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COMPARATIVE STUDY OF BRAND AND GENERICS OF OMEPRAZOLE CAPSULES AVAILABLE IN THE SAUDI MARKET

Saira Zahoor [1], Hajer Alghamdi [1], Mohammed S. Khalid [2], Hawra Al-Mubarak [1] and Hassan M. Ghonaim [*1]

Department of Pharmaceutics [1], Department of Pharmacology [2], College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Kingdom of Saudi Arabia.

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Correspondence to Author:
Hassan M. Ghonaim

Associate Professor,
Department of Pharmaceutics,
College of Clinical Pharmacy,
Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Kingdom of Saudi Arabia.

E-mail: hmghonaim@iau.edu.sa

ABSTRACT: Proton Pump Inhibitors (PPIs) are widely used acid suppression medications for many conditions. PPIs class includes many drugs, such as omeprazole, lansoprazole, pantoprazole and esomeprazole, available orally in a tablet/capsule form. PPI's products have reasonably high prices with quality differences that most healthcare providers must know. Therefore, this study aimed to compare the quality of PPIs for brand and generics in the Saudi market. Gastric ulcers result from an imbalance involving gastric protection and aggressive factors. Gastric protection depends on several factors, such as the release of prostaglandin E2 (PGE2), bicarbonate secretion, gastric mucus production, and gastric mucosal blood flow regulation. Factors leading to gastric offensives are the hypersecretion of H.C.L. or pepsin. Ethanol is well known to induce gastric ulcers via multi-factorial mechanisms such as the impairment of gastric defensive factors like mucus dissolution or by increasing offensive factors such as acid secretion or gastrin release. Our study reveals that the gastroprotective effect of PPIs marketed in Saudi Arabia has significantly protected the gastric mucosa against ethanol challenge.

INTRODUCTION: The first proton pump inhibitor discovered was omeprazole. Initially, it was only a chemical structure with an observed antisecretory effect and severe toxic effect. However, basic and applied research operated together to reach an acceptable balance between the efficacy and safety of omeprazole [1].

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PPIs have a structure that resembles histamine H2 receptor antagonists, which aim for stomach acid reduction [5]. The mainly used PPI's omeprazole brand is tested in this study along with their locally manufactured generics to assess their bioequivalence and quality [2, 4]. Multiple studies in different countries have proven that the substitution with generic formulation significantly impacts cost savings for individual and national levels [3, 6, 7].

MATERIALS AND METHODS: We will assess the bioequivalence of the local generics compared to the brand omeprazole capsules **Table 1** by using chemical and physical quality control tests according to United States Pharmacopeia (U.S.P.) [8]

and Saudi Food and Drug Authority's (SFDA) regulations [7].

TABLE 1: MARKETED PRODUCTS, BRAND, AND GENERICS OF OMEPRAZOLE

Omeprazole	Pack size	Brand/Generic
Gasec 20 mg	28 capsules	Brand
Omiz 20mg	14 capsules	Generic
Risek 20mg	14 capsules	Generic

Weight Variation Test: As per U.S.P., the physiochemical parameters, including the weight variation test, are performed to ensure that all the capsules in a batch are of the same weight; 20 capsules are weighed collectively and individually for brand (Gasec) 20mg and generics O (Omiz) 20mg and R (Risek) 20mg by using an analytical balance. The average weight is compared with the individual weights of all capsules. The percentage difference is determined.

Dissolution Test:

Chemicals & Reagents: Potassium Dihydrogen Phosphate (KH_2PO_4) Sodium Hydroxide (NaOH) pellets, Hydrochloric Acid (H.C.L.) & Distilled water.

Glassware and Materials: Marketed omeprazole capsules brand and generics, measuring flask, graduated cylinder, pipette, beaker, glass rod, test tubes, test tubes stand, funnel, filter paper, pipette pump, goggles,

Equipment/ Apparatus: Analytical balance, UV-Visible Spectrophotometer, and Dissolution apparatus. This test determines the rate at which the drug from the dosage forms dissolves and forms the drug solution. Unless and until a drug is dissolved, it will never be absorbed.

