Compatibility of proton pump inhibitors in a preservative-free suspending vehicle

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ABSTRACT

Objectives To evaluate the microbiological and physicochemical compatibility of commonly used proton pump inhibitors (PPIs) esomeprazole, lansoprazole, omeprazole and pantoprazole compounded at a single concentration using SyrSpend SF Alka and stored at refrigerated temperatures (omeprazole was also stored at room temperature because it has the most widespread use).

Methods Compatibility was assessed by measuring the per cent recovery at varying time points throughout a 90-day period. Quantification of the APIs was performed by a validated high performance liquid chromatography (HPLC-UV) method. This same assay was also used to determine the dosage content uniformity of the suspensions. Microbiological stability ('test in use') was assessed during 60 days and total aerobic microbial count (TAMC), total combined yeasts and moulds count (TYMC), detection of *Escherichia coli* and pH determination were performed. Antimicrobial effectiveness testing was determined following European Pharmacopoeia guidelines.

Results Beyond-use dates of maximum 60 days for omeprazole (5 mg/mL), pantoprazole (3 mg/mL) and esomeprazole (3 mg/mL) were established. All suspensions that met the physicochemical criteria for stability also met the content uniformity criteria. The suspensions showed no antimicrobial efficiency against bacteria, yeasts and moulds as SyrSpend SF Alka is an unpreserved vehicle, but the 'test in use' showed that the suspensions can remain microbiologically stable for up to 60 days.

Conclusions SyrSpend SF Alka can be used to compound palatable (taste-masking properties) preservative-free oral suspensions with almost all commonly used PPIs.

INTRODUCTION

Proton pump inhibitors (PPIs) esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, known to be highly effective for treatment of gastro-oesophageal reflux disease, ulcers and gastrointestinal bleeding,¹ are also commonly used for paediatric patients^{2–5} and patients with enteral feeding tubes.^{1 6–8} A recent study found the incidence of gastro-oesophageal reflux disease to be highest among young children,⁹ and stress ulceration has been reported to be present in 70–100% of all critically ill patients.¹⁰

Paediatric patients are often unable to swallow PPIs in a solid dosage form (tablets or capsules) and critically ill patients frequently rely on enteral nutrition. Intravenous administration of PPIs is

preferably avoided due to possible complications, cost restrictions and patient discomfort.¹ Therefore, PPIs (crushed or as raw powder) are usually administered in the form of an oral suspension for these patient groups.

Preparation of PPI suspensions from the (intact) granules out of commercial capsules or granulates for suspension may be complicated by the instability of the medication at acidic pH and by the time-consuming compounding procedures.¹ These PPI suspensions also figure among the formulations that most frequently obstruct enteral feeding tubes.¹¹ Therefore, pharmacists frequently turn to extemporaneously preparing liquid formulations for the PPIs, demonstrated by the fact that omeprazole and lansoprazole are reported to be the most commonly compounded formulations in the hospital setting.^{12 13}

Traditionally, simplified 8.4% sodium bicarbonate suspension has been used for compounding omeprazole and lansoprazole oral liquids because its high pH protects the PPI against degradation.^{6 14} However, preparing these sodium bicarbonate formulations can be time-consuming,¹ can be troublesome due to their high sodium content¹⁵ and does not result in a palatable formulation, which is important for compliance in paediatric therapy.¹⁶

In this sense, use of ready-to-use suspending vehicles can be of great value to the healthcare team. One of these vehicles is SyrSpend SF Alka, a starch-based powder that can be reconstituted to make a taste-masking oral liquid vehicle whose composition is detailed in table 1. It includes calcium carbonate to adjust the pH to >7 to prevent PPIs from degradation.^{17 18} It does not contain traditionally used suspension excipients that can have toxicological effects, induce allergic reactions or cause irritation, such as sugar,^{19 20} ethanol,^{21 22} propylene glycol,^{23 24} sorbitol,^{25 26} benzyl alcohol^{27–29} and common food allergens.^{30 31} It is also a preservative-free vehicle to facilitate administration to neonates.³² Although it seems to be an adequate vehicle to be used in common pharmaceutical practice, its compatibility with PPIs has not yet been demonstrated, except for omeprazole at 2 mg/mL.¹⁸

