Stability of an extemporaneously prepared tadalafil suspension

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Purpose. The stability of an extemporaneously prepared tadalafil oral suspension was studied.

Methods. An oral suspension of tadalafil 5 mg/mL was prepared by thoroughly grinding 15 20-mg tadalafil tablets in a glass mortar. Thirty milliliters of Ora-Plus and 30 mL of Ora-Sweet were mixed and added to the powder to make a final volume of 60 mL. Three identical samples of the formulation were prepared and placed in 2-oz amber plastic bottles with child-resistant caps and stored at room temperature (23–25 °C). A 1-mL sample was withdrawn from each of the three bottles with a micropipette immediately after preparation and at 7, 14, 28, 57, and 91 days. After double dilution (1:10 and 0.1:5 v/v) to an expected concentration of 10 μg/mL with methanol and mobile phase, respectively, the samples were assayed in duplicate using stability-indicating high-performance liquid chromatography. The samples were visually examined for any color change and evaluated for pH changes on each day of analysis. Taste evaluation was performed at the beginning and end of the study. Stability was defined as the retention of at least 90% of the initial concentration.

Results. At least 99% of the initial tadalafil concentration remained throughout the 91-day study period. There were no detectable changes in color, odor, taste, and pH, and no visible microbial growth was observed in any sample.

Conclusion. An extemporaneously prepared suspension of tadalafil 5 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet was stable for at least 91 days when stored in amber plastic bottles at room temperature.

Index terms: Chromatography, liquid; Color; Compounding; Concentration; Hydrogen ion concentration; Odors; Stability; Storage; Suspensions; Tadalafil; Taste; Temperature; Vasodilator agents; Vehicles

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Pulmonary hypertension affects both adult and pediatric patients and is characterized by an increase in pulmonary arterial pressure and pulmonary vascular resistance that can lead to heart failure and death.[1] In pediatric patients, pulmonary hypertension can be caused by cardiac and noncardiac abnormalities, including bronchopulmonary dysplasia, transposition of the great arteries, left-to-right shunting in the heart, chronic hypoxia, and scoliosis. Maintenance therapy for pediatric patients with pulmonary hypertension includes calcium channel blockers, phosphodiesterase-5 (PDE5) inhibitors, endothelin receptor antagonists, and prostacyclin agonists.[1]

The PDE5 enzyme isoform is highly expressed in pulmonary vascular smooth muscle and breaks down cyclic guanosine monophosphate (cGMP) to 5´-GMP. Inhibiting PDE5 increases endothelial cGMP, causing smooth muscle relaxation.[2] The most commonly used PDE5 inhibitor for the treatment of pediatric pulmonary hypertension is sildenafil.[2] Sildenafil suspension can be extemporaneously compounded from commercial tablets; however, it must be given three to four times daily in pediatric patients.[2,3]

Tadalafil, another PDE5 inhibitor, has been evaluated for the treatment of pulmonary hypertension in adult patients. A randomized study by Galie et al.[4] found that tadalafil

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40 mg orally daily in patients older than 12 years improved both exercise capacity and quality-of-life measures and reduced clinical decline. Due to its longer half-life, tadalafil can be given once daily and therefore is more convenient to dose compared with sildenafil. Currently, tadalafil is not approved for use in children and is available only in tablet formulations. There is a need for a tadalafil formulation that can be accurately measured and administered to pediatric patients and to adult patients unable to swallow tablets.

A tadalafil suspension can be extemporaneously compounded from tadalafil tablets; however, there are currently no data on the stability of a liquid formulation. The objective of this study was to assess the physical and chemical stability of a tadalafil suspension over 91 days when stored at room temperature.

Methods

Sample preparation. An oral suspension of tadalafil 5 mg/mL was prepared by thoroughly grinding 15 20-mg tablets of tadalafil[a] in a glass mortar. Thirty milliliters of Ora-Plus[b] and 30 mL of Ora-Sweet[c] were mixed and added to the powder to yield a final volume of 60 mL. Details of the procedure are provided in the appendix.

Three identical samples of the formulation were prepared and placed in 2-oz amber plastic bottles with child-resistant caps.[d] Each bottle was stored at room temperature (23–25 °C). After thorough but gentle shaking by hand to prevent foaming, a 1-mL sample was withdrawn from each of the three bottles with a 5-mL micropipette immediately after preparation and at 7, 14, 28, 57, and 91 days. After double dilution (1:10 and 0.1:5 v/v) to an expected concentration of 10 µg/mL with methanol and mobile phase, respectively, the samples were assayed in duplicate using high-performance liquid chromatography (HPLC).

HPLC analysis. A modification of the stability-indicating reverse-phase HPLC methods described by Aboul-Enein and Ali[5] and Cheng and Chou[6] was used. The instrumentation included a constant-flow-rate solvent delivery system[e] and a C_{18} column.[f] A variable-volume injector,[g] an ultraviolet-light detector[h] set at 230 nm, and a recording integrator[i] were also used. The mobile phase consisted of aqueous 0.05M monobasic potassium phosphate (pH 3 with dilute phosphoric acid) and acetonitrile (60:40 v/v) delivered at a flow rate of 1.5 mL/min.

