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Post-marketing Assessment of Esomeprazole and Lansoprazole Enteric Coated Products Available in Saudi Arabia Based on Quality Control

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by authors MAI, DHA, AMA and TNA. The first draft of the manuscript was written by authors MAI and DHA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Esomeprazole (ESM) and Lansoprazole (LNZ) are proton pump inhibitors, used in the treatment of peptic ulcer and gastroesophageal reflux disease. Different marketed generic products for both drugs are now available in Saudi market as enteric coated dosage form. Different factors can affect the drug release from enteric coated formulation, and therefore, the final product should be tested.
Methodology: In this study three different ESM generic products (20 and 40 mg) and four LNZ generic products (15 and 30 mg) were assessed and compared to the innovator products based on quality control tests.

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Results: For ESM, it was found that the content uniformity results for the innovator product (Nexium®) and all other generic products lies between 85-115% with relative standard deviation (RSD) less than 6%. Also, the calculated Acceptance values (AV) was less than 15% (L1), which met the US Pharmacopeia. The *in-vitro* dissolution test in acid stage for Nexium® and other ESM generic products was less than 10% which met the requirement. In case of LNZ, 4 different generic enteric coated pellets filled in capsules were studied and compared to its innovator (Lanzor®), the content uniformity results showed that all products met the requirement with AV less than 15%. The *in-vitro* dissolution studies showed that all products met the requirement and release less than 10% of the drug in the acidic media, except LNZ-P2 containing both 15 and 30 g LNZ, which exhibited release more than 10% in the acids stage.
Conclusion: post-marketing assessments for drug products play an important rule to figure out the non-effective products.

Keywords: Esomeprazole; lansoprazole; delayed release; Proton Pump Inhibitors (PPIs) enteric coated; quality control.

1. INTRODUCTION

Oral solid dosage forms are price-saving, taken by patient easily and have a high level of patient compliance. They are a non-invasive since it is taken orally without the aid of special instrument to administer the drug [1].

Solid oral dosage forms could enhance the stability of drug product during their shelf-life. However, drug bioavailability from such formulations could be affected by gastrointestinal tract (GIT) physiological conditions such as a difference in pH, first-pass metabolism and enzymes [2].

According to United State Pharmacopeia (USP), delayed-release drug products are solid dosage forms that release the drugs at a time later than immediately after administration (i.e., there is a lag time exhibited to attain plasma levels). Enteric coatings are proposed to prevent drug release in the acidic medium, and release it starting from alkaline medium thereafter [3]. The main target of enteric coating is the protection of the stomach from local irritation of some drug, such as NSAID's [4], and shielding drugs that are unstable or sensitive at gastric pH [5,6] such as proteins and enzymes macromolecules, because they are hydrolyzed rapidly and inactivated in gastric pH [6,7].

The concept of enteric coated tablets or pellets is based on coating these dosage forms with gastric resistant polymers, which control drug dissolution in the gastric pH, and allow drug release in the intestine where the enteric coat decomposes [8-10].

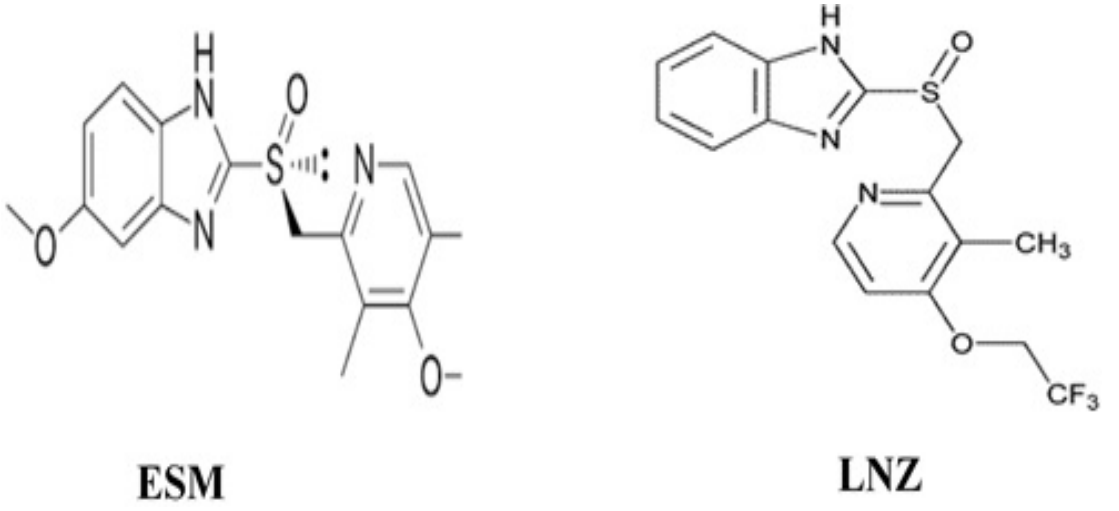

Fig.1. Chemical structures of ESM and LNZ

Proton pump inhibitors are working through block proton pump in the stomach. Hence acid secretion is reduced. It acts by inhibiting H, K-ATPase enzyme, and suppresses gastric acid secretion [11]. The most common PPIs examples are omeprazole, lansoprazole, rabeprazole, Esomeprazole, and Pantoprazole. They are used for treating gastrointestinal diseases particularly peptic ulceration, Zollinger–Ellison syndrome and reflux esophagitis [12].

