52 ± 0.55	96.55 ± 0.41	T = 90	100.55 ± 0.65	98.79 ± 0.30
ATROPINE SULFATE 0.1 MG/ML			**ONDANSETRON HYDROCHLORIDE 0.8 MG/ML**		
T = 0	100 ± 0.39	100 ± 0.39	T = 0	100 ± 0.65	100 ± 0.65
T = 7	99.28 ± 0.80	98.77 ± 0.42	T = 7	99.88 ± 0.55	100.60 ± 0.51
T = 14	94.88 ± 0.80	97.94 ± 0.74	T = 14	100.97 ± 0.50	100.22 ± 0.45
T = 30	94.97 ± 0.72	94.35 ± 0.96	T = 30	100.38 ± 0.18	100.41 ± 0.28
T = 60	94.36 ± 0.35	96.30 ± 0.79	T = 60	99.18 ± 1.53	99.29 ± 0.63
T = 90	95.44 ± 0.66	94.64 ± 0.65	T = 90	99.59 ± 0.21	99.74 ± 0.20
GLUTAMINE 250 MG/ML			**OXANDROLONE 3 MG/ML**		
T = 0	100 ± 0.53	100 ± 0.53	T = 0	100 ± 0.73	100 ± 0.73
T = 7	99.22 ± 0.78	101.39 ± 0.64	T = 7	99.24 ± 0.59	97.12 ± 0.77
T = 14	100.80 ± 0.35	100.78 ± 0.42	T = 14	99.60 ± 0.34	99.87 ± 0.44
T = 30	101.25 ± 0.27	101.85 ± 0.23	T = 30	98.28 ± 0.48	96.79 ± 0.87
T = 60	99.13 ± 0.36	98.96 ± 0.51	T = 60	93.38 ± 2.14	99.96 ± 1.02
T = 90	99.53 ± 0.52	99.45 ± 0.56	T = 90	98.59 ± 0.43	98.84 ± 0.41
LEVOFLOXACIN 50 MG/ML			**PREGABALINE 20 MG/ML**		
T = 0	100 ± 0.24	100 ± 0.24	T = 0	100 ± 0.32	100 ± 0.32
T = 7	99.25 ± 0.71	101.26 ± 0.36	T = 7	99.05 ± 0.32	100.44 ± 0.16
T = 14	101.60 ± 0.25	101.18 ± 0.25	T = 14	99.16 ± 0.59	99.75 ± 0.33
T = 30	102.34 ± 0.48	99.63 ± 0.30	T = 30	98.13 ± 0.37	100.27 ± 1.34
T = 60	99.51 ± 0.37	99.37 ± 0.85	T = 60	100.67 ± 0.37	100.96 ± 0.28
T = 90	100.13 ± 0.16	99.64 ± 0.40	T = 90	98.73 ± 0.54	100.33 ± 0.28
METOPROLOL TARTRATE 10 MG/ML			**RIBOFLAVIN 10 MG/ML**		
T = 0	100 ± 0.61	100 ± 0.61	T = 0	100 ± 0.68	100 ± 0.68
T = 7	96.03 ± 0.32	100.46 ± 0.64	T = 7	102.92 ± 0.80	98.99 ± 0.61
T = 14	97.88 ± 0.90	99.92 ± 0.58	T = 14	101.37 ± 0.63	98.92 ± 0.49
T = 30	102.03 ± 0.99	101.49 ± 1.70	T = 30	102.05 ± 0.38	99.85 ± 0.36
T = 60	96.37 ± 0.24	97.23 ± 1.20	T = 60	102.38 ± 0.61	99.73 ± 0.66
T = 90	100.69 ± 0.19	100.81 ± 0.16	T = 90	101.77 ± 0.33	99.99 ± 0.33

- Caking
- Floculation
- Macroscopically visible crystal growth
- Phase separation
- Precipitation
- Turbidity

The 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%.[26,28,29] Figure 1 graphically represents the stability of the APIs in SyrSpend SF PH4 (liquid) in terms of absolute nominal concentration.

Alprazolam Oral Suspension

Allen and Erickson[30] evaluated 1-mg/mL alprazolam oral suspensions compounded with Ora-Sweet and Ora-Plus (Perrigo) (50:50, v/v) or cherry syrup (Robinson Laboratories) mixed with 1:4 with

simple syrup, prepared from tablets. They found out that all suspensions remained stable for up to 60 days of storage, both at 5°C and 25°C (losses of 7% to 9% for cherry syrup and less than 5% for Ora-Plus-containing suspensions), which is a lower storage period than the one found in our study (90 days).

Levofloxacin Oral Suspension

For levofloxacin, VandenBussche et al[31] evaluated 50-mg/mL oral suspensions prepared from tablets in Ora-Plus and strawberry syrup (50:50, v/v/). HPLC analysis demonstrated that the suspensions remained stable for 57 days when packaged in amber, plastic prescription bottles and stored at 3°C to 5°C or 23°C to 25°C, in contrast with the 90-day period of stability found here.

