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Chemical Stability of Diphenhydramine in "Magic Mouthwash" Stored at Room and Refrigerated Temperatures for 90-Days

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OBJECTIVE This study aimed to investigate the chemical stability of diphenhydramine in a pediatric "Magic Mouthwash" preparation, specifically a 1:1 mixture of aluminum hydroxide/magnesium hydroxide/simethicone (Mylanta comparable product) and liquid diphenhydramine over 90 days under different storage conditions.

METHODS A high-performance liquid chromatography-ultraviolet method was developed for quantifying diphenhydramine in the mouthwash. A total of 10 bottles of mouthwash were prepared, with half stored in the refrigerator and half kept at room temperature. The method was applied to analyze the stability of diphenhydramine in the mouthwash preparations, with 5-mL aliquots removed from each bottle at 0, 1, 7, 14, 30, 60, and 90 days. Stability was defined as maintaining 90–110% of the initial concentration.

RESULTS Both storage conditions (room temperature: 19.3 ± 0.8°C; refrigeration: 3.01 ± 0.3°C) maintained stable temperatures. The pH remained stable (room temperature: 8.34 ± 0.4; refrigeration: 8.38 ± 0.4). Diphenhydramine concentrations stayed within the 90–110% range for the entire study duration under both conditions. No statistically significant differences in diphenhydramine concentration were observed between storage conditions or over time.

CONCLUSION The pediatric "Magic Mouthwash" demonstrated stable pH and diphenhydramine potency over 90 days, regardless of whether it was stored at room temperature or refrigerated. This supports the feasibility of bulk preparation and extended storage of this formulation, providing a safe and effective alternative to lidocaine-containing mouthwash for pediatric patients.

ABBREVIATIONS HPLC, high-performance liquid chromatography; UV, ultraviolet

KEYWORDS oral mucositis; "Magic Mouthwash"; diphenhydramine; stability; pediatrics

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Introduction

"Magic Mouthwash" is a mixture of medications routinely prepared by pharmacists in hospitals and community settings to treat oral mucositis. The product has various recipes, with the most common formulation containing equal parts of Mylanta (or a comparable product with aluminum hydroxide, magnesium hydroxide, and simethicone), diphenhydramine, and viscous lidocaine. This combination is commonly referred to as BMX.[1,2] Additionally, a kit is available to compound this product. The FIRST - Mouthwash BLM kit contains 0.1 grams diphenhydramine, 0.8 grams lidocaine, 1.58 grams aluminum hydroxide, 1.58 grams magnesium hydroxide, and 0.158 grams simethicone per 4 ounces.[3] Viscous lidocaine should not be used in "Magic Mouthwash" preparations for young children due to the risk of cardiovascular and other systemic side effects.[4] Furthermore, viscous lidocaine carries a Boxed Warning from the Food and Drug Administration regarding its use in infants and children, which lists potential side effects such as seizures, cardiopulmonary arrest, and death in patients under the age of 3 years.[5,6] Owing to these risks, an alternative preparation is recommended for pediatric patients, which excludes lidocaine. This alternative to the BMX preparation for "Magic Mouthwash" is a 1:1 mixture of Mylanta and diphenhydramine. Diphenhydramine exerts an anti-inflammatory effect, while the components of Mylanta help restore oral pH and coat the oral surfaces.[2] Furthermore, pediatric oncology patients tend to have lower salivary pH, making them vulnerable to dental caries.[7] The relatively higher pH of "Magic Mouthwash" helps correct the oral pH in these patients and combats flare-ups of oral mucositis, which are more common in pediatric oncology patients than in adults.[8] Commercially available compounding kits with extended beyond-use dates contain the

lidocaine. Thus, pediatric-suitable "Magic Mouthwash" preparations must be compounded.[9] The stability of lidocaine in "Magic Mouthwash" preparations has been established,[1] and the stability of diphenhydramine has been investigated in various aqueous media.[11–13] However, data supporting the stability of diphenhydramine when mixed with aluminum hydroxide (200 mg), magnesium hydroxide (200 mg), and simethicone (20 mg) per every 5 mL (eg, Mylanta) or a comparable product for pediatric "Magic Mouthwash" is lacking. As such, we investigated the chemical stability of diphenhydramine in a "Magic Mouthwash" preparation suited for children.

