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In Vitro Release Kinetics Study of Different Brands of Esomeprazole Sustained Release Tablets Available in Bangladesh

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ABSTRACT

Commercially available four national and four international brands of esomeprazole magnesium sustained release matrix tablets were studied in simulated gastric medium (pH 1.2) for 2 hours and simulated intestinal medium (pH 6.8) for 8 hours time period using USP reference dissolution apparatus. All the national and international brands complied with the USP *in-vitro* dissolution specifications for drug release in simulated gastric medium. However, one of the national brands (Code: MP-1) and one of the international brands (MP-7) failed to fulfill the official requirement of 80% drug release within 8th hour in simulated intestinal medium. Drug release of that national and international brand were 70.49% and 67.05% respectively within the specified time period, however one national brand (Code: MP-4) released 103.46 % drug within 8th hour in intestinal medium. Drug release profiles were analyzed for zero order, first order and Higuchi equation to reveal the release kinetics perspective of esomeprazole magnesium sustained release matrix tablets. It was found that zero order release kinetics was the predominant release mechanism than first order and Higuchi release kinetics for those brands (Code: MP-2, MP-3, MP-4, MP-5, MP-6 and MP-8) which complied with the USP *in vitro* dissolution specification for drug releases. On the other hand, first order release kinetics was predominant for one national and also one international non compliant brands (Code: MP-1 and MP-6).

Key Words: *In vitro* dissolution, Sustained release, Market preparations, Kinetic analysis, Esomeprazole, National brand, International brand.

INTRODUCTION

Esomeprazole, the *S*-isomer of omeprazole, irreversibly inhibits the gastric parietal H^+/K-ATPase enzyme involved in the production of hydrochloric acid in the stomach. It acts as proton pump inhibitor, used to treat gastroesophageal reflux disease (GERD), erosive esophagitis, and gastric ulcer etc. (Martindale, 2005). The process of *in vitro* dissolution played a vital role in liberating the drug from the tablet matrix and marking whether it is available for subsequent gastrointestinal absorption. The *in vitro* dissolution of the drug from the tablet matrix depends on many factors, which include not only the physiochemical properties of drug, but also the nature of formulation and the process of manufacturing (Augsburger *et al,* 1983). Hence in vitro dissolution analysis of pharmaceutical dosage form has emerged a very important parameter that ensured product quality as well as for differentiating among formulations of the same therapeutic agent (Ayres *et al.,* 1984). For sustained release tablets the role of *in vitro* dissolution becomes still more crucial as an additional coating step involved in the manufacturing process (Lordi, 1992). *In vitro* dissolution study is an important tool in the evaluation of the best formulation and also in the understanding of possible risks related to specific gastrointestinal environment, dose dumping, food effects on bioavailability and interaction with other drugs (Sungthongjeen *et al.,* 1999). Today dissolution studies are the most frequently used tools in the development, characterization and utilization processes of controlled release formulations (Longer *et al*., 1990).

In Bangladesh there are a number of pharmaceutical companies manufacturing and marketing sustained release matrix tablet of esomeprazole. Besides the national brands, there are few international brands also available in drug stores. This study deals with the comparative *in vitro* dissolution or *in vitro* bioavailability characteristics of sustained release matrix tablets of most commonly available national and international brands of esomeprazole in Bangladesh.

MATERIALS AND METHODS

Drug: Esomeprazole magnesium (Square Pharmaceuticals, Bangladesh); **Solvents and reagents:** Hydrochloric acid (Merck, Germany); ortho-phosphoric acid (Merck, Germany); Potassium di hydrogen phosphate (Merck, Germany); Sodium Hydroxide (Merck, Germany); **Equipments:** Single Punch Tablet press (Shanghai-Tianhe Pharmaceutical Machinery Company); UV Spectrophometer (Shimadzu, Japan); Digital pH meter (Hach Company, USA); Electronic Hardness tester (Ereweka, Germany); Tablet Dissolution Tester (Electrolab, India); Sartorius Electronic Balance.

Dosages forms

Four national and four international brands of marketed (production date not more than four months ago from the time of purchase) esomeprazole sustained release matrix tablets of the test drug were collected from various stores. The samples were properly checked for their manufacturing license number, batch number, and date of manufacture and expiry dates before purchasing. These were randomly coded (MP-1, MP-2, MP-3 and MP-4) for national brands and (MP-5, MP-6, MP-7 and MP-8) for international brands. The labeled active ingredient was esomeprazole 20 mg and packaged in strip or in blister packing. The strip or blister packs stored at 25±2°C for four weeks before the dissolution study in order to evaluate any change in organoleptic properties.

