Stability and viscosity of a flavored omeprazole oral suspension for pediatric use

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Purpose. The stability and viscosity of preparations of a commercially available, flavored, immediate-release powder for oral suspension (omeprazole–sodium bicarbonate) during refrigerator and room temperature storage were investigated.
Methods. Omeprazole–sodium bicarbonate 20-mg packets were suspended to initial omeprazole concentrations of 0.6 and 2 mg/mL, and omeprazole–sodium bicarbonate 40-mg packets were suspended to initial omeprazole concentrations of 1.2, 2, 3, and 4 mg/mL. Suspensions were stored at 4 °C in darkness (refrigerated) or 22–25 °C (room temperature) in light for one week. A third set of suspensions was stored refrigerated for one month. Omeprazole's stability was quantified after 0, 6, 12, 24, 48, and 168 hours in one-week samples and after 0, 7, 14, 21, and 28 days in one-month samples using high-pressure liquid chromatography. Viscosities of refrigerated suspensions were measured after 0, 1, and 7 days.
Results. Refrigerated suspensions retained >98% and >96% of their initial omeprazole concentrations after one week and one month, respectively. Stability of room temperature suspensions was concentration dependent. After one week, the 0.6- and 1.2-mg/mL suspensions retained 87.2% and 93.1% of their respective initial omeprazole concentrations, whereas the 2-, 3-, and 4-mg/mL suspensions retained >97% of their initial omeprazole concentrations. Suspension viscosities varied 10-fold over the concentrations studied, but all were within the viscosity ranges of other commercially available oral suspensions. Prolonged refrigeration did not increase the suspensions' viscosities.
Conclusion. Omeprazole–sodium bicarbonate suspensions of 0.6–4 mg/mL omeprazole were stored at 4 °C in darkness for up to 28 days. The viscosities of refrigerated suspensions did not increase over 7 days. Except for the 0.6 mg/mL preparations, suspensions stored at room temperature in the light retained >90% of their initial omeprazole content after 7 days, despite turning yellow.

Index terms: Antacids; Color; Concentration; Gastrointestinal drugs; Omeprazole; Pediatrics; Photodecomposition; Sodium bicarbonate; Stability; Storage; Suspensions; Temperature; Viscosity
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Proton-pump inhibitors (PPIs) are substituted pyridylmethylsulfinyl benzimidazole compounds that act to inhibit gastric acid secretion by selectively and irreversibly inhibiting the stomach's parietal cells' H^+,K^+-ATPase.[1] Since first introduced in the late 1980s, PPIs have become the medications of choice in the treatment of acid-related disorders, including gastroesophageal reflux disease (GERD), duodenal and gastric ulcers, and Zollinger–Ellison syndrome. Of five PPIs currently approved for use in treating these disorders, lansoprazole and omeprazole are approved for use in children older than one and two years of age, respectively.[2,3]

The activity of PPIs is dependent on the weakly basic nature of the pyridyl nitrogen, which has a pK_a near <4.[1,4] At neutral pH, PPIs are inactive, remaining as lipophilic prodrugs that can freely cross cell membranes. At pH <4, the pyridyl nitrogen becomes protonated, which initiates a structural rearrangement to form a reactive cyclic sulfenamide, the pharmacologically active form of the drug.

The structural features of PPIs that make them pharmacologically active also render them unstable and subject to degradation. For this reason, most oral PPI dosage forms are enteric-coated tablets or extended-release capsules containing enteric-coated granules. The enteric coatings protect the PPIs from degradation by stomach acid.[1]

Administration of enteric-coated PPIs is problematic in pediatric,

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elderly, or critically ill patients who may be unable to swallow solid dosage forms. Recommendations for administration in these patients involve opening capsules and mixing the enteric-coated granules into soft acidic foods or flushing granules through nasogastric tubes with liquids. Such methods have significant drawbacks. Flushing granules through nasogastric tubes is time-consuming and may lead to clogging of tubes.[5,6]

Oral administration of enteric-coated granules to pediatric patients is fraught with problems. Children may be too young to swallow even soft foods, or they may chew the granules, which compromises the enteric coating and leads to drug inactivation.[5] Also, adjusting pediatric dosages of granule-containing PPI formulations by weight is difficult and not recommended.

