Proton pump inhibitors (PPIs) are widely used for the treatment of various acid-related disorders. The five PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) are currently available in various formulations for i.v. and oral delivery. For patients who have difficulty swallowing, the contents of an open capsule containing enteric-coated pellets of omeprazole, lansoprazole, or esomeprazole can be given in slightly acidic fruit juice, applesauce, or yogurt. Other extemporaneously compounded liquid formulations such as sodium bicarbonate suspensions or solutions combined with omeprazole, lansoprazole, or pantoprazole have also been used. However, there are clinical situations in which gastric acid suppression is necessary for patients who are unable to take medications by mouth (e.g., patients in nursing homes or those in intensive care units). For such patients, administration of acid-suppressive therapy i.v. or via nasogastric or gastrostomy tube is frequently required.

In previous investigations, omeprazole and lansoprazole pellets were found to offer poor and unpredictable delivery through nasogastric tubes. However, 98–99% delivery of esomeprazole magnesium pellets was observed in vitro when the pellets were dispersed in 50 mL of tap water as a delivery medium for tube delivery. When compared with tap water as a delivery medium, no differences in pellet retention were observed when 30% and 50% Ora-Plus were used; thus, these Ora-Plus concentrations are feasible alternatives to tap water for nasogastric tube delivery of esomeprazole pellets.

Conclusion. Administration of esomeprazole magnesium enteric-coated pellets dispersed in tap water or Ora-Plus through size 14 French nasogastric tubes in vitro delivered over 99% of capsule contents, regardless of the Ora-Plus concentration used. For immediate bedside administration, Ora-Plus at 50% concentration is a feasible alternative to water when delivering the pellets through size 14 French tubes, while 30% Ora-Plus is an alternative to water for all tubes studied.
water and administered in one step over 30 seconds; pellets that were not delivered were retained in the syringe used to inject the liquid into the tube. Although an effective delivery method, administering esomeprazole in this manner is somewhat cumbersome: The catheter requires gentle shaking and the tip requires elevation and lowering to prevent accumulation of the pellets near the tip, which facilitates the formation of a large bolus or blockage due to simultaneous catheter tip egress. Further, use of another administration method (50 mL of water administered in two steps of 25 mL each) showed reduced pellet delivery (78% pellet delivery with undelivered pellets being predominantly retained in the syringe). We postulated that if the esomeprazole pellets were suspended into a thicker liquid, they might pass through the syringe and tube with less clumping and easier flow. Ora-Plus (Paddock Laboratories, Minneapolis, MN) is a multi-ingredient suspension liquid containing microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, and carrageenan as thickeners; simethicone as an antifoaming agent; sodium phosphate and citric acid as buffering agents; and potassium sorbate and methylparaben as preservatives. Since Ora-Plus has a pH of 4.2, it may provide the thickening effects desired without removing enteric coating. Esomeprazole, like other PPIs, is acid labile and is hence formulated with an acidic enteric-coated polymer that shields it from the gastric environment of the stomach. Suspending the enteric-coated pellets in a slightly acidic environment with a pH close to that of orange juice, apple juice, or yogurt (3.8, 3.2, and 3.9, respectively) would help preserve the drug’s integrity until absorption occurs in the alkaline environment of the duodenum. In an in vitro model where esomeprazole was dispersed in 100 mL of cultured milk (pH 4.4) for 30 minutes and added to 500 mL of 0.1 M hydrochloric acid (pH 1) (simulating stomach conditions), resulting in a final pH of 1.3, Ora-Plus should similarly not affect gastric pH substantially.

The objective of the study was to determine the optimal medium for delivery of esomeprazole magnesium enteric-coated pellets dispersed in various concentrations of Ora-Plus suspension through commonly used nasogastric and gastrostomy tubes using a previously used standardized in vitro protocol.

**Methods**

In phase A, 60 size 14 French standard nasogastric tubes were used to compare esomeprazole magnesium pellet delivery via tap water (0%) or 30, 50, or 70% Ora-Plus concentrations (15 tubes for each). In phase B, tap water and the concentration that yielded the best pellet delivery in phase A were used with the narrower size 8 French (20 tubes) nasogastric tubes and shorter size 20 French tubes (20 tubes) gastrostomy tubes. We evaluated pellet delivery using size 14 French tubes first since (1) the bore size fell between that of the size 8 and 20 French tubes, (2) the size 20 French tubes are substantially shorter than the size 8 and 14 French tubes, and (3) this is the tube type most used in previous studies.