Esomeprazole (ESM); 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2yl) methylsulfinyl] benzimidazol-1-ide, the omeprazole S-isomer, is the first single isomer proton pump inhibitor (PPI) approved to treat peptic ulcer, peptic/stomach ulcer, gastroesophageal reflux disease and Zollinger-Ellison syndrome [13]. EMS (daily dose of 20-40 mg) suppresses gastric acid secretion by specific inhibition of the H+ /K+ -ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide.

Lansoprazole (LNZ) is a benzimida-zole derivative; (2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole) is one of the PPIs with potent and irreversible inhibition of gastric acidity. LNZ is widely used in treatment of acid reflux and peptic ulcer in a daily dose from 15 – 30 mg [14]. LNZ is a prodrug of substituted benzimidazole with selective and irreversible proton pump inhibitor activity. LNZ prodrug is transformed to an active sulfonamide derivative in the acidic media which able it to binds to the gastric proton pump H^+/K^+ ATPase. This irreversible but selective binding will inactivate the ATPase and reduce the gastric acid secretion [15].

The stability of both ESM magnesium and LNZ is pH dependent; it degrades rapidly in the acidic stage, but under alkaline conditions, these active pharmaceutical ingredients (APIs) exhibit good stability [16,17]. Therefore, improving the bioavailability of ESM and LNZ by a delivery system can protect the drug from an acidity found in the stomach. ESM is available on the market as oral stable dosage forms (enteric coated tablets and capsules containing enteric coated pellets).

The growing number of proton pump inhibitors containing marketed pharmaceutical products increases the questions about the enteric coating efficiency of generic substitution. In our previous work [18]. The pharmaceutical quality control of 6 generic pantoprazole (PPIs) enteric coated tablets in 2 local markets was assessed relative to the innovator product. The obtained data showed that all tested pharmaceutical tablets did not exhibit cracks, swelling or disintegration in the acidic medium, and no drug release within 2 hours was observed. However, an exception was noticed for one product, whose tablets exhibited complete disintegration with 20 minutes.

In the present study, the pharmaceutical quality of 3 generic ESM enteric coated solid dosage forms (enteric coated tablets and capsules containing enteric coated pellets), in addition to 4 generic LNZ hard gelatin capsules containing enteric coated pellets available in Saudi market will be assessed relative to the innovator product (Nexium® and Lanzor®, respectively).

2. MATERIALS AND METHODS

2.1 Materials

Saudi Pharmaceutical Industries & Medical Appliances Corporation; SPIMACO (Buraydah, Saudi Arabia) donated esomeprazole raw material. Lansoprazole was gifted by Lupin Pharmaceuticals Ltd (Pune, India). Various esomeprazole products available in Saudi markets were included in this study, Table 1. Innovator product (Nexium® 20 and 40 mg) and other generic products with similar strengths (ESM-P1, ESM-P2 and ESM-P3) were adopted in the study. Table 2. show different LNZ generic products used in this study compared to the innovator product (Lanzor®) with a same strength.

2.2 Methods

2.2.1 Standard calibration curves

Accurately weighed 10 mg of ESM using (Analytical Balance, Model no. B203-S, Mettler Toledo, (Switzerland)) was dissolved in 100 ml methanol (100 µg/ml) (Stock solution-I). Different aliquots were prepared for the calibration curve. The Calibration curve was made in both acidic medium (0.1N HCl) and phosphate buffer (Disodium hydrogen phosphate and potassium di-hydrogen phosphate) pH 6.8 based on USP guidelines [19].

Table 1. Esomeprazole marketed products in Saudi Arabia

Product	Strength (mg)	Batch No. /Lot No.	Manufacturing Date	Expiry Date
Nexium® (tablets)	20 mg	ZBWG	05-2018	03-2020
Esomeprazole magnesium	40 mg	ZLVS	12-2017	11-2019
ESM-1 (tablets)	20 mg	JS1327	08-2017	08-2020
Esomeprazole magnesium trihydrate	40 mg	JS6838	12-2017	12-2020
ESM-2 (tablets)	20 mg	PY2497	04-2018	04-2020
Esomeprazole magnesium	40 mg	PY2392	04-2018	04-2020
ESM-3	20 mg	SE6046	06-2018	06-2020
Esomeprazole magnesium dihydrate (enteric coated pellets in hard capsules)	40 mg	SE5777	06-2018	06-2020

Table 2. Lansoprazole marketed products in Saudi Arabia

Product*	Strength (mg)	Batch No./ Lot No.	Manufacturing date	Expiry date
Lanzor®	15 mg	7TC9A	12-2017	11-2019
	30 mg	8K56A	05-2018	03-2020
LNZ-1	15 mg	106277	12-2017	12-2020
	30 mg	104212	08-2017	08-2020
LNZ-2	15 mg	854043	04-2018	04-2020
	30 mg	854045	04-2018	04-2020
LNZ-3	15 mg	NA**		
	30 mg	16DN88	01-2017	01-2020
LNZ-4	15 mg	NA		
	30 mg	s0057	09-2017	09-2020

**All products are enteric coated pellets filled in hard gelatin capsules; **NA: Not available*

In the case of 0.1 N HCl (pH 1.2), serial dilutions were made from the previous stock in light protected volumetric flasks, and the absorbance values for these dilutions were measured at 271 nm (UV spectrophotometer, Model Biochrom Libra S22, Bichrom Ltd., Amersham Biosceneces UK Ltd. (Cambridge, England). In the case of buffer solution (pH 6.8), serial dilutions were made from the sock solution using buffer solution in light protected volumetric flasks, and the absorbance values for these dilutions were measured at scan at 302 nm.