Homogeneous liquid suspensions of PPIs permit greater ease of administration orally or via nasogastric tube, and they also simplify dosage adjustments for children. Homogenous suspensions of omeprazole and lansoprazole can be prepared by dissolving enteric-coated granules in a solution of 8.4% sodium bicarbonate. However, these preparations are intensely salty and bitter and undesirable as orally administered formulations, especially in children.

In 2004, omeprazole–sodium bicarbonate, an immediate-release omeprazole powder for oral suspension,[a] became commercially available; it contains sweeteners and additional flavorings to improve palatability.[7,8] Omeprazole–sodium bicarbonate is dispensed as single, ready-to-use packets that, with the addition of 30 mL of water, provide either 20 or 40 mg of omeprazole homogeneous suspension buffered with sodium bicarbonate (20 meq per packet).[8] Suspensions have a peach–mint flavor.

Previous studies have investigated the stability of omeprazole in extemporaneously prepared, unflavored omeprazole–bicarbonate suspensions.[6,9,10] However, no data are available on the stability of omeprazole in flavored suspensions. This study reveals the effects of refrigerated and ambient storage of omeprazole–sodium bicarbonate suspensions prepared to final omeprazole concentrations ranging from 0.6 to 4 mg/mL. The study also shows the effect of refrigerated storage on omeprazole–sodium bicarbonate fluidity as a function of suspension concentration.

Methods

Sample preparation. Individual packets of omeprazole–sodium bicarbonate powder containing either 20[b] or 40[b] mg omeprazole were dissolved in tap water in clear plastic 50-mL conical polypropylene tubes.[c] Powders from 20-mg packets were suspended to initial omeprazole concentrations of 0.6 and 2 mg/mL, and powders from 40-mg packets were suspended to initial omeprazole concentrations of 1.2, 2, 3, and 4 mg/mL. Volumes of water used for omeprazole–sodium bicarbonate suspensions are indicated in Table 1. For short-term stability determinations, six tubes of each omeprazole–sodium bicarbonate suspension concentration were prepared. Three tubes were stored for one week at 4 °C in darkness, and three were stored at room temperature (22–25 °C) in continuous light. For extended storage stability determinations, tubes of each omeprazole–sodium bicarbonate suspension concentration were prepared in triplicate and stored at 4 °C in darkness for 28 days.

To assess the stability of omeprazole during suspension storage, aliquots of approximately 80 µL were removed from all tubes immediately after preparation (time 0) and at specific times throughout the storage period. For preparations stored for one week, aliquots were removed at 6, 12, 24, 48, and 168 hours (7 days). For extended storage experiments, aliquots were removed at 7, 14, 21, and 28 days. Before removing aliquots, tubes were mixed well to ensure uniform resuspension of insoluble materials that had settled during storage.

Because of the potential for volume error due to difficulty in pipetting thicker, more concentrated suspensions, the exact volume of an aliquot

Table 1.
Preparation of Immediate-Release Omeprazole–Sodium Bicarbonate Suspension

Omeprazole Concentration (mg/mL)	Omeprazole Packet Size (mg)	Volume of Tap Water Added (mL)	Final Volume of Solution, (mL)	Sodium Bicarbonate Concentration (%)[a]
0.6	20	30.0[b]	33.5	5.0 (0.6 M)
2.0	20	6.5	10.0	16.8 (2 M)
1.2	40	30.0[b]	33.5	5.0 (0.6 M)
2.0	40	16.5	20.0	8.4 (1 M)
3.0	40	9.8	13.3	12.6 (1.5 M)
4.0	40	6.5	10.0	16.8 (2 M)

[a]Molarity indicated in parentheses.
[b]Volume recommended by manufacturer.

was calculated from the weight of the aliquot (determined on a tared electronic balance) and the density of the suspension from which it was taken. The densities of suspensions were determined by weighing them and dividing by the final suspension volumes.

Omeprazole extraction and analysis. For determination of omeprazole concentrations in aliquots, a method of omeprazole extraction and assay by reverse-phase high-performance liquid chromatography (HPLC) was developed on the basis of previously published methods.[9,11]

Extraction of omeprazole from suspension aliquots was a two-step process, begun when aliquots were collected and completed on the day of HPLC injection. For the first step of the extraction, 9 volumes of methanol[d]/15 mM sodium phosphate buffer[e] (1:1, v/v, pH 7.4) were added to the aliquots, and the samples were mixed by inversion and agitation using a benchtop vortex mixer. The methanol/phosphate-containing aliquots were immediately placed at –80 °C, where they remained until the day of HPLC analysis. The addition of methanol before freezing was to minimize omeprazole degradation that might occur as a result of freezing and thawing or subsequent sample handling.