So, the faster the dissolution rate, the more rapidly the drug will be absorbed. The temperature of the dissolution fluid is maintained at 37°C. After each period of an interval, a sample of fluid was withdrawn and assayed. It is replaced by fresh fluid immediately. The procedure is repeated until the drug content is diminished substantially and used to assess drug release by U.V.- a visible spectrophotometer. The dissolution test was carried out in two stages, acidic and basic, because it is enteric coated formulations by running two capsules of each product. The parameters are shown in **Table 2.**

TABLE 2: DISSOLUTION PARAMETERS FOR OMEPRAZOLE

Parameters	Acid Stage	Buffer Stage
Apparatus	II	II
Medium	500mL of 0.1N HCL	900ml of pH 6.8 Phosphate Buffer
Sample Interval	120 minutes	10,20,30,45 and 60 minutes
Revolution Per Minutes	100 RPM	100 RPM
Temperature	$37^oC \pm 0.5^oC$	$37^oC \pm 0.5^oC$
Tolerance	N.M.T. 10%	N.M.T. 75%
Lambda Max	305 nm	305 nm

Preparation for Acidic Medium: Measure 8.3mL of pure concentrated hydrochloric acid, pour into a flask containing enough water, and make up the volume up to 1000mL to get 0.1 N H.C.L. solution.

Preparation of Phosphate Buffer pH 6.8: Weighed 6.8g of Potassium Dihydrogen Phosphate (KH_2PO_4) and 0.89 g of Sodium Hydroxide in sufficient water and adjusted the pH with 0.1N H.C.L. & NaOH 0.1N and made up the volume to 1000mL.

Acid Stage: Maintain the temperature at $37^oC \pm 0.5^oC$. We placed a capsule in each vessel containing 500mL 0.1 N H.C.L. Set the stated 100 revolutions per minute and run the sample for 120 minutes using dissolution apparatus type II. After specific time intervals, we measured the absorbance at 305 nm using the same medium and scanned absorbances on the U.V. visible spectrophotometer.

Buffer Stage: Removed the acidic medium from vessels &added the fresh medium of buffer pH 6.8 in the vessels. Maintain the temperature at $37^oC \pm 0.5^oC$. Set the stated 100 revolutions per minute and run the same sample for 60 minutes. After specific time intervals of 10,20,30,45 and 60 minutes, we picked 5mL of sample and replaced it immediately with the same fresh medium to maintain the volume of 900mL. After specific time intervals, we measured the absorbance at 305 nm using the same medium as a blank and scanned absorbances on the U.V. visible spectrophotometer.

Antiulcer Study of Omeprazole: To study the gastroprotective effect of omeprazole on ethanol-induced gastric erosion in rats, the chemicals and drugs included male albino Wistar rats weighing 160-180gindividually were used. They were

obtained from Institute for Research and Medical Consultation (IRMC) of Imam Abdulrahman bin Faisal University.

Animals: Rats were acclimatized at 25 ± 1°C (humidity 55±5 %) on a 12h light-dark cycle (light on at 07.00) in standard wire meshed plastic cages for 4 to 5 days before the commencement of the experiment. The animals were fed a standard laboratory diet and water ad libitum and fasted for at least 12 hours before the experiment [9, 10]. All the procedures were carried out according to the Animal Experimentation Ethics Committee of the University. The allocation of animals to all groups was randomized. *In-vivo* experimental protocols were approved by the Institutional Review Board (I.R.B**.)** IRB-UGS-2018-05-245.

Experimental Design: The ulcer is induced by administering ethanol to animals.

Ethanol Gastric Ulcer Induction: The animals are divided into five groups of six animals in each. To induce ulcers with ethanol, all the animals fasted for 24 hours before administering ethanol. Then, all groups received ethanol (50 % v/v or 95°) (in distilled water) in a dose of 10 mL/kg orally *via* a stainless-steel intubation needle [11, 12] except group-I, which received the vehicle and served as a negative control. The groups are divided as follows:

Group A: Negative control receive vehicle (Normal saline).

Group B: Positive control: - Receives ethanol (50% v/v or 95%) 1 mL/ 100g orally **[11, 12]**

Group C: Omeprazole brand Gasec 20 mg/kg; p.o, 1 hour before ethanol administration **[13]**

Group D: Omeprazole generic Omiz, 20 mg/kg; p.o, 1 hour before ethanol administration.