Metoprolol Tartrate Oral Suspension

Allen and Erickson[32] evaluated 10-mg/mL metoprolol tartrate oral suspensions compounded with Ora-Sweet and Ora-Plus (50:50, v/v) or cherry syrup mixed with 1:4 with simple syrup, prepared from tablets. They found out that all suspensions presented losses in API content lower than 3% after 60 days of storage in the dark, both at 5°C and 25°C. Gupta and Maswoswe[33] reported that 5-mg/mL aqueous mixtures prepared from metoprolol tartrate tablets were stable for 16 days at 25°C. Peterson et al[34] evaluated metoprolol tartrate 10-mg/mL suspensions (compound tragacanth powder–3g; concentrated chloroform water–1.25 mL; syrup–12.5 mL; distilled water–qs 100 mL). The suspensions were packaged in amber glass bottles and stored at 5°C to 7°C or 21°C to 25°C. The HPLC analyses revealed no loss in API content at 60 days refrigerated and a 10% loss in 28 days at room temperature. All these metoprolol studies reported a shorter period of stability during storage compared to our results, showing that the formulation used here possesses a higher storage capacity for this API, comparatively.

Ondansetron Hydrochloride Oral Suspension

The same improved stability was observed for ondansetron HCl. Williams et al[35] assayed four 0.8-mg/mL ondansetron HCl suspensions, compounded with: Cherry Syrup USP; Syrpalta (HUMCO); Ora-Sweet (Perrigo); and Ora-Sweet Sugar-Free (Perrigo). All suspensions remained stable for 42 days, when stored at 4°C, lower than what was found in this study.

Oxandrolone Oral Suspension

As for the oxandrolone oral suspension, data from literature shows that the stability of the vehicle used in this study is comparable with other vehicles. For instance, Johnson et al[36] evaluated oxandrolone oral suspension (1 mg/mL) prepared using oxandrolone tablets in 1:1 mixtures of Ora-Plus and either Ora-Sweet or Ora-Sweet SF, stored in 2-oz amber, plastic bottles, and at room temperature (23°C to 25°C). They reported that at least 98% of the original oxandrolone concentration remained in both formulations at the end of the 90-day study period (a slightly higher loss than the one from the present study).

Atropine Sulfate, Glutamine, Nitrofurantoin, Pregabalin, Riboflavin Oral Suspensions

Lastly, to the best of the authors' knowledge, no study concerning the stability of atropine sulfate, glutamine, nitrofurantoin, pregabalin, and riboflavin in oral suspensions was performed until the submission of this study for publication.

CONCLUSION

As the results showed, oral suspensions of alprazolam, atropine sulfate, glutamine, levofloxacin, metoprolol tartrate, nitrofurantoin, ondansetron HCl, oxandrolone, pregabaline, and riboflavin prepared with SyrSpend SF PH4 are stable for at least 90 days when stored both at refrigerated and at room temperatures. This indicates the probable success of validating the APIs evaluated in this study for the multiple dosages likely to be used in clinical applications by pharmacists or drug manufacturers interested in using oral suspensions for drug administration.

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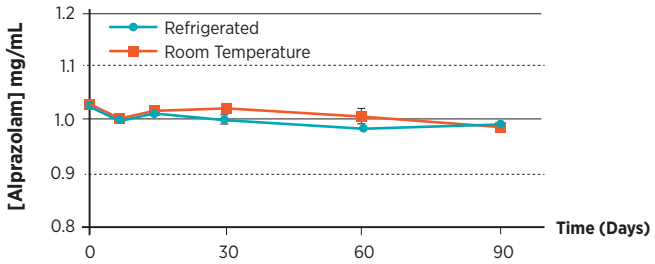
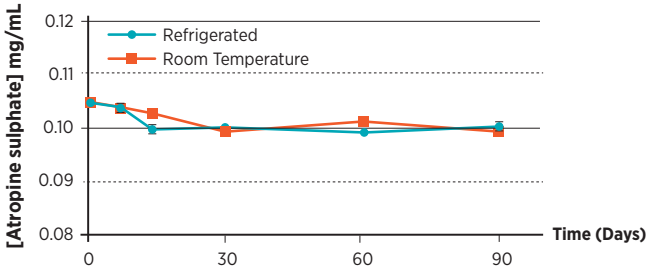
FIGURE 1. PLOT OF ACTIVE PHARMACEUTICAL INGREDIENTS IN SYRSPEND SF PH4 (LIQUID) THROUGHOUT THE COMPATIBILITY STUDY.

