Development of Rapid and Simple Analytical Method for Some Proton Pump Inhibitors (PPIs) Using HPLC

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ABSTRACT

A simple, selective and rapid reversed phase High Performance Liquid Chromatographic (HPLC) method for the analysis of Lansoprazole (LNS), Omeprazole (OMP) and Esomeprazole (ESOMP) has been developed and validated. HPLC-UV detector equipped with RP-C18 column, mobile phase (Water: Acetonitrile: TEA, 60: 40: 0.5 V/V/V pH=7 adjusted with phosphoric acid) and a flow rate of 1ml/min were used for the quantification for each compound. The analytical method parameter was the same except for the wave lengths; they were 285, 280, 303 nm; and the retention times were 7 min, 4.5 min and 5 min for LNS, OMP and ESOMP, respectively. Method validation was performed for each compound, and all the parameters were acceptable. Therefore, the method could be used as a simple, rapid and efficient option for the analysis of LNS, OMP, and ESOMP during routine tests in pharmaceutical industries because all the parameters (mobile phase, column, flow rate) of the method are the same except for the wave length which should be changed for each compound, and the change of the wave length does not need more than 2 minutes.

Keywords: Lansoprazole, Omeprazole, Esomeprazole, HPLC, Validation.

INTRODUCTION

Proton Pump Inhibitors (PPIs) are Benzimidazole derivative[1,8] ; they include Lansoprazole (LNS), Omeprazole (OMP), Esomeprazole (ESOMP), Rabeprazole, and Pantoprazole. PPIs have shown great efficacy in the treatment of stomach hyperacidity compared with H_2 antagonists. PPIs are used to treat gastric hyperacidity such as GERD, gastric ulcer, gastric disorders associated with usage of NSAIDs. PPIs have low side effects and drug interactions, and they have similar activity.[2,9]

Three compounds of PPIs have been studied in this article:

1. Lansoprazole (LNS) is chemically 2-({3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl} sulfinyl benzimidazole. It has an empirical formula of $C_{16}H_{14}F_3N_3O_2S$, and a molecular weight of 369.36, **Figure (1)** shows its formula:[3,5]

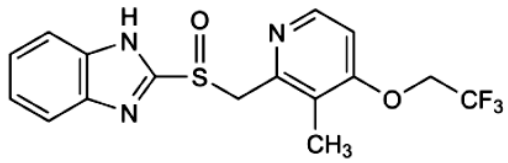

Figure (1): Lansoprazole

2. Omepraozle (OMP) is chemically 5-methoxy-2-[(RS)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-1H-benzimidazole, It has an empirical formula of $C_{17}H_{19}N_3O_3S$, and a molecular

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weight of 345.42, **Figure (2)** shows its formula:[3,4]

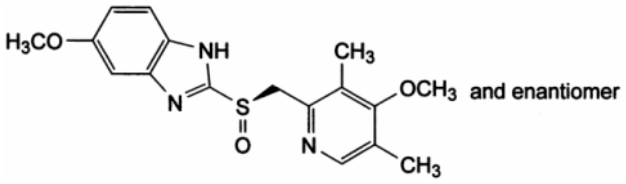

Figure (2): Omeprazole

3. Esomeprazole (ESOMP) is the S enantiomer of Omeprazole, it's available as Mg salt, it has an empirical formula of $(C_{17}H_{18}N_3O_3S)_2Mg.3H_2O$ and a molecular

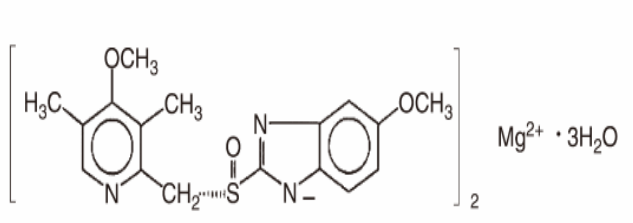

Figure (3): Omeprazole

These three compounds LNS, OMP, and ESOMP are supplied in Syrian market as enteric coated pellets filled in capsules. Previous research has mentioned many analytical methods for determination and quantification of LNS, OMP, and ESOMP. These methods used different techniques such as UV spectroscopy[12,13,16], HPLC connected to UV detector[7,10,11], HPLC/MS[14,15], and Capillary Zone Electrophoresis[6], and they were used to analyze each compound alone, in different parameter. Furthermore, they were uneconomic and could not be used in routine tests.