Table 1: Multiple coefficients ($R^{2)}$ and diffusion exponent (n) values of different brands of national and international esomeprazole magnesium sustained release tablets available in Bangladesh Pharma market

Code	Multiple coefficient of determination (R^2)			Diffusion exponent(n)
	Zero order	First order	Higuchi	
MP-1	0.95	0.91	0.89	1.05
MP-2	0.99	0.92	0.90	1.10
MP-3	0.99	0.93	0.87	1.20
MP-4	0.99	0.90	0.85	1.0
MP-5	0.98	0.91	0.88	1.11
MP-6	0.98	0.93	0.87	1.05
MP-7	0.98	0.95	0.90	0.99
MP-8	0.92	0.94	0.92	0.89

In vitro dissolution study

These studies were conducted at 37±0.5°C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six section assembly according to the USP XXIII procedure with minor modification (USP XXII and NF XVII, 1995). For *in vitro* dissolution studies, simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 6.8) were used as dissolution media.

a*) Preparation of simulated gastric medium (0.1 N HCl pH 1.2)*

For 0.1N HCl, 11.4 ml of hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml.

b) Preparation of simulated intestinal medium (Buffer pH 6.8)

20 ml sodium hydroxide (25%) was diluted with 0.1 N Hydrochloric acid to 1000 ml adjusting pH 6.8 by the addition of 1.2 ml *O*-phosphoric acid. The dissolution test was performed using 900 ml medium at 37±0.5°C and 100 rpm.

The medium was preheated to 37°C and then added to the vessels. After that paddle rotation was started and the system was allowed to equilibrate for 15 min. Each vessel, vessel position, and corresponding tablet result were assigned the same number. Thus, for each sub sample of six

tablets tested simultaneously, every individual tablet result was identified with a particular vessel and position. The total duration of dissolution was 12 hours in which the first 2 hours the tablet matrices were subjected to simulated gastric media (0.1N HCl pH 1.3) and the later 10 hours the tablet matrices were subjected to simulated intestinal media.

Acid stage

900 ml of 0.1N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour, 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 305 nm.

Buffer stage

After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ±0.05) was adjusted with addition of 1.2 ml *O*-phosphoric acid. The operation was continued for 10 hours. At every one-hour interval, sample (10 ml) of the solution was withdrawn from the dissolution medium and immediately replaced with equal volumes of fresh dissolution medium. The withdrawn samples (10ml) was then filtered and diluted, analyzed at 305 nm for esomeprazole by UV spectrophotometer. The amounts of drug present in the samples were calculated from calibration curves constructed from the standard solution of USP reference standard test drug.

RESULTS AND DISCUSSION

Commercially available four national brands (Code: MP-1, MP-2, MP-3 and MP-4) and four international brands (Code: MP-5, MP-6, MP-7 and MP-8) of esomeprazole sustained release tablets were studied for their *in vitro* dissolution behavior in simulated gastric medium (pH 1.2) for 2 hours time period and in simulated intestinal medium (pH 6.8) for 8 hours time period using USP reference dissolution apparatus to observe the release kinetics of the matrix tablets (Table 1 and Fig. 1-4).

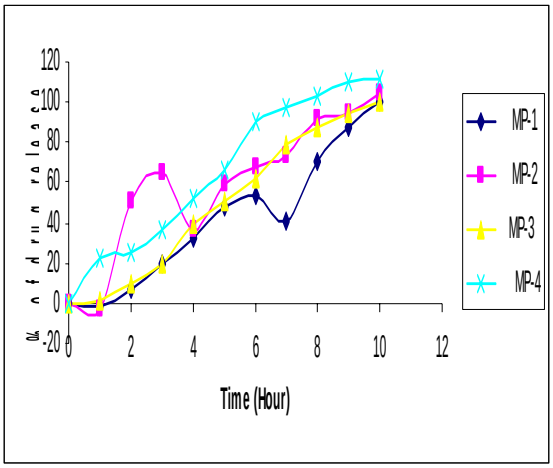

Figure 1a: Zero order plot of release kinetics of four national brands.

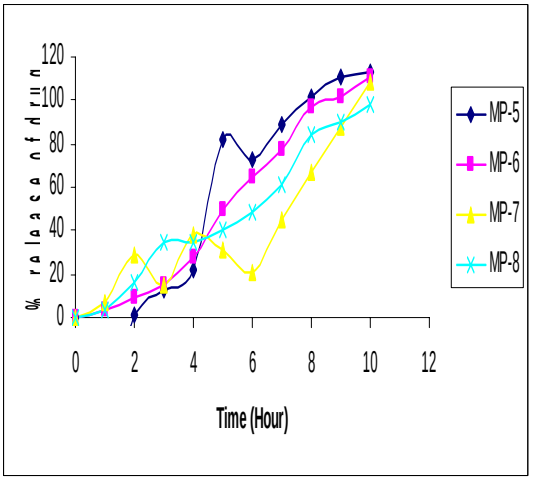

Figure 1b: Zero order plot of release kinetics of four international brands.