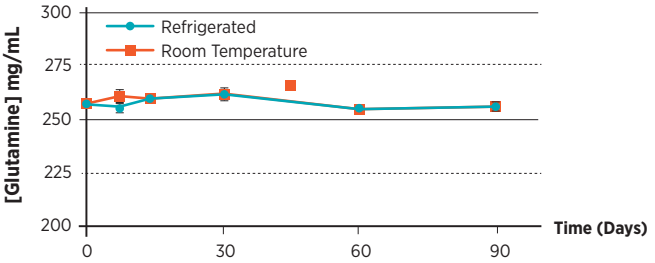
A – Alprazolam 1.0 mg/mL



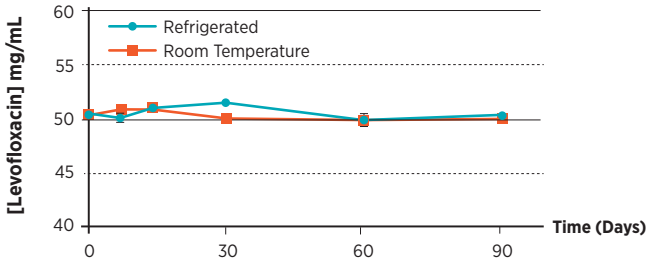
B – Atropine sulfate 0.1 mg/mL



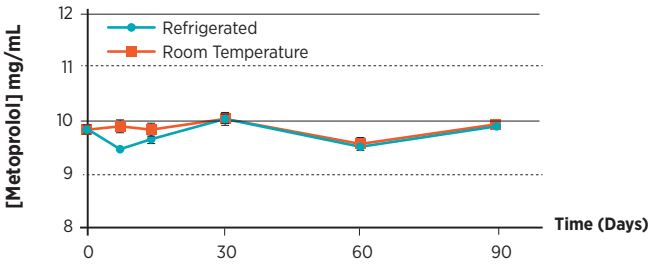
C – Glutamine 250.0 mg/mL



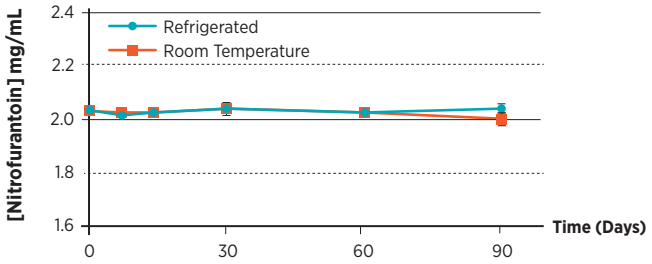
D – Levofloxacin 50.0 mg/mL



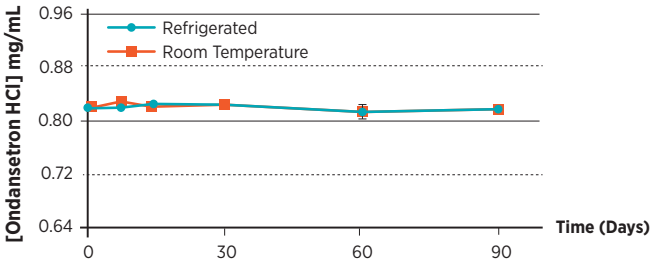
E – Metoprolol tartrate 10.0 mg/mL



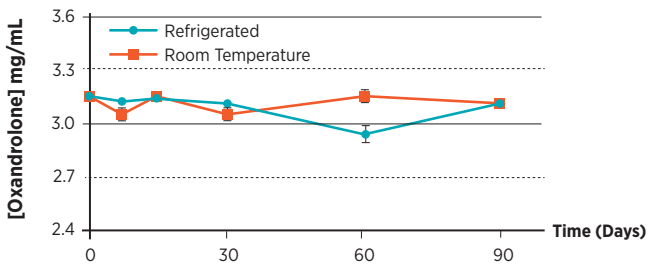
F – Nitrofurantoin 2.0 mg/mL



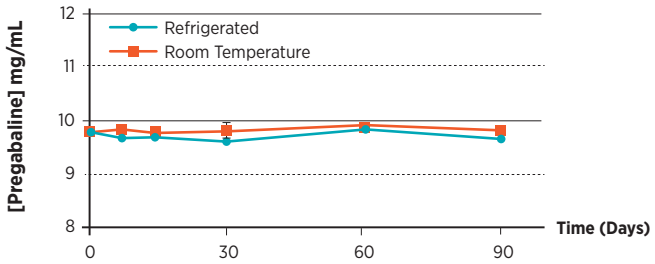
G – Ondansetron HCl 0.8 mg/mL



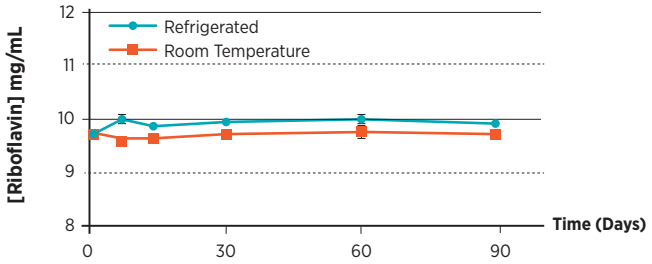
H – Oxandrolone 3.0 mg/mL



I – Pregabaline 20.0 mg/mL



J – Riboflavin 10.0 mg/mL



Dashed lines represent the lower and upper limits, corresponding to 90% and 110% of labeled concentration. Values represent mean ± SD (*n*=6).

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