Stability of Extemporaneously Prepared Sodium Benzoate Oral Suspension

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Abstract
The stability of extemporaneously prepared sodium benzoate oral suspension in cherry syrup and Ora-Sweet was studied. Oral solutions of 250-mg/mL sodium benzoate were prepared in either cherry syrup or Ora-Sweet. To a beaker, 50 grams of Sodium Benzoate Powder USP was dissolved and filtered, the solution was divided equally into two parts, and each aliquot was added into two separate calibrated 100-mL amber vials. In the first vial, cherry syrup was added to make a final volume of 100 mL. In the second vial, Ora-Sweet was added to give a final volume of 100 mL. This process was repeated to prepare three solutions of each kind and all were stored at room temperature. A 250-µL sample was withdrawn immediately after preparation and again at 7, 14, 28, 60, and 90 days for each sample. At each time point, further dilution was made to an expected concentration of 0.25 mg/mL with sample diluent, and the samples were assayed in triplicate by stability-indicating high-performance liquid chromatography. Stability was defined as the retention of at least 90% of the initial concentration. At least 92% of the initial concentration of sodium benzoate in cherry syrup and at least 96% of the sodium benzoate in Ora-Sweet remained throughout the 90-day study period. There were no detectable changes in color and no visible microbial growth in any sample. Extemporaneously compounded suspensions of sodium benzoate in cherry syrup or Ora-Sweet were stable for at least 90 days when stored in a 4-oz amber plastic bottle at room temperature in reduced lighting.

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Stability of Extemporaneously Prepared Sodium Benzoate Oral Suspensions

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INTRODUCTION
Urea cycle disorders (UCDs) are genetic disorders that result from defective metabolism of nitrogenous waste produced by the breakdown of nitrogen-containing molecules such as proteins. A mutation or deficiency in any or all essential enzymes and cofactors in the urea cycle result in accumulation of ammonia as well as precursor metabolites in the blood. Depending on the severity of the mutation, symptoms may include vomiting, lethargy, permanent brain damage, coma, and death.

Individuals with UCDs consume a low-protein diet and are often treated with nitrogen ammonia scavengers. One substance used to remove nitrogenous waste is sodium benzoate. Sodium benzoate is the sodium salt of benzoic acid that conjugates with nitrogen-containing glycine to form the molecule hippurate. Hippurate can then be excreted by the kidneys, thereby removing nitrogenous waste from the bloodstream. One mole of hippurate contains, and allows for removal of, one mole of nitrogenous waste.

Currently, Sodium Benzoate USP is only available as a powder. UCD affects adults, children, and newborns. All subsets of patients can have difficulty taking oral tablets or capsules, therefore, a liquid formulation is often used. While the efficacy of liquid formulations of sodium benzoate has been established, currently, there is no data available on the stability of sodium benzoate in suspension. The purpose of this study was to evaluate the 90-day stability of sodium benzoate in either cherry or Ora-Sweet syrup.

METHODS
SAMPLE PREPARATION
Sodium benzoate 250-mg/mL solutions were compounded (formulation and method of preparation shown below) using Sodium Benzoate Powder USP (Lot MKBL2285V; Sigma-Aldrich, St. Louis, Missouri). To a beaker, 50 grams of the sodium benzoate powder was added to 100 mL of sterile water. Once the powder was fully dissolved and filtered, the solution was divided equally into two parts, and each aliquot was added into two separate calibrated 100-mL amber vials. In the first vial, cherry syrup was added to make a final volume of 100 mL. In the second vial, Ora-Sweet was added to give a final volume of 100 mL. This process was repeated to prepare three solutions of each kind and all were stored at room temperature. A 250-μL sample was withdrawn immediately after preparation and again at 7, 14, 28, 60, and 90 days for each sample. At each time point, further dilution was made to an expected concentration of 0.25 mg/mL with sample diluent, and the samples were assayed in triplicate by stability-indicating high-performance liquid chromatography. Stability was defined as the retention of at least 90% of the initial concentration. At least 92% of the initial concentration of sodium benzoate in cherry syrup and at least 96% of the sodium benzoate in Ora-Sweet remained throughout the 90-day study period. There were no detectable changes in color and no visible microbial growth in any sample. Extemporaneously compounded suspensions of sodium benzoate in cherry syrup or Ora-Sweet were stable for at least 90 days when stored in a 4-oz amber plastic bottle at room temperature in reduced lighting.

