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Pharmacokinetics and Bioequivalence Study of Two Proton Pump Inhibitor Products

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Omeprazole (OPZ) efficiently suppresses acid secretion in the parietal cells of the stomach. It is widely recommended as proton pump inhibitor (PPI) in Egypt. Presence of many products containing omeprazole available in the Egyptian market raises questions of generic substitution and/or therapeutic equivalence. The aim of the study was to compare the pharmacokinetic parameters and relative bioequivalence properties of two oral omeprazole formulations, Gastroloc® and Pepzol® enteric coated capsules, in healthy subjects. A randomized, two-way crossover study was conducted to study the pharmacokinetic parameters of the OPZ products in 24 healthy human volunteers in compliance with the Declaration of Helsinki and ICH guidelines. After oral administration and at specified time intervals, blood samples were collected and analyzed for plasma OPZ content using a validated HPLC method. The Pharmacokinetic parameters such as AUC_{0-12}, C_{max}, T_{max}, $t_{1/2}$ and elimination rate constant were determined from plasma concentration-time profile for both formulations by a non-compartmental method. The statistical analysis of the data obtained in this study showed no significant difference between the tested OPZ products. The

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results indicated that the tested products have similar bioavailability profiles and therefore can be considered bioequivalent based on the obtained data of AUC, C_{max}, and T_{max}.

Keywords: Omeprazole; bioavailability; pharmacokinetics; peptic ulcer; human volunteers; bioequivalence.

1. INTRODUCTION

Peptic ulcer may results from erosion in the gastrointestinal (GI) mucosa, which could happen in stomach (gastric ulcer) or in duodenum (duodenal ulcer). Approximately all ulcers are caused by administration of non-steroidal anti-inflammatory drugs (NSAIDs) or *Helicobacter pylori* infection [1,2]. Peptic ulcer can lead to life-threatening complications if perforation or bleeding takes place [3-5]. This could lead to a significantly lower health-related quality of life in patients with peptic ulcer compared to the general population [6].

Patients at increased risk of peptic ulcer are elder, those with a history of previous GI events such as bleeding and those who are long term treated with NSAIDs [7,8]. A study of patients with osteoarthritis found that up to 17% of patients developed gastric ulcer 12 weeks of beginning treatment with non-selective NSAIDs such as ibuprofen and diclofenac [9]. Minimizing the risk of potentially serious GI events in long-term NSAIDs users is clearly appropriate, especially for those patients at increased risk.

In the past few years, GI acid suppression has improved the management of peptic ulcer symptoms [10]. Proton pump inhibitors (PPIs) are the most effective agents for suppressing gastric acid secretion and are the drugs of choice for the treatment of hyper-gastric acid disorders. PPIs have been shown to be efficacious in the prevention of peptic ulcers and upper GI symptoms related to administration of NSAIDs [11].

Omeprazole (OPZ), one of the PPI, is a substituted benzimidazole that inhibits gastric acid secretion by altering the activity of H^+ / K^+ ATPase, which is the final common step of acid secretion in parietal cells [12,13]. OPZ is used in the treatment of dyspepsia, peptic ulcer disease, gastro-esophageal reflux disease, laryngopharyngeal reflux, Zollinger-Ellison syndrome and eradication of *Helicobacter pylori* infection, when combined with antibiotics [14]. It is one of the most widely prescribed drugs internationally and is available over the counter in some countries [15].

Bioequivalence has gained considerable importance during the last three decades because of its application to brand and generic drugs. Bioequivalence became important for the approval of generic drugs globally. Because generic drugs could be used instead of innovator products in the market place, the safety and efficacy of generic drugs should be compared to the safety and efficacy of the corresponding innovator drugs. Assessment of interchangeability between the generic and the innovator product is carried out by a study of bioequivalence [16].

Bioequivalence of two formulations of the same drug comprises equivalence with respect to the rate and extend of their absorption. The area under concentration time curve ($AUC_{0-\infty}$) generally serves as the characteristic of the extent of absorption while the peak concentration (C_{max}) and the time of its occurrence (T_{max}), reflect the rate of drug absorption from the formulations [17]. The present study was designed to evaluate and compare the pharmacokinetics properties and relative bioavailability of two OPZ enteric capsules products after single oral administration of 40 mg dose in fasting healthy male volunteers.