Within this context, this study was designed to evaluate the compatibility of commonly used PPIs (esomeprazole, lansoprazole, omeprazole and pantoprazole) compounded with SyrSpend SF Alka in order to determine their beyond-use dates. For that purpose, we evaluated the microbiological and physicochemical stabilities as well as the content uniformity of the suspensions stored at refrigerated temperature (omeprazole was also stored at room

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Table 1 SyrSpend SF Alka composition

Ingredient	Function	Safety references
Modified food starch	Suspending agent	FDA 21CFR 172.892 ⁵⁹
Calcium carbonate	pH adjustment	FDA GRAS listed ⁶⁰
Sucralose	Sweetener	FDA, EC Scientific Committee on Food ^{61 62}

temperature because it has the most widespread use). Rabeprazole was not included in this study since the safety and efficacy of a rabeprazole suspension has never been demonstrated in the literature and rabeprazole is far less frequently prescribed than the other PPIs.³³ To the best of the authors' knowledge, there is no previous study in the literature dealing with the individual stability of these four PPIs in the referred concentrations, compounded in a single taste-masking, alkaline, oral liquid vehicle.

MATERIALS AND METHODS

Reagents, reference standards and materials

All PPI raw materials and SyrSpend SF Alka (powder for reconstitution) were obtained from Fagron (batch number 12F19-U01-005190; St Paul, Minnesota, USA) and HPLC-grade reagents (Carvalhaes, 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 total organic carbon content of <10 ppb) was also used throughout the experiments. The reference standards were work standards obtained using primary USA Pharmacopeia (USP, Rockville, Maryland, USA) reference materials. All of 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 min immediately before use. All volumetric glassware and analytical balances were previously calibrated.

Preparation of PPI suspension samples

The PPI 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 PPI was placed in a mortar and triturated until a fine powder was obtained; (4) the triturated PPI was added to the SyrSpend SF Alka and mixed; (5) about 80 mL of purified water was added, mixing thoroughly; (6) sufficient water was added to bring the volume to 100 mL and then mixed well; (7) the final product was packaged in low-actinic plastic prescription bottles and labelled.

For lansoprazole, 8.5% pellets were used. The pellets were placed in a glass mortar and 5 mL absolute ethanol was added. The pellets were allowed to rest for 5 min to soften the coating, and then they were triturated to form a fine powder. The ethanol was left to evaporate completely. After that, the protocol continued from step (4) above.

The final concentrations in the suspensions were: esomeprazole magnesium trihydrate 3.0 mg/mL, lansoprazole 3.0 mg/mL, omeprazole 5.0 mg/mL and pantoprazole (as sodium sesquihydrate salt) 3.0 mg/mL. The suspensions were immediately assayed at T=0. The omeprazole suspensions were separated into two different bottles; one sample was stored at controlled refrigeration (2–8°C) and the other at controlled room

temperature (20–25°C) during the study, as these are the official temperature ranges for storage according to the USP (temperature and humidity were checked in real time throughout the experiment using a calibrated digital thermo-hygrometer; Incoterm, Brazil). The other suspensions were stored only refrigerated, which is the recommended storage condition for any preservative-free suspension.³⁴ All samples were protected from light.

Chromatographic conditions

HPLC analyses were performed on a qualified and calibrated chromatography system (Young Lin) comprising 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).

The chromatographic determinations were based upon USP methods for PPIs or their final products, with modifications when necessary. The standards were diluted in the mobile phase. Samples were prepared as follows: (1) appropriate aliquots of each suspension were pipetted and transferred to a suitable volumetric flask to achieve the work concentrations described below; (2) two-thirds of the flask capacity were filled with mobile phase and then agitated by sonication for 20 min; (3) mobile phase was added to the flask volume; (4) this solution was filtered in filter paper and then in cellulose membrane filters (0.45 μm) and transferred to HPLC vials for automatic injection. For all analyses, the columns were connected with a pre-column with the same packing (4.0 × 3.0 mm; 5 μm) from the same vendor and the injection volume was 20 μL.

For esomeprazole magnesium trihydrate (work concentration 50 μg/mL), the mobile phase consisted of a mixture of acetonitrile and Solution A (0.725 g monobasic sodium phosphate and 4.472 g dibasic sodium phosphate in 1000 mL; a 250 mL of this solution diluted to 1000 mL with water, with pH adjusted to 7.6) (35:65) at a flow rate 1.0 mL/min. Separation was achieved in a L7, 4.0 mm×15 cm column (Kromasil) at 25°C; detection was performed at 280 nm.