For LNZ, 10 mg of the pure drug was weighted accurately ESM and dissolved in 100 ml methanol to perform a stock solution (SS) (100 µg/ ml). Different aliquots were prepared for the calibration curve. The Calibration curve was made in both acidic medium (0.1N HCl) and phosphate buffer pH 6.8 based on USP 27 Dissolution ⟨711⟩ guidelines. The absorbance values were measured at 334 nm and 282, respectively. For content uniformity, LNZ calibration curve was made in 0.1N NaOH and the absorbance was measured at 219 nm [20].

2.2.2 Weight variation

The weight variation test of ESM and LNZ marketed products (enteric coated tablets or capsules containing enteric coated pellets) was performed by following the general harmonized chapter of "USP 34〈905〉UNIFORMITY OF DOSAGE UNITS" [21]. On an analytical balance (Mettler, Switzerland) ten units of each product were weighed individually. The average weight was measured as well as the relative standard deviation (RSD).

For LNZ capsules, the test was performed on 10 individual units for each product. Each capsule was emptied and the content of which was weighed on an analytical balance. The average weight of the content and RSD were calculated.

2.2.3 Uniformity of dosage unit

In compliance with the general harmonized chapter "USD 34 – 905 – UNIFORMITY OF DOSAGE UNITS," [20], the value of ESM and LNZ was evaluated. For ESM, the UV spectrophotometer (Model Biochrom Libra S22, Bichrom Ltd., Amersham Biosceneces UK Ltd

Cambridge, England) at the wavelength 302 nm used to analyze Esomeprazole formulations. Ten individual units were placed each one in a volumetric flask of 250 ml and 40 ml of methanol was added, and the dispersion was sonicated to dissolve the dosage forms then the volume was completed to 250 ml with buffer. The average content and relative standard deviation were calculated.

Concerning LNZ capsules, the content was examined using UV Spectrophotometer at wavelength 219 nm. Individual capsules were placed in a 100 ml light protected volumetric flask and 70 ml of 0.1 N NaOH was added. The dispersion was sonicated to facilitate the capsule to dissolve and then the volume was completed to 100 ml with 0.1 N NaOH. The mixture was then filtered, and 0.1 ml of the previously mentioned solution was placed in a 100 ml volumetric flask and the volume was completed with the same solvent and the absorbance was measured [18]. The average content and standard deviation were calculated.

2.2.4 Calculation of Acceptance Value (AV) for weight variation and content uniformity

The acceptance values for weight variation and dosage unit "content" uniformity were calculated as follows:

$$AV = |M - \bar{X}| \, ks$$

Where $\bar{X}$ is the average of weights or content, k is constant depends on the size of sample: for 10 capsules, k is 2.4; while for 30 capsules, k is 2.0, M is a constant value depending on sample mean ($\bar{X}$):

- If is $98.5 \leq \bar{X} \geq 101.5$, $M = \bar{X}$
- If $\bar{X}$ is < 98.5, M = 98.5
- If $\bar{X}$ is > 101.5, M = 101.5

The calculated AV should be less than 15.0 (L1), and no single unit deviates by more than L2% (generally, 25%) from the reference value M. i,e., No unit < 0.75 M and no unit > 1.25 M in case of L2. It means no unit outside 75 -125 of % Label Claim in case of L2.

2.2.5 Tablet hardness

Tablet hardness testing is used to test the breaking point and structural integrity of ESM tablets prior to storage, transportation, and handling before usage. The tablet crushing strength was tested by (Pharmatest Test System (WHT 32.V02.09.00/15, Multicheck, Germany)). A tablet was placed between the anvils and the crushing strength, which causes the tablet to break, was recorded.

2.2.6 Tablet friability

ESM tablets strength was tested by a friabilator (Type TA3R, Erweka Apparatebau), tablets were weighted before putting them inside a friabilator. The test was operated with 100 revolutions in 4 min then de-dust the tested tablet before weighing them. The weight loss percentage was calculated by reweighing the tablet.

2.2.7 Tablet disintegration

Disintegration test of ESM marketed tablets was performed according to USP 701"Disintegration Test'' for delayed release dosage forms using a disintegration tester (Station Disintegration Tester (ED-2L) Electrolab (India) Private Limited). A minimum of 6 tablets of each product were tested and placed in the disintegration basket. For the first hour, the disintegration was done in acid media by using 0.1 N HCl maintained at 37 ± 2 ^{o}C for 1 h. If after 1 hour no dosage unit shows evidence of disintegration, cracking, or softening, proceed with the buffer stage which is composed of 0.05 M phosphate buffer, pH 6.8, maintained at 37 ± 2 ^{o}C.