2. MATERIALS AND METHODS

2.1 Materials

Omeprazole (OPZ) was gift from EPICO pharmaceutical company, Egypt. Phenacetin, acetonitrile, potassium dihydrogen phosphate and tri-basic sodium phosphate were obtained from Sigma-Aldrich, St. Louis, MO, USA. All other chemicals were of reagent grade and all solvents were HPLC grade and used as received.

2.2 Products Studied

Two available commercial OPZ products were used in this study. Pepzol® 40 mg capsules

(Al-Hekma pharma, Cairo, Egypt), batch number 060 and Gastroloc® 40 mg capsules (Sigma pharmaceutical industries, Cairo, Egypt), and batch number 12741.

2.3 Dissolution Study

Dissolution test of OPZ products was carried out using a USP dissolution apparatus type I (ERWEKA, DT-700, Germany) at a rotation speed of 50 rpm in 900 ml dissolution medium at 37±0.5℃. The dissolution media were simulated gastric fluid (0.1 N HCl of pH 1.2 for 2 h) and simulated intestinal fluid (phosphate buffer solution of pH 6.8 for 3 h and pH 7.4 till the end of the test). Dissolution medium was adjusted to the required pH values (6.8 and 7.4) by the addition of specific amount of tri-basic sodium phosphate. Five ml aliquots of the dissolution fluid were removed at specified time intervals, filtered and replaced with fresh dissolution medium and assayed for the amount of OPZ by spectrophotometer (Spectro UV-Vis Double PC 8 Auto Cell Scanning Spectrophotometer UV-VIS Double Beam Model UVD-3000 Labomed INC., CA, USA.) at wavelength 237 nm against blank [18]. At the end of the dissolution test, OPZ products were able to release up to 90% of their drug content.

2.4 Pharmacokinetics Study

2.4.1 Subjects

For the assessment of the pharmacokinetics and bioequivalence twenty-four Egyptian healthy male adult volunteers participated in randomized two-period crossover experiment. The average ages were 23 to 39 years (mean 26.7 ± 0.4 years). The average body weight was 77.24 ± 3.6 kg and the average height was 175.3 ± 5.06 cm. Prior to inclusion of the subjects to study, the subjects were judged healthy on the basis of the purpose, the nature of the study and any possible risks were explained and it was made clear, that any subject may withdraw voluntarily from the study at any time without prejudice. Before starting the trial, volunteers were subjected to medical and clinical examination. After explaining these, the volunteers were asked to sign consent forms. Verbal assurance was taken from all volunteers that they have not taken any drugs one week preceding the experiment day. Two weeks were kept as a wash out period before crossover study and no medication was allowed one week before and during the study. The volunteers fasted for 12 hours before the studies. Food was allowed 3 hours after dosing. During the study all subjects remained under close medical supervision and were supplied uniform diets. At the beginning of the experiment, each subject received one capsule of either Pepzol® or Gastroloc® (equivalent to 40 mg OPZ).

2.4.2 Blood sampling

Venous blood samples were withdrawn by an indwelling catheter into heparin-containing tubes immediately just before dosing and after specific time intervals of drug administration. The blood samples were centrifuged at 5000 rpm for 15 minutes (CT5, Germany) and the separated plasma samples were frozen until analysis.

2.4.3 Analysis of OPZ in human plasma

In the present study, a specific and validated HPLC method for the determination of omeprazole in plasma was adopted [19] with some modification. It allows the analysis of OPZ in plasma at concentrations ranging from 0.2 – 40 µg/ ml. Plasma sample (0.5 ml) was transferred into a 10 ml culture tube, 25 µl of phenacetin methanol solution (40 µg/ml) as an internal standard, and 5 ml of ethyl acetate were added to the sample. For the calibration graphs, different amounts (0.2, 0.4…….40 ml) of OPZ standard solution (10 µg/ml) were added at the beginning of the procedure to blank serum. The sample mixture was agitated on a vortex mixer for 2 minutes after each addition, and then centrifuged for 10 min at 3500 rpm. The supernatant was carefully separated to another clear tube and evaporated in a water bath at 35℃ under a stream of nitrogen. The residue was dissolved in 100 µl of the mobile phase, vortex for 1 minute, centrifuged at 3500 rpm and 50 µl of clear supernatant was injected onto the liquid chromatograph for analysis under the above mentioned condition. Concentrations of OPZ in unknown samples were calculated with reference to the prepared calibration curve. The samples of spiked plasma were processed as described above. The calibration curve was obtained by plotting the ratio of the peak area of the analyte to that of the internal standard against the amount of the analyte added.

