Compatibility of caffeine, carvedilol, clomipramine hydrochloride, folic acid, hydrochlorothiazide, loperamide hydrochloride, methotrexate, nadolol, naltrexone hydrochloride and pentoxifylline in SyrSpend SF PH4 oral suspensions

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Received 28 January 2016
Revised 29 February 2016
Accepted 1 March 2016
Published Online First
24 March 2016

ABSTRACT

Objectives The objective of this study was to evaluate the compatibility of 10 commonly used active pharmaceutical ingredients (APIs) compounded in oral suspensions using a globally available suspending vehicle (SyrSpend SF PH4 liquid): caffeine 10.0 mg/mL, carvedilol 1.0 mg/mL, clomipramine hydrochloride 5.0 mg/mL, folic acid 1.0 mg/mL, hydrochlorothiazide 5.0 mg/mL, loperamide hydrochloride 1.0 mg/mL, methotrexate 2.5 mg/mL, nadolol 10.0 mg/mL, naltrexone hydrochloride 1.0 mg/mL and pentoxifylline 20.0 mg/mL, stored at both controlled refrigerated (2–8°C) and room (20–25°C) temperature.

Methods Compatibility was assessed by measuring the per cent recovery at different time points throughout a 90-day period. Quantification of the APIs was performed by high performance liquid chromatography (HPLC-UV) using a stability-indicating method.

Results Methods were adequately validated. Forced degradation studies showed that at least one parameter influenced the stability of the APIs. All suspensions were assayed and showed API contents of between 90% and 110% over 90 days.

Discussion Given the percentage of recovery of the APIs within the suspensions, the expiration date of the final products (API+vehicle) was found to be at least 90 days for all suspensions, for both controlled refrigerated and room temperature.

Conclusions The results suggest that SyrSpend SF PH4 liquid is a stable suspending vehicle for compounding APIs from different pharmacological classes.

INTRODUCTION

Extemporaneous preparation of oral liquid dosage forms is a common and important pharmacy practice for patients who require non-standard doses, have swallowing difficulties or receive medication via an enteral feeding tube.¹ Oral liquids are commonly employed in paediatrics^{2–3} and in the general adult population, where recent studies have demonstrated a swallowing difficulty prevalence of up to 22.4%.^{4–5}

Oral liquids are relatively quick and easy to prepare with a limited need for compounding equipment, and allow for flexibility in dosage adjusted from a single strength preparation.²

The main challenge with compounding oral liquid formulations is the limited availability of

data to support the physical, chemical and microbiological stability of the formulations.^{1–6} In a UK survey it was found that the shelf life of more than half (54%) of extemporaneous formulations was inadequately supported.² Due to the limited availability of scientific data, there is little harmonisation of the concentrations or formulations of compounded oral liquids.^{2–7} This poses a patient safety concern and a risk for medication errors.⁷ There have been demands for the publication of scientifically verified, palatable extemporaneous formulations with standardised oral liquid concentrations to increase patient safety and adherence.^{2–8}

The objective of this study was to evaluate the physical and chemical compatibility of the 10 frequently used active pharmaceutical ingredients (APIs) listed in table 1, compounded at a single concentration using SyrSpend SF PH4 (liquid) and stored at both refrigerated and room temperature.

SyrSpend SF is an internationally available, GMP produced, ready-to-use taste-masking oral liquid vehicle. Its suspending properties are derived from starch without traditionally used excipients that can have toxicological effects, induce allergic reactions or cause irritation, such as sugar,^{9–10} ethanol,^{11–12} propylene glycol,^{13–14} sorbitol,^{15–16} benzyl alcohol^{17–19} and common food allergens.^{20–21} The compatibility of SyrSpend SF with a large number of APIs has already been demonstrated.^{22–33} Its detailed formulation can be found in table 2, along with safety references.

In this study, the combined physical and chemical compatibility was assessed, as a deficit in either of the two would result in an out of specification result during analysis. The concentration for each API study was selected based on commonly prescribed concentrations for children or adults. To the best of the authors' knowledge, there is no previous study in the literature dealing with the stability of these APIs compounded using SyrSpend SF PH4 (liquid).

MATERIALS AND METHODS

Reagents, reference standards and materials

All raw materials and SyrSpend SF PH4 (liquid) were obtained from Fagron (São Paulo, Brazil). High performance liquid chromatography (HPLC)-grade reagents (Vetec, Rio de Janeiro, Brazil) were used. Ultrapure water obtained with an

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To cite: Polonini HC, Silva SL, de Almeida TR, et al. *Eur J Hosp Pharm* 2016;**23**:352–358.

