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Stability Of Sildenafil Citrate Oral Suspension With Syrspend® Sf

Original Paper

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Abstract Aim: Sildenafil citrate is a drug used to treat erectile dysfunction (ED) and pulmonary arterial hypertension (PAH). As for both clinical applications, the only available dosage form is tablets; there is a clear need for a safe oral liquid, especially for children. The objective of this study was to determine the stability of sildenafil citrate in SyrSpend® SF PH4, a suspending agent containing neither sorbitol nor alcohol.
Material/Methods: The studied sample was compounded into a 2.5-mg/mL suspension and stored in low-actinic plastic bottles at temperatures between 2 and 8°C and at room temperature conditions. Six samples were assayed at each time point out to 92 days by a high-performance liquid chromatography (HPLC) method. The method was validated for its specificity through forced-degradation studies.
Results: The samples remained within 90–110% of the initial concentration throughout the course of the study.
Conclusions: On the basis of the data collected, the beyond-use date of this product is at least 92 days when protected from light at both refrigerated and room temperature storage conditions.

Keywords *Compatibility – Stability – Compounding – Oral suspension – SyrSpend – Sildenafil*

CONFLICT OF INTEREST

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INTRODUCTION

Sildenafil citrate is used to treat erectile dysfunction (ED) in adult males and pulmonary arterial hypertension (PAH) in both children and adults. National Institute of Health (NIH) has defined ED as the permanent inability of a man to attain and/or maintain penile erection sufficient to permit satisfactory sexual intercourse (NIH, 1993). Abdo et al. (2006) defined it as a condition clearly compromising the quality of life. The main treatment for ED is the use of oral phosphodiesterase type 5 (IF5) inhibitors, amongst which sildenafil citrate is best known and most widely used (Toledo, 2013; Afif-Abdo, 2007). IF5 inhibitors increase relaxation of smooth muscle and dilation of the sinusoids body, resulting in an increased blood flow, allowing penile erection (Porst et al., 2012; Montorsi et al., 2010). PAH is characterised by progressive destruction of the pulmonary vasculature and associated with high morbidity and mortality, especially in children (Tissot & Beghetti, 2009). Sildenafil is most widely used in PAH by relaxing the blood vessels in the lungs and reducing blood pressure and has contributed to improved survival in this group, from a historical less-than-1-year survival in untreated children with severe PAH in the 1980s to a 97% 5-year survival rate (Tissot & Beghetti, 2009; Martínez et al., 2003; Humpl et al., 2005; Keller et al., 2004; Kothari & Duggal, 2002; Ladha et al., 2005; Leibovitch et al., 2007; Namachivayam et al., 2006; Barnett & Machado, 2006). However, it must be conceded that most of the agents mentioned are used off-label in children

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and the use is based mainly on experience in adults with PAH (Dodgen & Hill, 2015). For both ED and PAH, the only commercially available dosage form of sildenafil citrate is tablets. Sildenafil is available as a tablet only and the dosage in newborns ranges from 0.3 to 8 mg/kg/day (Huddleston et al., 2009). In addition, up to 22.4% of the adult population have swallowing difficulties, which highlights the importance of liquid formulations with adequate quality and stability for both paediatric patients and adults (Lau et al., 2003; Schirm et al., 2003).

The objective of this study was to determine the stability of sildenafil citrate in SyrSpend® SF, a suspending agent containing neither sorbitol nor alcohol or other excipients to be avoided in children (Gershanik et al., 1982). Currently, the stability of a large number of other active pharmaceutical ingredients (APIs) has already been shown in SyrSpend® SF (Vu et al., 2008; Geiger et al., 2012a, 2012b; Sorenson & Whaley, 2013; Geiger et al., 2013a, 2013b; Sorenson et al., 2012; Whaley et al., 2012a, 2012b; Voudrie & Allen, 2010; Voudrie et al., 2011; Geiger et al., 2015; Ferreira et al., 2016; Polonini et al., 2015; Polonini et al., 2016a, 2016b, 2016c). Sildenafil stability in SyrSpend® SF (2.5 mg/mL) was assessed throughout a 92-day period at both controlled refrigerated (2–8°C) and room temperature.