Group E- Omeprazole generic Risek 20 mg/kg; p.o, 1 hour before ethanol administration.

Two hours after ethanol administration, all rats were killed by an overdose of chloroform. The stomachs were rapidly removed, opened along their greater curvature, and cleaned gently by dipping them in saline. The mucosal damage was examined grossly under magnifying lens [14]. The severity of mucosal damage was assessed by modifying a previously reported [15]-rating scale. Based on the severity of the mucosal damage, the specimen was assigned an ordinal score as per the scoring scheme. For example, a specimen with five punctiform lesions, two small ulcers, and a large ulcer was assigned a score of 3.0. However, the control specimens did not exhibit the formation of lesions or ulcers and accordingly had a score of '0'. The scores were averaged [16] the ulcer incidence [15], and the ulcer length (mm) [17] was tabulated, where mean ulcer score **Table 3** [16] percentage of ulcer incidence [16] cumulative ulcer length (mm) [16] and ulcer index [17] were calculated. To calculate the Ulcer index [18].

TABLE 3: THE ESTIMATE OF THE ULCERATION INDICES

Observation Score	Score
No lesions	0.0
Punctiform lesions (lesions less than 1 mm)	0.5
Five or more punctiform lesions	1.0
One to five small ulcers (1-2 cm)	2.0
More than five small ulcers or one large ulcer (2-4 mm)	3.0
More than one large ulcer (greater than 4 mm)	4.0

Ulcer index = (UN + US+ UP) x 10 rise to power -1

Where, UN = Average number of ulcers per animal, U.S. = Average of severity score, UP = percentage of animals with an ulcer.

The percentage protection was calculated using the formula [19].

Control means ulcer index ethanol - Test mean ulcer index $_{PPI}$

Inhibition (%) = Control means ulcer index $_{ethanol}$ × 100

Statistical Analysis: Data obtained from the animal experiments were expressed as mean ± S.E.M. statistical tests. A one-way analysis of variance (ANOVA) followed by the Tukey posthoc test was used to analyze any differences between the groups subjected to testing. A p-value of less than 0.05 was statistically significant.

RESULTS AND DISCUSSION: The weight variations test results showed no significant difference between the brand and generic product, and the average weight for all products is similar, as shown in **Table 4.**

TABLE 4: WEIGHT VARIATION RESULTS OF OMEPRAZOLE

Product name	Average weight for capsule
Gasec	280 mg
Omiz	290 mg
Risek	300 mg

The results of the Omeprazole dissolution test proved that all the products passed the test, and all met the U.S.P. quality expectations of tolerance of not more than 10% within 120 minutes in the acid stage and released more than 75% of the drug within 60 minutes in the buffer stage. Drug"Generic O" has the highest percentage of drug release, i.e., 98.51% within 30 minutes, compared to the brand "Brand B," which reached the maximum percentage of drug release, 94.41% within 45 minutes. Drug "Generic R" passed the test but with the lowest percentage of drug release of 88.60% within 45 minutes, are shown in **Fig. 1.**