All the national and international brands complied with the USP *in vitro* dissolution specification, i.e., 25% drug release within 2 hours in simulated gastric medium. After a comprehensive *in vitro* dissolution study, it denoted that the three national brands (Code: MP-2, MP-3 and MP-4) and three international brands (Code: MP-5, MP-6 and MP-8) fulfilled the USP *In vitro* dissolution specification (80% drug release within 8th hours) in simulated intestinal medium. Due to formulation defects, one of the national brands (Code: MP-1) and one of the international brands (MP-7) were failed to fulfill the USP *in vitro* dissolution specification i.e., 80% drug release within 8th hours in simulated intestinal medium and one national brand (Code: MP-4) released 103.46% drug within 8th hours in the simulated intestinal medium. The amount of drug present in each tablet was determined by spectroscopic method and except two; all the brands met the official standard.

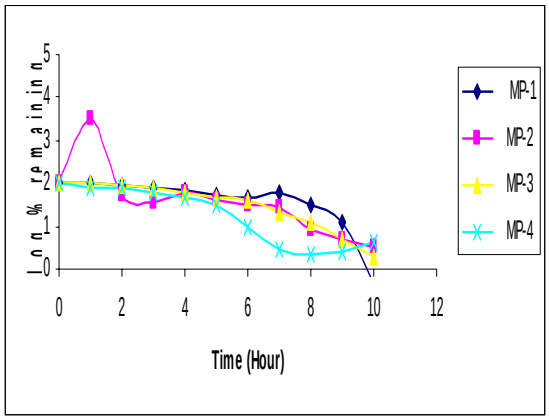

Figure 2a: First order plot of release kinetics of four national brands.

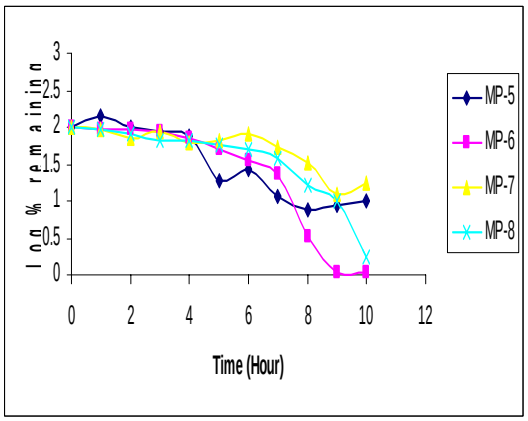

Figure 2b: First order plot of release kinetics of four international brands

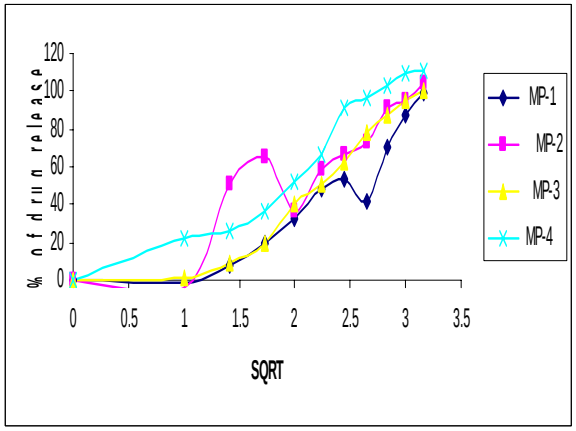

Figure 3a: Higuchi plot of release kinetics of four national brands.

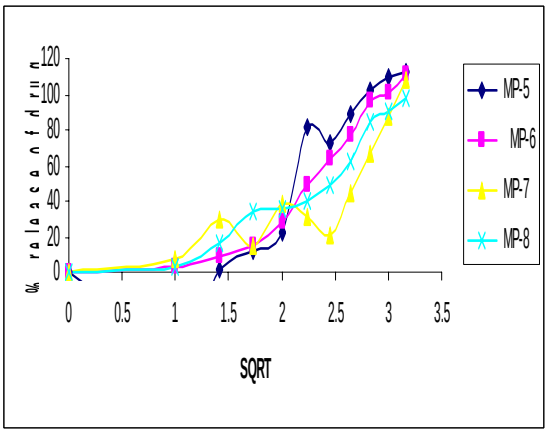

Figure 3b: Higuchi plot of release kinetics of four international brands.

The drug release mechanism was determined by multiple coefficients (r^2) and diffusion exponent (n) for each individual brands (Table 1). A zero order release kinetics was predominant than the first order and Higuchi release kinetics for the national three brands (Code: MP-1, MP-2 and MP-4) and three international brands (Code: MP-5, MP-6 and MP-8). It was focused that the drug release of those brands followed diffusion method and concentration independence from the matrix of tablet. First order release was predominant than the zero order and Higuchi release kinetics for one national and one international non compliant brands (Code: MP-1 and MP-7).

CONCLUSION

This study revealed that most of the commercially available brands of esomeprazole magnesium sustained release tablets in Bangladesh met the official specification and few of them failed which might have some formulation problems. The study also emphasized the need of constant surveillance on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for the patients in Bangladesh.

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