2.2.8 *In-vitro* dissolution

Dissolution tests for ESM from marketed products were performed by using (DT-70 dissolution test instrument, manufactured by Pharma Test, Germany) in accordance with USP 27 Dissolution ⟨711⟩ using apparatus 2 (paddle). The paddle was applied at 100 round per minute (rpm). The test includes the following two stages:

2.2.8.1 Acid stage

Three hundred milliliters of 0.1 N HCl for each vessel was used as the dissolution medium (0.1 N HCl, pH 1.2). The dissolution percentage within 120 minutes was measured. The samples were collected at 15, 30, 45, 60, 90 and 120 min and examined by spectrophotometry at wavelength of 271 nm.

2.2.8.2 Buffer stage

After ending of the acid stage, each vessel was completed to 1000ml with buffer solution, composed of 61.05 g of disodium hydrogen

phosphate in 5 liters of distilled water at pH 6.2. The samples were collected at 5, 10, 15and 30 min. The amount of esomeprazole dissolved in the dissolution medium (0.1N HCl + Buffer) was determined by spectrophotometry at wavelength.

Dissolution tests for LNZ marketed products were performed in accordance with USP 27 Dissolution ⟨711⟩ using apparatus 2 (paddle) with a rotation speed of 75 rpm. The temperature was adjusted at 37 ^{o}C. The test was accomplished in two stages as per the USP 27 Dissolution ⟨711⟩ requirements for delayed release tablets. First, the dissolution was performed in 475 ml of 0.1N HCl for 1 hour. A sample of 5 ml was withdrawn every 15 minutes. The amount of lansoprazole dissolved in the dissolution medium was detected by spectrophotometry at wavelength of 334 nm against 0.1N HCl as a blank. Subsequently, the media render alkaline by adding 425 ml of buffer concentrate to obtain 900 ml of phosphate buffer pH 6.8. The test was completed for an extra 1 hour. A sample of 5 ml was withdrawn with 0.45 µm filter and the absorbance was measured at 282 nm against fresh buffer solution as a blank.

The similarity factor is a measure of the similarity of two respective dissolution profiles (brand and generics), It is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves:

$$f2 = 50 \times \log \{[1+(1/n) \sum(R_t-T_t)^2]^{-0.5} \times 100\}$$

Where n is the number of sample points, Rt is the percent of brand release and Tt is the percent of generic formulations release. According to FDA guidelines, f2 value between 50 and 100 indicates similarity between two dissolution profiles [22].

3. RESULTS AND DISCUSSION

3.1 Properties of ESM Marketed Products

ESM marketed tablets' properties are listed in Table 3. Generally, it was found that the tablets of the innovator products (nexium®) was very hard with a hardness of 25.16±1.99 and 30.31±1.85 for 20 mg and 40 mg strength, respectively. The hardness of all generic products, with different strength, were also very high and ranged between 22-30 kp except that for ESM- P2 (20 mg) which showed lower tablet hardness with a value of 12.05±0.76 kp. Moreover, the ESM marketed tablets exhibited acceptable friability, in which the friability value for all marketed product are complying with USP limit (NMT 1%).

Concerning disintegration of ESM marketed products, all the tested products showed no evidence of disintegration, cracks or swelling in 0.1 N HCl, except one generic product (ESM-1 of 20mg and 40mg), which showed complete disintegration of all the tablets after 40 min, which indicates inappropriate enteric coating of the tablets. However, the disintegration of all the products in phosphate buffer (pH 6.8) met USP requirements.

3.2 Weight Variation of ESM Formulations (Tablets and Capsules)

The weight variation test was performed by measuring the weight of 10 units for each product containing 20mg and 40mg of ESM.

Table 3. Properties of marketed esomeprazole tablets

Product	Weight uniformity		Content uniformity		Friability (%)	Hardness (kp)
	Weight (%)	AV	ESM content (%)	AV		
Nexium® 20 mg tablets	101.35±1.03	2.47	101.49 ±4.79	11.50	0.44	25.16±1.99
ESM-P1 20mg tablets	103.56±0.92	4.27	101.45±4.72	11.33	0.25	22.96±1.56
ESM-P2 20 mg tablets	103.17±0.40	2.63	101.10±4.35	8.04	0.36	12.05±0.76
ESM-P3 20 mg capsules	102.22±1.92	5.33	101.74±6.21	14.90	N/A	N/A
Nexium® 40 mg tablets	99.98±1.06	2.54	102.58±3.95	10.56	0.24	30.31±1.85
ESM-P1 40 mg tablets	99.93±0.47	1.13	103.68±4.33	12.67	0.18	23.81±1.31
ESM-P2 40 mg tablets	99.99±0.89	2.13	103.43±4.13	11.83	0.27	23.16±1.4
ESM-P3 40 mg capsules	99.98±0.90	2.14	102.10±2,27	6.05	N/A	N/A

The average mean of all weights, the acceptance value; AV (between 85% - 115%) and RSD% (Not less than 6.0%) in accordance with USP pharmacopeia (USP 34) were calculated and reported. In case of more than one individual unit is outside the range 85% - 115% and 20 dosage forms are tested, and no units are out of limit 75%-125%. The weight variation test for the innovator product Nexium® 20 mg showed that the AV for weight uniformity was less than 15 (2.47) for the 10 units with an average weight of 101.35±1.03%, Table 3. The AV for weight variation of generic products ESM-1, ESM-2, ESM-3 containing 20 mg drug was 4.27, 2.63 and 5.33.