The stability of extemporaneously prepared sodium benzoate oral suspension in cherry syrup and Ora-Sweet was studied. Oral solutions of 250-mg/mL sodium benzoate were prepared in either cherry syrup or Ora-Sweet. To a beaker, 50 grams of Sodium Benzoate Powder USP was dissolved and filtered, the solution was divided equally into two parts, and each aliquot was added into two separate calibrated 100-mL amber vials. In the first vial, cherry syrup was added to make a final volume of 100 mL. In the second vial, Ora-Sweet was added to give a final volume of 100 mL. This process was repeated to prepare three solutions of each kind and all were stored at room temperature. A 250-μL sample was withdrawn immediately after preparation and again at 7, 14, 28, 60, and 90 days for each sample. At each time point, further dilution was made to an expected concentration of 0.25 mg/mL with sample diluent, and the samples were assayed in triplicate by stability-indicating high-performance liquid chromatography. Stability was defined as the retention of at least 90% of the initial concentration. At least 92% of the initial concentration of sodium benzoate in cherry syrup and at least 96% of the sodium benzoate in Ora-Sweet remained throughout the 90-day study period. There were no detectable changes in color and no visible microbial growth in any sample. Extemporaneously compounded suspensions of sodium benzoate in cherry syrup or Ora-Sweet were stable for at least 90 days when stored in a 4-oz amber plastic bottle at room temperature in reduced lighting.

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tion was divided equally into two parts, and each aliquot was added into separate calibrated 100-mL amber, oval prescription vials with child-resistant closures (Total Pharmacy Supply, Arlington, Texas). Four liters of cherry syrup was prepared by adding 4 mL of cherry flavoring to Simple Syrup NF (sucrose 85%, purified water, 0.01% citric acid, methylparaben 0.1%). In the first vial, prepared cherry syrup (Lot 114729:02; University of Rochester Medical Center Compounding Service, Rochester, New York) was added to make a final volume of 100 mL. In the second vial, Ora-Sweet flavored vehicle syrup (Lot 6256027; Perrigo, Minneapolis, Minneapolis) was added to give a final volume of 100 mL. This preparation was repeated in triplicate to provide a total of six sodium benzoate 250-mg/mL samples (three in cherry syrup and three in Ora-Sweet).

The samples were stored at room temperature (23°C to 25°C) in low-light conditions. At days 0, 7, 14, 28, 60, and 90, a 250-μL aliquot from each sample was diluted and filtered using a 45-micron filter (syringe filter, nylon,45-micron, 13 mm diameter; CELLTREAT Scientific Products, Pepperell, Massachusetts) to an expected concentration of 0.25 mg/mL with the sample diluent (50:50 v/v acetonitrile and sterile water). Each of the six samples at each time point was assayed in triplicate by high-performance liquid chromatography (HPLC).

**REVERSE-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY**

Reverse-phase HPLC was performed using a Shimadzu model LC2010A instrument (Shimadzu Scientific Instruments, Marlborough, Massachusetts) with Shimadzu LC Solution Software. The HPLC was equipped with a C18 Li 4.6-mm × 15-cm diameter, 5-μm particle column (Ascentis, L × I.D. 15 cm × 4.6 mm; Supelco, Bellefont, Pennsylvania) maintained at 25°C and an ultraviolet detector set at 230 nm. The mobile phase used was aqueous monobasic potassium phosphate (0.020 M) and acetonitrile (30:70, v/v) with phosphoric acid delivered at a flow rate of 0.5 mL/minute. The retention time of sodium benzoate was 10.9 minutes.

