



## STUDYING THE RELEASE RATIO OF SOME PPI'S IN DIFFERENT BIORELEVANT DISSOLUTION MEDIA

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## ABSTRACT

Lansoprazole, Omeprazole, and Esomeprazole are Benzimidazole derivatives; they belong to proton pump inhibitors group (PPIs). PPIs are used for treatment of peptic ulcer, GERD, and other gastrointestinal disorders. Dissolution test in Compendial and different biorelevant media had been applied to some Syrian generic products. Dissolution profiles of these products had been studied, and a comparison between dissolution profiles was made to predict the in-vivo behavior. It was found that some products have reasonable behavior and an acceptable dissolution profiles in biorelevant media, while other products do not comply with the compendial dissolution test.

**Keywords:** LNS, OMP, ESOMP, Biorelevant dissolution media, Dissolution profile, Dissolution test.

## INTRODUCTION

Proton Pump Inhibitors (PPIs) are substituted Benzimidazole compounds and prototype anti-secretory agent. They act by interaction with H<sup>+</sup>/K<sup>+</sup> ATPase in the secretory membranes of the parietal cells. They are widely used for the prophylaxis and treatment of gastro-duodenal ulcers, for the treatment of symptomatic gastro-esophageal reflux, and are very effective in the treatment of Zollinger–Ellison syndrome. PPIs include: Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole and Rabeprazole. They are supplied in different pharmaceutical dosage forms.<sup>1</sup> In Syria they are supplied as enteric coated pellets filled in capsules. These compounds are found in many generic names in Syrian market.

Lansoprazole (LNS) is: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] Benzimidazole. Its empirical formula is C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S with a molecular weight of 369.37; **Fig. (1)** Shows its structure:<sup>2</sup>

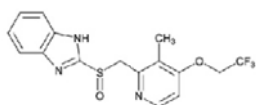


Fig. 1: Lansoprazole

Omeprazole (OMP) is: 5-methoxy-2-[[[4-methoxy-3, 5-dimethyl-2-pyridinyl] methyl] sulfinyl]-1Hbenzimidazole. Its empirical formula is C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S, with a molecular weight of 345.42; **Fig. (2)** shows its structure:<sup>3</sup>

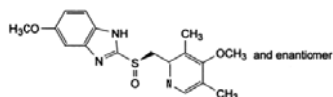


Fig. 2: Omeprazole

Esomeprazole (ESOMP) is bis [(S)-5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]sulfinyl]-1 H-benzimidazole] magnesium trihydrate. Esomeprazole is the S-enantiomer of omeprazole. Its empirical formula is (C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>S) 2Mg.3H<sub>2</sub>O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis, **Fig. (3)** Shows its structure:<sup>4</sup>

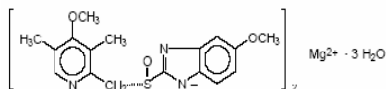


Fig. 3: Esomeprazole

Previous researches have studied dissolution tests only for Omeprazole from different Spanish,<sup>5</sup> and Egyptian generic products.<sup>6</sup> Other researchers have studied modified dissolution tests for Lansoprazole.<sup>7</sup> All these studies were done only in compendial media and they were not tested in biorelevant media. No research was done on Syrian generic products neither in compendial nor in biorelevant media.

In addition, Some of these studies employed dissolution media described in the pharmacopeias (so-called "compendial approach"),<sup>8,9,10,11</sup> while others added synthetic surfactants to compendial media.<sup>12,13,14</sup> As these conditions do not comprehensively represent the gastrointestinal (GI) tract environment, it can be inferred that the results can only be interpreted on an empirical basis. As a part of a general drive to develop predictive *in vitro* models, biorelevant media were proposed and have evolved over the last decade as a tool for *in vitro* biorelevant dissolution tests.<sup>15,16,17</sup> Recently, the media have been updated to more nearly represent both the pre- and postprandial states in the proximal gut.<sup>18,19,20,21</sup>

The aim of this study is to develop a rapid and simple analytical method for quantification of some proton pump inhibitors (PPIs) Using HPLC,<sup>22</sup> and to study *in-vitro* dissolution test for some Syrian generic products in order to compare the dissolution profile in compendial and biorelevant media, which enables to predict the *in-vivo* behavior of these products. In this study, it was found that some products comply with compendial dissolution test while other products do not, because of their defects during industrial preparation. In addition, the behavior in biorelevant media had been studied and a comparison between dissolution profiles had been made.