Concerning the weight variation for the brand Nexium® 40 mg, the calculated AV for weight uniformity was 2.54 for the 10 units, and the average weight was 99.98±1.06%. The AV for weight variation of generic products ESM-1, ESM-2, ESM-3 containing 40 mg drug was 1.13, 2.13 and 2.14. The results showed that the acceptance value of weight variation for all ESM products containing 20 mg and 40 mg drug met the AV requirement, since it did not exceed L1 of 15%.

Weight variation test for LNZ was performed on innovator and generic products containing 15 and 30 mg of lansoprazole (Table 4). The percentage of weight of the innovator LNZ products with label claimed 15 and 30 mg was 100.35% and 97.46% and RSD of 1.07% and 1.32%, respectively. The percentage of weight of all generic products with labeled claimed of 15 mg ranged between 98.18 to 104.60% with RSD less than 6% (Table 4). While for that containing 30 mg, it ranged between 91.65% to 96.7% with RSD less than 6% (Table 4).

The AV for LNZ weight variation was also calculated. The Av for Lanzor® containing 15 and 30 mg was 4.1 and 4.16, respectively. The AV values for all generic products were less than 15 (L1) as shown in Table 3.

The results of weight variation of LNZ met the USP Pharmacopeia requirement that stated that the weight variation should lies between 85 to 115% with RSD not more than 6% and AV not exceeding 15% (L1).

3.3 Content Uniformity

The content uniformity of esomeprazole is applied on products with strengths 20 mg and 40mg and the results have been analyzed according to USP pharmacopeia [21], Table 3.

The content uniformity results for the innovator product Nexium® 20 mg indicated that all the individual unit measurements were within the range of 85-115% with an RSD of 4.73%, with AV of 11.50. The content uniformity of the generic products containing 20 mg (ESM-P1, ESM-P2 and ESM-P3) was calculated, the results showed that AV of drug content was 11.33, 8.04 and 14.90, indicating acceptable content uniformity. In addition, The RSD % values of generic products ESM-P1, ESM-P2 and ESM-P3 were 4.72, 4.31 and 6.11 respectively.

The content uniformity for Nexium®, ESM-P1, ESM-P2 and ESM-P3 containing 40 mg drug showed an acceptable content uniformity as the calculated AV was in the range less than 15 (10.56, 12.67, 11.83 and 6.05, respectively), which lies between 85 -115%, with RSD of 3.85, 4.18, 4.0 and 2.23, respectively.

The content uniformity of LNZ in different products with different strengths (15 and 30 mg) was determined and the data were analyzed according to USP Pharmacopeia [21] (Table 4). The content uniformity results for the innovator product for both strength 15 mg and 30 mg was 103% and 104% with RSD less than 6%, respectively and therefore, they met the USP requirements.

The content uniformity for the generic products with labeled claimed of 15 mg ranged between 97.65% to 101.6% with RSD less than 6%, which also met the USP requirement. The content uniformity for LNZ generic products with labeled claimed of 30 mg ranged between 99.17% to 104.2% with RSD of 30 mg compared to 104.37% for LNZ innovator product. The results complied with the USP requirement. The acceptance value was also calculated for all products (Table 4). Generally, the reported data showed that the content uniformity of lansoprazole from products containing 15 mg was acceptable and none of the products exceeded the limit of L1 (15%). In addition, the AV of the generic products were less than that of the innovator (Table 4). The reported data for LNZ products with label claim of 30 mg showed AV less than L1 (15%). The Av values for Products 1, 2 and 4 were less than that of the innovator. In case of product 3, the AV was

higher (14.93) compared to 14.17 for the innovator. The AV for product 3 was just below the boarder of L1.

3.4 *In vitro Dissolution*

3.4.1 *In vitro* release of ESM

The *in vitro* release profiles of ESM from the brand product (Nexium®) and generic products containing 20 mg drug are displayed in Fig. 2 For brand product, ESM showed very slow dissolution in the acid stage (1.4± 0.81), which is according to USP guidelines for ESM delayed release dosage forms (Not more than 10% of the labeled amount of ESM is dissolved in 120 minutes). Also, ESM showed slow release from ESM-1 (5.5%± 0.76), and ESM-3 (2.2% ± 0.47) generic products, while no drug release was recorded in the case of ESM-2 marketed product containing 20 mg drug.

Regarding ESM release in the buffer stage (pH 6.8), a high release rate ESM has been shown from a brand product containing 20 mg drug, in which 90.0%±3.43 was released at the end of the dissolution period, Fig. 2 The drug exhibited release rates of 95.5% ±4.76 and 105.2%±5.79 from generic products ESM-1and ESM-3, respectively. However, only 58.9% ±4.56 of the drug label claim was released from ESM-2 generic product within 30 min in this stage.