Frozen omeprazole–sodium bicarbonate suspension aliquots were thawed at room temperature in darkness. The thawed tubes were then maintained in darkness at 4 °C until they could be processed. All samples were thawed and processed as rapidly as possible after removal from the –80 °C freezer.

Thawed samples were remixed and then centrifuged for one minute in a microcentrifuge to pellet insoluble materials. The final extraction step was completed by adding 9 volumes of 100% acetonitrile[f] to the supernatant and centrifuging for three minutes to remove precipitated excipient materials. For injection into the HPLC system,[g] a 50-µL aliquot of the supernatant was diluted 1:10 with methanol/15 mM sodium phosphate buffer, pH 7:4 (40:60, v/v). Injection volumes ranged from 30 to 100 µL.

The HPLC column configuration consisted of a C_{18} silica column[h] fitted with a C_{18} silica precolumn.[i] Mobile phase was methanol/acetonitrile/15 mM sodium phosphate buffer (40:10:50 v/v/v, pH 7.4). The flow rate was 1 mL/min and the detector wavelength was 300 nm.

Calibration standards were prepared by using the mobile phase to dilute a 1-mg/mL stock solution of pure omeprazole[j] (dissolved in 100% methanol) to 1 and 10 µg/mL. Volumes of these working standards equivalent to 0.02, 0.05, 0.1, and 0.2 µg of omeprazole were injected to obtain calibration curves. The stock solution and aliquots of the working standards were stored at –80 °C.

Standard curves were produced by the software included in the HPLC system. Standard curves were linear and highly reproducible, with r^2 values always greater than 0.999. The coefficient of variation for the slope of the standard curves over a six-month period was 1.5% (n = 18 curves).

The stability-indicating capacity of the HPLC assay was assessed by forced degradation of omeprazole in acid. A 40-mg packet was prepared to 1.2 mg/mL omeprazole. From each of duplicate 2-mL samples, 100-µL aliquots were removed to determine the time 0 omeprazole concentration in each tube. To the remaining 1.9 mL in each tube, 140 µL of either 12 *N* hydrochloric acid (HCl)[k] or tap water was added, and additional 100-µL aliquots were removed after 15 and 30 minutes of incubation at room temperature. All aliquots were extracted and analyzed by HPLC as described above.

All reagents used for extraction, dilution and separation were HPLC or analytical grade.

Viscosity determinations. To determine if storage time at 4 °C had an effect on the viscosity of omeprazole–sodium bicarbonate suspensions, they were subjected to shear stress in a rotational viscometer. Viscosity, which is the inverse of fluidity, is measured in units of Pascal-seconds (Pa-sec).[12]

Omeprazole–sodium bicarbonate was prepared by the same method that was used for the stability determinations (Table 1). Samples were prepared in duplicate 300-mL batches by combining the contents of multiple packets and bringing to volume with tap water prechilled to 4 °C. Suspensions were stored in glass jars at 4 °C in darkness.

Viscosity measurements of 60-mL aliquots of each suspension were taken immediately after suspension (time 0) and after one and seven days of storage using a rotational viscometer.[l] Samples were subjected to a constant shear rate of 110/sec for 120 seconds at 4 °C. Preliminary experiments had shown that viscosity became constant for preparations analyzed in this study 80 seconds into the run. Therefore, viscosities reported here are those recorded at 80 seconds.

Microbiological analysis. Aliquots from omeprazole–sodium bicarbonate 40-mg suspensions stored for one week under light and room temperature conditions were plated on chocolate, MacConkey, and blood agar plates. Plates were incubated for five days at 35 °C under 6% carbon dioxide and examined daily for microbial growth.