In both phases, the appropriate volume of water was added (25, 17.5, 12.5, or 7.5 mL) to a 60-mL catheter-tip syringe with the plunger removed. One esomeprazole 40-mg capsule was then opened and the content emptied into the syringe. The syringe volume was brought up to the 25-mL mark using Ora-Plus. The plunger was then replaced and, with the tip up, the syringe shaken until the pellets in the tip moved into the body of the syringe. A volume of 5 mL of air separated the liquid and the plunger in the syringe, which was shaken vigorously for 15 seconds before the catheter tip was inserted into the end of the respective nasogastric or gastrostomy tube. With side-to-side shaking as dictated by the location of pellets in the syringe, all contents were emptied, leaving behind the 5-mL pocket of air. An additional 25 mL of tap water was added to the syringe, the contents were again shaken vigorously for 15 seconds, and the entire contents were emptied into the tube with similar side-to-side shaking as needed. Time was measured from the initiation of capsule emptying into the syringe to the administration of the final volume of water (25 mL tap water). To ensure consistency, the same investigator set up the tube as shown in Figure 1 and was responsible for esomeprazole administration.

All capsules were assumed to have 1240 pellets based on our previously conducted study. At the end of each administration, pellet retention counts for the syringe and the tube were performed by two individuals. When necessary, the tubes and syringes were cut open for count accuracy. An amber-colored coffee filter (size 2 filtering capacity) was placed at the end of the tube to collect any remaining pellets. For phase B, a similar method was used except for two things. First, a Luer-Lok syringe was used with the size 8 French tube. Second, the size 20 French gastrostomy tube was set up simulating the positioning of a gastrostomy tube in a supine patient (Figure 2) (set up to lie horizontally rather than a sideways J shape as with the size 14 French and size 8 French tubes).

Sample size was determined at an $\alpha = 0.05$, a power of 0.8, a difference between groups of 20 pellets (less than 2% of pellets), and a standard deviation of 10 pellets (less than 1% of pellets). Using these assumptions, a sample size estimate of 6 tubes per group was derived. We used 15 tubes per group in phase A and 10 tubes in phase B.

Data were collected as the number of pellets retained in the syringe.
and the tube. An analysis of variance (ANOVA) with Bonferroni’s post hoc analysis was used to compare the data from phase A, and Student’s t test was used for data from phase B. Where necessary, Fisher’s exact test was used for dichotomous variables.

Results

Phase A. As shown in Table 1, the mean numbers of pellets (syringe and tube) retained in the tap water (0%) and 30%, 50%, and 70% Ora-Plus concentrations were 1.4, 3.9, 4.6, and 9.0, respectively. Assuming 1240 pellets were in each capsule, there was greater than 99% delivery across all concentrations. ANOVA revealed a statistically significant difference among the various concentrations for pellets retained in the syringe, pellets retained in the tube, total pellets retained, and time from initiation of capsule emptying into the syringe until the final volume of water was administered (all p values <0.03). Bonferroni post hoc t tests revealed a significant difference between the tap water and 70% Ora-Plus groups for pellet retention in the syringe and total pellet retention (both p values <0.02). The 70% Ora-Plus concentration also retained a statistically significant number of pellets in the tube when compared to the other Ora-Plus concentrations and tap water (p values <0.003 for all comparisons). Time from initiation of capsule emptying into the syringe to final water administration was significantly shorter when tap water was used as a delivery medium compared with all the Ora-Plus concentrations (all p values <0.001).

Phase B. For phase B of the study, the 30% Ora-Plus concentration, which showed the best pellet delivery in phase A, was used along with water in the size 8 French and 20 French gastrostomy tubes. The mean numbers of pellets retained (Table 2) in the size 8 French tubes were 106.8 and 3.0 pellets in the tap water and 30% Ora-Plus concentrations, respectively. Fisher’s exact test categorizing the data in groups of greater or less than 10 total retained pellets revealed no difference between tap water and 30% Ora-Plus with the size 8 French tubes.
(p = 0.211). One of the 10 trials with the size 8 French nasogastric tube resulted in retention of 988 pellets in the water dispersion group. When this one trial was removed, an average ± S.D. of 9 ± 14 pellets was retained in the remaining nine trials of size 8 French tubes, which was similar to the 30% Ora-Plus group.