## EXPERIMENTAL

## Materials

Lansoprazole RS (lot: 078K1098), Omeprazole RS (lot: 069K1700), Esomeprazole (lot: 127K47123), and Sodium taurocholate (Sigma & Aldrich), Sodium chloride, sodium hydroxide pellets, and potassium phosphate monobasic (Merck, Germany). Hydrochloric acid (37%, fuming), ethanol, methanol, ortho-phosphoric acid 85% (SCP England). Lethcine and Sodium borate (Himedia, India).

## Equipments

Beakers of different volumes, volumetric flasks of different volumes, Erlenmeyers, graduated cylinders, filtration funnel, filtration paper, nylon filter 0.45 μ (Chromtech), volumetric pipette, micropipette (Dragonmed), sensitive balance (Sartorius), Ultra sonic bath (Grant XB2), electric stirrer and heater, pH paper (Merck, German), pH

meter (Thermo – Orion), Dissolution apparatus (Pharma Test PTW II, Germany). HPLC system consisted of:

- High Performance Liquid Chromatography (HPLC - Shimadzu Prominence, Japan)
- UV detector (PDA)
- Pump (prominence LD 10)
- CBM (Shimadzu- LD10)
- Column: RP-18 (250mm×4.6 mm, particle size 5 µm).
- Mobile phase: water-acetonitrile-TEA (60:40:0.5, v/v) (pH 7.0).
- Flow rate: 1.0 ml/min, 20 µl loop injector.
- Column temperature: ambient temperature.
- Wavelength: 285, 280, 303 nm (PDA detector) for LNS, OMP, ESOMP respectively.

## Methods

### Reference samples

Reference samples were collected for each compound of PPI products:

Lansoprazole (Prevacid, TAP Pharmaceuticals): 2 samples.

- Omeprazole (Losec, Astra Zenica): 2 samples.
- Esomeprazole (Nexium, Astra Zenica): 2 samples.

### Samples

Samples of LNS, OMP, and ESOMP were collected from 3 different batches, which are available in Syrian market, samples' numbers which have been collected are as follows:

- Lansoprazole: 21 samples.
- Omeprazole: 27 samples.
- Esomeprazole: 30 samples.

### Sample preparation

- **Acid stage:** pellets were collected from each vessel after 1 hour for LNS, and 2 hours for OMP and ESOMP. Samples were analyzed by HPLC in order to calculate the residual amount of LNS, OMP, or ESOMP.
- **Buffer stage:** samples were collected from each vessel at different periods as mentioned in the compendial test. The 5 ml sample was filtered with nylon filter 0.45 µ, the filtrate was kept in the refrigerator protected from light till all the samples were collected, then they were injected in HPLC sample by sample in order to calculate the released amount of the drug.

### Compendial dissolution protocol

The compendial dissolution test for LNS and OMP is fully described in the United States Pharmacopoeia 30 (USP 30), and the dissolution test of ESOMP capsules is described in the FDA web site (as mentioned in the references). **Table (1):** summarize the protocols of dissolution test for LNS, OMP and ESOMP.

### Preparation of biorelevant media

Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid. The use of biorelevant media can have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation. In addition, biorelevant dissolution testing could be used to assess bioequivalence of post-approval formulation changes in certain kinds of drugs.<sup>26,27,28,29,30</sup> The formulation and preparation instructions for the biorelevant media developed by Dr. Dressman's group are fully detailed in the **Table (2)**.