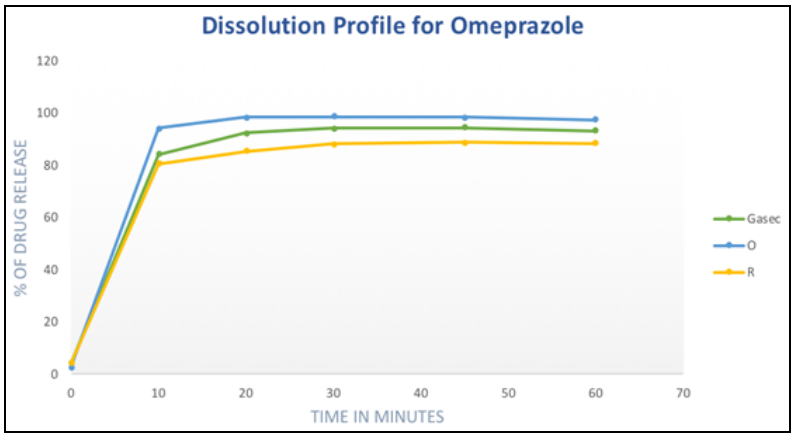


FIG. 1: ILLUSTRATING DISSOLUTION PROFILE FOR OMEPRAZOLE BRAND AND GENERICS

Ulcer ethanol induction in stomachs of rats and protection by the brands and generics of proton pump inhibitors omeprazole, as results showed in **Fig. 2** and **Table 5**, ethanol (95% v/v (1ml/100g; p.o) administration caused multiple gastric lesions in addition to sever hemorrhagic steaks in all the animals (*n*=8) (ulcer incidence of 100%). The ulcer index was calculated as 14.27 ± 0.68mm. The lesion index was almost nil in the control group treated with the vehicle (0.9% NaCl).

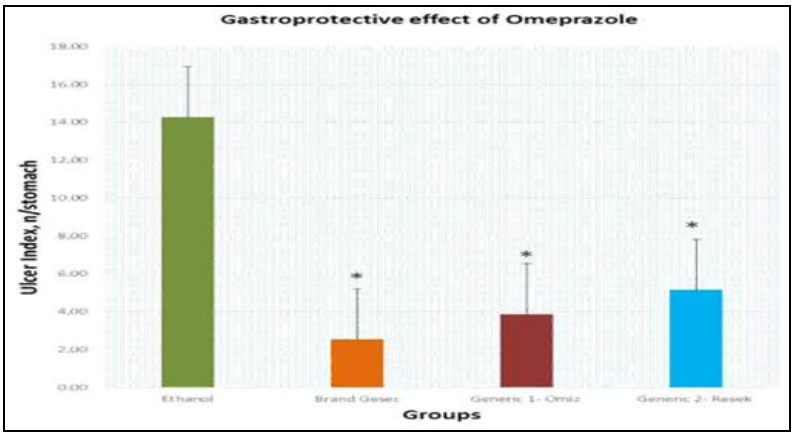


FIG. 2: ULCER INDEX SCORED THE FUNDIC REGION OF THE STOMACH IN RATS SUBJECTED TO ETHANOL. WHEN COMPARED TO GENERIC OMIZ AND RISEK WITH ITS BRAND GESEC (20 MG/KG) TREATMENT. The data were expressed as mean ± S.E.M. (n = 8). Results were analyzed statistically using one-way ANOVA with the Tukey Multiple Comparisons tests as a posthoc test. *Significantly different from the ethanol group at P < 0.05. The minimum level of statistical significance was set at P 0.05.

The findings suggest that pre-treating n/animals with a single dose of omeprazole (20mg/kg; p.o) prior to ethanol has significantly prevented ulcer lesion formation, whereas in brand B only two rats showed ulcer with ulcer incidence of 25% (*n*=2/8) and significantly reduced (*P*<0.05) ulcer index of 2.55±0.28 mm with a percentage ulcer inhibition of 82.13% when compared to the ethanol control

group. However, the rats pre-treated with omeprazole generic O [only three rats showed ulcer with ulcer incidence of 37.5% (*n*=3/8] and generic R [4 rats showed ulcer with ulcer incidence of 50% (*n*=4/8] showed a significant reduction in ulcer index of 3.88±0.59mm (72.81% inhibition) and 5.15+0.20mm (63.91% inhibition) respectively **Fig. 2** and **Table 5** when compared to the ethanol control group. The brand and generic omeprazole exerted significant protection against damage produced by ethanol ($p < 0.05$).

TABLE 5: PROTECTIVE EFFECTS OF OMEPRAZOLE BRAND AND ITS GENERICS AGAINST THE ETHANOL-INDUCED GASTRIC ULCER IN RATS

Group No. (*n*=8)	Treatment	Dose	% of ulcer Incidence	Mean Ulcer scores	Cumulative Ulcer length (mm)	Ulcer Index (mm)	Inhibition (%)
A	Normal Saline	Vehicle (0.9% NaCl)	0% (0/10)	0.00	0.00	0.00	--
B	Ethanol	95% v/v (1ml/ 100g; p.o)	100% (8/8)	9.52±0.16	33.13±0.68	14.27±0.68	0.00
C	Brand	20mg/kg; p.o	25 % (2/8)	0.23+0.16	0.26±0.28	2.55±0.28*	82.13%
D	Generic 1-	20mg/kg; p.o	37.5% (3/8)	0.31+0.19	0.94±0.59	3.88±0.59*	72.81%
E	Generic 2-	20mg/kg; p.o	50(4/8)	0.42+0.20	1.06±0.53	5.15+0.20*	63.91%

Data were expressed as mean ± S.E.M. (n = 8). Results were analyzed statistically using one-way ANOVA with the Tukey Multiple Comparisons tests as a post hoc test. Gastric lesions were measured, summed, and scored from one to five. *Significantly different from the ethanol group at $P < 0.05$.