Table 1 Concentrations of the suspensions used in the study

API	Concentration in suspension (mg/mL)	Action and use
Caffeine	10.0	Central nervous system stimulant
Carvedilol	1.0	β-Adrenoceptor antagonist; arteriolar vasodilator
Clomipramine hydrochloride	5.0	Monoamine reuptake inhibitor; tricyclic antidepressant
Folic acid	1.0	Vitamin B component
Hydrochlorothiazide	5.0	Thiazide diuretic
Loperamide hydrochloride	1.0	Opioid receptor agonist; antidiarrhoeal
Methotrexate	2.5	Dihydrofolate reductase inhibitor; cytostatic
Nadolol	10.0	β-Adrenoceptor antagonist
Naltrexone hydrochloride	1.0	Opioid receptor antagonist
Pentoxifylline	20.0	Vasodilator

API, active pharmaceutical ingredient.

AquaMax-Ultra 370 Series system (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 USP (Rockville, Maryland, USA) reference materials. All 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 min 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) consisting 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 μL and a software controller (Clarity).

Chromatographic conditions

The chromatographic determinations were performed accordingly to the official USP method for each API, with minor modifications when necessary. The mobile phase used for each API is given in table 3. The standards were diluted in the mobile phase unless otherwise stated. All columns were from Phenomenex (Torrance, California, USA), unless otherwise stated. The columns were connected with a pre-column with the same packing (4.0×3.0 mm, 5 μm) from the same manufacturer as the particle column. The injection volume was 20 μL for every chromatographic analysis.

Validation of the HPLC method

The methods and their acceptance criteria were established based upon the protocols defined by USP⁴⁹ and ICH (International Conference on Harmonization).⁵⁰

The 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 criteria were defined as a percentage of discrepancy between the peak areas lower than 2%. In addition, the specificity of the method was obtained through comparison of standard chromatograms with and without the matrix. All analyses were run in triplicate.

For precision, the test was designed to assess the degree of variation among the series of measurements obtained by the same analyst (repeatability) and between two analysts and 2 days (within-laboratory variations, intermediate precision) for solutions of the API at work concentrations. Repeatability was determined by consecutively analysing six replicates by a single analyst in a single day. Intermediate precision was also performed on six replicates, but in 2 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, and within range of the corresponding calibration curves. Per cent recovery was calculated from the concentration measured relative to the theoretical concentration spiked.

For linearity, the test was conducted by plotting three standard curves (genuine replicates, from three separate samplings), each constructed from the API concentrations of 70–130% of work concentrations in order to assess the linear relationship between the concentration of the analyte and the obtained areas, and in the presence of the SyrSpend SF PH4 (liquid) matrix. For this purpose, the data for each concentration range of the curve after fitting by the ordinary least squares method were evaluated by analysis of variance (ANOVA) and subjected to the least squares method to determine the correlation coefficient of the calibration curve.

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 Eqs. (1) and (2), respectively:

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

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

Table 2 SyrSpend SF PH4 (liquid) composition

Ingredient	Function	Safety references
Purified water	Liquid phase	N/A
Modified food starch	Suspending agent	FDA 21CFR 172.892 ³⁴
Sodium citrate	Buffering agent	FDA GRAS listed ³⁵
Citric acid	Buffering agent	FDA GRAS listed ³⁵
Sucralose	Sweetener	FDA, EC Scientific Committee on Food ^{36, 37}
Sodium benzoate*	Preservative	FDA GRAS listed, EC Scientific Committee on Food, WHO Expert Committee on Food Additives ^{38–41}
Malic acid	Buffering agent	FDA GRAS listed ⁴²
Simethicone	Anti-foaming agent	WHO Expert Committee on Food Additives ⁴³

*Even though the WHO mentions an acceptable daily intake of 5 mg/kg bodyweight sodium benzoate, it is known that this ingredient can cause metabolic acidosis and neurotoxicity in pre-term neonates and infants (<6 months) due to immature metabolism capacity.^{44–47} The concentration of sodium benzoate in SyrSpend SF PH4 (liquid) is low (<0.1%) compared to the concentrations reported in the literature in connection with fatal accidents,⁴⁴ and much lower than concentrations to which neonates are still being exposed in hospital settings today.⁴⁸ However, as precaution compounds can also use SyrSpend SF PH4 (dry), a similar, preservative-free, vehicle (ingredients: modified food starch, sodium citrate, citric acid and sucralose) with similar API compatibility.²⁹

API, active pharmaceutical ingredient; FDA GRAS, Food and Drug Administration Generally Recognized as Safe.