**Table 1: Dissolution protocols for pharmaceutical compendial dissolution test of Lansoprazole, Omeprazole and Esomeprazole.**

Drug name	Dosage form	USP apparatus	Speed (RPMs)	Medium	Volume	Recommended sampling times (minutes)
Lansoprazole <sup>23</sup>	Capsule (Delayed Release)	II (Paddle)	75	Acid stage: 0.1 N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8	Acid stage: 500 Buffer stage: 900	Acid stage: 60 Buffer stage: 15, 30, 45 and 60
Omeprazole <sup>24</sup>	Capsule (Delayed Release)	II (Paddle)	100	Acid stage: 0.1 N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8	Acid stage: 300; Buffer stage: 1000	Acid stage: 120 Buffer stage: 10, 20, and 30
Esomeprazole <sup>25</sup>	Capsule (Delayed Release)	II (Paddle)	100	Acid stage: 0.1 N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8	Acid stage: 300; Buffer stage: 1000	Acid stage: 120 Buffer stage: 10, 20, 30, 45 and 60

**Table 2: Composition of biorelevant media developed by Dr. Dressman's group**

Composition	FaSSGF	FeSSGF Early	FeSSGF Middle	FeSSGF Late	FaSSIF	FeSSIF
Sodium taurocholate	80 µm	—	—	—	3 mM	15 mM
Lecithin	20 µm	—	—	—	0.75 mM	3.75 mM
Pepsin	0.1 mg/ml	—	—	—	—	—
NaH <sub>2</sub> PO <sub>4</sub> .H <sub>2</sub> O	1.977 g	—	—	—	1.977 g	—
NaOH pellets	—	—	—	—	0.174 g	4.04 g
Sodium chloride	34.2 mM	148(mM)	237.02(mM)	122.6(mM)	3.093 g	11.874 g
Acetic acid	—	—	17.12(mM)	—	—	8.65 g
Sodium acetate	—	—	29.75(mM)	—	—	—
Ortho-phosphoric acid	—	—	—	5.5(mM)	—	—
Sodium dihydrogen phosphate	—	—	—	32(mM)	—	—
Milk/buffer	—	1:0	1:1	1:3	—	—
Hydrochloric acid/Sodium hydroxide qs.	pH= 1.6	pH= 6.4	pH= 5	pH= 3	pH=6.5	pH=5

### FaSSGF

The stomach is the port of entry into the GI tract for orally administered drug products. Under fasting conditions, it is well known that the pH in a healthy human stomach is acidic, ranging

between 1 and 3.<sup>31,32</sup> For poorly soluble weak bases, the pH conditions for dissolution are the most favorable in a fasted, healthy stomach. Compared with simple aqueous buffers like Simulated

Gastric Fluid without pepsin (SGFsp), gastric fluids have a low surface tension in addition to a low pH.<sup>33</sup> A medium representing the fasted conditions in a human stomach, so-called Fasted-State Simulated Gastric Fluid (FaSSGF), was proposed by Vertzoni et al. in 2005.<sup>34</sup> The medium was designed to embrace the important aspects of human basal gastric juice plus a glass of water normally given with a dosage form. With respect to the applications of FaSSGF, the medium is able to predict the solubility of poorly soluble drugs in the fasted stomach rather well.<sup>34, 35</sup>

#### FaSSGF

Milk (full-fat [3.5%], long-life, UHT-treated) has been considered as a good starting point for medium design because its ratio of carbohydrate/protein/fat is similar to that observed in the stomach after administration of meals.<sup>31</sup>

#### FaSSIF<sup>36</sup>

##### Preparation of blank FaSSIF

Dissolve 1.74 g of NaOH (pellets), 19.77 g of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ , and 30.93 g of NaCl in 5 liters of purified water. Adjust the pH to exactly 6.5 using 1 N NaOH or 1 N HCl.

##### Preparation of FaSSIF

Dissolve 3.3 g of sodium taurocholate in 500 ml blank FaSSIF. Add 11.8 ml of a solution containing 100 mg/ml lecithin in methylene chloride, forming an emulsion. The methylene chloride is eliminated under vacuum at about 40°C. Draw a vacuum for fifteen minutes at 250 mbar, followed by 15 minutes at 100 mbar. This results in a clear, micellar solution, having no perceptible odor of methylene chloride. After cooling to room temperature, adjust the volume to 2 L with blank FaSSIF. For dissolution tests a volume of 500 ml is recommended.

#### FeSSIF<sup>36</sup>

##### Preparation of blank FeSSIF

Dissolve 20.2 g of NaOH (pellets), 43.25 g of glacial acetic acid, and 59.37 g of NaCl in 5 litres of purified water. Adjust the pH to exactly 5.0 using 1 N NaOH or 1 N HCl.