METHODS

Chemical Reagents

Sildenafil citrate raw powder was received from Fagron US (Lot 0911227111; St. Paul, Minnesota). SyrSpend® SF PH4 (liquid) was received from Fagron US – formally Gallipot (Lot 1110358V14; St. Paul, Minnesota). High-performance liquid chromatographic (HPLC) grade acetonitrile (Lot DG353; Honeywell Burdick and Jackson, Muskegon, Michigan), dibasic sodium phosphate heptahydrate (Lot 115824; Fisher, Fairlawn, NJ) and phosphoric acid (Lot 40350080404; CCI, Columbus, Wisconsin) were used in this study. HPLC-grade water was supplied by filtering deionised water from a Millipore Elix through a Millipore Simplicity (Billerica, Massachusetts).

Equipment and Chromatographic Conditions

Two different types of HPLCs were used. The first, used for validation and the stability study, was a Perkin Elmer 200-Series (Waltham, Massachusetts) equipped with a quaternary gradient solvent delivery system, a dual wavelength UV/VIS detector, a 100-vial programmable autosampler with a Peltier tray, 200-µL sample loop and a 250-µL syringe. The second HPLC system, used for forced degradation studies, was a Varian Prostar (Palo Alto, California) equipped with a tertiary gradient solvent delivery system, a photodiode array detector (PDA), an 84-vial programmable autosampler with a 100-µL sample loop and a 250-µL syringe. The Perkin Elmer HPLC was operated and the data was collected using Perkin Elmer Totalchrom chromatography software, whilst the Varian HPLC used Galaxie chromatography software. The mobile phase for the HPLC method was prepared by adding 5.3 g of dibasic sodium phosphate heptahydrate to 650 mL of HPLC-grade water and 350 mL of HPLC-grade acetonitrile. The mobile phase was adjusted to pH 6.5 with 85% phosphoric acid and delivered at 1.5 mL/min. Chromatographic separation was achieved using a 150 mm × 4.6 mm Phenomenex (Torrance, California) Gemini C8 column with 5-µL particle packing. The mobile phase was used as solvent to dilute the standard and assay preparations to 25 µg/mL sildenafil citrate. The assay was monitored following a 100-µL injection.

Validation of Forced-Degradation Studies to Determine the Characteristics of the HPLC Method

Sildenafil citrate samples were stressed and assayed at 293 nm to determine the specificity of the HPLC method to any possible degradation product produced during the storage of an oral suspension. Sildenafil citrate was diluted to 25 µg/mL in solutions of acid (0.1M HCl), base (0.1M NaOH) and hydrogen peroxide (3.5%), in addition to exposure to ultraviolet light at 365 nm and heat at 70°C for 3 h. Any extraneous peaks found in the chromatogram were labelled and the resolution was determined between the degradant and the sildenafil citrate. Purity calculations were performed in Galaxie on the sildenafil citrate peak using the controlled unstressed standard as a reference.

For determining the linearity of the method, the test was conducted by the plotting three standard curves in the range of 2.49–99.55 µg/mL and a determination coefficient higher than 0.99 was considered adequate. Precision of the method was assessed through repeatability: it was determined by consecutively analysing six replicates by a single analyst in a single day. An injection precision of <5% relative to the coefficient of variation (CV) was considered acceptable. Accuracy measurements were performed by the same analyst by injecting the chromatographic samples to which the matrix was added (at the same concentration levels performed for the linearity test (n = 3 for each concentration level)). The result was expressed as a percentage of recovery and compared with the analytical curve obtained from linearity.

Preparation of Sildenafil Citrate Suspension Samples

The sildenafil citrate suspension was prepared by adding 250 mg of sildenafil citrate to a low actinic prescription bottle. An aliquot of SyrSpend® SF PH4 (liquid) was added to the bottle to achieve a final volume of 100 mL. The final concentration was 2.5 mg/mL sildenafil citrate. The suspensions were stored at temperatures between 2 and 8°C and at room temperature storage conditions for the duration of the study.