Statistical analysis. Effects of storage time on omeprazole concentration and viscosity were determined by one-way repeated-measures analysis of variance for each sample and storage condition. For main effects, statistical significance was set a priori at $p < 0.05$. When a significant main effect was detected, paired t tests were conducted to identify values significantly different from values at time 0. All statistical analyses were

conducted with SPSS version 11.0.2 (SPSS Inc., Chicago, IL). To control for Type I errors, significance levels for post hoc tests were determined using Holm's sequential Bonferroni procedure.[13]

Results

The HPLC assay for omeprazole was stability indicating. The addition of 140 μL of concentrated HCl to a 2-mL aliquot of omeprazole–sodium bicarbonate suspended to 1.2 mg/mL omeprazole resulted in most of the omeprazole being degraded within 15 minutes (Figure 1). Degradation products that appeared with acid treatment did not interfere with the ability to detect remaining intact omeprazole. Control samples in which water was added instead of acid showed no significant loss of omeprazole over the 30-minute incubation period (data not shown).

Omeprazole–sodium bicarbonate suspensions refrigerated in darkness showed no appreciable degradation of omeprazole during either short-term or long-term storage. Samples stored for a week showed less than 2% loss of omeprazole (Table 2). After 28 days of refrigerated dark storage, losses of 2–4% were noted for three suspensions (Table 3). Specifically, after 28 days, the 0.6- and 2-mg/mL suspensions made with powders from 20-mg packets had omeprazole concentrations that averaged 97.5% and 97.7% of the initial concentrations, respectively. The 1.2-mg/mL suspension made with powders from 40-mg packets had 96.2% of the mean starting concentration. However, none of these decreases in omeprazole concentration were statistically significant.

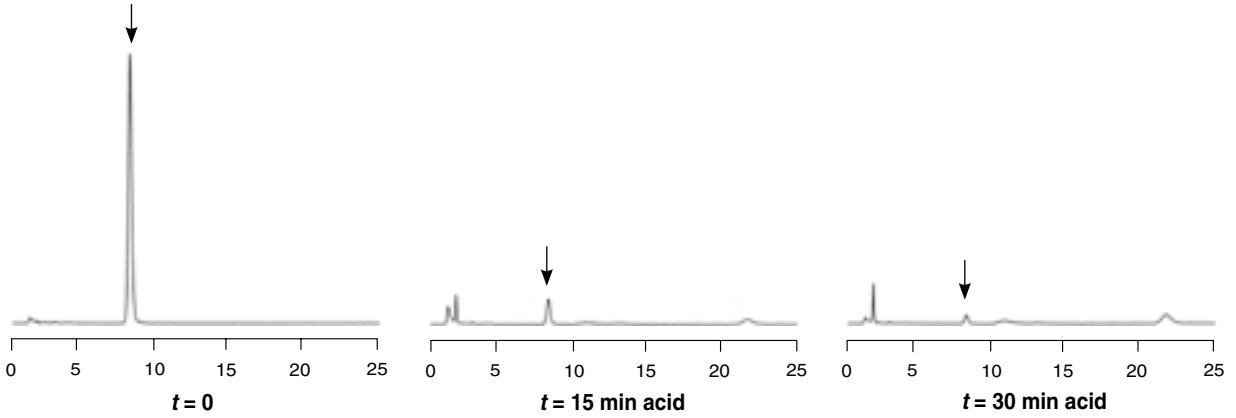
Storage at room temperature in the light resulted in omeprazole degradation in the 0.6- and 1.2-mg/mL suspensions (Table 2). After 48 hours, the mean omeprazole concentration of the 0.6-mg/mL suspensions made with powders from 20-mg packets was 96.6% of the mean starting concentration. After one week, the mean omeprazole concentration in the 0.6-mg/mL suspensions had declined to 87.2% of the starting concentration, statistically significant for this sample ($p = 0.018$). In the 1.2-mg/mL suspensions made with powders from 40-mg packets, the mean concentration after 48 hours was 97.2% of the starting concentration; after one week, the mean concentration had declined to 93.1% of the starting concentration. Suspensions prepared to 2, 3, and 4 mg/mL showed no more than 2.5% degradation after one week of storage at room temperature.

All freshly prepared suspensions were white in color. Refrigerated samples did not change color even after one month of storage. Samples stored at room temperature in the light began to turn yellow after 24 hours, and color intensity increased with duration of storage. The 0.6- and 1.2-mg/mL samples exhibited a more intense color change than the 2-, 3-, and 4-mg/mL samples. No colonies or other evidence of bacterial or fungal growth were detected on any of the culture media for any of the suspensions tested.