##### Preparation of FeSSIF

Dissolve 16.5 g of sodium taurocholate in 500 ml of blank FeSSIF. Add 59.08 ml of a solution containing 100 mg/ml lecithin in

methylene chloride, forming an emulsion. The methylene chloride is eliminated under vacuum at about 40°C. Draw a vacuum for fifteen minutes at 250 mbar, followed by 15 minutes at 100 mbar. This results in a clear to slightly hazy, micellar solution having no perceptible odor of methylene chloride. After cooling to room temperature, adjust the volume to 2 L with blank FeSSIF. The recommended volume for simulating conditions in the upper small intestine after a meal is one liter.

## RESULTS AND DISCUSSION

### Compendial dissolution test

After applying dissolution test for LNS (21 samples), OMP (27 samples) and ESOMP (30 samples) - each samples was injected 3 times in HPLC system - the dissolution profile between the drug's percentage released and time was made for different generic products. Charts (1), (2), (3) show the comparison between dissolution profiles for each one of PPIs for different generic products used in this study:

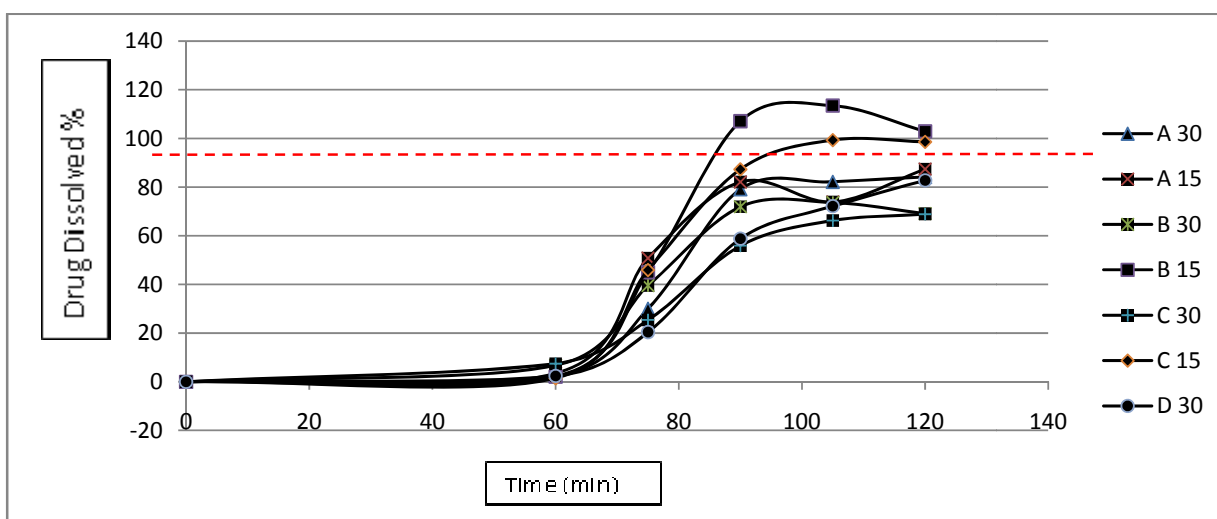
In the acid stage, the acceptable criterion for all products is not more than 10 %. While the acceptable criteria in buffer stage is not less than 80% for LNS and 75 % for both OMP and ESOMP;<sup>23,24,25</sup> hence as shown in the previous charts, there are some generic products which do not comply with the compendial dissolution test. Looking for the reasons for this, it was found that these unacceptable products were in the form of crushed pellets filled in capsules Fig. (4), Fig. (5), Fig. (6). so when these pellets and powders contact with the gastric fluids (HCl 0.1 M) they degraded and turned into degradation products. Later, when continuing the test with the intestinal fluids (buffer stage) the amount released is low because the initial amounts of the active material degraded in the acid stage. But for ESOMP, some of these generic products were in form of tablets contain compressed pellets Fig. (7) and Fig. (8), which delayed the diffusion of the liquids into the initial pellet and in turns decrease the dissolution ratio.

### Dissolution test in biorelevant media

#### FaSSGF and FeSSGF

The generic products of LNS, OMP, and ESOMP which showed the best dissolution rate in compendial test were chosen to evaluate the dissolution profile in FaSSGF and FeSSGF (full fat, UHT treated milk).