The aim of this research was to use an RP-HPLC connected to UV detector with fixed parameters to analyze three compounds of PPIs (LNS, OMP, ESOMP) in order to use an easy, simple, and specific analytical method which enables us to perform an accurate and sensitive analysis for routine tests. In this research a single and isocratic mobile phase, RP-C_{18} column and a flow rate = 1 ml/min have been used for the three compounds, but the wave length was changed for each compound. Analytical method validation was done for each compound, and the results showed acceptable values.

EXPERIMENTAL

A. Chemical and Reagents

Lansoprazole RS (Sigma & Aldrich, Germany, Lot №: 078K1098), Omeprazole RS (Sigma & Aldrich, Germany, Lot №: 069K1700), and Esomeprazole RS (Sigma & Aldrich, Germany, Lot №: 127K47123). HPLC grade solvents (water, methanol, acetonitrile, and triethylamine) were purchased from Merck, Germany. Sodium hydroxide, hydrochloric acid, and orthophosphoric acid were purchased from SCP England. HPLC grade ethanol was purchased from Scharlau, Spain.

B. Equipments

Different volumes of beakers, volumetric flasks, graduated cylinders, and Erlenmeyers were used. Filtration funnel, filtration paper, HPLC nylon filter 0.45µ (Chromtech), micropipette (Dragonmed), sensitive balance (Sartorius), ultrasonic bath (Grant XB2), magnetic stirrer, electric heater, pH-meter (Thermo – Orion), and pH paper (Merck, Germany) were also used.

C. Method

A High Performance Liquid Chromatography system with the following specifications:

- 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 adjusted with phosphoric acid).
- Flow rate: 1.0 ml/min, 20 µl loop injector.
- Column temperature: ambient temperature.
- Wavelength: 285, 280, and 303 nm (PDA detector) for LNS, OMP, and ESOMP respectively.

D. Standards Preparation

- LNS standard solution: to a 50 ml volumetric flask, 10 mg of LNS RS accurately weighted was transferred and dissolved in 1 ml of methanol, the volume was completed with phosphate buffer (pH=6.8) to the

mark. The solution was used to prepare five standards with concentrations (8, 16, 24, 32, and 44 µg/ml).

- OMP standard solution: to a 50 ml volumetric flask, 10 mg of OMP RS accurately weighted was transferred and dissolved in 10 ml of ethanol; the volume was completed with sodium borate (0.01 M) to the mark. The solution was used to prepare five standards with concentrations (16, 24, 32, 40, and 48 µg/ml).
- ESOMP standard solution: to a 50 ml volumetric flask, 10 mg of ESOMP RS accurately weighted was transferred and dissolved in 10 ml of ethanol; the volume was completed with sodium borate (0.01 M) to the mark. The solution was used to prepare five standards with concentrations (16, 24, 32, 40, and 48 µg/ml).

RESULTS AND DISCUSSION

A standard solution of LNS with a concentration of 24 µg/ml was injected in the HPLC system. **Figure (4)** shows the chromatogram of LNS standard solution; it has a sharp peak and there are no interferences, impurities, or tailing of the peak.

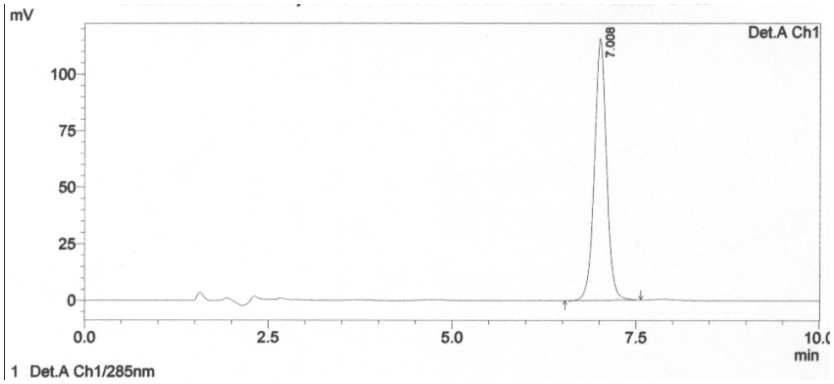

Figure (4): Lansoprazole chromatogram

Standard solutions of OMP and ESOMP were also injected in the HPLC system. **Figure (5)** and **Figure (6)** show the chromatograms of OMP and ESOMP. It's clear that the peaks were sharp, without any interferences or tailing.