Table 3 Chromatographic conditions used in the compatibility studies

API	Mobile phase composition	Work concentration (µg/mL)*	Column	Flow (mL/min)	UV detection wavelength (nm)
Caffeine	Acetonitrile, tetrahydrofuran, and buffer (0.82 g/L of anhydrous sodium acetate) (25:20:955), adjusted with glacial acetic acid to a pH of 4.5	200.0	Microsorb-MV 100 C18, 50×4.6 mm (Varian)	1.0	275
Carvedilol	Acetonitrile and pH 2.0 monobasic potassium phosphate buffer (31:69)	40.0	Kromasil 100-5C8, 150×4.6 mm; at 55°C	1.0	254
Clomipramine hydrochloride	20.0 mL of a 55 g/L sodium 1-heptanesulfonate solution in glacial acetic acid, 2.0 mL of triethylamine, 478 mL of water, and 522 mL of acetonitrile. The pH was adjusted with phosphoric acid to 3.2±0.1	320.0	Luna 5 µm C18(2) 100 Å, 300×3.9 mm (Phenomenex)	1.0	254
Folic acid	Methanol and 1 M phosphate buffer pH 4.0 (12:88)	100.0	Zorbax Eclipse XDB-C8, 250×4.6 mm, 5 µm (Agilent)	0.9	280
Hydrochlorothiazide	Acetonitrile and 0.1 M monobasic sodium phosphate (1:9), adjusted with phosphoric acid to a pH of 3.0±0.1	150.0	Zorbax Eclipse XDB-C18, 250×4.6 mm, 5 µm (Agilent)	2.0	254
Loperamide hydrochloride	Acetonitrile and pH 2.0 monobasic potassium phosphate buffer (37:63)	10.0	Kromasil 100-5 C8, 150×4.6 mm; at 55°C	2.0	214
Methotrexate	Acetonitrile and buffer (0.2 M dibasic sodium phosphate and 0.1 M citric acid, 63:37) (10:90)	100.0	Zorbax Eclipse XDB-C18, 250×4.6 mm, 5 µm (Agilent)	1.2	302
Nadolol	5.62 g of sodium hydrochloride and 1.97 g of sodium acetate in 1000 mL of water. To this mixture, 4 mL of glacial acetic acid and 800 mL of methanol were added	400.0 (in methanol)	Zorbax Eclipse Plus Phenyl-Hexyl, 150×4.6 mm, 3.5 µm (Agilent); at 45°C	1.0	270
Naltrexone hydrochloride	600 mL of 0.05 M buffer solution (7.0 g of monobasic sodium phosphate in 1 L of water), 1.1 g of sodium 1-octane sulfonate monohydrate and 400 mL of methanol, and adjusted with dilute sodium hydroxide to a pH of 6.7	250.0	Luna 5 µm C18(2) 100 Å, 150×3.9 mm (Phenomenex)	1.0	280
Pentoxifylline	Acetonitrile and a solution composed of 50 mM monobasic potassium phosphate buffer, adjusted with phosphoric acid to a pH of 3.2 (30:70). The buffer was prepared with 0.8 g/L of ammonium acetate in water; to each litre of this solution, 10 mL of triethylamine were added, and the final buffer was adjusted with phosphoric acid to a pH of 5.0	80.0	Zorbax Eclipse XDB-C18, 250×4.6 mm, 5 µm (Agilent)	1.0	280

*Diluted with mobile phase, unless specified otherwise.
API, active pharmaceutical ingredient.

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

Preparation of API suspension samples

The API suspensions were prepared using the following general protocol: (i) the required quantity of each ingredient for the total amount to be prepared was calculated; (ii) each ingredient was accurately weighed; (iii) the API was placed in the mortar and triturated until a fine powder was obtained; (iv) a small amount of the SyrSpend SF PH4 (liquid) was added to the powder and mixed to form a uniform paste; (v) the SyrSpend SF PH4 (liquid) continued to be added in approximately geometric portions almost to volume, mixing thoroughly after each addition; (vi) sufficient SyrSpend SF PH4 (liquid) was added to bring the volume to 300 mL, and then mixed well; and (v) the final product was packaged in low-actinic prescription bottles and labelled.