**Chart (4), Chart (5), and Chart (6)** explain the dissolution profiles for Lansoprazole, Omeprazole, and Esomeprazole respectively.



**Chart 1: Dissolution profile of Lansoprazole in acid stage and buffer stage. All tested products are acceptable except C30 & B30. The microscopic examination showed that these capsules contained crushed pellets and powders which explain unacceptable dissolution rates. (A, B, C, and D are generic products which were used in this study, 15 and 30 refers to the dosage)**

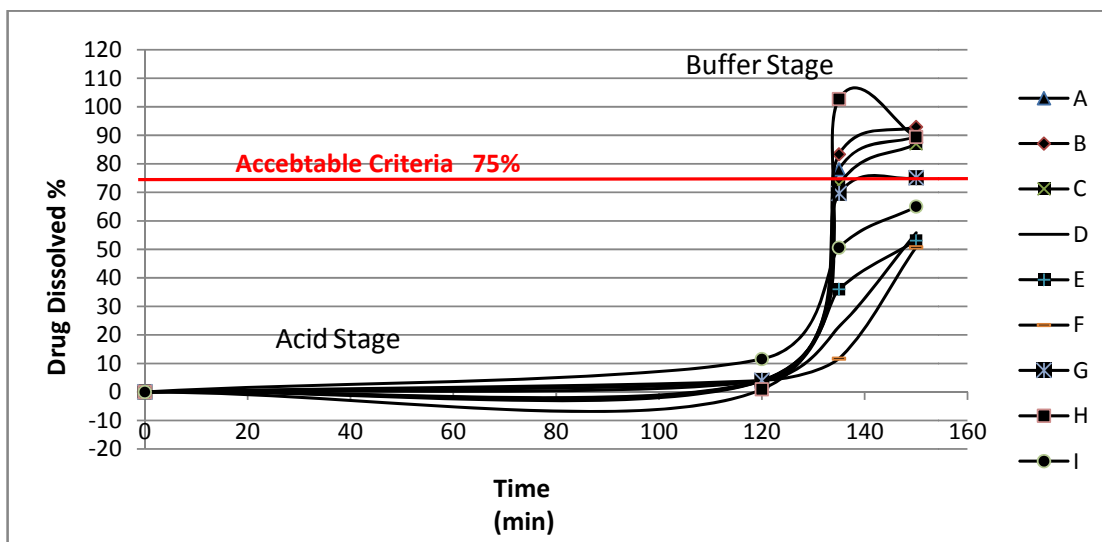


Chart 2: Dissolution profile of Omeprazole in acid stage and buffer stage. All tested products are acceptable except D, E, F and I. The microscopic examination showed that these capsules contained crushed pellets and powders which explain unacceptable dissolution rate. (A, B, C .... are generic products which were this study)