Methods

A high-performance liquid chromatography method with ultraviolet detection (HPLC-UV) was developed for the quantification of diphenhydramine in a high-pH "Magic Mouthwash" preparation. In brief, the chromatographic conditions included an isocratic separation with 10 mM of triethylammonium acetate in water (A) and acetonitrile (B). The mobile phase was delivered in a 55%A/45%B ratio at a flow rate of 0.400 mL/min on an Agilent Eclipse XDB-C18 column (150 x 4.6 mm; 3.5-µm particle size). The column was maintained at 50°C, and the UV detector set at 227 nm. For the stability investigation, 10 bottles of 60-mL "Magic Mouthwash" using the 1:1 vol/vol ratio of components were prepared. The products used were Leader Children's Allergy Relief (Lot 14191, Exp 04/26) and GERICARE Geri-Lanta (Lot AAR015, Exp 03/25). The GERICARE Geri-Lanta contains aluminum hydroxide (200 mg), magnesium hydroxide (200 mg), and simethicone (20 mg) per every 5 mL. Thirty-milliliter syringes were used to separately measure the 2 components of the mouthwash, which were pale pink and opaque after vigorous mixing. The bottles used were 4-oz polypropylene amber child-resistant syrup bottles. The bottles were randomly assigned to room temperature or refrigerated storage, and the temperature in each storage condition was recorded on each sampling day.

Additionally, the pH of the prepared mouthwashes was recorded at study initiation and on each sampling day using a benchtop pH meter. Baseline quantification of diphenhydramine in each bottle was conducted at the initiation of the study and was defined as the benchmark for 100% recovery. Five samples from each condition (refrigerated and room temperature) were evaluated in triplicate for diphenhydramine recovery on study initiation and days 1, 7, 14, 30, 60, and 90. Five-milliliter aliquots were removed from each bottle after 30 seconds of vortex mixing on each sampling day. Each aliquot was further partitioned into three 1-mL samples to allow for replicates from each bottle. Each sample was filtered using a 0.22-µm nylon filter and injected into the HPLC without further dilution. As such, the target diphenhydramine concentration in each sample was 1.25 mg/mL due to the initial concentration on the product label of 12.5 mg/5mL. A fresh calibration curve was prepared daily to facilitate the quantification of diphenhydramine in the samples, and the pH from each individual bottle was measured on each sampling day. The calibration curve concentrations were 0.3125, 0.6250, 0.9375, 1.250, and 1.5625 mg/mL, representing 25%, 50%, 75%, 100%, and 125% of the target concentration, respectively. Percent error and percent relative standard deviation were assessed across 4 days (n = 3 each day) at each calibration concentration. Percent diphenhydramine recovery was calculated for all samples of each condition to stay within 90–110% of the initial concentration.[14] Statistical analyses of the data were conducted using GraphPad Prism (version 9.5.1) to assess the stability of diphenhydramine across conditions. A Welch's *t*-test was used to investigate pH differences between the 2 study groups. Diphenhydramine concentrations in samples between groups and across the 90-day study duration were compared using a 2-way analysis of variance with a threshold of $p = 0.05$. Additionally, a Dunnett's multicomparison post-hoc test was applied to examine statistically significant differences between time 0 and subsequent time points in each treatment group.

Results

The HPLC-UV assay demonstrated reproducible and accurate quantification of diphenhydramine at all concentrations. These data are summarized in Table 1.

Room temperature (19.3 ± 0.8°C) and refrigerator temperature (3.01 ± 0.3°C) remained stable and within acceptable ranges for the 90-day duration of the study. No statistically significant difference in pH was found between room temperature mouthwash (8.34 ± 0.4) and refrigerated mouthwash (8.38 ± 0.4), as determined by a Welch's *t*-test ($p = 0.6267$).

There was no statistically significant difference in the initial diphenhydramine concentrations between the bottles assigned to the 2 storage conditions (*t*-test, $p = 0.6788$). For room temperature preparations, diphenhydramine concentration was measured to be 1.276 ± 0.080 mg/mL initially, which was assigned to the "100% recovery" benchmark. Likewise, refrigerated preparations showed an initial diphenhydramine concentration of 1.264 ± 0.076 mg/mL. As the study progressed, the 2-way analysis of variance yielded no statistically significant differences in diphenhydramine concentration between the 2 conditions or throughout the study sample days. The 90-day diphenhydramine concentrations were 1.219 ± 0.062 and 1.239 ± 0.077 mg/mL for room temperature and refrigerated samples, respectively. The concentration of diphenhydramine in all preparations stayed within the desired 90–110% recovery range for the entire study.[14] These data are shown in Figure 1. After 90 days of storage, recovery of diphenhydramine was 95.5% in room temperature samples

Table 1. Precision and accuracy for the quantification of diphenhydramine using HPLC-UV

	Intraday Validation (n = 3 per day)		Interday Validation (n = 12)	
Diphenhydramine Concentration, mg/mL (% Assay Level)	% RSD Range	% Error Range	% RSD	% Error
0.3125 (25%)	1.36–2.92	0.93–4.51	2.05	2.90
0.6250 (50%)	1.15–4.83	2.58–3.19	2.69	2.83
0.9375 (75%)	0.14–3.13	0.81–4.39	1.78	1.93
1.250 (100%)	2.28–3.32	0.86–3.46	2.77	2.29
1.5625 (125%)	0.99–2.61	0.65–2.91	1.84	1.40

RSD, relative standard deviation; HPLC-UV, high-performance liquid chromatography-ultraviolet

Precision (represented by %RSD) and accuracy (represented by % error)

Figure 1. Mean diphenhydramine concentration found in samples for duration of stability study.