For lansoprazole (work concentration 100 μg/mL), the mobile phase consisted of a mixture of acetonitrile, water and triethylamine (40:60:1), with pH adjusted to 10 with phosphoric acid, at a flow rate of 1.0 mL/min. Separation was achieved in a L1, 4.6 mm×25 cm column (Agilent) at 25°C; detection was performed at 280 nm.

For omeprazole (work concentration 50 μg/mL), the mobile phase consisted of a mixture of acetonitrile and 50 mM sodium phosphate pH 8.5 solution (25:75) at a flow rate of 1.0 mL/min. Separation was achieved in a L1, 3.9 mm×15 cm column (Agilent) at 35°C; detection was performed at 302 nm.

For pantoprazole sodium (work concentration 50 μg/mL in water), the mobile phase consisted of a mixture of acetonitrile and 50 mM dibasic sodium phosphate (4:6), with pH adjusted to 7.0, at a flow rate of 2.0 mL/min. Separation was achieved in a L1, 4.6 mm×25 cm column (Phenomenex) at 25°C; detection was performed at 280 nm.

Validation of the HPLC method and stability-indicating characteristics (extended specificity)

The methods and their acceptance criteria were established on the basis of the USP³⁴ and ICH International Conference on Harmonization (ICH) guidelines.³⁵ Specificity, precision, accuracy, linearity and limits of detection and quantification were determined following a protocol described in a previous study.³⁶ In this protocol, during specificity determination a stressing test

was also conducted (acid, alkaline, ultraviolet light, heat and oxidising stresses).

Physical and chemical stabilities

The PPI samples were assayed by HPLC at predetermined time points to verify the compatibility of the PPI in SyrSpend SF Alka. The samples were shaken manually for 1 min to simulate patient shaking during dosing. Occurrence of physical phenomena (precipitation, turbidity, macroscopically visible crystal growth, odour generation, phase separation, flocculation or caking) was checked. A detailed protocol is described by Ferreira *et al.*³⁶ Samples were withdrawn at 0 (baseline), 7, 14, 30, 60 and 90 days (T=0, 7, 14, 30, 60 or 90) and assayed six times at each time point.

Uniformity of dosage units/content uniformity

To ensure dosing accuracy of the suspensions over time, the uniformity of dosage units from the suspensions was determined by applying an adaptation of the British and European Pharmacopoeias content uniformity for liquid dosage forms calculation.^{37–38} Smeets *et al* have provided a smaller set-up (n=6 instead of n=10) with the same statistical confidence to calculate the acceptance value (AV) for small-scale preparations as used in compounding pharmacies.³⁹

Microbiological stability

A 'test in use' was conducted to evaluate if normal utilisation of the unpreserved PPI suspensions would result in microbiological contamination.⁴⁰ SyrSpend SF Alka was prepared with 100 mL water and stored at refrigerated temperature (2–8°C) for 60 days. The bottle was opened every day for a few seconds at regular room temperature (15–25°C) with no product withdrawal. At T=0, total aerobic microbial count (TAMC), total combined yeasts and moulds count (TYMC), detection of *Escherichia coli* and pH determination were performed. At T=15, T=30 and T=60, TAMC, TYMC and pH determination were repeated.

Antimicrobial effectiveness testing was also performed following European Pharmacopoeia 2015 guidelines.³⁸ Briefly, a series of containers of the product to be examined (SyrSpend SF Alka) was inoculated, each with a suspension of one of the test organisms to give an inoculum of 10^5 – 10^6 micro-organisms per mL of the preparation. The volume of the suspension of inoculum did not exceed 1% of the volume of the product. The inoculated product was maintained at 20–25°C and protected from light. A suitable sample from each container was removed at 0 hours and at appropriate intervals (2, 7, 14 and 28 days) to determine the number of viable micro-organisms by plate count. The results were given as the $\log_{10}$ reduction in the number of viable micro-organisms against the value obtained for the inoculum.

RESULTS AND DISCUSSION

Validation and forced degradation test

All the results of the validation studies of all methods of analyses (table 2) met the respective acceptance criteria, proving the methods to be adequate for the study.

