Published in final edited form as:

J Pharm Sci. 2017 July ; 106(7): 1859–1864. doi:10.1016/j.xphs.2017.04.008.

In Vitro Evaluation of Nasogastric (NG) Tube Delivery Performance of Esomeprazole Magnesium Delayed-Release Capsules

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Abstract

Enteral feeding tubes are used to deliver food or drugs to patients that cannot swallow. To deliver delayed-release drugs that are formulated as enteric coated granules to these patients via feeding tubes requires that they be suspended in water prior to administration. Importantly, the suspension of enteric granules in water of varying pH can cause damage to the enteric coating and affect the bioavailability of the drug. Here, analytical methods for testing acid resistance stability and particle size distribution (PSD) of esomeprazole granules were utilized to monitor the integrity of the granule enteric coating after water pretreatment and delivery through an oral syringe and nasogastric (NG) tube. Granules from esomeprazole magnesium delayed-release capsules were transferred to an oral syringe, suspended in water, and delivered on the bench through a NG tube. Subsequently, acid resistance stability, (*i.e.*, the amount of drug released after 2-hour acid dissolution) was determined via HPLC and the particle size distributions (PSD) were measured with a laser diffraction system. All of the granules demonstrated acid resistance stability when the granules were delivered immediately (0 min incubation) through the oral syringe and NG tube. By contrast, some granules demonstrated significant drug release during acid exposure after a 15-min incubation period which mimics a possible delay in delivery of the drug from the syringe by the caregiver. A bimodal PSD was observed with these granules, which was attributed to debris from damaged enteric coating and particle agglomeration. The methods developed in this study could be used to distinguish batches with suboptimal product quality for delivery using NG tubes and to confirm the substitutability of generic drug products for this alternative route of administration.

Introduction

Proton pump inhibitors, a class of drugs that include esomeprazole, are commonly used to manage acid-related disorders by irreversibly inhibiting the proton pump (H⁺/K⁺/ATPase) function.¹⁻³ Esomeprazole magnesium is the (S)-isomer of omeprazole and is used to inhibit

gastric acid secretion and for the treatment of acid-related disorders including gastroesophageal reflux disease (GERD), ulcers, and gastrointestinal (GI) bleeding.⁴⁻⁶ Esomeprazole can also be used as a preventive medication to decrease the risk of stress-induced gastrointestinal tract bleeding (SGIB), which is a common occurrence in intensive care patients.⁷

Esomeprazole is available as a capsule that contains granules. Because esomeprazole is an acid labile drug, the granules are formulated with an enteric coating to prevent degradation in stomach acid.^{5,7,8} Once the drug reaches the intestine where the pH is greater than 5.6, the enteric coating dissolves and the drug is released.⁹

Esomeprazole delayed-release capsules can be administered orally or administered through a NG tube. NG tubes are a type of feeding tube used for the delivery of food or medicine from the nose to the stomach and are commonly used for patients who also require gastric acid suppression. However, if the enteric coating on the granules is damaged during drug delivery through the NG tube or when the granules are suspended in water, the esomeprazole will degrade in the acidic environment of the stomach. In addition, administration through a feeding tube creates the potential risk for the medication to clog or adhere to the sides of the NG tube.^{8,10}

The approved labeling for esomeprazole magnesium delayed-release capsules states that the capsule contents can be delivered through an oral syringe and NG tube. For patients with feeding tubes in place, the esomeprazole capsule can be opened and the contents can be suspended in water and immediately delivered.¹¹ Administration of esomeprazole through an oral syringe and NG tube provides similar bioavailability to the oral dosage form.⁶ A previous study determined that esomeprazole granules dispersed in tap water and administered through an 8 French NG tube delivered almost all (>98%) of the esomeprazole capsule contents, indicating a low risk of tube obstruction.^{12,13}

As noted above, the pH and ionic strength of the water used to suspend the granules may have an effect on the integrity of the enteric coating. In the present study, benchtop *in vitro* methods to monitor the robustness of the enteric coating after water pretreatment and delivery through an 8 French polyurethane NG tube were developed. This work investigated acid resistance stability, particle size distribution, and the percentage of esomeprazole recovered after delivery through a NG tube.