**FORCED DEGRADATION**

To test the ability of the HPLC method to detect degradation, decomposition of sodium benzoate was forced by allowing samples of each preparation to be exposed to three different degradation conditions: 1) pH 2 with 1 M hydrochloric acid, 2) pH of 12 with 1 M sodium hydroxide, or 3) 3% hydrogen peroxide. Each solution was incubated at 60°C for 24 hours, and an additional sample in 3% hydrogen peroxide was placed in direct sunlight for 7 days. The most pronounced degradation was observed in the 3% hydrogen peroxide sample incubated at 60°C for 24 hours. Approximately 12% degradation in cherry syrup and 14% degradation of the parent compound in Ora-Sweet were achieved. In these samples, in addition to the sodium benzoate peak at 10.9 minutes, an unidentified degradation peak was observed at a retention time of 4.8 minutes. Approximately 13% degradation in cherry syrup and 9% degradation in Ora-Sweet was achieved with the acidic solution. Approximately 10% degradation in cherry syrup and 10% degradation in Ora-Sweet was achieved with the sodium hydroxide solution. Approximately 7% degradation in cherry syrup and 10% degradation in Ora-Sweet was achieved with the 3% hydrogen peroxide solution that was in direct sunlight for 7 days.

**STANDARD SOLUTIONS AND STANDARD CURVE**

A 250-mg/mL stock solution of analytical grade sodium benzoate (Supelco) was prepared in 50:50 (v/v) acetonitrile in sterile water. Standard samples of sodium benzoate were prepared by diluting the stock solution with sample diluent to 1.0 mg/mL, 0.5 mg/mL, 0.25 mg/mL, 0.125 mg/mL, and 0.0625 mg/mL sodium benzoate. The standards were prepared at day 0, and aliquots were frozen at -20°C. Each standard was assayed in triplicate at every time point of the analysis. A standard curve was produced by linear regression of the peak heights of sodium benzoate against sodium benzoate concentration. The standard curve was linear (average \( r^2 = 0.985 \)) over the working range of concentrations. The between-day and within-day coefficients of variation for the sodium benzoate assay were 1.92% and 1.15%, respectively.
SAMPLE ANALYSIS

Each of the sodium benzoate samples was shaken thoroughly by hand for approximately 15 seconds immediately before the assay. Ten microliters of each sample was assayed in triplicate according to the HPLC method described above. The samples were visually inspected for color change on each day of analysis. Because each commercial vehicle contained effective preservatives, microbiological testing was not performed.

DATA ANALYSIS

The stability of sodium benzoate in cherry syrup and Ora-Sweet was determined by calculating the percentage of the initial concentration remaining at each time interval +/- the standard deviation of replicates. Stability was defined as the retention of at least 90% of the initial concentration.

RESULTS AND DISCUSSION

Currently, Sodium Benzoate USP is only available as a powder. The 250-mg/mL sodium benzoate suspensions were prepared in this study using cherry syrup or Ora-Sweet. The results from this study indicate that sodium benzoate was chemically and physically stable in the two suspensions. The RP-HPLC data of the compounded suspensions are summarized in Table 1. Both suspensions remained stable (at least 90% of initial concentrations) throughout the 90-day study period. There was no detectable change in color and no visible presence of microbial growth in any samples. The bioavailability of sodium benzoate formulations in the current study has not been evaluated. However, the absorption and therapeutic effectiveness of a drug in a suspension compounded from a powder is unlikely to differ appreciably from the original dosage form.

Before this study, no stability data had been published on the preparation of sodium benzoate suspension. In the absence of stability information from documentation, literature, or stability tests, USP Chapter 795: Pharmaceutical Compounding—Nonsterile Preparations recommends a maximum beyond-use date that is "no longer than 14 days or the earliest expiration of any ingredient used, whichever is shorter, and stored at controlled room temperatures." The results of this study will have a particular benefit for infants and children with UCDs, as well as others who require a liquid formulation of sodium benzoate. In addition, the extended stability will benefit compounding pharmacies by reducing workload and increase convenience for families, who will be able to refill their prescriptions less frequently.

CONCLUSION

Extemporaneously compounded suspensions of sodium benzoate 250 mg/mL in cherry syrup or Ora-Sweet were stable for at least 90 days when stored in 4-oz amber, plastic bottles at room temperature in low-light conditions.

REFERENCES


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