The *in vitro* drug release patterns of the drug from the brand and generic products containing 40 mg ESM are displayed in Fig. 3 The drug exhibited also very slow dissolution rate from the brand product in the acid stage (4.0 ± 1.0%) as well as from ESM-1 (6.1±0.70), and ESM-2 (1.4 ± 0.63) and ESM-3 (1.7 ± 0.36) generic products. Concerning the release profiles of ESM marketed products containing 40 mg drug in the buffer stage (pH 6.8), the brand product showed a high drug release (94.45%±5.08) at the end of the dissolution period, Fig. 3 Also, high release rates were recorded from generic products ESM-1, ESM-2 and ESM-3, in which 99.15%±3.44, 108.0%±5.19 and 102.05%±2.78 release rates were observed, respectively.

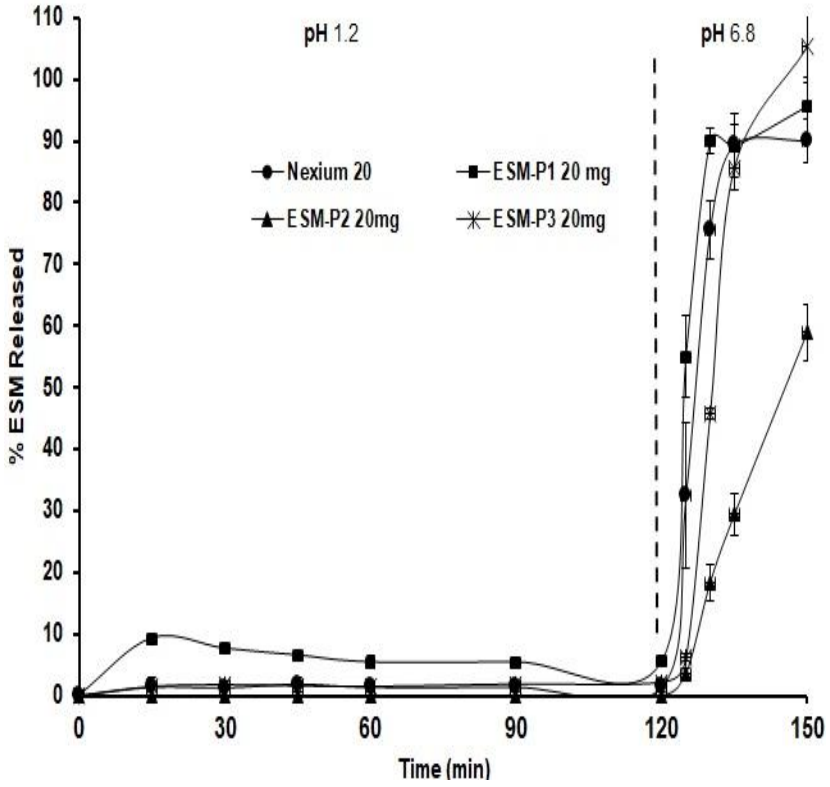

Fig. 2. *In vitro* release profiles of ESM from enteric coated marketed products containing 20 mg drug

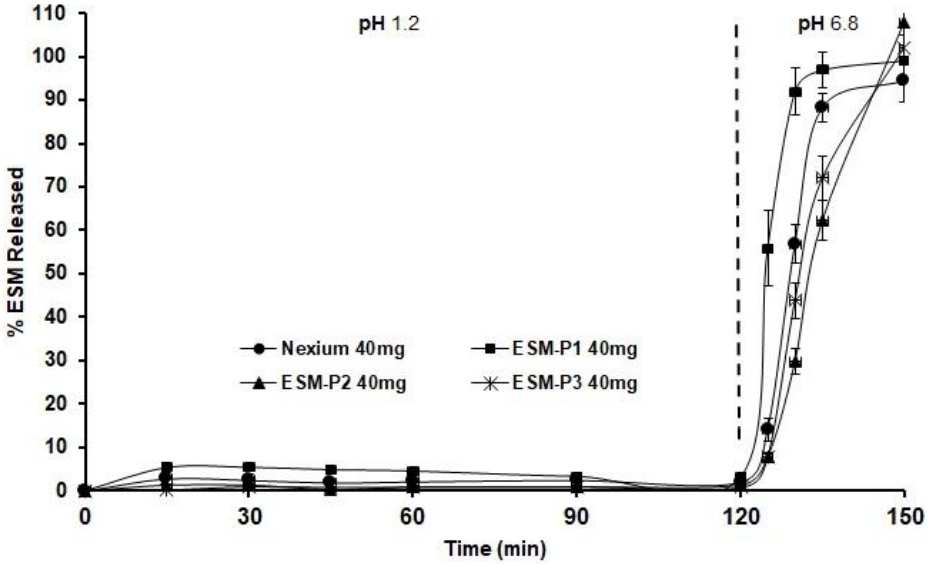

Fig. 3. *In vitro* release profiles of ESM from enteric coated marketed products containing 40 mg drug