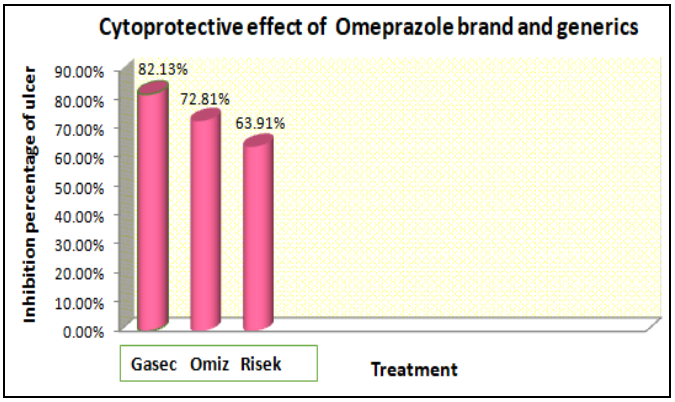


FIG. 3: GASTROPROTECTIVE INDEX OF PPIS BRAND AND GENERICS MARKETED IN SAUDI ARABIA IN THE STOMACH OF RATS SUBJECTED TO ETHANOL (% V/V (95% V/V, 1ML/100G; P.O). COMPARISON OF PROTON PUMP INHIBITORS BRAND WITH THEIR RESPECTIVE GENERIC'S TREATMENT. The data were expressed as mean S.E.M. (n = 8). Results were analyzed statistically using one-way ANOVA with Tukey Multiple Comparisons as a posthoc test. The minimum level of statistical significance was set at P 0.05

Our study reveals the comparative study of the gastroprotective effect of brands and generics of PPIs marketed in Saudi Arabia has significantly protected the gastric mucosa against ethanol challenge (in ethanol model) as shown by reduced values of lesion index as compared to the control group suggesting its potent cytoprotective effect **Fig. 3.** Macroscopic examination of rat stomachs of the control group administered normal saline and rat stomach from the groups treated with ethanol (95% v/v (1ml/100g; p.o), the PPI's brand and generics were presented in **Fig. 4.** Rats of Group A (control group), which administered normal saline, showed zero ulcer incidence as no one developed an ulcer from the total rats (*n*=8) of this group (all stomachs are of normal type). In addition, a gross study of the control group's gastric lumina showed an apparent normal gastric mucosa regarding a normal rouge and mucous covering layer **Fig. 4A.**

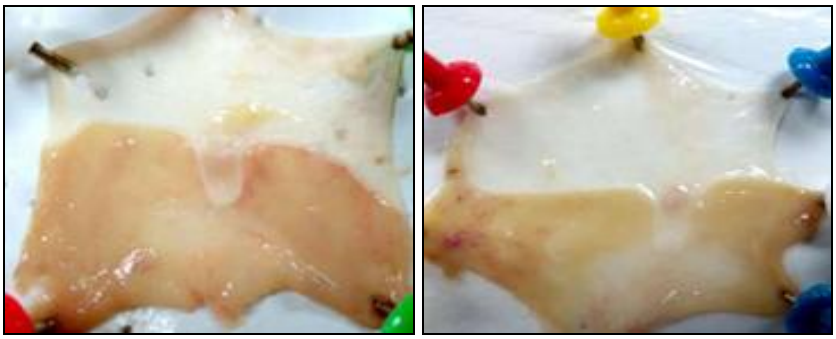
A rat stomach that received ethanol (95% v/v-1ml/100g; p.o), showed severe ulcer incidence by evidence of the changes in the area of gastric ulcer and gastric blood flow at entire gastric mucosa and ulcer margin widespread hemorrhaging/ hemorrhagic streaks as indicated by the numerous red spots which are severe blood clots **Fig. 4B.**