2.4.4 Chromatographic conditions

OPZ was analyzed using HPLC Waters system consisting of auto-sampler, model no. 717 plus, binary HPLC pump (model no. 1525), Dual λ

Absorbance (model no. 2487). The separation was performed by using Bondapack C18, 10 µm, (150 x 3.9 mm) from Hewlett-packard USA. The mobile phase composed of acetonitrile 20 mM KH_2PO_4 buffer pH 7.4 (30:70, v/v) and was pumped at a flow rate of 1 ml/min. Effluent was monitored at a wavelength of 302 nm. The injection volume was 50 µl.

2.4.5 Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was employed to analyze plasma drug concentration-time data for OPZ in human volunteers. The parameter C_{max} and T_{max} were obtained directly from the plasma concentration-time curve for each subject. The elimination rate constant, terminal slope (k) of the concentration-time curve was determined by log-linear regression of at least the last three data points. Elimination half-life ($t_{½}$) of the terminal log linear phase was calculated as 0.693/k (Laurian Vlase et al., 2010). Area under the plasma concentration-time curve (AUC_{0-12}) was calculated using the trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-12} + C_{12}/k$, where C_{12} is the last measurable concentration. The mean residence time (MRT) was calculated as follows:

$$MRT = AUMC_{0-\infty} / AUC_{0-\infty}$$

where $AUMC_{0-\infty}$ is the area under the first moment curve, which could be calculated from the plasma concentration–time curve [20].

2.5 Statistical Analysis

The data were expressed as the mean ± SD. The data were evaluated by one-way ANOVA followed by the Tukey-Kramer test for multiple comparisons. A probability value of ≤ 0.05 was used as the criterion for significance.

3. RESULTS AND DISCUSSION

Food and Drug Administration (FDA) recommends that *in vivo* bioequivalence studies be accompanied by *in vitro* dissolution profiles. I*n vitro/in vivo* correlation is a scientific approach to describe the relationship between an *in vitro* attribute of a dosage form such as the rate or extent of drug release and a relevant *in vivo* response such as plasma drug concentration or amount of drug absorbed. This model relationship facilitates the rational development and evaluation of extended-release dosage forms as a surrogate for bioavailability and/or bioequivalence testing, as well as a tool for formulation screening and setting of the dissolution/drug release acceptance criteria. The dissolution data was analyzed to calculate the percent cumulative OPZ released at different time intervals. This test was done in triplicates (Fig. 1).

From the dissolution study, both OPZ products have the ability to withstand almost intact on the acidic pH medium for two hours (only 5% of OPZ was released from each formulation) which is due to the enteric coat of both formulations as

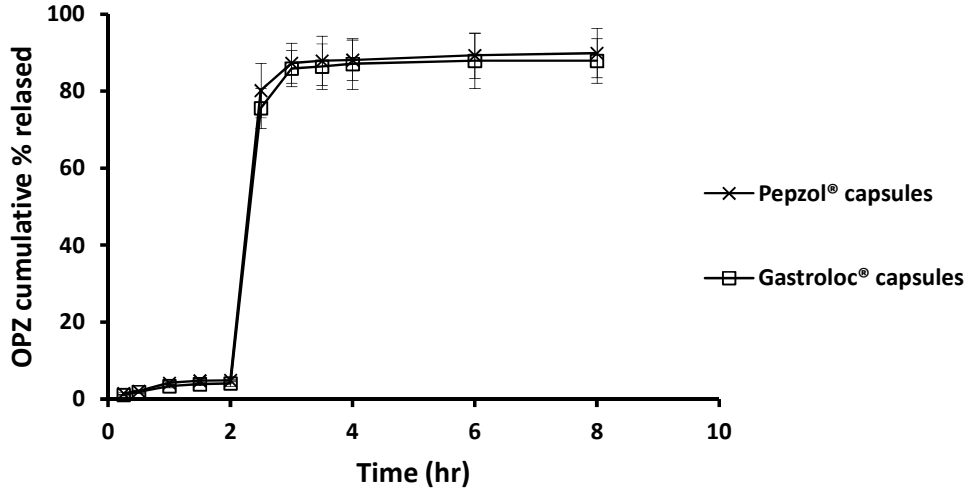

Fig. 1. Dissolution profile of OPZ from Pepzol® and Gastroloc® enteric coated capsules in different pH media

well as the low solubility of OPZ in acidic pH medium [21]. By increasing the pH of the dissolution medium to 6.8 and 7.4 there was a blast in OPZ release from both tested formulations due to the higher solubility of the drug in these relatively high pH media. There was no significant difference in the release profile from Pepzol® and Gastroloc® capsules that reflects pattern, rate and extent of release of OPZ.