The final concentrations in the bottles are summarised in [table 1](#). The suspensions were immediately assayed at $T=0$, and then separated into two different 150 mL bottles: one sample was stored at the USP recommended refrigerated temperature (2–8°C) and the other at room temperature (20–25°C), for the duration of the study (temperature and

humidity were checked in real time throughout the entire experiment, using a calibrated, digital Incoterm thermo-hygrometer). Both samples were protected from light. Before analyses, the bottles were shaken until the API was optically uniformly dispersed.

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 product produced during storage of the oral suspension: (i) dilution in acid (0.1 M HCl, at 25°C); (ii) dilution in base (0.1 M NaOH, at 25°C); (iii) exposure to ultra-violet light at 365 nm (at 25°C); and (iv) heating at 70°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 3](#)). The stock solutions were sonically dispersed for 10 min 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 labelled. The resolution was also determined between the degradation products and the API peaks. A resolution of 1.5 between the peaks was considered full separation.

Table 4 Summary of linearity study for validation of the HPLC method

API	Linearity				Specificity		Precision		Intermediate precision		Accuracy	
	Range (µg/mL)	Analytical curve	R ²	ANOVA significance of regression (F)	ANOVA lack of fit (F)	LOD (µg/mL)	LOQ (µg/mL)	Discrepancy (%)	Repeatability (CV, %)	Intermediate precision (CV, %)	Recovery (%)	
Caffeine	140.5–261.0	y=71.2x+132.5	0.999	1.4×10 ⁴	1.74	0.02	0.08	[1.90]	0.61	0.59	99.8	
Carvedilol	28.2–52.3	y=79.1x–34.2	0.990	1.3×10 ³	2.58	0.12	0.40	[0.23]	1.97	2.07	98.9	
Clomipramine hydrochloride	224.1–416.2	y=23.3x–206.2	0.997	5.4×10 ³	3.01	0.01	0.02	[1.52]	0.65	2.49	99.5	
Folic acid	70.1–130.2	y=61.0x+680.0	0.993	1.9×10 ³	3.67	0.01	0.02	[0.77]	0.83	2.80	99.9	
Hydrochlorothiazide	105.1–195.2	y=10.4x+26.6	0.997	4.8×10 ³	2.81	0.02	0.07	[0.01]	1.00	1.40	99.8	
Loperamide hydrochloride	7.2–13.4	y=207.7x–59.2	0.994	2.1×10 ³	2.06	0.48	1.60	[0.74]	0.64	3.13	100.7	
Methotrexate	70.3–130.6	y=43.5+113.5	0.995	2.7×10 ³	2.51	0.03	0.09	[0.12]	0.29	0.70	100.3	
Nadolol	280.3–520.5	y=2.3x–67.4	0.996	3.3×10 ³	2.36	0.003	0.01	[0.37]	0.73	1.04	100.1	
Naltrexone hydrochloride	175.2–325.4	y=3.3x–100.6	0.998	6.5×10 ³	1.23	0.001	0.003	[1.62]	0.69	1.51	99.8	
Pentoxifylline	56.4–104.8	y=31.6x+12.9	0.997	3.8×10 ³	3.40	0.05	0.16	[0.27]	0.25	0.45	101.1	

Acceptance criteria were: R²>0.99, F (significance of regression) >4.67, F (lack of fit) <3.71, 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). ANOVA, analysis of variance; API, active pharmaceutical ingredient; CV, coefficient of variation; HPLC, high performance liquid chromatography; LOD, limit of detection; LOQ, limit of quantification (20 µL injections).

Physical and chemical stability study

The API samples were HPLC-assayed at pre-determined time points to verify the feasibility of using the API in SyrSpend SF PH4 (liquid). The samples were shaken manually for 1 min to simulate patient dosing and then adequate volumetric 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 properly in order to obtain work solutions in the concentration described in the Chromatographic conditions section. Sampling times were: initial (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 immediately assayed six times at each time point (samples were diluted, sonicated for 10 min 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 per cent recovery with respect to T=0, using the HPLC method (results given as percentage±SD).

RESULTS AND DISCUSSION

The results of specificity, precision, accuracy and linearity tests for method validation are listed in [table 4](#). All analysis

methods met the respective acceptance criteria, demonstrating that the methods were adequate for quantification purposes.

Data from these stability-indicating studies are summarised in [table 5](#). The data indicate that the conditions influencing the chemical stability of the APIs varied greatly from each other, but the HPLC method was able to detect any degradation.