A rat stomach that received omeprazole (dose of 20mg/kg; p.o) brand B, showed a normal gastric mucosa with a small area of congestion covered by a thick layer of mucosa **Fig. 4.** A rat stomach that received omeprazole (dose of 20mg/kg; p.o) generic O shows ulcer incidence by evidence of mild blood spots with a small area of congestion **Fig. 4D** and **Fig. 4E** shows the rat stomach, treated with generic R, wide spread of blood spots and mild congestion showing hemorrhagic steaks. Gastric ulcers result from an imbalance involving

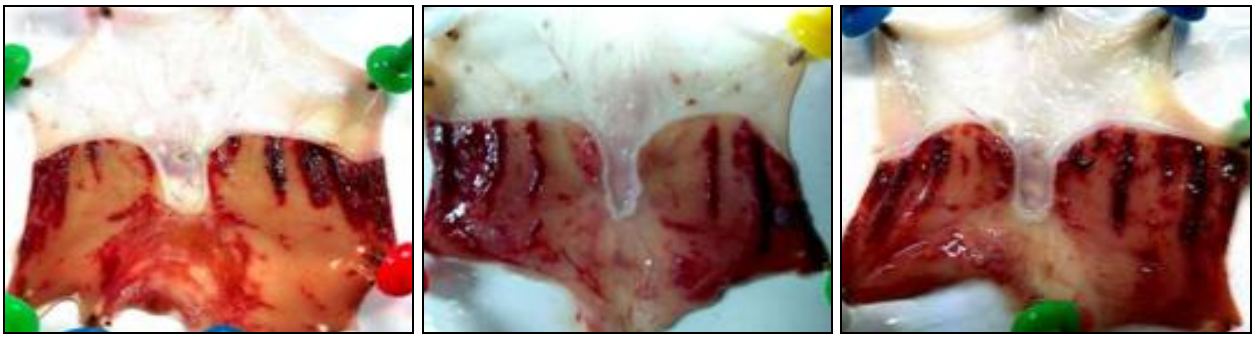
gastric protection and aggressive factors [20]. Gastric protection depends on several factors, such as the release of prostaglandin E2 (PGE2), bicarbonate secretion, gastric mucus production, and gastric mucosal blood flow regulation. Factors leading to gastric offensives are the hypersecretion of H.C.L. or pepsin. Ethanol is well known to induce gastric ulcers *via* multi-factorial mechanisms such as the impairment of gastric defensive factors like mucus dissolution [21] or by increasing offensive factors such as acid secretion or gastrin release [22].

In the ethanol model, the brands and generics of PPIs omeprazole significantly decrease the gastric acid and pepsin output, indicating a decrease in offensive acid and pepsin secretion. Conversely, on the defensive factors, PPIs significantly increased gastric mucin secretion and prevented the gastric mucosal damage induced by ethanol. Omeprazole showed a better reduction of gastric acid secretion and the protection percentage, which is high in omeprazole brand B 82.13% compared to its two generics, O and R (72.81% and 63.91%, respectively) treated group **Fig. 4**. The cytoprotective effect of omeprazole is due to increased expression of COX-2 protein and elevated levels of PGE2.