The tested OPZ products were administered with about 240 mL of water to subjects under fasting conditions. Water was allowed as desired except for 1 hour before and after drug administration. Subjects received standardized meals 4 hours after drug administration at the same time in each period of the study. For most dosage forms that release drug intended to be systemically available, FDA recommends use of a two-period, two-sequence, and two-treatment, single-dose, and crossover design for bioequivalence studies. In this design, each study subject received each product in random order.

FDA recommends drawing blood samples at appropriate times to describe the absorption, distribution, and elimination phases of the drug. Sampling should continue for at least three or more terminal elimination half-lives of the drug. Therefore in this study samples were collected for 12 h after drug administration. Also FDA recommends that, the exact timing for sample collection depends on the nature of the drug and the rate of input from the administered dosage form. At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of elimination rate constant (K) from linear regression.

Bioequivalence frequently relies on the pharmacokinetic parameters. FDA recommends that the rate of drug absorption after single-dose could be assessed by measuring the peak drug concentration (C_{max}) obtained directly from the data. Also the time-to-peak drug plasma concentration (T_{max}) can provide important information regarding the rate of drug absorption. Regarding the extent of drug absorption, both the area under the plasma concentration-time curve from time zero to last time point with a measurable concentration ($AUC_{0\text{-}end}$) and the area under the plasma concentration-time curve from time zero to time infinity ($AUC_{0\text{-}\infty}$) could be very helpful.

To evaluate the pharmacokinetic properties and bioavailability of two commercial available OPZ products (Pepzol® and Gastroloc® capsules), an individual comparative single-dose cross-over study was carried out in 24 healthy male volunteers. The mean plasma concentrations of OPZ from two brands of OPZ 40 mg capsules are shown in Fig. 2. All calculated pharmacokinetic parameters: C_{max}, t_{max}, $t_{½}$, k, $AUC_{0\text{-}12}$, $AUC_{0\text{-}\infty}$ and MRT for both formulations are given in Table 1. For bioequivalence evaluation various statistical modules were applied to $AUC_{0\text{-}12}$ and $AUC_{0\text{-}\infty}$ and C_{max} as per current FDA guideline [22].

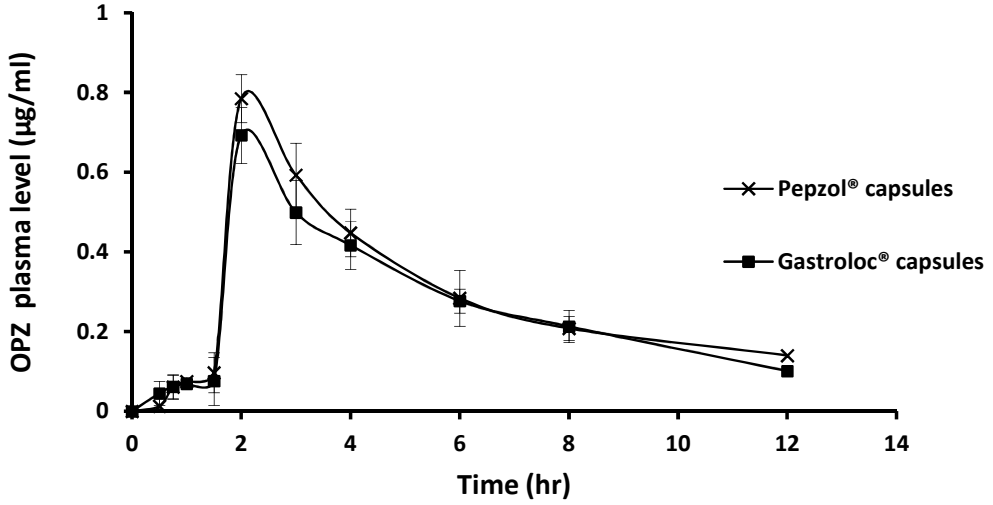

Fig. 2. Plasma concentration-time curve after oral administration of 40 mg of Pepzol® and Gastroloc® enteric coated capsules in human volunteers

Table 1. Pharmacokinetic parameters after oral administration of 40 mg of Pepzol® and Gastroloc® enteric coated capsules in human volunteers