Stability Study

The sample of sildenafil citrate suspended in SyrSpend® SF PH4 (liquid) at a concentration of 2.5 mg/mL was submitted for stability. The initial submitted sample was assayed and then split into two containers. The sample was packaged in low actinic plastic prescription bottles and stored at refrigerated storage conditions between 2 and 8°C and at room temperature storage conditions. Time points for the study were initial (T = 0), 7 days (T = 7), 14 days (T = 14), 30 days (T = 30), 61 days (T = 61) and 92 days (T = 92). The evaluation parameter was percent recovery assay and also appearance, taste, odour and pH. The stability of the sildenafil citrate in suspension was defined by the percent recovery with respect to T = 0 using the validated HPLC method. The sample stock was prepared six times by adding 100 µL of suspension to a 10-mL volumetric flask and diluting to volume with mobile phase. The average and coefficient of variation of all replicate injections (n = 3) at each time point were used to calculate the percent recovery.

RESULTS AND DISCUSSIONS

As a first step of our work, the HPLC method was monitored in order to verify its applicability to the main objective of this study, which is the inference for the stability of sildenafil citrate in SyrSpend® SF PH4 (liquid). A summary of the HPLC method parameters can be found in Table 1, which provides the data for peak tailing, range of the analytical curve, its coefficient of determination (linearity), precision and accuracy (in terms of percentage of recovery). All data are within international guidelines acceptance criteria (Council of Europe, 2015; ICH, 2005), which are coefficient of determination higher than 0.99 for linearity, coefficient of variation lower than 5% for precision (in terms of repeatability, intra-assay variation) and percentage of recovery within 98.0% and 102.0% of the target value for accuracy. Figure 1 depicts typical chromatograms of standard and simple, confirming specificity of the method. With a peak tailing lower than 2.0 and a theoretical plate number over 4,000, good separation capacity for the HPLC column was demonstrated.

Evaluation of possible degradation was also conducted to identify the decomposition of the APIs and assure sufficient separation by chromatographic analysis. The decomposition profile of the API varied for different stressing conditions. Sildenafil citrate was stable to acid, base, light and heat, but oxidiser created significant degradation. The degradants present were all completely separated from the analyte with acceptable resolution (>1.5).

The suspension compounded with SyrSpend® SF PH4 (liquid) was prepared and its stability profile was traced. The initial concentration of the suspension was 2.59 mg/mL, which was set as the baseline for all other time points tested. The results were expressed in terms of percentage of recovery (Table 2). The assay results varied between 2.57 (T = 30) and 2.59 mg/mL (T = 0) for the room temperature storage condition and between 2.56 (T = 7) and 2.61 mg/mL (T = 61) for the refrigerated storage condition. All sample preparations at each time point were within specification, with a maximum variability in the assays of CV = 4.21% (T = 30) for room temperature conditions and 4.91% (T = 92) for refrigerated conditions. All time points showed a similar chromatographic profile and clear degradant separation. In addition to the assay, appearance, taste and odour were evaluated and remained exactly the same as T = 0 throughout the whole study. Initial pH was measured as 4.21 and also remained constant during the study.

By the exposed, the sildenafil citrate suspension compounded with SyrSpend® SF PH4 (liquid) presented equal to or better physicochemical stability than other vehicles. Roque et al. (2013) developed two different oral liquid formulations of

Table 1. Summary of the HPLC parameters used in the stability study of sildenafil citrate in SyrSpend® SF PH4 (liquid).

Parameter	Result
Peak tailing	1.31 (CV = 0.23)
Theoretical plates	4126.82 (CV = 0.59)
Linearity	
Range	2.49–99.55 mcg/mL
Determination coefficient	0.9996
Precision (repeatability, n = 6)	CV = 1.06%
Accuracy	Recovery = 99.74%

CV, coefficient of variation.