Table 4. Properties of marketed lansoprazole capsules

Product	Weight uniformity		Content uniformity	
	Weight (%)	AV	LNZ content (%)	AV
Lanzor® (15 mg)	100.35 ± 1.71	4.10	103.45 ± 5.03	14.02
LNZ-P1 (15 mg)	104.60 ± 1.48	6.65	96.65 ± 4.71	12.16
LNZ-P2 (15 mg)	98.18 ± 0.81	2.26	101.60 ± 4.42	10.68
Lanzor® (30 mg)	97.46 ± 1.30	4.16	104.37 ± 4.71	14.17
LNZ-P1 (30 mg)	96.87 ± 1.82	6.00	101.90 ± 5.32	13.67
LNZ-P2 (30 mg)	96.54 ± 1.29	5.05	99.29 ± 5.02	12.04
LNZ-P3 (30 mg	91.65 ± 2.36	12.52	104. 20 ± 4.75	14.93
LNZ-P4 (30 mg)	94.96 ± 0.97	5.87	99.17 ± 5.82	13.97

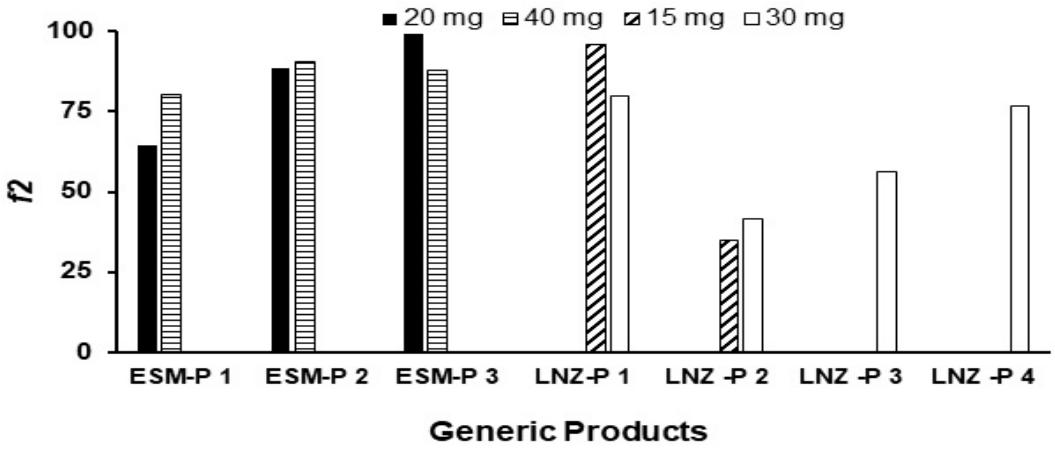

Fig. 4. Similarity factor (f2) of ESM and LNZ enteric coated marketed products

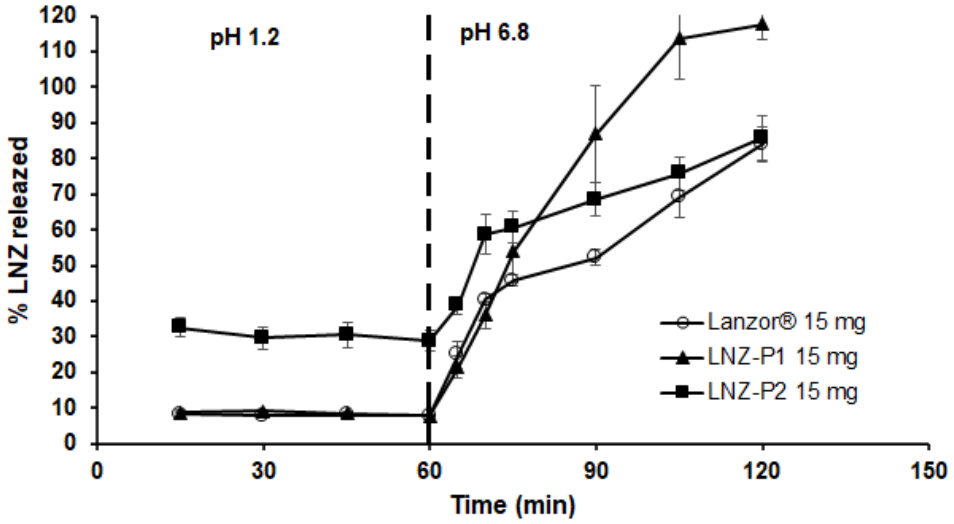

Fig. 5. *In vitro* release profiles of LNZ from enteric coated marketed products containing 15 mg drug