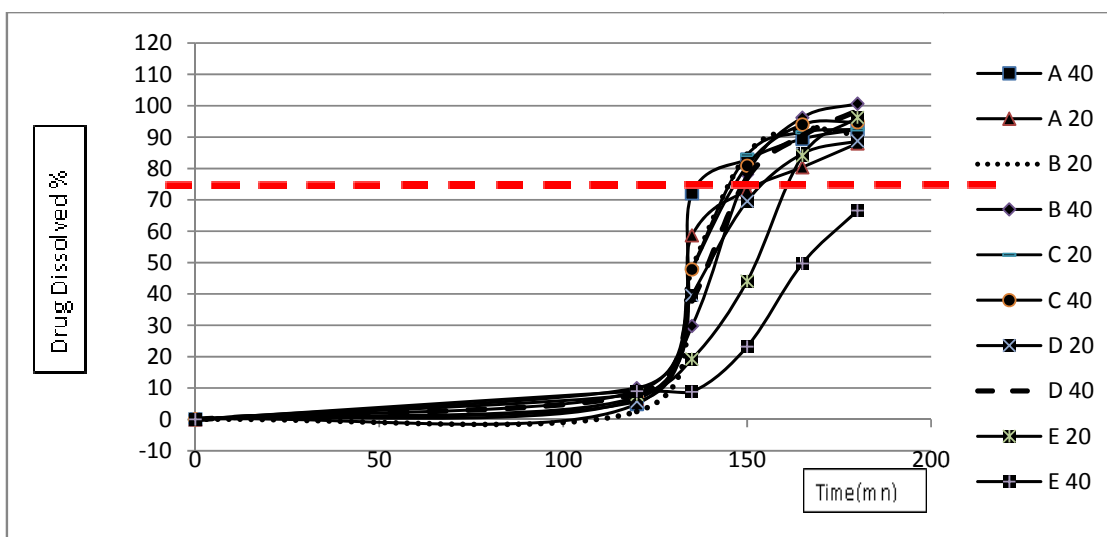


Chart 3: Dissolution profile of Esomeprazole in acid stage and buffer stage. All tested products are acceptable except E40. The optical examination showed that this product is in form of tablet contains compressed pellets. (A, B, C, D and E are generic products which were used in this study, 20 and 40 refers to the dosage)

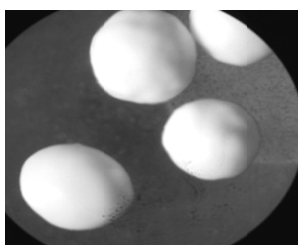


Fig. 4: the form of normal pellets



Fig. 5: crushed pellets



Fig. 6: other crushed pellets



Fig. 7: Cualompressed pellets



Fig. 8: Esomeprazole Tabs. (Contain compressed pellets)

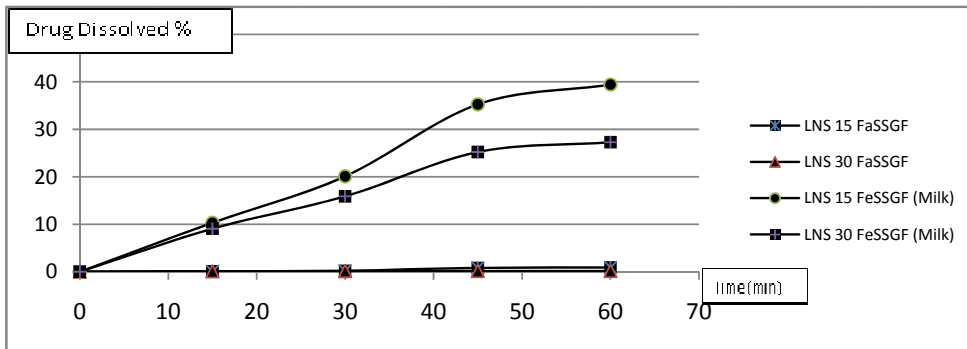


Chart 4: Dissolution profile of Lansoprazole in biorelevant media (FaSSGF and FeSSGF), dissolution rate vs time.

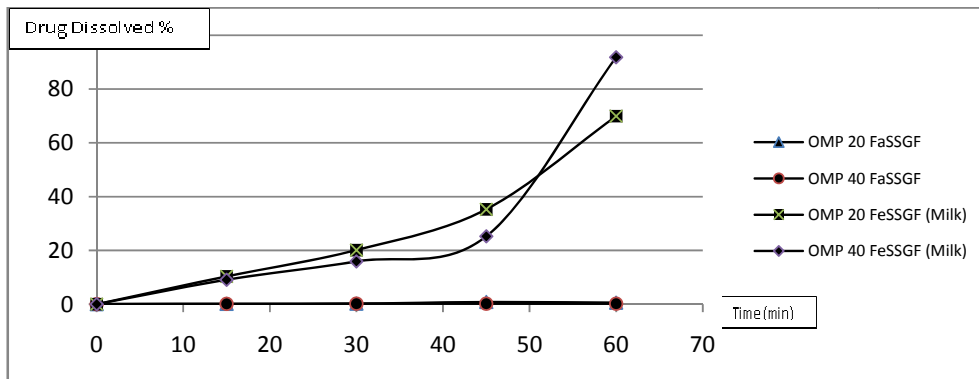


Chart 5: Dissolution profile of Omeprazole in biorelevant media (FaSSGF and FeSSGF), dissolution rate vs time.