Across the range of suspension concentrations analyzed, viscosities varied 10-fold from 0.02 to 0.21 Pa-sec. Storage for up to one week in the cold did not result in any increase of viscosity in any of the suspensions (Table 4). In fact, viscosity appeared to slightly decrease during storage for all but the two most dilute suspensions.

To determine how the viscosity of the omeprazole–sodium bicarbonate suspensions compared to other commercially available oral suspensions, viscosity determinations were also made on a pediatric acetaminophen suspension[m] and on a buffered, chocolate-flavored product for use in preparing oral suspensions of enteric-coated PPI granules.[n] The acetaminophen suspension had a

Figure 1. Chromatograms showing the time course of omeprazole degradation by acid. Omeprazole was quantified in 100-μL portions of a 2-mL omeprazole–sodium bicarbonate suspension (1.2 mg/mL omeprazole prepared using omeprazole–sodium bicarbonate 40-mg packets) taken before and after addition of 140 μL 12 *N* hydrochloric acid. Horizontal axes show retention time in minutes. Omeprazole retention time = 8.1 minutes. Arrows indicate omeprazole peaks.



viscosity of 0.349 Pa-sec, whereas the flavored buffer product had an initial viscosity of 0.157 Pa-sec that increased slightly over time. Viscosities of the omeprazole–sodium bicarbonate suspensions were less than or similar to these other oral suspensions.

Discussion

A drawback of liquid suspensions of omeprazole and other PPIs is the potential for degradation due to the acid lability of the compounds. The stability of PPIs is increased at alkaline pH,[14,15] and previous studies have demonstrated that PPIs dissolved in 8.4% (1 M) sodium bicarbonate are stable[6,9,10,16-18] and bioavailable.[18-20]

The *United States Pharmacopeia* (*USP*) criterion for omeprazole delayed-release capsules is that omeprazole content must be between 90% and 110% of the labeled amount.[21] A 90% cutoff has been the criterion used in previously published reports that assessed the stability of unflavored omeprazole suspensions prepared to 2 mg/mL in 8.4% sodium bicarbonate.[6,9,10] Quercia et al.[9] concluded that these unflavored suspensions were stable for 30 days in the refrigerator and for two weeks at room temperature when stored in glass vials. Phillips et al.[10] determined that such suspensions could be stored in clear glass containers for up to six months in the refrigerator and for one week at room temperature without significant loss of omeprazole. DiGiacinto et al.[6] concluded that unflavored omeprazole–bicarbonate suspensions stored in plastic amber syringes were stable for 45 days in the refrigerator and for two weeks at room temperature.

This study was undertaken to determine the stability of omeprazole

Table 2.
Stability of Omeprazole in Immediate-Release Omeprazole–Sodium Bicarbonate Suspension

Storage Condition	Packet Size (mg)	Target Omeprazole Concentration (mg/mL)	% ± S.D. Omeprazole Remaining[a]				
			6 hr	12 hr	24 hr	48 hr	168 hr
4 °C, dark	20	0.6	99.6 ± 0.8	99.3 ± 1.4	100.0 ± 1.0	99.7 ± 0.8	99.4 ± 0.6
	20	2.0	100.5 ± 0.1	101.8 ± 1.7	101.2 ± 1.6	101.8 ± 1.7	101.6 ± 1.2
	40	1.2	99.5 ± 3.6	102.0 ± 4.3	101.3 ± 6.4	101.2 ± 5.1	98.9 ± 5.3
	40	2.0	98.6 ± 1.1	98.8 ± 0.4	99.3 ± 0.4	99.3 ± 0.1	98.9 ± 0.7
	40	3.0	101.4 ± 0.9	98.4 ± 1.3	100.3 ± 0.9	100.7 ± 1.2	102.3 ± 0.8
	40	4.0	99.9 ± 0.3	100.9 ± 0.9	99.5 ± 2.7	98.9 ± 1.8	99.8 ± 4.3
RT[b], light	20	0.6	99.3 ± 1.9	100.7 ± 2.3	98.4 ± 3.1	96.6 ± 2.3	87.2 ± 2.9[c]
	20	2.0	101.9 ± 1.0	101.5 ± 1.6	101.9 ± 0.6	101.4 ± 0.5	99.5 ± 0.6
	40	1.2	98.3 ± 4.2	99.3 ± 3.9	98.8 ± 5.3	97.2 ± 7.6	93.1 ± 4.0
	40	2.0	100.9 ± 1.2	100.3 ± 1.5	101.1 ± 1.8	100.8 ± 2.3	97.5 ± 2.8
	40	3.0	99.8 ± 0.9	100.3 ± 0.9	100.7 ± 1.5	100.7 ± 2.2	101.5 ± 0.9
	40	4.0	97.0 ± 1.6	99.4 ± 1.2	100.3 ± 0.6	100.1 ± 0.9	100.4 ± 0.2