Experimental

Materials

Nexium® Delayed-Release Capsules (20 and 40 mg) from AstraZeneca (London, United Kingdom) were used in this study. Omeprazole reference standard was purchased from USP (Rockville, MD, USA). 8 French polyurethane NG tubes were purchased from Corpak MedSystems (Buffalo Grove, IL, USA). Sixty mL oral syringes were purchased from Novaplus (Irving, TX, USA). Hydrochloric acid, ethanol, sodium phosphate tribasic, sodium phosphate monobasic monohydrate, sodium phosphate dibasic, and acetonitrile were purchased from Fisher Scientific (Waltham, MA, USA). A 4.6 × 150 mm Zorbax Eclipse

Plus C18 column with 5 μ m packing was purchased from Agilent (Santa Clara, CA, USA). Type 1 deionized water was obtained from an Elga Purelab Flex System (Woodbridge, IL, USA).

Percent Recovery Studies

The percentage of esomeprazole recovered was determined after suspension in deionized (DI) or tap water and delivery through a polyurethane NG tube. The pH of the water used to suspend the granules was measured with an Orion pH meter (Thermo Fisher Scientific Waltham, MA, USA) calibrated with pH 4, 7 and 10 buffers and the conductivity of the water was tested with a traceable conductivity meter (Fisher Scientific, Waltham, MA, USA). All samples were prepared in the following manner: an esomeprazole magnesium delayed-release capsule was opened and the contents transferred to a 60 mL oral syringe. Fifty mL of DI or tap water was used to suspend the granules in the oral syringe. The syringe was shaken vigorously for fifteen seconds before attaching to the NG tube. The granules were delivered at an approximately forty-five degree angle through the NG tube. The tube was flushed before and after drug delivery with twenty mL of water, according to the NG tube instructions. Then, the recovered granules that had passed through the NG tube were dissolved in a pH 11 tribasic sodium phosphate diluent and sonicated for five min to completely dissolve all remaining granules. This solution was diluted to a final concentration of 0.04 mg/mL esomeprazole in water, assuming recovery of all granules after delivery through the NG tube. The USP monograph HPLC assay for Esomeprazole Magnesium Delayed-Release Capsules with UV detection at 302 nm was used to determine the amount of esomeprazole recovered.¹⁴

Acid Resistance Measurements

The esomeprazole samples were prepared as described in the percent recovery studies. The drug product insert instructions indicate that the granules should be delivered immediately, but a fifteen min incubation time was also tested to investigate the robustness of the enteric coating. After suspension in water, the esomeprazole granules were delivered through the oral syringe and NG tube directly into a USP dissolution apparatus II with the paddle operating at 100 rpm. Mechanical calibration of the dissolution apparatus was performed based on ASTM.¹⁵ The dissolution vessels contained 300 mL of 0.1 M HCl maintained at 37.0 ± 0.5 °C. The dissolution medium was prepared using a degassing procedure previously described.¹⁶ Because esomeprazole is an acid labile drug,¹⁷ the granules (and not the dissolution media) were analyzed. After 2 h, the dissolution medium was carefully removed, leaving the granules clustered together at the bottom of the vessel. Tribasic sodium phosphate pH 11 diluent was added to the granules and the solution was placed on a horizontal shaker for twenty min. A five min sonication was performed to completely dissolve any remaining granules. Assuming there was no drug release during the acid resistance test, a concentration of 0.2 mg/mL esomeprazole solution was prepared in pH 11 tribasic sodium phosphate diluent. This solution was diluted to a final concentration of 0.04 mg/mL esomeprazole in water. The USP monograph HPLC assay for Esomeprazole Magnesium Delayed-Release Capsules with UV detection at 302 nm was used to determine the amount of drug remaining after acid dissolution.¹⁴

Particle Size Distribution

The particle size distributions of the esomeprazole granules were measured with a Malvern Mastersizer 3000 laser diffraction system with the HydroMV sample unit (Malvern Instruments Ltd, United Kingdom). Deionized water was used as the dispersant with a stirring speed of 1000 rpm. Opaque particle and Fraunhofer Approximation were chosen as analysis mode parameters. Each sample was measured as three consecutive 30 s signal collections, and the average values were reported.