Parameters	Pepzol® capsules	Gastroloc® capsules
Dose (mg)	40	40
T_{max} (h)	2	2
C_{max} (µg/ml)	15.8±1.1	13.3±0.9
K (hr^{-1})	0.157±0.08	0.176±0.09
$t_{1/2}$ (hr)	4.41±0.43	3.94±0.41
$AUC_{0\text{-}end}$ (µg.h/ml)	3.42±0.37	3.14±0.32
$AUC_{0\text{-}\infty}$ (µg.h/ml)	4.31±0.34	3.71±0.33
MRT (hr)	6.53±0.35	6.17±0.37
$AUMC_{0\text{-}\infty}$ (µg.h^2/ml)	28.15±1.2	22.90±1.7
C_{max}/ $AUC_{0\text{-}end}$ (h^{-1})	0.23±0.01	0.22±0.01

The mean value of $AUC_{0\text{-}12}$ of Pepzol® and Gastroloc® capsules were 3.31 µg.h/ml and 3.14 µg.h/ml, respectively, while the mean value of $AUC_{0\text{-}\infty}$ were 4.42 µg.h/ml and 3.71 µg.hr/ml for the same products. These values were in good agreement with reported ones [23,24]. On the basis of these values it was concluded that the two products did not show any unusual pharmacokinetics values for OPZ. There was no significant difference in the values of $AUC_{0\text{-}12}$ and $AUC_{0\text{-}12}$ between the tested OPZ products. The 90% confidence interval also fell within the bioequivalence criteria. Two one-sided t-tests [25] were also performed on the ratio of mean $AUC_{0\text{-}12}$ of Pepzol® capsules to mean $AUC_{0\text{-}12}$ of Gastroloc® capsules which was found to be 1.09. It was accepted that the probability for the ratio (T/R) to lie within 0.8 and 1.2 was 0.90.

The mean C_{max} was 15.8 and 13.3 µg/ml for Pepzol® and Gastroloc® capsules respectively; these values were in good agreement with reported ones [23,24], assuring further the lack of any unusual OPZ pharmacokinetics from the tested products. There was no significant difference between the tested products regarding the value of the C_{max}. The 90% confidence interval also fell within the bioequivalence criteria. Two one-sided t-tests (US FDA) were also performed on the ratio of mean C_{max} of Pepzol® capsules to mean C_{max} of Gastroloc® capsules which was found to be 1.19. In addition, there was no significant difference between the tested products regarding Tmax, $AUMC_{0\text{-}\infty}$, and MRT.

4. CONCLUSION

The statistical comparison of $AUC_{0\text{-}12}$ and $AUC_{0\text{-}\infty}$ and C_{max} clearly indicated no significant difference in the two brands of OPZ 40 mg capsules. 90% confidence intervals for the mean ratio (T/R) of $AUC_{0\text{-}end}$ and $AUC_{0\text{-}\infty}$ and C_{max} were entirely within the FDA acceptance range. Based on pharmacokinetic and statistical results of this study, it can be concluded that Pepzol® capsules is bioequivalent to Gastroloc® capsules; i.e. they deliver the same amounts of OPZ to the systemic circulation with the same rates and that the two products can be considered interchangeable in medical practice.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Iijima K, Kanno T, Koike T, Shimosegawa T. Helicobacter pylori-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. World J Gastroenterol. 2014;20(3):706-13.
2. Tsibouris P, Kalantzis C, Apostolopoulos P, Zalonis A, Isaacs PE, Hendrickse M, Alexandrakis G. Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding. World J Gastrointest Endosc. 2014;6(12): 612-9.
3. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;13(3):728–738.
4. Sikes DH, Agrawal NM, Zhao WW, Kent JD, Recker DP, Verburg KM. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. Eur J Gastroenterol Hepatol. 2002;13(10):1101–11.