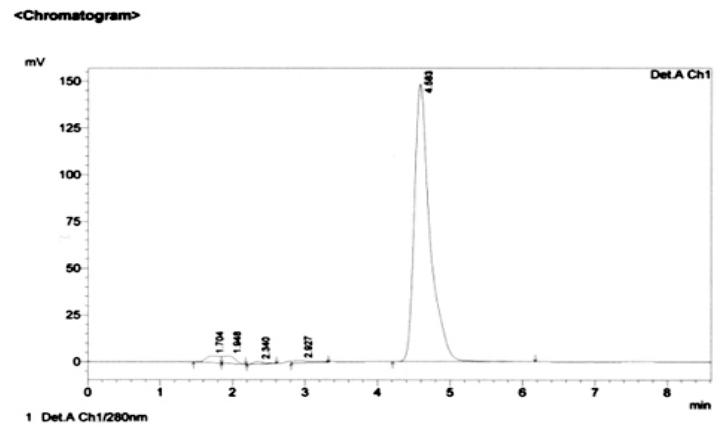

Figure (5): Omeprazole chromatogram

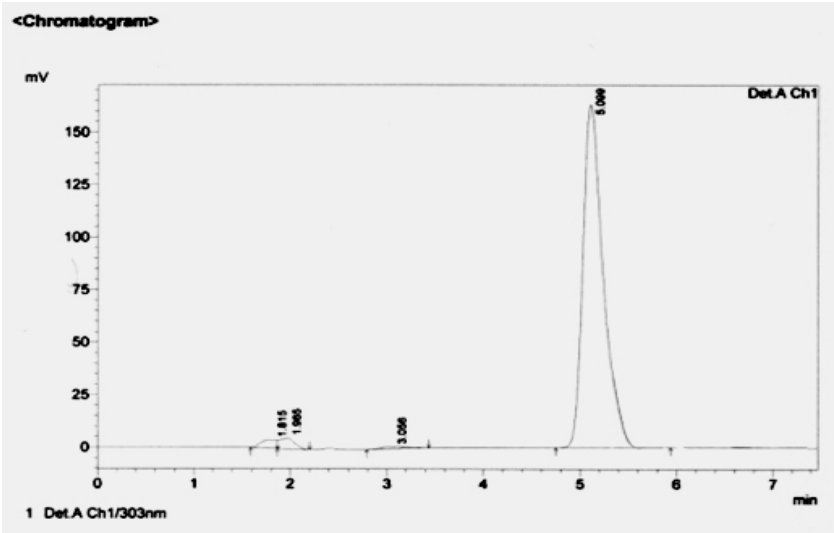

Figure (6): Esomeprazole chromatogram

Analytical Method Validation

- **Linearity** [17,18]

Five standard solutions of LNS were prepared with the concentrations (8, 16, 24, 32, and 44 µg/ml). Each solution was injected six times in the HPLC. **Figure (7)** shows the linearity of Lansoprazole.

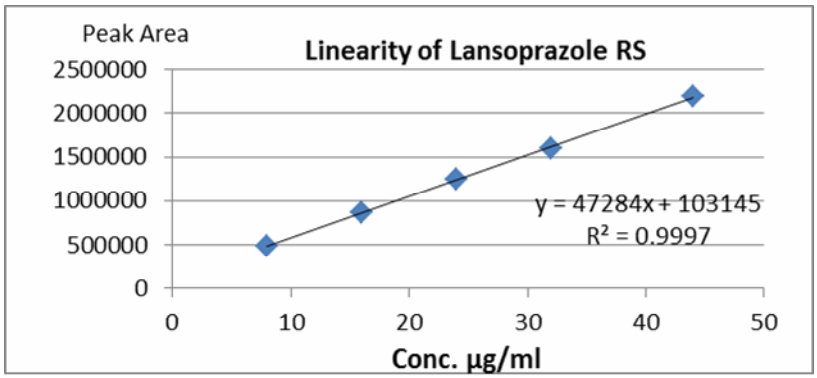

Figure (7): Lansoprazole linearity

The correlation coefficient of LNS (R^2) was 0.9997**.** To calculate the linearity of OMP and ESOMP five standard solutions were prepared with the concentrations (16, 24, 32, 40, and 48 µg/ml), the results are shown in **Figure (8)** and **Figure (9)**.