Imaging Analysis

Two lots were selected for imaging: one with significant drug release during acid resistance and the other lot demonstrating no significant drug release during acid resistance measurements. A digital microscope (Keyence VHX-500) was used to capture the images in Figure 4A and 4B. The images shown in Figure 4C and 4D were captured with a JEOL IT300 LV SEM (scanning electron microscope). Images were taken in high vacuum mode with an acceleration voltage of 25 kV.

Results and Discussion

Administration of Esomeprazole through a NG Tube

Esomeprazole magnesium is used for the treatment of acid-related disorders and to inhibit gastric acid secretion.¹⁸ Esomeprazole magnesium delayed-release capsules, depicted in Figure 1A, are available in 20 and 40 mg strengths. Multiple lots of both strengths were used to test percent recovery through the NG tube, acid resistance, and particle size distributions. The average weights (n=3) of the granules are 84.1 ± 3.2 mg for 20 mg capsules and 170.7 ± 2.5 mg for 40 mg capsules, respectively.

To administer esomeprazole through a NG tube, the granules need to be suspended in water. The pH values of different sources of water vary, and there was a concern that suspending the granules in water of varying pH could affect the enteric coating of the esomeprazole granules. Two sources of water were used to suspend the granules. The pH values were 6.0 for DI water and 9.4 for the St. Louis laboratory tap water. In addition to the varying pH, the conductivity of the two types of water also varied. The resistance of the deionized water used to suspend the granules was 18.2 MΩ. Because carbon dioxide from the atmosphere can be easily absorbed into the water, conductivity measurements for high purity deionized water with a conventional standard was not possible. The reported conductivity of deionized water (with 18.2 MΩ resistivity) at 25 °C is 0.055 microsiemens (μS)/cm.¹⁹ The conductivity of the tap water used to suspend the granules was measured as 302 μS/cm at 25°C. The effect of the type of water used to suspend the granules was investigated in regards to percent recovery, acid resistance measurements, and particle size distributions.

Percent Recovery Studies

Administration of a medication through a NG tube creates a concern that the drug could partially block or completely obstruct the tube, especially with small bore (12 French) NG tubes used for pediatric patients. Previous studies determined that >98% of the esomeprazole granules were recovered after dispersion in tap water and administration through an 8

French NG tube.^{12,13} In addition to the size of the NG tube, the percent recovery of esomeprazole can also be influenced by the material used to manufacture the NG tube (polyurethane, silicone, or polyvinyl chloride) as well as the design of the tube (*e.g.*, length and number and type of exit ports).²⁰

The present study determined the percent recovery of esomeprazole after suspension in DI or tap water and immediate delivery through an 8 French polyurethane NG tube. A depiction of the nasogastric tube used for this work is shown in Figure 1B. The granules were suspended in 50 mL of DI or tap water (Figure 1C) in a 60 mL oral syringe attached to a NG tube. After delivery through the NG tube, the granules were dissolved in pH 11 diluent and analyzed using HPLC with UV detection. All percent recoveries were 98.0% with an average of $103.0 \pm 3.6\%$ of label claim ($n=6$, 2 lots of 20 mg or 40 mg dose). There was no statistical difference between suspending the granules in DI or tap water. These results indicate that the risk of blockage or obstruction of the tube was low because nearly all granules were recovered after drug delivery through a small bore NG tube.