[Figure 1](#) shows the compatibility of the APIs in SyrSpend SF PH4 (liquid) in terms of absolute nominal concentration. The figure also shows the relative per cent of recovery (initial sampling time=100%) at T=90 days. For the suspensions to be considered compatible, the relative percentage recovery should be 90–110%. At each sampling time, the visual appearance of the suspension was also evaluated to verify homogeneity (data not shown). Throughout the entire study, no phenomena such as precipitation, turbidity, macroscopically visible crystal growth, odour generation, phase separation, flocculation or caking were observed.

All suspensions were stable throughout the duration of the study (at least 90 days), whether stored under refrigeration or at room temperature, as no visual, odour or assay changes were detected. Losses in API content, with respect to T=0, were no

Table 5 Summary of the stability-indicating study for the APIs (results presented as the average of three replicates, at the work concentration)

API	Acid %d*	Alkali %d*	UV light %d*	Heat %d*
Caffeine	[–2.96]	[–11.75]	ND	ND
Carvedilol	[–8.05]	[–28.70]	[5.46]	[2.17]
Clomipramine hydrochloride	[7.98]	[2.74]	ND	ND
Folic acid	[–91.90]	ND	[–42.41]	ND
Hydrochlorothiazide	[8.56]	[8.50]	[13.04]	[–27.50]
Loperamide hydrochloride	ND	[–7.90]	[89.27]	[3.33]
Methotrexate	[–3.23]	[–10.87]	[10.31]	[5.83]
Nadolol	[11.81]	[10.03]	[–9.54]	[–4.89]
Naltrexone hydrochloride	[11.48]	ND	ND	[3.38]
Pentoxifylline	ND	[–10.13]	[–2.45]	ND

*%d indicates percentage of discrepancy between the API peak without degradation (negative control) and the peak of a sample subjected to one of the cited accelerated-degradation factors.

Bold numbers indicate factors that led to high interference with the analytical peak of the API.

API, active pharmaceutical ingredient; ND, not detected (below the maximum acceptable of 2%).

Figure 1 Plot of active pharmaceutical ingredients (APIs) in SyrSpend SF PH4 throughout the compatibility study (dashed lines represent the lower and upper limits, corresponding to 90 and 100% of labelled concentration). Values represent the relative average per cent recovery ($n=6$). (A) Caffeine; (B) carvedilol; (C) clomipramine hydrochloride; (D) folic acid; (E) hydrochlorothiazide; (F) loperamide hydrochloride; (G) methotrexate; (H) nadolol; (I) naltrexone hydrochloride; (J) pentoxifylline.

greater than 10% and generally within 5%, which indicates good stability of the APIs and their chemical compatibility with the vehicle used.

CONCLUSIONS

This study showed that the APIs were all compatible with SyrSpend SF PH4 (liquid) for 90 days after preparation,

when stored refrigerated and at room temperature. As the results showed, SyrSpend SF PH4 (liquid) is compatible with a wide range of APIs from diverse pharmacological classes. These results validate APIs for use at various dosages in oral suspensions for drug administration. Thus, SyrSpend SF is shown to be an alternative vehicle for use by compounders.

Key messages

What is already known on this subject

- Oral liquids are safe alternatives to solid dosage forms, particularly for elderly and paediatric patients with dysphagia.
- The use of a ready-to-use suspending vehicle such as SyrSpend SF PH4 is convenient for pharmacists as it offers a safe, time-saving and well-studied option.
- The compatibility of SyrSpend SF PH4 with some active pharmaceutical ingredients (APIs) has already been established, but it is important to determine the compatibility of each specific API with the suspending vehicle as stability is the result of individual behaviour within the vehicle.

What this study adds

- We focused on 10 APIs: caffeine 10.0 mg/mL, carvedilol 1.0 mg/mL, clomipramine hydrochloride 5.0 mg/mL, folic acid 1.0 mg/mL, hydrochlorothiazide 5.0 mg/mL, loperamide hydrochloride 1.0 mg/mL, methotrexate 2.5 mg/mL, nadolol 10.0 mg/mL, naltrexone hydrochloride 1.0 mg/mL and pentoxifylline 20.0 mg/mL.
- The use by date was ≥ 90 days for all these suspensions for both storage conditions.
- This is the first report of the compatibility of this vehicle with these APIs.

Contributors HCP conceived of the study and wrote the manuscript. SLS and TRA performed the analyses and helped with data interpretation. MAFB and AOF coordinated the study. All authors contributed to refinement of the study protocol and approved the final manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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