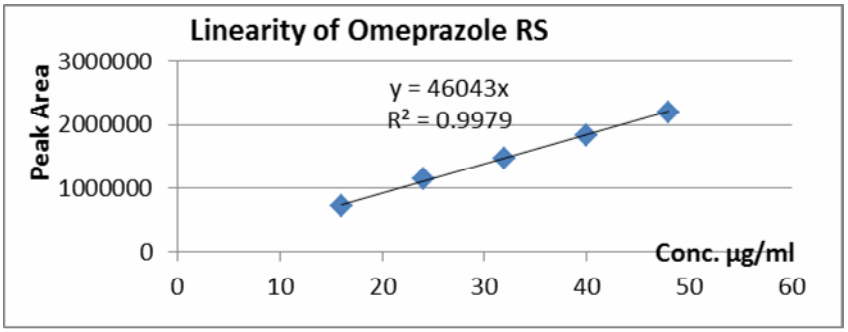

Figure (8): Omeprazole linearity

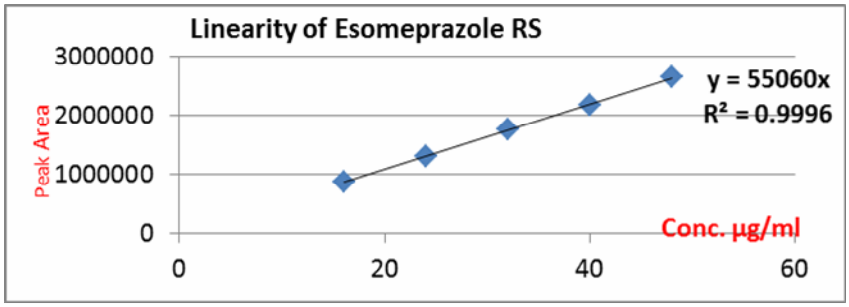

Figure (9): Esomeprazole linearity

It's clear that the linearity of OMP and ESOMP is 0.9979 and 0.9996, respectively. Therefore, all the values of the linearity are acceptable for the three compounds because R^2 <1.

- **Range** [17,18]

The range of an analytical procedure is the interval between the upper and lower concentrations (amounts) of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. Linearity, precision and accuracy were confirmed in the interval (8, 16, 24, 32, and 44 µg/ml) for LNS and in the interval (16, 24, 32, 40, and 48 µg/ml) for both OMP and ESOMP.

- **Accuracy** [17,18]

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or as an accepted reference value, and the value found. The following concentrations of LNS have been used to study the accuracy of LNS (8, 16, 24, 32, and 44 µg/ml), **Table (1)** shows the accuracy of Lansoprazole:

Table (1): Accuracy of Lansoprazole

Conc.	Mean of Peaks' area	Calc. Concentration	Spike Recovery	Average	RSD %
8	485524	8.086858134	101.0813322	101.0966441	0.014319544
8	485633	8.089163353	101.1101079		
8	485589	8.088232806	101.098492		
16	859633	15.99881567	99.92251684	100.3600481	0.746240704
16	869499	16.20746976	101.2248147		
16	859711	16.00046527	99.93281273		
24	1245710	24.16388207	100.5894176	100.5539246	0.034190355
24	1244930	24.14738601	100.5207783		
24	1245280	24.15478809	100.551578		
32	1595734	31.56647069	98.54339585	98.52108809	0.107118401
32	1596799	31.58899416	98.61368508		
32	1593655	31.52250233	98.40618334		
44	2197865	44.30082057	100.5698978	100.5699298	0.474554183
44	2207809	44.51112427	101.0472046		
44	2187923	44.09055917	100.092687		

As shown in **Table (1)** the RSD% of LNS is less than 1% which means the accuracy of LNS is acceptable.

Similarly, the accuracy of OMP and ESOMP were also calculated, and they are shown in **Table (2)** and **Table (3)**.

Table (2): Accuracy of Omeprazole

Conc. µg/ml	Mean of Peaks' area	Calc. Concentration	Spike Recovery	Average	RSD %
16	735231	14.41601145	100.1111906		
16	734831	14.40816847	100.0567255		
16	736882	14.44838337	100.3359956	100.1679706	0.147792021
24	1119574	21.95200094	101.629634		
24	1124621	22.05095979	102.0877768		
24	1109231	21.749201	100.6907454	101.4693854	0.7018555
32	1460123	28.62930139	99.40729648		
32	1482522	29.06848885	100.932253		
32	1479923	29.01752907	100.7553093	100.3649529	0.831027472
40	1825382	35.79110214	99.41972815		
40	1852761	36.32793475	100.9109299		
40	1825382	35.79110214	99.41972815	99.91679539	0.861662645
48	2196573	43.06921433	99.69725539		
48	2222820	43.5838513	100.8885447		
48	2209764	43.32785632	100.2959637	100.2939213	0.593901662

