

OPTIMIZATION OF THE BIOEQUIVALENCE STUDY OF ESOMEPRAZOLE CAPSULE CONTENTS AFTER IN VITRO SUSPENSION IN SOFT FOODS USING HPLC

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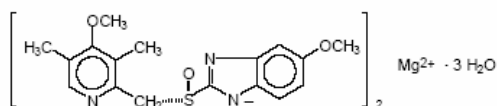
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Abstract: A bioequivalence study for the selection of the alternative and feasible mode of administration of esomeprazole pellets suspended in some common soft liquid foods has been done. 20 mg of four different brands esomeprazole pellets suspended in yogurt, orange juice, apple juice and milk were analyzed in the gastric environment using dissolution tester and high performance liquid chromatography. The release of the esomeprazole active was found more the 90% using these liquid foods except milk. The optimal release of the active was found in the system of apple juice (97.06%). Administration of the esomeprazole pellets suspending in apple juice may be a practical alternative for patients who cannot swallow an intact capsule.

Keywords: Bioequivalence, Esomeprazole pellets, Soft foods, Gastric environment, Dissolution.

1 Introduction

Esomeprazole magnesium, content of delayed release capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl)magnesium trihydrate, a compound that is widely used as a proton pump inhibitor for the treatment of various acid-related disorders. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 3H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is: Esomeprazole is currently supplied in Bangladesh as 20 mg or 40 mg capsule



containing pellets. Many patients in Bangladesh have difficulty in swallowing capsules containing enteric coated pellets of esomeprazole because of general abrasion, hyperactive gag reflex, or dysphagia [1-3]. However, there are situations in which gastric acid suppression is necessary for patients who are unable to take medication by mouth [4]. For such patients modes of administration other than an intact capsule are desirable. Extemporaneously compounded liquid formulations such as sodium bicarbonate suspension or solutions combined with different proton pump inhibitors have been used [5]. About 98~99% delivery of esomeprazole magnesium pellets was observed in vitro when the pellets were dispersed in tap water [6]. Stability of esomeprazole capsule contents in different common soft liquid foods and water were also studied [7].

The objective of the study was to determine the optimal medium for the delivery of esomeprazole magnesium enteric coated pellets suspended in different soft liquid foods.

2 Experimental

2.1 Collection and Preparation of Media and Sample

Apple juice (Cyprina), orange juice (ACME), yogurt (Aarong) and milk (Milk Vita -1.5% fat) were collected locally. HCl (0.1M) solution was prepared from 37% HCl (Merck, Germany). Four different brands of esomeprazole capsules such as, Nexium (AstraZeneca, Sweden), Sergel (Healthcare Pharm. Ltd), Neptor (Novartis Bangladesh

Ltd.), Maxpro (Renata Ltd.) were collected and analyzed.

Single esomeprazole 20-mg capsule contents were weighed and emptied into individual USP vessels of dissolution tester (Erweka, Germany) containing 100mL of liquid soft foods. After 30 minutes, 500 mL of hydrochloric acid (0.1M) was added to each vessel. After 2 hours dissolution pH values were measured using hand pH meter (Hanna HI98127, USA), and the pellets were collected and transferred into a 250-mL volumetric flask containing approximately 100-mL water. 50 mL phosphate buffer solution (pH 11.0 phosphate buffer- 965.3 ml of 0.1M disodium hydrogen phosphate solution was mixed with 34.7 ml of 0.1M sodium hydroxide, to obtain 1000 mL. The pH was adjust to 11.0 ± 0.05 with phosphoric acid or sodium hydroxide) was added and the mixture was agitated in the mechanical shaker machine for 20 minutes. After another 5 minutes in an ultrasonic bath at ambient temperature the flask was shaken by hand and 50 mL of 95% ethanol was added. Next the flask was shaken by hand again, and the contents were filtered through 0.45 μ filter paper. The filtrate was diluted to 5 times with water [7].

2.2 Standard Preparation

About 20 mg of esomeprazole working standard was weighed and was transferred to a 50 ml volumetric flask. Methanol (40 ml) was added and was sonicated to dissolve. It was made volume up to the mark with

Methanol. 10 ml of this solution was diluted to 50 ml with the dissolution media.