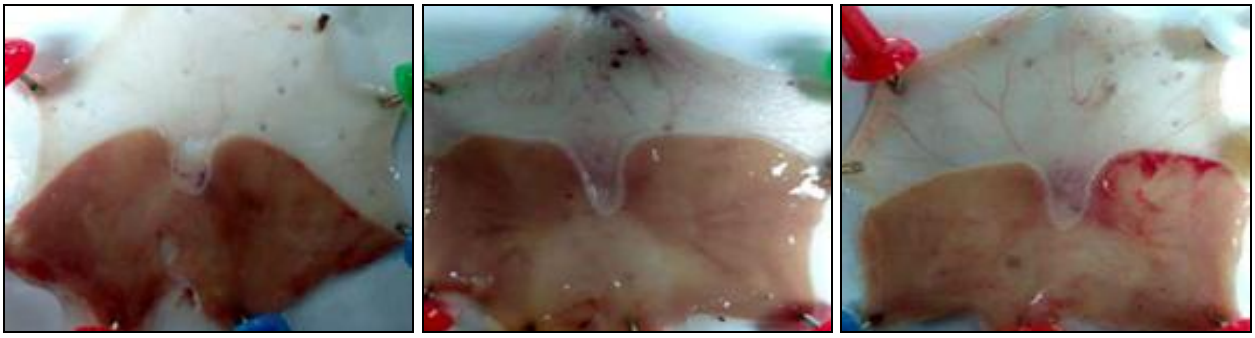
It also showed increased gastric pH and reduced gastric acid secretion, possibly due to the inhibition of gastric mucosa enzymes, carbonic anhydrase II (C.A.), and CA IV, which are abundant in the gastric parietal cells and the secretory canaliculi walls. This inhibition potentiates the inhibitory effect on the proton pump inhibitors like omeprazole [23].



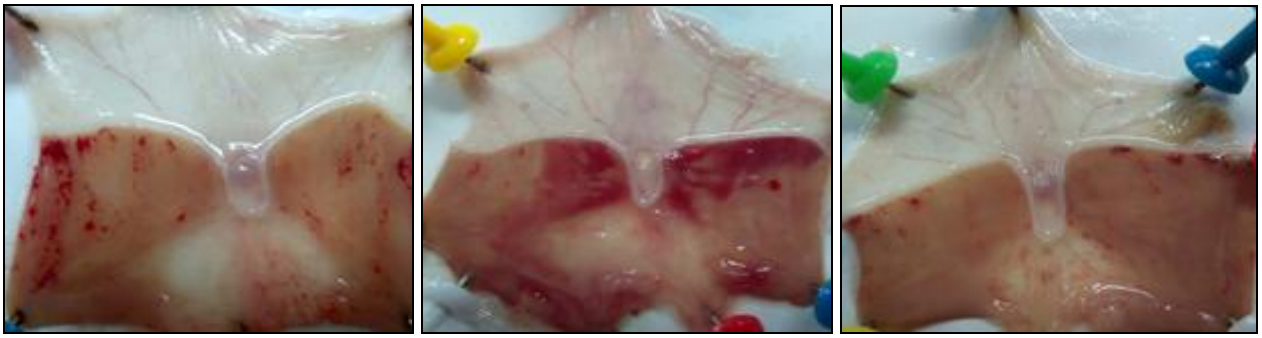
4A: GROUP A: NORMAL CONTROL (NORMAL STOMACH)



4B: GROUP B: ETHANOL 95% V/V (1ML/100G ;P.O)-TOXICANT GROUP



4C: GROUP C: OMEPRAZOLE BRAND - GASEC (20MG/KG)



4D: GROUP D: OMEPRAZOLE GENERIC 1- OMIZ (20MG/KG)

4E: GROUP E: OMEPRAZOLE GENERIC 2 - RISEK (20MG/KG)

FIG. 4: ILLUSTRATION OF AN ETHANOL-INDUCED GASTRIC ULCER IN RATS AND ITS PREVENTION OF FORMATION BY PPI'S BRANDS AND ITS GENERIC. (THE ANIMALS WERE GIVEN OMEPRAZOLE TWO HOURS BEFORE ADMINISTERING ABSOLUTE ETHANOL (95% V/V, 1ML/100G; P.O). ANIMALS WERE KILLED TWO HOURS AFTER ETHANOL INGESTION)

CONCLUSION: Based on this current study, all generics showed good potential, including weight variation, disintegration time, and dissolution tests. However, there is no significant difference between brand and generics, so the results support the generic substitutions of omeprazole. The results of our animal study agreed with study [24] of Sener *et al.* (2001). In addition, Robert *et al*. (1979) study 25 showed that intra-gastric administration of ethanol consistently caused hemorrhagic lesions in the stomach mucosa, and pre-treatment of rats with omeprazole prevented the gastric ulcerogenic significantly. Furthermore, they decreased the U.I. values while disagreeing [26] with Blandizzi *et al.* (2000). Omeprazole generic Omiz does not provide more protection than omeprazole brand Gasec cytoprotective action in ethanol-induced gastric ulcers in rats.

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