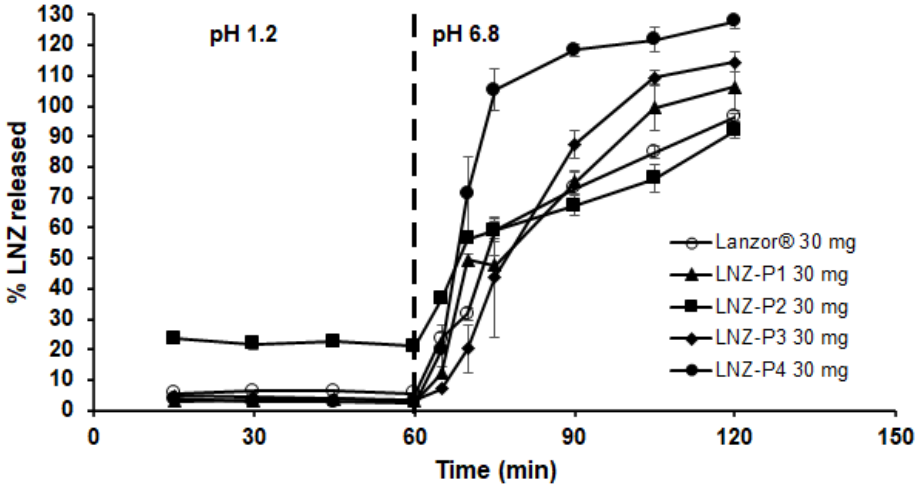

Fig. 6. *In vitro* release profiles of LNZ from enteric coated marketed products containing 30 mg drug

Fig. 4 shows the values of the similarity factor (*f2*) of ESM and LNZ generic products. It is evident from the results that (*f2*) of ESM products containing 20 mg drug was between 64. 27 and 98.95 and for generic products containing 40 mg ESM, it was between 80.27 and 87.75, demonstrating dissolution profiles similarity in of all ESM enteric coated products according to FDA requirements.

3.4.2 *In vitro* release of LNZ

Fig. 5 showed the dissolution profile for LNZ innovator and generic products containing 15 mg of the drug. The innovator product release 7.85± 0.27% of LNZ after 60 minutes in the acid stage, the release of the drug increase after shifting the pH to 6.8 and it reach 83.97 ± 4.86% at the end of the dissolution test. Product 1 exhibited a percentage dissolution of 7.75±0.26%, which complied with the USP guidelines. After that, a complete dissolution was observed in the buffer stage. Product 2 showed differ profile, more than 10% of the labeled amount of LNZ was released in the acid stage (32.43 ± 2.69%) and about 85.72 ± 6.05% of LNZ was released in the buffer stage. This may indicate inappropriate enteric coating of product 2.

Moreover, those products exhibit the same manner of dissolution from capsules loaded with 30 mg LNZ enteric coated pellets, Fig. 6. The innovator LNZ product release 5.5±0.37% in the acid stage which then reach 96.24±1.48% at the end of the dissolution run in the buffer stage. Generally, it was observed that all generic products except product 2 had a lower dissolution rate in acid stage than the innovator (2.55 to 3.65%), product 2 exhibited higher release rate in acid stage (22.85±2.83%) compared to the innovator product. In addition, a complete dissolution (100%) in the buffer stage was observed for all generic products. The release of LNZ from products 3 and 4 showed higher release rate in the buffer stage compared to the innovator. It was observed that a complete release of LNZ from product 3 occurred within 45 min from starting the dissolution in the buffer stage, while it needs only 15 minutes for product 4 to show complete dissolution.

The dissolution test of LNZ capsules, containing enteric coated pellets of the drug, showed that the innovator and all generic products, except product 2, complies with the USP guidelines and release less than 10% of LNZ in the acid stage.

Concerning LNZ generic products containing 15 mg drug, LNZ-P1 showed a similarity factor of 95.52, while LNZ-P2 showed a similarity factor of 34.84, which is non-complying generic with FDA specification, Fig. 4. In the case of generic products containing 30 mg LNZ, LNZ-P1, LNZ-P3 and LNZ-P4 showed *f2* values 56.13 and 79.74, while LNZ-P2 containing 40 mg drug showed a non-complying similarity factor (34.84), (Fig. 4).

ESM and LNZ tablets and capsules containing enteric-coated pellets are marketed as generic drugs under different brand names. Hence, to know the difference in efficacy between a brand and generic products, the pharmaceutical quality of generic drugs should be tested based on the innovator as a reference. Generic pharmaceutical products should be formulated to maintain a similar effect as an innovator drug or even better.

ESM and LNZ are extremely unstable in their aqueous solution, at low pH values. Therefore, these APIs are formulated as an enteric coat dosage form [23]. Any abnormality in the enteric coat will lead to the release of the drug in the acidic medium, which results in the destruction of the released amount of drug. The malfunction in the enteric coat could be due to the type and concentration of coating material, the type of solvent and/or the curing time [24].

4. CONCLUSION

The presented study showed that ESM and LNZ brand generic products are complying with the compendia guidelines in terms of the uniformity of dosage unit weight and drug content as well. In addition, ESM products showed minimum release in the acidic buffer, in which less than 10% of the ESM label claim was released from all brand and generic enteric coated oral solid dosage forms containing both 20 mg and 40 mg drug. In contrast, LNZ generic product 2 containing 15 mg and 30 mg showed high release in the acid stage, indicating that this generic product failed to pass USP guidelines for delayed release solid dosage forms and didn't fulfil FDA requirements for enteric coated products. This could be attributed to inappropriate enteric tablet coating that caused drug release in the acid stage, which designates non-effective product. Thus, firmer control of the marketed products by local regulatory authorities should be applied concerning such issues.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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