The results of the stability-indicating studies are summarised in online supplementary table S1. The decomposition profile of the PPIs was notably similar (see online supplementary figure S1 for chromatograms and additional information on typical HPLC responses for the PPIs). Acidic stress led to total destruction of the PPIs, and oxidising stress led to the same result for lansoprazole and esomeprazole magnesium trihydrate. UV exposure led

Table 2 Summary of validation of HPLC methods

PPI	Linearity		R ²	ANOVA significance of regression (F)	ANOVA lack of fit (F)	LOD (µg/mL)	LOQ (µg/mL)	Specificity Discrepancy (%)	Precision Repeatability (CV, %)	Intermediate precision (CV, %)	Accuracy recovery (%)
	Range (µg/mL)	Analytical curve									
Esomeprazole magnesium trihydrate	37.07–65.13	$y=25.38x-77.04$	0.9956	2926.96	2.73	2.01	6.71	[1.33]	1.27	1.27	99.45
Lansoprazole	70.07–130.13	$y=3.57x-12.47$	0.9967	3966.78	3.57	0.02	0.06	[0.11]	0.53	0.59	100.37
Omeprazole	35.70–66.30	$y=37.85x+22.42$	0.9974	5084.23	0.05	0.04	0.14	[1.75]	0.55	0.98	100.05
Pantoprazole sodium	10.50–19.50	$y=48.10x-27.11$	0.9960	3213.12	3.32	1.91	6.35	[0.79]	0.36	1.17	99.18

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 PPIs in the concentrations used in the suspensions (mg/mL).
CV, coefficient of variation; LOD, limit of detection; LOQ, limit of quantification; PPI, proton pump inhibitor.

Figure 1 Plot of proton pump inhibitors (PPIs) in SySpend SF Alka throughout the compatibility study (dashed lines represent the lower and upper limits corresponding to 90% and 110% of labelled concentration). Values represent mean $\pm$ SD (n=6). (A) Esomeprazole magnesium trihydrate 3.0 mg/mL. (B) Lansoprazole 3.0 mg/mL. (C) Omeprazole 5.0 mg/mL. (D) Pantoprazole sodium 3.0 mg/mL.

to fewer discrepancies between the various PPIs with or without exposure to stress conditions, but it also achieved up to 22% of the difference among the analytical peaks. Only heat exposure did not lead to degradation (except for lansoprazole), confirming the susceptibility of these molecules to degradation, and that the method is stability-indicating in being able to detect the decomposition of the PPIs.

Physicochemical stability and content uniformity

Chemical stability results of each suspension are depicted in figure 1, which graphically represents the stability of the PPIs in SySpend SF Alka in terms of absolute nominal concentration. Detailed results expressed as the relative per cent of recovery (initial sampling time=100%) are shown in online supplementary table S2. For the suspensions to be considered stable, the relative per cent of recovery should lie within 90–110%, according to the USP, British Pharmacopoeia and European Pharmacopoeia.^{34 37 38} At each sampling time the suspensions were visually inspected to evaluate their homogeneity/physical stability. Throughout the whole study, no precipitation, turbidity, macroscopically visible crystal growth, odour generation, phase separation, flocculation or caking was observed. A colour change was observed only for the omeprazole suspension and will be discussed below.

Esomeprazole magnesium trihydrate was chemically and physically stable for up to 90 days when stored at refrigerated temperature. Few studies are available dealing with the compatibility of esomeprazole in liquid formulations. Kupiec *et al*⁴¹ found esomeprazole 0.4 and 0.8 mg/mL as the sodium salt in infusion solutions (5% dextrose, 0.9% sodium chloride, and lactated Ringer's injection) to be chemically and physically

Figure 2 Indicative colour chart of omeprazole stability in SySpend SF Alka. Section 1 represents acceptable colour changes while Section 2 represents unacceptable colouring of the suspension.

stable for at least 2 days at room temperature and 5 days under refrigeration. SySpend SF Alka is thus a substantially more stable vehicle for this PPI in comparison to this previous work.