[a] $n = 3$.
[b] RT = room temperature, 22–25 °C.
[c] $p = 0.018$ from the concentration at time 0.

Table 3.
Stability of Omeprazole in Immediate-Release Omeprazole–Sodium Bicarbonate Suspension in Darkness at 4 °C

Packet Size (mg)	Target Omeprazole Concentration (mg/mL)	% ± S.D. Omeprazole Remaining[a]			
		7 Days	14 Days	21 Days	28 Days
20	0.6	99.3 ± 1.0	97.8 ± 1.3	98.0 ± 1.6	97.5 ± 0.8
20	2.0	99.9 ± 0.3	99.3 ± 1.0	99.0 ± 0.9	97.7 ± 0.5
40	1.2	98.3 ± 0.7	98.9 ± 2.6	98.5 ± 0.9	96.2 ± 3.9
40	2.0	101.3 ± 0.9	99.5 ± 3.1	100.2 ± 1.4	100.8 ± 1.4
40	3.0	99.1 ± 1.2	100.4 ± 1.5	100.9 ± 1.9	100.5 ± 0.8
40	4.0	99.6 ± 1.8	101.1 ± 1.2	102.0 ± 1.2	101.5 ± 1.2

[a] $n = 3$.

Table 4.
Viscosity of Immediate-Release Omeprazole–Sodium Bicarbonate Suspension in Darkness at 4 °C

Packet Size (mg)	Omeprazole Concentration (mg/mL)	Mean ± S.D. Viscosity[a] (Pa-sec)		
		0 hr	24 hr	7 Days
20	0.6	0.020 ± 0.001	0.020 ± 0.001	0.020 ± 0.000
20	2.0	0.214 ± 0.001	0.209 ± 0.001	0.187 ± 0.002
40	1.2	0.020 ± 0.001	0.020 ± 0.000	0.020 ± 0.000
40	2.0	0.043 ± 0.002	0.043 ± 0.000	0.042 ± 0.000
40	3.0	0.100 ± 0.001	0.096 ± 0.004	0.093 ± 0.003
40	4.0	0.208 ± 0.001	0.210 ± 0.000	0.203 ± 0.010
ChocoBase[b]	...	0.157 ± 0.003	0.192 ± 0.003	0.183 ± 0.009
Children's Tylenol[c]	...	0.349	0.349	0.349

[a] $n = 2$.
[b] Prepared according to manufacturer's instructions but without omeprazole.
[c] Single sample measured at 25 °C.

in a commercially available omeprazole powder for suspension that, unlike extemporaneous suspensions examined in earlier studies, contains flavorings and other excipient materials. The study examined omeprazole–sodium bicarbonate suspensions prepared over final omeprazole concentrations ranging from 0.6 to 4 mg/mL. When prepared according to package instructions, final omeprazole concentrations for the 20- and 40-mg packets are 0.6 and 1.2 mg/mL. Higher concentrations than 1.2 mg/mL were also investigated because they are more useful for pediatric use because the volume per dose is reduced.

No significant omeprazole degradation was detected in samples refrigerated for up to one month, irrespective of suspension concentration. All omeprazole–sodium bicarbonate suspensions showed 2% or less degradation after one week, and no more than 2–4% degradation after one month, which fulfilled the *USP* criterion. For samples stored at room temperature in the light, all but the 0.6-mg/mL suspension fulfilled the *USP* criterion for up to one week of storage.

The rate of degradation at room temperature in the light appeared to be influenced by the concentration of the omeprazole–sodium bicarbonate suspension. For the first 24 hours of storage, all samples were relatively stable. After 24 hours of storage, however, the 0.6- and 1.2-mg/mL samples exhibited degradation that increased with increasing storage time. While degradation was accelerated in the 1.2-mg/mL samples, these suspensions still retained 93.1% of their initial omeprazole concentration after one week of storage. However, the 0.6-mg/mL samples retained only 87.2% of the mean starting concentration after one week, a statistically significant difference.