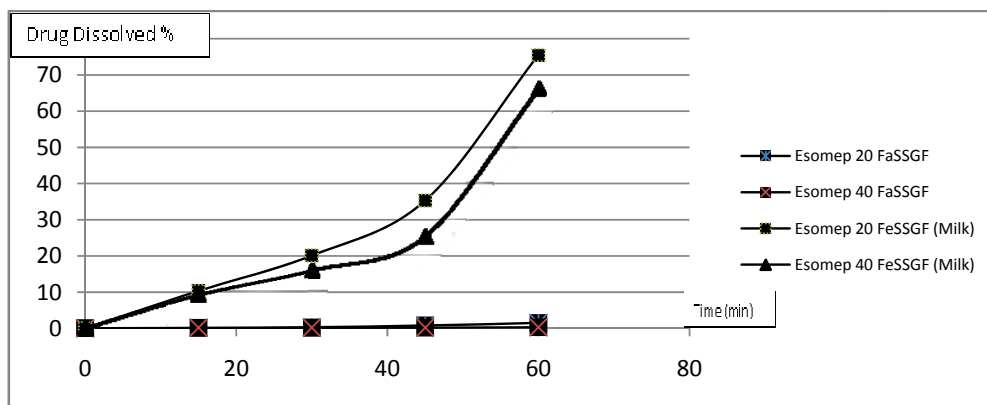
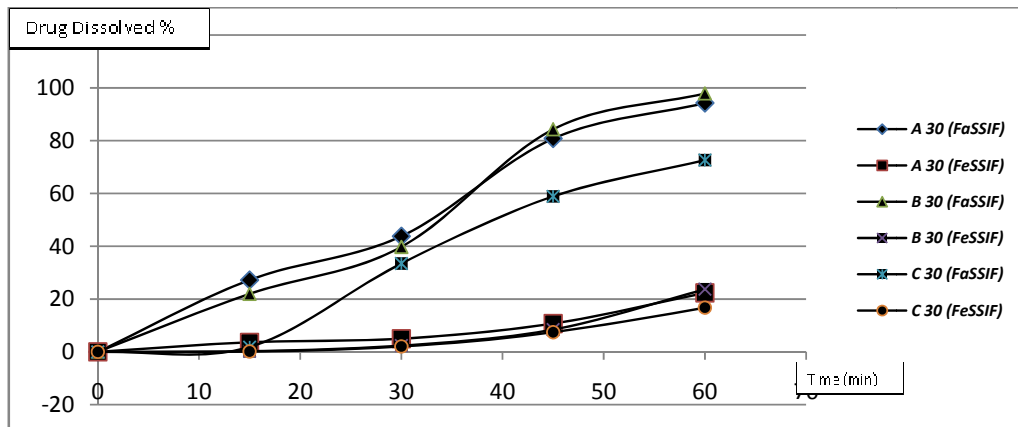


Chart 6: Dissolution profile of Esomeprazole in biorelevant media (FaSSGF and FeSSGF), dissolution rate vs time.

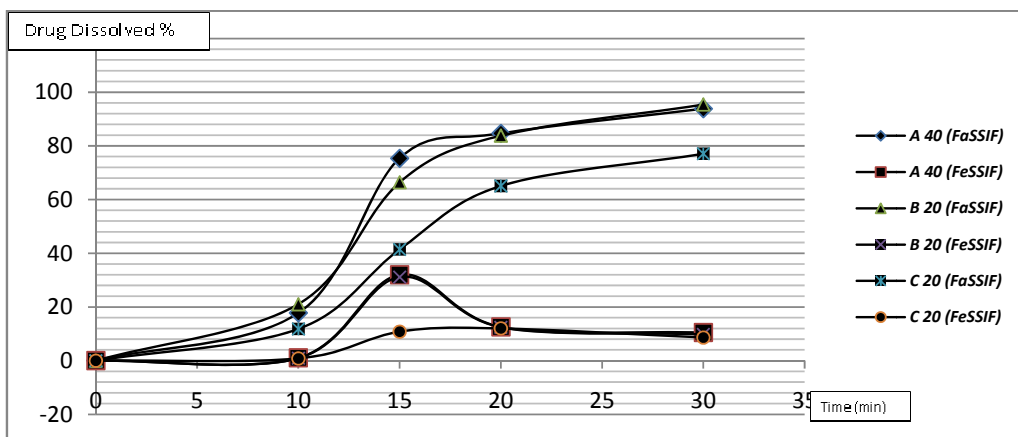
As noticed in **chart (4)**, Lansoprazole was not released in the FaSSGF medium, but it was released in the FeSSGF medium. These results can be explained by the influence of food on the pH of stomach's content. The FeSSGF (full fat, UHT treated milk) raised the pH to about 4-4.5. This increase in the pH value allowed the dissolution of some pellets of Lansoprazole to reach about 40 % of the labeled dosage. The same thing can explain the charts of Omeprazole and Esomeprazole, **chart (5)** and **chart (6)** respectively.