Acid Resistance Studies

Proton pump inhibitors, including esomeprazole, are formulated as delayed-release preparations with an enteric coating. The enteric coating prevents acid degradation in the stomach and allows for targeted absorption in the jejunum.^{1,21} The robustness of the enteric coating was investigated by performing acid resistance measurements. Esomeprazole granules were analyzed after delivery through a combination of an oral syringe and an 8 French NG tube followed by a two hour dissolution in 0.1 M HCl (pH 1.2). The label instructions for NG tube administration indicate that the granules should be delivered immediately. However, a 15 min incubation time was also tested to investigate the robustness of the enteric coating with a delay between preparation and delivery of the granules that might occur in a clinical setting.

All of the lots demonstrated little esomeprazole release (<10% of label claim) during the acid resistance test when esomeprazole granules were delivered immediately (no incubation) through the oral syringe and NG tube. By contrast, when the granules were suspended in DI water and delivered through a NG tube after a fifteen min incubation (Figure 2 and Table 1) four out of six lots demonstrated significant drug release (35% of label claim). Similarly, with tap water instead of deionized water, three out of six lots demonstrated significant drug release (>34% of label claim) when the granules were suspended and delivered through a NG tube after a 15 min incubation. Thus, DI and tap water can cause enteric coating damage after a 15 min incubation period. Overall, if esomeprazole granules were not immediately delivered through the NG tube as indicated in the drug product instructions, the enteric coating may be damaged which could affect the bioavailability and therapeutic effect of esomeprazole.

Where significant drug release was observed, the acidic media changed from a colorless solution to yellow in a short time (less than 10 min). In addition, at the end of the 2 hour test, the media was a dark red color and the granules had disintegrated into small pieces. By contrast, if little or no drug release occurred; the acidic media remained colorless and the

granules remained their original white color at the end of the 2 hour test. Thus, the color of the acid media was an indicator of enteric coating damage.

Particle Size Distribution

Esomeprazole granules have a smaller diameter in comparison to other proton-pump inhibitors, such as lansoprazole and omeprazole.^{6,13} The smaller granule diameter makes esomeprazole an ideal drug for nasogastric tube administration.

The PSD of neat (untreated) esomeprazole granules was measured. As shown in Table 2, the median particle size values ranged from $552 \pm 11 \mu\text{m}$ to $594 \pm 4 \mu\text{m}$, $n=3$. The difference in the PSD may be due to lot-to-lot variations in the granule batches. A larger granule size did not correspond to a more robust enteric coating as some of the larger granules had significant drug release during the acid resistance measurements (*e.g.*, 20 mg Lot 3). In addition, granules having similar particle sizes from various lots (40 mg dosage) demonstrated different acid resistance results. Thus, the particle size of the neat granules was not an indicator of the robustness of the enteric coating.

As shown in Figure 3, some of the lots (20 mg, Lot 2; 20 mg, Lot 3; and 40 mg, Lot 1) demonstrate a bimodal distribution after incubation in DI water for 15 min. Smaller and larger particles, as indicated by $D_x(10)$ and $D_x(90)$ in Table 2 are observed after incubation in three of the four acid resistance measurements that demonstrated significant drug release after a 15 min incubation in DI water and in all cases in which the drug release was greater than forty percent. The smaller particles may be debris from damaged enteric coating and the larger particles may be a result of particle and coating agglomeration.

Imaging of Esomeprazole Particles

Microscopy and SEM were used to investigate the shape and surface morphology of the neat granules. Two lots were selected for imaging: one without significant drug release during acid resistance measurements after a 15 min incubation in DI water (20 mg, Lot 1) and the other with significant release after a 15 min incubation in DI water (20 mg, Lot 2).

There was no noticeable difference in the microscope or SEM images of the neat granules shown in Figure 4. However, not all granules are the same size and shape (Figure 4A and 4B). As shown in Figure 4C and 4D, a few granules had defects in the enteric coating, but these were observed for both lots that were imaged. In some cases, granules consisted of two particles encased in one enteric coating layer. Therefore, microscope imaging of the esomeprazole granules did not provide additional information that correlates the integrity of the enteric coating or particle size with drug release.