A possible explanation for reduced stability of the more dilute suspensions is that they may not have sufficient buffering capacity to permit prolonged room temperature storage. Each omeprazole–sodium bicarbonate packet provides 20 meq (1.68 g) of sodium bicarbonate, which is intended to protect the drug from acid degradation in an adult stomach when taken as a single dose. When prepared in 30 mL water according to the manufacturer's instructions, the 0.6- and 1.2-mg/mL suspensions therefore contain 5.0% sodium bicarbonate. Suspensions prepared to 2, 3, and 4 mg/mL omeprazole contain 8.4–16.8% sodium bicarbonate (Table 1).

In this study, all omeprazole–sodium bicarbonate suspensions stored at room temperature in the light began to turn yellow after 24 hours, with the two most dilute suspensions exhibiting the most intense color change over the course of a week. Previous studies have also noted that omeprazole–bicarbonate suspensions change color upon storage at room temperature in the light.[6,9,10] Discolorations appear to be largely due to acid-induced decomposition of omeprazole.[14,22] Upon addition of acid, omeprazole suspensions immediately turn pale yellow and become dark yellow to brown with heating.[14] Omeprazole solutions that degrade completely without alkaline stabilizing agents typically turn purple upon prolonged storage.[22]

While light may also contribute to omeprazole degradation, the extent of that contribution is not clear. DiGiacinto et al.[6] observed that 2-mg/mL suspensions stored in amber syringes exhibited slight yellowing after one week at room temperature; in that study, samples could be stored at room temperature for up to 14 days without significant (>10%) loss of omeprazole. However, Quercia et al.[9] found that suspensions in glass vials were stable for the same amount of time, noting that under these conditions, suspensions gradually turned from white to brown.

Although additional studies are necessary to determine the precise relationship between omeprazole loss and light-induced or temperature-induced color changes, it appears that the color change to yellow is not necessarily an indicator that the suspension can no longer be used, especially if the preparation has been at room temperature for only a few days. While yellowing may indicate the beginning of acid-induced degradation, HPLC analysis of omeprazole–sodium bicarbonate suspensions showed that, with the

exception of the 0.6-mg/mL suspension, omeprazole content was still greater than 90% of the preparations' starting concentrations after one week at room temperature. Moreover, room temperature storage does not appear to promote any microbial growth in suspensions.

Refrigeration did not cause the viscosity of omeprazole–sodium bicarbonate suspensions to increase over time, regardless of concentration. While a 5-fold decrease in the amount of water added did result in a 10-fold increase in viscosity, the viscosities of the most concentrated omeprazole–sodium bicarbonate suspensions were still comparable to those of other commercially available suspensions. Therefore, concentrated suspensions stored for up to a week are still fluid enough to be poured or drawn into a syringe.

Homogeneous buffered suspensions of PPIs prepared to concentrations of 2 mg/mL and above are useful for treating acid-related disorders in pediatric patients because they permit ease of dose adjustment. Suspensions prepared to higher PPI concentrations also permit administration in the smaller volumes more readily tolerated by infants and young children. This study demonstrates that omeprazole–sodium bicarbonate prepared to 2 mg/mL or higher omeprazole concentrations is sufficiently stable and fluid to allow a single packet to provide multiple doses, resulting in potential cost and time savings for caregivers of pediatric patients.

When administering omeprazole–sodium bicarbonate suspensions that have been prepared to concentrations higher than those recommended by the manufacturer, sufficient sodium bicarbonate must be present in the dose to protect the omeprazole from degradation by stomach acid. An estimate of this minimum requirement was obtained by calculation using a previously published maximal rate of acid production measured in a pediatric population, 0.24 meq/kg/hr.[23] Assuming a gastric transit time of 2.25 hours (children with GERD often have reduced gastrointestinal motility[24]) and a 13-kg patient (one-year-old child at the 97th percentile of growth[25]), the extent of acid exposure will be $0.24 \times 13 \times 2.25 = 7$ meq; therefore, 7 meq of sodium bicarbonate is necessary to neutralize this quantity of acid.