5. Aabakken L. Current endoscopic and pharmacological therapy of peptic ulcer bleeding. Best Pract Res Clin Gastroenterol. 2008;22:243–59.
6. Barkun A, Leontiadis G. Systematic review of the symptom burden, quality of life impairment and costs associated with peptic ulcer disease. Am J Med. 2010; 123:358–66 e2.
7. Lanas A, Tornero J, Zamorano JL. Assessment of gastrointestinal and cardiovascular risk in patients with osteoarthritis who require NSAIDs: The LOGICA study. Ann Rheum Dis. 2010; 13(8):1453–1458.
8. Hawkey CJ, Svedberg LE, Naesdal J, Byrne C. Esomeprazole for the management of upper gastrointestinal symptoms in patients who require NSAIDs: a review of the NASA and SPACE double-blind, placebo-controlled studies. Clin Drug Investig. 2009;13(10): 677–687.
9. Yuan YH, Wang C, Yuan Y, Hunt RH. Meta-analysis: Incidence of endoscopic gastric and duodenal ulcers in placebo arms of randomized placebo-controlled NSAID trials. Aliment Pharmacol Ther. 2009;13(3):197–209.
10. Na Liu, Lili Liu, HongBo Zhang, Prakash Chandra Gyawali, Dexin Zhang, Liping Yao, Yan Yang, KaiChun Wu, Jie Ding, DaiMing Fan. Effect of intravenous proton pump inhibitor regimens and timing of endoscopy on clinical outcomes of peptic ulcer bleeding. Journal of Gastroenterology and Hepatology. 2012;27:1473–1479.
11. Sugano K, Kinoshita Y, Miwa H, Takeuchi T. On behalf of the Esomeprazole NSAID Preventive Study Group. Randomised clinical trial: Esomeprazole for the prevention of nonsteroidal anti-inflammatory drug-related peptic ulcers in Japanese patients. Aliment Pharmacol Ther. 2012;13(2):115–125.
12. Xiaofang H, Xi Z, Chunhua Y, Qiuyang Z, Edaire C, David HW, Thai HP, Stuart JS, Rhonda FS. In oesophageal squamous cells exposed to acidic bile salt medium, omeprazole inhibits IL-8 Expression through Effects on Nuclear Factor-κB and Activator Protein-1.Gut. 2014;63(7):1042–1052.
13. Shahran Ala, Fatemeh Zanad, Mohammad Reza Shiran. Population pharmacokinetics of omeprazole in a random Iranian population. Caspian J Intern Med. 2013; 4(3):712-716.
14. Whaley PA, Voudrie MA, Sorenson B. Stability of omeprazole in SyrSpend SF Alka (reconstituted). Int J Pharm Compd. 2012;16(2):164-6.
15. Wei Li, Su Zeng, Lu-Shan Yu, Quan Zhou. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. Therapeutics and Clinical Risk Management. 2013;9:259–271.
16. Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. Clinical Therapeutics. 2003; 25(11):2875–2890.
17. Christians U, Klawitter J, Clavijo CF. Bioequivalence testing of immunosuppressants: concepts and misconceptions. Kidney Int Suppl. 2010; 115:S1-7.
18. Hamdan II. *In vitro* study of the interaction between omeprazole and the metal ions Zn(II), Cu(II), and Co(II). Pharmazie. 2001;56(11):877-81.
19. Vlase L, Neag M, Popa A, Muntean D, Leucuta SE. Pharmacokinetic interaction between fluoxetine and omeprazole in healthy male volunteers: A prospective pilot study. Curr Ther Res Clin Exp. 2010;71(6):360-8.
20. Laurian Vlase, Maria Neag, Adina Popa, Dana Muntean, Sorin E. Leucuta pharmacokinetic interaction between fluoxetine and omeprazole in healthy male volunteers: A prospective pilot study. Current Therapeutic Research. 2010;71(6): 360-368.
21. El-Badry M, Taha EI, Alanazi FK, Alsarra IA. Study of omeprazole stability in aqueous solution: Influence of cyclodextrins. J Drug Del Sci Tech. 2009; 19(5):347-351.
22. Blume HH, Midha KK, eds. Bio-international 2: Bioavailability, bioequivalence and pharmacokinetics. Medpharm Scientific Publishers, Stuttgart, Germany; 1995.
23. Schaltenbrand R, Huber R, Cotoraci CA, Mascher H, Potthast H, Hole U. Bioequivalence between omeprazole MUPS 20 mg as tablet and omeprazole MUPS 20 mg as tablet encapsulated in a hard gelatine capsule. Int J Clin Pharmacol Ther. 2001;39(10):453-9.

24. Jian Liu, Jian-zhong Shentu, Li-hua Wu, Jing Dou, Qi-yang Xu, Hui-li Zhou, Guo-lan Wu, Ming-zhu Huang, Xing-jiang Hu, Jun-chun Chen. Relative bioavailability and pharmacokinetic comparison of two different enteric formulations of omeprazole. J Zhejiang Univ-Sci B (Biomed & Biotechnol). 2012;13(5):348-355.

25. US Food and Drug Administration, FDA Guidelines, Bioequivalence Food and Drug Administration, Division of Bioequivalence, Office of Generic Drugs, Rockville, MD; 1992.

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