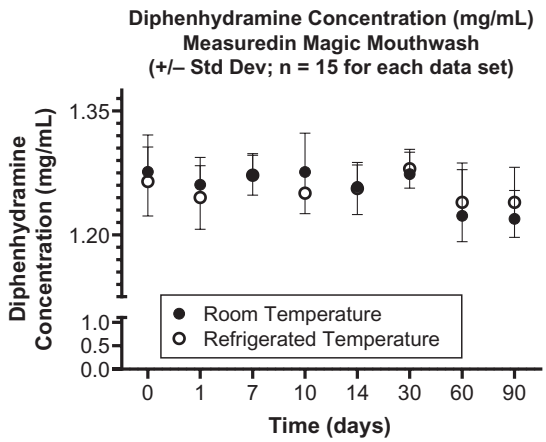

Table 2. Measured diphenhydramine concentrations (mg/mL) and percentage recovery relative to initial concentration for the 90-day stability investigation

Timepoint, days	Room Temperature	Refrigerated Temperature
0	1.276 ± 0.080 (100)	1.264 ± 0.076 (100)
1	1.261 ± 0.059 (98.8)	1.245 ± 0.070 (98.4)
7	1.273 ± 0.046 (99.1)	1.272 ± 0.044 (100.6)
10	1.276 ± 0.085 (99.9)	1.250 ± 0.045 (98.9)
14	1.258 ± 0.048 (98.6)	1.256 ± 0.057 (99.3)
30	1.273 ± 0.048 (99.8)	1.280 ± 0.042 (101.2)
60	1.223 ± 0.101 (95.8)	1.239 ± 0.086 (98.0)
90	1.219 ± 0.062 (95.5)	1.239 ± 0.077 (98.0)

Percentage recovery in parenthesis, n = 15 for each data point

and 98.0% in refrigerated samples compared with the initial concentration. Calculated concentrations and recovery data for the entire study are shown in

Figure 2. Comparison of diphenhydramine recovery across the 90-day storage.

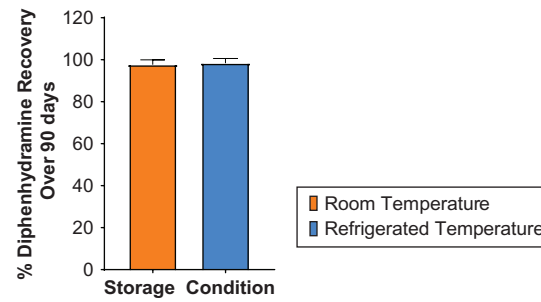

Table 2. The average recovery over 90 days is shown in Figure 2 for the mouthwash preparations at room and refrigerated temperatures. Finally, no change in the physical characteristics was detected between refrigerated and room temperature samples for the duration of the study.

Discussion

The stability of the mouthwash pH under both room and refrigerated conditions confirmed that the pH maintenance provided by the Geri-Lanta components was not affected by temperature. The relatively high pH maintained by the aluminum hydroxide and magnesium hydroxide in Geri-Lanta likely helped preserve the stability of the diphenhydramine component. Previous research has shown that diphenhydramine degrades less in basic pH conditions compared with acidic pH environments.[13]

One limitation of this study was the low room temperature conditions relative to the USP metric (20–25°C).[15] Despite this, there is no evidence that diphenhydramine stability would be negatively impacted at USP-defined room temperature, given that the difference between our refrigerated and room conditions did not initiate degradation. Furthermore, the stability of the preparation's pH provides additional confidence that the

mixture would sustain at a slightly higher room temperature. While the USP allows excursions of 15–30°C to still be considered controlled room temperature, other pharmacopeias define room temperature as 15–25°C.[15–17] Finally, other investigators have demonstrated the thermal stability of diphenhydramine in basic solutions.[12]

Conclusions

These data support the preparation of bulk "Magic Mouthwash" using Mylanta (or a comparable product) and diphenhydramine (1:1 vol/vol) for pediatric patients. Mouthwash pH and diphenhydramine potency remained stable for 90 days, regardless of storage condition. Additionally, multiple withdrawals from the bulk container did not affect product stability.

Article Information

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