The mean total numbers of pellets retained in the syringe and the size 20 French tube together were 3.0 and 2.8 pellets for tap water and 30% Ora-Plus concentrations, respectively. No differences were seen between groups with regard to pellet retention in the syringe, tube, or total pellet retention (all p values >0.886). The time from initiation of capsule emptying into the syringe until the final volume of water was administered was significantly shorter using tap water compared with 30% Ora-Plus irrespective of the tube (all p values <0.021).

Though we collected tube discharge in a filter, there were no instances where counting was necessary.

Discussion

The results of our study support findings from previous studies and show excellent delivery of esomeprazole pellets using tap water as a medium for tube delivery. The one group (water through a size 8 French tube) that had less than 99% delivery was predicated on one tube run that had an exceptionally high retention rate. When that run was excluded, the group yielded greater than 99% delivery. However, this suggests that there is a potential for syringe clogging with the water-only medium, but we did not have enough power to show that it was significant. A larger study should be conducted to clarify this issue.

A previous study evaluating esomeprazole delivery methods showed 77.7% esomeprazole delivery with water when using a similar two-part method through size 14 French tubes. Our study shows a 99% delivery using the same model and method while evaluating three times the number of tubes compared to that study. Such differences suggest the presence of technique variances, an issue that can be of clinical relevance and can also have associated cost implications.

Though we did not quantitate the number of side-to-side shakes required during different administration methods, we noticed that the Ora-Plus method may require less
syringe shaking than with tap water, which may help reduce interadministrator variability. Further study is necessary to confirm that less shaking is required when Ora-Plus is used. Tube displacement in a patient can also occur as a result of normal movement, further reinforcing the importance of a less cumbersome nasogastric drug administration method.8

When compared with tap water as a delivery medium, no difference in pellet retention was observed when 30% or 50% Ora-Plus was used; thus, these Ora-Plus concentrations are feasible alternatives to tap water for nasogastric tube delivery of esomeprazole pellets. It seems that 70% Ora-Plus would not be an effective alternative to water as a delivery medium as it retains a significantly greater number of pellets and takes longer to administer. Since only the 30% Ora-Plus concentration and tap water were used to determine tube delivery in different tubes, only these mediums can be recommended for esomeprazole delivery when these tube types are used.

Water had a faster delivery time compared with the other concentrations, probably since using Ora-Plus requires an extra step while preparing the syringe. However, all concentrations yielded an esomeprazole to Ora-Plus exposure time and delivery time of less than three minutes, which incorporated syringe preparation, a travel distance of approximately 10 feet simulating near bedside syringe preparation in a patient room, and a two-part drug administration method.

Since only one individual performed drug administration, the study did not incorporate intra-administrator variances, hence increasing internal validity. In vivo, the distal catheter tip resides in an acidic medium. Though our in vitro model did not reflect this, the enteric coating of the esomeprazole pellets prevents dissolution in an acidic medium and hence should not affect our results. The lack of long-term stability data is a potential study limitation as well.

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**Table 1.** Delivery of Esomeprazole Magnesium Pellets through Size 14 French Nasogastric Tubes Using Various Delivery Methods

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Tap water (0%)</td>
<td>15</td>
<td>1.1 ± 1.3</td>
<td>0.3 ± 0.7c</td>
<td>1.4 ± 1.6</td>
<td>105.4 ± 10.9</td>
<td>99.9</td>
</tr>
<tr>
<td>Ora-Plus (30%)</td>
<td>15</td>
<td>3.7 ± 4.6</td>
<td>0.3 ± 0.8c</td>
<td>4.0 ± 4.4</td>
<td>154.9 ± 24.5d</td>
<td>99.7</td>
</tr>
<tr>
<td>Ora-Plus (50%)</td>
<td>15</td>
<td>4.5 ± 6.2</td>
<td>0.1 ± 0.4d</td>
<td>4.6 ± 6.3</td>
<td>151.4 ± 20.7d</td>
<td>99.6</td>
</tr>
<tr>
<td>Ora-Plus (70%)</td>
<td>15</td>
<td>6.5 ± 5.6d</td>
<td>2.5 ± 3.1</td>
<td>9.0 ± 7.2d</td>
<td>170.5 ± 30.1d</td>
<td>99.3</td>
</tr>
</tbody>
</table>