2.3 Preparation of mobile phase

Mobile phase was prepared by mixing with 350mL acetonitrile & 500mL phosphate buffer (pH 7.3). This mixture was diluted to 1000 mL with distilled water. Phosphate buffer - pH 7.3 was prepared by dissolving 6.8 gm of monobasic potassium phosphate in water to obtain 250 ml of solution. 250 ml of this solution was mixed with 36.9 ml of 0.2M NaOH and was volume with distilled water up to 1000 mL. The pH was adjusted to 7.3 ± 0.05 with phosphoric acid or potassium hydroxide. The mixture was filtered, degassed and used as mobile phase.

2.4 Chromatographic Condition

High Performance Liquid Chromatography (HPLC- Shimadzu Prominence, Japan) with 1.0 mL/min flow rate, 20 μ l loop injector, ambient column oven temperature and detection wavelength 302 nm (PDA detector) was used for this analysis. Hypersil 0.250 m long and 4.6 mm internal diameter column, packed with octadecylsilyl silica gel (5 μ m) was used for chromatographic analysis.

3 Results and Discussion

The suspensions of esomeprazole enteric coated pellets from four different brands products in yogurt, orange juice, apple juice and milk were analyzed.

The pH of esomeprazole enteric coated pellets suspended in yogurt, apple juice, orange juice and milk were determined, which is shown in the Table 1.

Table 1 Mean pH of esomeprazole pellets in common liquid foods to an acidic environment.

Liquid Foods	Initial pH of Liquid Foods	pH of the Suspension in Liquid Foods and 500ml 0.1M HCl	Mean pH \pm Standard Deviation
Yogurt	3.76	1.41, 1.40, 1.35, 1.39	1.38 ± 0.03
Orange juice	3.80	1.31, 1.37, 1.32, 1.40	1.35 ± 0.04
Apple juice	3.16	1.33, 1.34, 1.28, 1.37	1.33 ± 0.04
Milk	6.82	3.45, 3.41, 3.39, 3.43	3.42 ± 0.03

The initial pH of the different types of soft foods was found quite acidic and almost similar except for system of milk. The pH of milk was found close to neutral (6.82). With

the addition of hydrochloric acid (0.1M HCl) to the suspension and subsequent dissolution, the pH of the suspension dropped significantly in all systems.

The potency of different brands esomeprazole capsule contents were evaluated using reverse phase HPLC and the results obtained are shown in the Table 2. The initial potency were found 99.42 ~ 101.50% for the four different brands esomeprazole capsule content.

Table 2 Initial potency of different brand esomeprazole capsule.

Esomeprazole Sample	Specification (%)	Initial Potency (%)
Sample-A	90.00 ~ 110.00	99.45
Sample-B		101.50
Sample-C		99.92
Sample-D		101.17

Table 3 shows the percent stability of esomeprazole pellets in common liquid foods. The bioequivalence of esomeprazole enteric-coated pellets was not affected by suspension in any of the soft foods tested, except milk. The decreased bioequivalence of the esomeprazole pellets in milk, which has a high buffering capacity, may have been due in part to its near-neutral pH, which caused dissolution of the enteric-coated polymer of the pellet, with release of its contents and rapid degradation after acid exposure.

Table 3 The stability of esomeprazole pellets in common liquid foods by HPLC method

Liquid Foods	Stability of esomeprazole pellets (%)	Mean Stability (%) \pm Standard Deviation
Yogurt	99.26, 91.90, 92.55, 91.63	93.83 \pm 3.6
Orange juice	98.28, 92.05, 95.20, 98.25	95.94 \pm 2.9
Apple juice	98.86, 96.90, 94.15, 98.33	97.06 \pm 2.1
Milk	58.15, 49.21, 53.60, 51.63	53.14 \pm 3.7

After addition of the esomeprazole pellets to an alkaline medium, more than 90% of the esomeprazole was recovered from all the soft liquid foods except the system containing milk (only 49 ~ 58% recovered). The percent stability of esomeprazole magnesium suspended in yogurt, orange juice and apple juice were found 93.83 (\pm 3.6), 95.94 (\pm 2.9)

and 97.06 (\pm 2.1) respectively in gastric environment, which is good.

4 Conclusion

Administration of esomeprazole enteric coated pellets suspended in yogurt, orange juice and apple juice were found in vitro delivered over 90% of the active. The optimum release of the esomeprazole active was found for the system of apple juice, which is about 97.06%. So, those patients [8] who have pain or difficulty with swallowing intact capsule can take the capsule contents suspended in apple juice for feasible and also comfortable administration of medication.

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