**FaSSIF and FeSSIF**

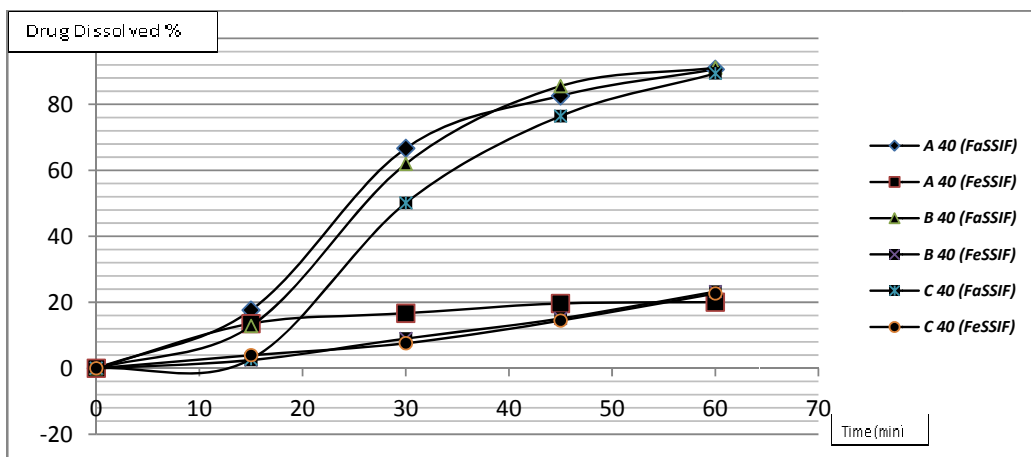
The generic products of LNS, OMP, and ESOMP which showed the best dissolution rate in compendial test were chosen to evaluate the dissolution profile in FaSSIF and FeSSIF. **Charts (7), (8), and (9)** explain the dissolution profiles in FaSSIF and FeSSIF for Lansoprazole, Omeprazole, and Esomeprazole respectively.



**Chart 7: Dissolution profile of Lansoprazole in biorelevant media (FaSSIF & FeSSIF), dissolution rate vs time. (A, B, and C are generic products which were used in this study, 15 and 30 refers to the dosage)**



**Chart 8: Dissolution profile comparison of cumulative Omeprazole dissolution vs time profiles using biorelevant methods in the FaSSIF & FeSSIF, (A, B, and C are generic products which were used in this study, 20 and 40 refers to the dosage)**



**Chart 9: Dissolution profile comparison of cumulative Esomeprazole dissolution vs time profiles using biorelevant methods in the FaSSIF & FeSSIF. (A, B, and C are generic products which were used in this study, 40 refers to the dosage)**

As noticed in **chart (7)**, Lansoprazole release in the FaSSiF medium, because the physical and chemical properties of this is close to the properties of compendial medium, except for the little amount of bile salts in the FaSSiF medium which has unremarkable effect on the dissolution profile.

On the other hand, the FeSSiF medium causes a decrease in the dissolution rate of Lansoprazole. This can be explained by the influence of the decreased pH value of this medium to about 5, and the degradable effect of bile salts on dissolved Lansoprazole.

Dissolution profile of Omeprazole **Chart (8)** and Esomeprazole **chart (9)** can be explained by the same way.

## CONCLUSION

Compendial dissolution test and biorelevant media's dissolution testing were carried out for 78 generic Syrian products of PPI group. The compendial test showed that some generic products were unacceptable because of industrial defects. Biorelevant tests showed that the presence of food in the stomach and in the intestinal tract affected the dissolution rate of the PPI products that were studied. The influence of food can be explained by the change of the pH values.

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