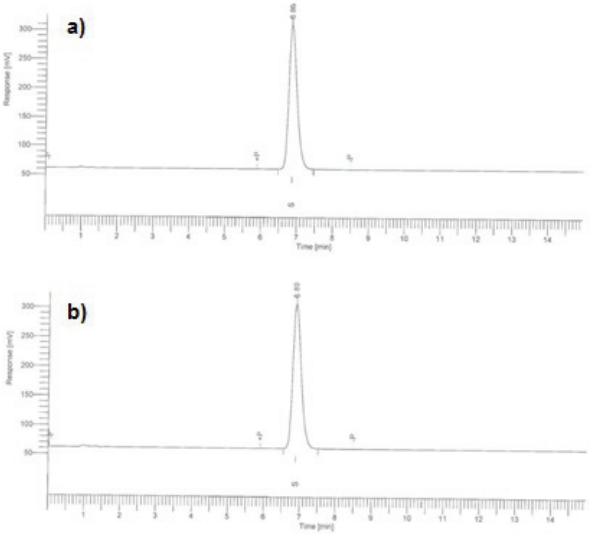

Figure 1. Typical chromatograms of sildenafil oral suspension in SyrSpend® SF PH4 obtained with the HPLC-validated method: (a) sildenafil standard; (b) oral suspension sample. Retention times of the chromatographic peaks show suitability of the method.

Table 2. Stability of sildenafil citrate in SyrSpend® SF PH4 (liquid).

Elapsed Time (days)	% Recovery	
	Room Temperature	Refrigerated Temperature (2–8 ºC)
T = 0	100.00	100.00
T = 7	99.94 ± 3.14	98.82 ± 1.45
T = 14	99.41 ± 2.10	99.41 ± 2.47
T = 30	99.13 ± 4.21	99.55 ± 1.36
T = 61	99.38 ± 2.85	100.72 ± 3.19
T = 92	99.57 ± 1.28	100.52 ± 4.91

Values expressed as the average of three replicates ± relative standard deviation (= coefficient of variation)

sildenafil citrate for paediatric use without preservatives, and the shelf-life of both formulations was three months (91 days); however, upon opening, aqueous solutions should be used within 10 days and kept refrigerated, and syrup solutions should be used within 14 days – which are significantly lower than what was obtained with our study.

A study by Nahata et al. (2006), for their turn, verified stability of two different extemporaneously prepared sildenafil formulations, prepared from crushed tablets and using two different suspending agents (1:1 mixture of Ora-Sweet® and Ora-Plus® and a 1:1 mixture of methylcellulose 1% and Simple Syrup NF). Both formulations were evaluated for physicochemical stability over a three-month period (91 days) under refrigerated conditions (4 and 8°C). No changes in pH, odour or physical appearance were observed throughout the study period, and the products remained stable after 91 days of preparation. Ora-Sweet® and Ora-Plus®, however, contain ingredients to be generally avoided in children, including glucose (Hill EM, Jijo A), carrageenan (Bhattacharyya S), glycerin (Maclaren NK), parabens (Rowe RC, European Commission, Weil, E) and sorbitol (Johnston KR, Payne ML, Pawar S and Pecar A). In addition, theses suspensions needed to be kept in refrigerator and were prepared from commercial tablets, not high-quality pharmaceutical raw materials (Jooste, 2011).

Lastly, Provenza et al. (2014) developed two oral liquid formulations of sildenafil citrate for paediatric use from pure powder: a suspension (containing citrate buffered solution, 'excipient for syrup' and distilled water) and a solution (containing citrate buffered solution, 'excipient for syrup sugar free' and distilled water). They showed that the suspensions presented better stability (90 days at 4 and 25 °C, whilst the solution was stable for 30 days when stored at 25 and 40 °C and 15 days at 4 °C, because of the formation of non re-dispersible sediment).

All these studies confirm that the sildenafil citrate suspension compounded with SyrSpend® SF PH4 (liquid) posses better physicochemical stability than other vehicles reported on the literature and ingredients that are safe for use in children.

CONCLUSION

When compounded from the raw powder, sildenafil citrate was stable in SyrSpend® SF PH4 (liquid) for 92 days at both room temperature and refrigerated conditions. The samples were still within specification at day 92 so the beyond-use date is concluded to be 92 days. The findings of this study show that SyrSpend® SF PH4 (liquid) is an acceptable oral syrup and suspending vehicle for preparing individually compounded sildenafil citrate suspensions. The formulations would be viable alternatives to commercially available tablets when that dosage form is found to be inappropriate whilst remaining alcohol-, sorbitol- and sugar-free.

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