aTime measured as seconds elapsed from initiation of capsule emptying into the syringe to the final volume of water administered.
bAssumes 1240 pellets per capsule.
cp < 0.003 with tap water or 30% or 50% Ora-Plus versus 70% Ora-Plus.
dp < 0.02 with Ora-Plus versus tap water.

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**Table 2.** Delivery of Esomeprazole Magnesium Pellets through Two Different Tubes Using Two Delivery Methods

<table>
<thead>
<tr>
<th>Delivery Method (Tube Type)</th>
<th>No. Tubes</th>
<th>No. Pellets Retained in Syringe</th>
<th>No. Pellets Retained in Tube</th>
<th>Total No. Pellets Retained</th>
<th>Delivery Time (sec)a</th>
<th>% Deliveryb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap water (size 8 French)</td>
<td>10</td>
<td>58.1 ± 159.3</td>
<td>48.7 ± 150.9</td>
<td>106.8 ± 309.9</td>
<td>114.1 ± 27.5</td>
<td>91.4</td>
</tr>
<tr>
<td>30% Ora-Plus (size 8 French)</td>
<td>10</td>
<td>2.1 ± 2.4</td>
<td>0.9 ± 2.8</td>
<td>3.0 ± 3.1</td>
<td>149.8 ± 17.6e</td>
<td>99.8</td>
</tr>
<tr>
<td>Tap water (size 20 French)</td>
<td>10</td>
<td>3.0 ± 3.8</td>
<td>0.0 ± 0.0</td>
<td>3.0 ± 3.8</td>
<td>81.6 ± 5.9d</td>
<td>99.8</td>
</tr>
<tr>
<td>30% Ora-Plus (size 20 French)</td>
<td>10</td>
<td>2.8 ± 2.0</td>
<td>0.0 ± 0.0</td>
<td>2.8 ± 2.0</td>
<td>131.5 ± 14.8e</td>
<td>99.8</td>
</tr>
</tbody>
</table>

aTime measured as seconds elapsed from initiation of capsule emptying into the syringe to the final volume of water administered.
bAssumes 1240 pellets per capsule.
cp < 0.003 with 30% Ora-Plus versus tap water.
dp < 0.002 with tap water and size 8 French tube versus tap water and size 20 French tube.
ep < 0.021 with 30% Ora-Plus and size 8 French tube versus Ora-Plus and size 20 French tube.
Several other alternatives such as lansoprazole delayed-release disintegrating tablets (Prevacid SoluTab, TAP Pharmaceutical Products Inc.) and immediate-release omeprazole powder with sodium bicarbonate (Zegerid, Santarus, Inc.) are now available for enteral tube delivery. However, only lansoprazole delayed-release disintegrating tablets and esomeprazole capsules delivered via nasogastric tube have been shown to have bioavailability similar to that of oral dosing.\textsuperscript{9-11}

**Conclusion**

Administration of esomeprazole magnesium enteric-coated pellets dispersed in tap water or Ora-Plus through size 14 French nasogastric tubes in vitro delivered over 99% of capsule contents, regardless of the Ora-Plus concentration used. For immediate bedside administration, Ora-Plus at 50% concentration is a feasible alternative to water when delivering the pellets through size 14 French tubes, while 30% Ora-Plus is an alternative to water for all tubes studied.

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\textsuperscript{a}Salem Sump, Mansfield, MA, lot 264945.
\textsuperscript{b}AstraZeneca, Wilmington, DE, lot 9348601.
\textsuperscript{c}Paddock Laboratories, lot 5153778.
\textsuperscript{d}VIASYS, Wheeling, IL, lot 16899.
\textsuperscript{e}Kimberly-Clark, Draper, UT, lot 312557.
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**References**