Lansoprazole was found not to be stable for the minimum period studied (ie, 7 days). This is not in accordance with the study by DiGiacinto *et al*⁴² who evaluated the stability of lansoprazole 3 mg/mL suspension prepared from capsules and mixed with sodium bicarbonate 8.4% injection. At room temperature 10% lansoprazole loss occurred in 8 hours; while refrigerated the sample showed 4% loss in 14 days and 12% loss after 21 days. Melkoumov *et al*⁴³ also evaluated a liquid formulation of lansoprazole and found a maximum stability of 7 days when stored at 4.5–5.5°C, but an extemporaneous formulation

Figure 3 Results of content uniformity test. Acceptance value (AV) must be <15.

consisting of lansoprazole microgranules in Ora-Blend maintained acceptable quality attributes when stored for only 3 days at 4.5–5.5°C. However, in both studies the sample preparations were significantly different from our work as they did not use crushed pellets for sample preparation; we used this form of raw material as it is more representative of common compounding practice.

As for omeprazole, the suspensions remained stable for up to 30 days at room temperature and at least 90 days refrigerated. This is in line with the findings of others for the stability of omeprazole suspensions. Whaley *et al*⁴⁴ studied omeprazole in the same vehicle but with a 2 mg/mL concentration and found that the product was stable for 92 days when stored under refrigerated conditions (2–8°C). This confirms that SyrSpend SF Alka could be a viable alternative to commercially available capsules when that dosage form is found to be inappropriate. Quercia *et al*⁴⁵ evaluated omeprazole 8.4% sodium bicarbonate mixtures. In this study omeprazole was stable for 30 days at –20°C and 4°C while the samples stored at room temperature had 8% loss in 14 days and 14% loss in 18 days. Phillips *et al*⁴⁶ evaluated a 2 mg/mL suspension compounded with 8.4% sodium bicarbonate. Refrigerated samples remained stable when stored for 24 weeks but room temperature samples had a 13% loss in 2 weeks and 25% in 4 weeks. Johnson *et al*⁴⁷ evaluated the stability of a reconstituted commercial omeprazole–sodium bicarbonate 2 mg/mL oral suspension stored at 3–5°C. A loss of only 2% in concentration throughout the 45 days of the study was observed. It is also important to note that the addition of bicarbonate to omeprazole suspensions can generate an

unpleasant taste, which could possibly lead to a low compliance rate for paediatric patients.^{48–49}

Although the omeprazole suspension in SyrSpend SF Alka stored at refrigerated temperature showed no chemical degradation of omeprazole, a slight grey/purple discolouration appeared and became more apparent with time. This discolouration was largely prevented at 2–8°C but, when left at room temperature for prolonged periods, the suspensions became dark purple. There are reports in the literature that confirm that the decomposition of omeprazole can be macroscopically seen to go through dark yellow, orange, purple, brown or black discolouration in aqueous media.^{41–50–54} The discolouration of omeprazole has been reported to be not harmful.⁵⁵ Based upon our results, figure 2 was designed and presents an indicative colour chart of omeprazole in SyrSpend SF Alka. The colour range presented in Section 1 shows acceptable colours of the omeprazole suspension while Section 2 shows the colour of suspensions where unacceptable omeprazole decomposition has occurred (ie, <90% omeprazole left).

Pantoprazole was also chemically and physically stable for at least 90 days at refrigerated temperature. This was superior to the findings of Dentinger *et al*⁵⁶ who studied pantoprazole 2 mg/mL oral suspensions extemporaneously prepared from tablets, sterile water and sodium bicarbonate.

Finally, all suspensions that met the physicochemical criteria for stability also met the content uniformity criteria (AV <15)^{37–38} (figure 3). In fact, the AV found in this study at all time points and storage temperatures is similar to—if not better than—those found in commercial solid dosage forms where Katori *et al*⁵⁷ report an AV of ≥3 for 279 evaluated lots of plain tablets and 168 lots of film-coated tablets sold in Japan. This indicates homogeneity and good resuspendability of the suspension and confirms that dose accuracy can be obtained with SyrSpend SF Alka suspensions, especially when used in combination with an oral syringe.⁵⁸

Microbiological stability

In addition to the physicochemical stability tests, antimicrobial effectiveness testing was performed on SyrSpend SF Alka after reconstitution. As expected, this preservative-free formulation showed no antimicrobial efficiency against bacteria, yeasts and moulds (table 3). However, when patient use was simulated during the ‘test in use’, the reconstituted suspension remained microbiologically stable to pH for up to 60 days (table 4). Intermediates and final microbial results complied with the