At the University of Missouri Hospital and Clinics, this bicarbonate requirement is followed when prescribing omeprazole–sodium bicarbonate to pediatric patients. Pediatric patients are typically prescribed age-adjusted or weight-adjusted dosages of omeprazole–sodium bicarbonate suspensions prepared to 2 mg/mL of omeprazole.[26] Because the 20- and 40-mg omeprazole–sodium bicarbonate packet sizes both contain 20 meq of sodium bicarbonate, a 2 mg/mL omeprazole suspension prepared with the 20-mg packet will contain 2 meq/mL sodium bicarbonate, whereas one prepared with the 40-mg packet will contain only 1 meq/mL. Therefore, in order to provide at least 7 meq of sodium bicarbonate in a dose from packets prepared to 2 mg/mL, the administered volume of suspension prepared from 40-mg packets can be no less than 7 mL; when prepared from 20-mg packets, the administered volume can be no less than 3.5 mL.

Because of the minimum sodium bicarbonate/volume requirement, the decision to prescribe either the 20- or 40-mg packet size is best determined by the amount of omeprazole a patient is to receive per dose. For pediatric patients requiring ≥14 mg omeprazole per dose, the 40-mg packet should be prescribed. For patients requiring <14 mg per dose, the 20-mg packet should be prescribed (Table 5).

Preparation of omeprazole–sodium bicarbonate to allow multiple doses from a single preparation involves combining several packets. At the University of Missouri Hospital and Clinics, children between one and two years of age who are diagnosed with acid reflux disorders are typically prescribed omeprazole at 1 mg/kg three times a day using suspensions prepared to 2 mg/mL.[26] For example, a one-year-old child weighing 10 kg would receive 10 mg of omeprazole per dose (i.e., 5 mL of a 2-mg/mL omeprazole–sodium bicarbonate suspension) three times a day. To provide an amount of suspension sufficient for two days' worth of dosage for that child, three 20-mg packets could be combined and water added to a final volume of 30 mL. The preparation can be stored in the

Table 5.
Guide for Preparation of Immediate-Release Omeprazole–Sodium Bicarbonate Suspension (2 mg/mL Omeprazole)

Drug (mg/dose)	Packet Size To Use (mg)	Volume Water To Add (mL)	Final Volume of Suspension (mL)	Sodium Bicarbonate (meq/mL)	Minimum Volume/Dose (mL)[a]
<14	20	6.5	10.0	2.0	3.5
≥14	40	16.5	20.0	1.0	7.0

[a]Minimum volume per dose to provide 7 meq of sodium bicarbonate.

refrigerator between doses, and caregivers should be instructed to shake the stored preparations before use to ensure a uniform suspension.

Conclusion

Omeprazole–sodium bicarbonate suspensions of 0.6–4 mg/mL omeprazole were stored at 4 °C in darkness for up to 28 days. The viscosities of refrigerated suspensions did not increase over 7 days. Except for the 0.6 mg/mL preparations, suspensions stored at room temperature in the light retained >90% of their initial omeprazole content after 7 days, despite turning yellow.

[a]Zegerid omeprazole powder for oral suspension, Santarus, San Diego, CA.

[b]20-mg packets, lot C4I00351; 40-mg packets, lot C5A0065.

[c]Sarstedt, Newton, NC.

[d]Fisher Scientific, St. Louis, MO, Catalog no. A452.

[e]Fisher Scientific.

[f]Fisher Scientific, Catalog no. A998.

[g]Model 10AVP, Shimadzu Scientific Instruments, Columbia, MD.

[h]Prevail, 5 µm, 15 cm × 4.6 mm i.d., Alltech Associates, Columbia, MD.

[i]Prevail All-Guard, 5 µm, 7.5 mm × 4.6 mm i.d., Alltech Associates.

[j]Sigma Chemical Co., St. Louis, MO, lot 111K1500.

[k]Fisher Scientific, St. Louis, MO, lot 01216P.

[l]Haake Model VT-550 Viscotester, Gebruder Haake GmbH, Karlsruhe, Germany.

[m]Children's Tylenol Suspension Liquid, cherry flavor, McNeil Pharmaceuticals, Fort Washington, PA, lot HHM116.

[n]ChocoBase for compounding oral suspension, Reflux Solutions, Columbia, MO, lot 12.13.04.

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