The stability-indicating capability of the assay was reevaluated in our laboratory. Degradation of tadalafil was forced by treating three 1-mL samples of the suspension with 3% hydrogen peroxide, 1 *N* sodium hydroxide to adjust to a pH of 12, or 1 *N* hydrochloric acid to adjust to a pH of 2. The solutions were then heated to 90 °C for two hours. The pH was corrected to 7, and the solutions were diluted with mobile phase to an expected tadalafil concentration of 10 µg/mL and assayed. Tadalafil in the Ora-Plus/Ora-Sweet suspension was degraded 12% by hydrogen peroxide, with an unidentified degradation peak at 2.06 minutes; the peak for tadalafil appeared at 3.5 minutes. There was little or no degradation by either acid or base.

Standard solutions and standard curve. A 0.2-mg/mL stock solution was prepared by solubilizing a 20-mg tadalafil tablet[a] in 100 mL of methanol on each day of sample analysis. Analytic-grade tadalafil powder was not available at the time of the study. Standard samples of tadalafil were prepared by diluting the stock solution with mobile phase to 8, 9, 10, 11, and 12 µg/mL. A solution of tadalafil 10 µg/mL was assayed in duplicate after approximately every 10th sample as an external control. A standard curve was produced by linear regression of the peak heights of tadalafil against tadalafil concentration. The standard curve was linear ($r^2 = 0.993$) over the working range of concentrations. The interday and intraday coefficients of variation for the tadalafil assay were 2.4% and 1.1%, respectively.

Sample analysis. Each tadalafil sample was shaken, as previously described, immediately before dilution and assay. All samples were centrifuged at 1000 rpm for two minutes to separate the insoluble tablet excipients. Five microliters of each sample was injected into the HPLC system, and each sample was assayed in duplicate. The samples were visually inspected for any color change, and the pH[j] of the samples was evaluated on each day of analysis. Taste evaluations were performed at the beginning (day 0) and end (day 91) of the study. Microbiological testing was not performed, since each vehicle contained preservatives.

Data analysis. The stability of tadalafil in the suspension was determined by calculating the percentage of the initial concentration remaining at each time interval. Stability was defined as the retention of at least 90% of the initial concentration.

Results and discussion

A mean of at least 99% of the initial concentration of tadalafil remained throughout the 91-day study period in all suspensions (mean ± S.D. of 99.13% ± 0.71% on day 7, 99.12% ± 0.99% on day 14, 99.63% ± 1.77% on day 28, 98.36% ± 1.18% on day 57, and 100.46% ± 2.36% on day 91). There were no detectable changes in color, odor, and taste, and no visible microbial growth was found in any sample. The preparation was sweet with no aftertaste. No appreciable change from the initial mean pH ± S.D. (4.4 ± 0.02) occurred in any of the samples. The bioavailability of the tadalafil formulation prepared in this study has not been evaluated. However, the absorption and therapeutic effectiveness of a drug in a suspension compounded

from crushed tablets are unlikely to differ appreciably from those of the original dosage form.

Conclusion

An extemporaneously prepared suspension of tadalafil 5 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet was stable for at least 91 days when stored in amber plastic bottles at room temperature.

[a]Tadalafil 20-mg tablets, Eli Lilly, Indianapolis, IN, lot A647476C.

[b]Ora-Plus, Paddock Laboratories, Minneapolis, MN, lot 9217189.

[c]Ora-Sweet, Paddock Laboratories, lot 8384259.

[d]2-oz amber prescription bottles with child-resistant caps, Owens Illinois Prescription Products, Perryburg, OH.

[e]HPLC pump, model 501, Waters Corporation, Milford, MA.

[f]Ultrasphere ODS C_{18} column (5-µm particle size, 4.6 × 150 mm), Beckman Coulter, Fullerton, CA.

[g]Variable-volume injector, model U6K, Waters.

[h]Tunable absorbance detector, model 486, Waters.

[i]Integrator–recorder, model 3394, Hewlett-Parkard Company, Avondale, PA.

[j]Alex pH 41 meter, Beckman Instruments, Irvine, CA.

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Appendix—Procedure for compounding tadalafil suspension, 5 mg/mL

1. Count out 15 20-mg tadalafil tablets.
2. Triturate the tablets in a glass mortar to produce a fine powder.
3. Mix 30 mL of Ora-Plus with 30 mL of Ora-Sweet; stir vigorously.
4. Levigate 30 mL of diluent into the tadalafil powder from step 2 via geometric dilution until a smooth suspension is formed.
5. Transfer the mixture into a 2-oz, child-resistant, amber plastic prescription bottle.
6. Rinse the contents of the mortar into the bottle with enough of the diluent to bring the final volume to the 60-mL mark as predetermined with a graduated cylinder.

Label the bottle "Shake Well Before Use" with an expiration date of 91 days after preparation.