Conclusions

The integrity of the esomeprazole granules after delivery through an oral syringe and NG tube is important to ensure absorption in the jejunum. In this work, *in vitro* methods were developed to monitor the robustness of the enteric coating of the esomeprazole granules after suspension in water and delivery through a NG tube.

No significant drug release was observed when esomeprazole granules were delivered immediately after preparation through the oral syringe and NG tube. However, some lots demonstrated significant drug release when the granule delivery through the NG tube was delayed 15-min after incubation in water. Thus, delay between preparation and administration in the clinic should be avoided. The particle size distribution of the neat granules did not correlate to the acid resistance results, but a bimodal distribution was observed for lots that demonstrate significant drug release (>40%) during acid resistance measurements. Microscope and SEM images did not show a visual difference between lots of neat granules that had significant drug release during acid resistance measurements and those with little drug release during acid resistance testing. Clogging of the NG tube was not observed regardless of incubation or type of water used to disperse the drug. Notably, in this study, one type of NG tube was investigated. However, additional parameters such as the material and design of the NG tube could be investigated in the future. The methods developed in this study could be used to evaluate in vitro equivalence and to assess the potential risks of delivering oral drug products through enteral feeding tubes after suspension in water.

Acknowledgments

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Table 1

Acid resistance test results (as % esomeprazole released) of 20 mg and 40 mg capsules delivered through NG tubes with 0 or 15 minute incubation in DI or tap water. The results in red show a significant amount of esomeprazole dissolved during acid resistance measurements.

Dosage (mg)	Lot	Incubation Time (min)	Water	% Esomeprazole Dissolved
20 mg	1	0	DI	0.9 ± 2.7
			Tap	3.6 ± 4.6
		15	DI	5.2 ± 2.5
			Tap	7.2 ± 5.8
	2	0	DI	2.2 ± 3.2
			Tap	3.4 ± 6.2
		15	DI	99.6 ± 0.1
			Tap	89.0 ± 4.2
	3	0	DI	2.1 ± 3.7
			Tap	8.4 ± 0.6
		15	DI	98.2 ± 0.7
			Tap	77.4 ± 17.4
40 mg	1	0	DI	2.9 ± 1.8
			Tap	2.0 ± 1.7
		15	DI	51.3 ± 7.7
			Tap	34.2 ± 5.8
	2	0	DI	5.5 ± 2.2
			Tap	5.6 ± 1.5
		15	DI	4.7 ± 3.2
			Tap	1.9 ± 2.4
	3	0	DI	0.1 ± 1.3
			Tap	3.6 ± 1.6
		15	DI	35.7 ± 1.4
			Tap	9.6 ± 0.8

Summary of PSD results of neat esomeprazole granules and esomeprazole granules after a 15 minute incubation in DI water. Smaller and larger particles (in comparison to the neat granules) are shown in red.

Table 2

Dosage (mg)	Lot	Incubation time (min)	Water	Dx (10)	Dx (50)	Dx (90)
20	1	15	DI	520 ± 5	597 ± 6	687 ± 6
		Neat Granules				
	2	15	DI	473 ± 2	572 ± 5	686 ± 13
		Neat Granules		21 ± 3	621 ± 25	939 ± 58
	3	15	DI	455 ± 10	567 ± 7	705 ± 24
		Neat Granules		31 ± 10	654 ± 15	900 ± 52
40	1	15	DI	478 ± 11	594 ± 4	707 ± 19
		Neat Granules		59 ± 9	607 ± 5	757 ± 13
	2	15	DI	461 ± 3	555 ± 1	664 ± 5
		Neat Granules		523 ± 1	588 ± 3	660 ± 3
	3	15	DI	458 ± 23	552 ± 11	658 ± 4
		Neat Granules		498 ± 18	601 ± 4	722 ± 26
				462 ± 7	554 ± 4	660 ± 3