Table 3 Antimicrobial effectiveness testing of reconstituted SyrSpend SF Alka

Germs	Test bacterial suspension (CFU/mL)	SyrSpend SF Alka reconstituted with 200 mL water									
		D0		D2		D7		D14		D28	
		Result (log red)	Result (CFU/mL)	Result (log red)	Result (CFU/mL)	Result (log red)	Result (CFU/mL)	Result (log red)	Result (CFU/mL)	Result (log red)	Result (CFU/mL)
<i>Staphylococcus aureus</i> ATCC 6538	4.2×10 ⁵	NR	3.8×10 ⁵	<1.2	>2.510 ⁴	<0.2	>2.5×10 ⁵	<0.2	>2.5×10 ⁵	<0.2	>2.5×10 ⁵
<i>Pseudomonas aeruginosa</i> ATCC 9027	5.4×10 ⁵	NR	2.8×10 ⁵	<1.3	>2.5×10 ⁴	<0.3	>2.5×10 ⁵	<0.3	>2.5×10 ⁵	<0.3	>2.5×10 ⁵
<i>Candida albicans</i> ATCC 10231	1.0×10 ⁴	NR	1.5×10 ⁵	NR	NR	NR	NR	0	>5×10 ⁴	0	>5×10 ⁴
<i>Aspergillus brasiliensis</i> ATCC 16404	1.1×10 ⁵	NR	1.0×10 ⁵	NR	NR	NR	NR	0	>5×10 ⁴	0	>5×10 ⁴

Acceptance criteria: Bacteria (D2=3, D7=3, D14=–, D28=no increase); Fungi (D2=–, D7=–, D14=2, D28=no increase). CFU, colony-forming unit; D, day; log red, log reduction; NR, not required.

Table 4 Microbiological 'test in use' of reconstituted SyrSpend SF Alka

Parameter	Results			
	D0	D15	D30	D60
Total aerobic microbial count (TAMC)	<10 CFU/mL	<10 CFU/ mL	<10 CFU/ mL	<10 CFU/ mL
Total combined yeasts and moulds count (TYMC)	<10 CFU/ mL	<10 CFU/ mL	<10 CFU/ mL	<10 CFU/ mL
<i>Escherichia coli</i>	Absent	NP	NP	NP
pH	9.92	9.85	10.09	10.06

Acceptance criteria: TAMC=10² CFU/mL, TYMC=10¹, *E. coli*=absence.
CFU, colony-forming unit; NP, not performed.

specifications for the suspension and the pH values were similar for the suspension at every time point. This test shows that the product is physically and microbiologically stable when prepared and stored at a temperature of 2–8°C. When not actively contaminated and exposed to opening once every day at room temperature, the suspension also remains stable. These results demonstrate that regular use of these suspensions by patients is not expected to generate microbial contamination or a fluctuation in the pH.

CONCLUSIONS

SyrSpend SF Alka showed different compatibility profiles for the PPIs studied and, based on the physicochemical and microbiological results, beyond-use dates of a maximum of 60 days for omeprazole (5 mg/mL), pantoprazole (3 mg/mL) and esomeprazole (3 mg/mL) have been determined. These results demonstrate that it is appropriate to use this suspending vehicle for PPIs in hospital and compounding centres worldwide.

What this paper adds

What is already known on this subject

- Oral liquids are appropriate alternatives to solid dosage forms, particularly for elderly and paediatric patients.
- Ready-to-use suspending vehicles are a useful resource for pharmacists as they constitute a safe, time-saving and better studied option.
- The stability of omeprazole at 2 mg/mL in SyrSpend SF Alka has already been shown, but it is important to determine the compatibility of each proton pump inhibitor (PPI) with the suspending vehicle as stability is a result of individual behaviour within the vehicle.

What this study adds

- We focused on four PPIs at refrigerated temperatures: esomeprazole (3 mg/mL), lansoprazole (3 mg/L), omeprazole (5 mg/mL, also at room temperature) and pantoprazole (3 mg/mL).
- For the first time, physicochemical stability throughout a 60-day period was determined for these PPIs in SyrSpend SF Alka.
- Also for the first time, microbiological stability was determined for these suspensions and antimicrobial effectiveness testing was performed for the vehicle.
- Beyond-use dates of 60 days for omeprazole (5 mg/mL), pantoprazole (3 mg/mL) and esomeprazole (3 mg/mL) were established.

Contributors HCP created the protocol, supervised the work and wrote the paper. SLS, SL, RA and AB performed the experiments and helped to write the manuscript. MAFB and AOF coordinated the entire work and revised/approved the final version.

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