Table (3): Accuracy of Esomeprazole

Conc. µg/ml	Mean of Peaks' area	Calc. Concentration	Spike Recovery	Average	RSD %
16	888548	14.52469146	100.8659129		
16	878719	14.36402125	99.75014757		
16	886520	14.49154066	100.635699	100.4172532	0.586637983
24	1301886	21.28134042	98.52472415		
24	1301260	21.27110748	98.47734944		
24	1310228	21.41770331	99.15603384	98.71936914	0.383819167
32	1787269	29.21567634	101.4433206		
32	1749899	28.60480588	99.32224266		
32	1753472	28.6632121	99.525042	100.0968684	1.169329602
40	2195207	35.88405394	99.67792762		
40	2180403	35.64205966	99.00572129		
40	2184287	35.70554965	99.18208237	99.28857709	0.35102443
48	2675236	43.73087045	101.2288668		
48	2643463	43.21149162	100.026601		
48	2654389	43.39009399	100.4400324	100.5651667	0.60739022

As shown in **Table (2)** and **Table (3)** the RSD% of OMP and ESOMP is less than 1% which means the accuracy for both is acceptable

- **Precision** [17,18]

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility.

➢ **Repeatability**

Repeatability expresses the precision under the same operating conditions over a short interval of time.

Repeatability is also termed intra-assay precision. The solution 16µg/ml for (LNS, OMP, and ESOMP) was injected nine times. Standard deviation and relative standard deviation of the response (peak area) was calculated.

Table (4): Repeatability of Lansoprazole

Conc. µg/ml	Peak Area	Mean of peaks' area	RSD %
16	859633	859913.8	0.45182
16	869499		
16	859711		
16	859810		
16	859543		
16	860344		
16	856543		
16	856399		
16	857742		

As shown in **Table (4)** the repeatability of Lansoprazole is acceptable because the RSD% of LNS is less than 1, in the same manner the repeatability of OMP and ESOMP were carried out and the RSD% of OMP was 0.401 and the RSD% of ESOMP was 0.466, the results are shown in **Table (5)** and **Table (6).**

Table (5): Repeatability of Omeprazole

Conc. µg/ml	Peak Area	Mean of peaks' area	RSD %
16	735231	734995	0.40138
16	733831		
16	734882		
16	739921		
16	732265		
16	731923		
16	739347		
16	732174		
16	735381		

Table (6): Repeatability of Esomeprazole

Conc. µg/ml	Peak Area	Mean of peaks' area	RSD %
16	888548	881363.4	0.466355
16	878719		
16	886520		
16	879374		
16	878119		
16	883275		
16	878992		
16	876347		
16	882377		

- **Intermediate Precision**

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc. The solution 16 µg/ml was injected 12 times at two different days. Relative standard deviation of peak area for the twelve injections was determined. **Table (7)** shows the results for LNS.

Table (7): Intermediate Precision of Lansoprazole

No. of Injection	Conc. µg/ml	Peak Area
Solution A		
1	16	859633
2	16	869499
3	16	859711
4	16	859810
5	16	859543
6	16	860344
Solution B		
1	16	876399
2	16	877545
3	16	879546
4	16	880973
5	16	887845
6	16	885364
Mean of peaks' area		**871351**
Standard deviation		**11127.41772**
RSD %		**1.277030464**

The RSD % is less than 2.5 so the result is acceptable, the same procedure was applied for OMP, ESOMP, and the results were RSD% = 1.059, RSD% = 0.8, respectively. The results are shown in **Table (8)** and **Table (9).**

Table (8): Intermediate Precision of Omeprazole

No. of Injection	Conc. µg/ml	Peak Area
Solution A		
1	**16**	735231
2	**16**	733831
3	**16**	734882
4	**16**	739921
5	**16**	732265
6	**16**	731923
Solution B		
1	**16**	742174
2	**16**	745381
3	**16**	728793
4	**16**	757743
5	**16**	742764
6	**16**	739347
Mean of peaks' area		**738688**
Standard deviation		**7825.18**
RSD %		**1.059**

Table (9): Intermediate Precision of Esomeprazole

No. of Injection	Conc. µg/ml	Peak Area
Solution A		
1	**16**	888548
2	**16**	878719
3	**16**	886520
4	**16**	879374
5	**16**	878119
6	**16**	883275
Solution B		
1	**16**	878992
2	**16**	876347
3	**16**	882377
4	**16**	897367
5	**16**	886653
6	**16**	869644
Mean of peaks' area		**882161**
Standard deviation		**7064.35**
RSD %		**0.80080**

- **Robustness**[17,18]

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. The following parameters have been changed for the study of Robustness:

- Flow rate: 0.8 and 1.2 ml/min.
- UV wavelength: 283 and 287 nm for LNS, 278 and 282 nm for OMP, 301 and 305 nm for ESOMP.

Table (10) and **Table (11)** show the results of flow rate modification and wave length modification of Lansoprazole

Table (10): Flow rate modification of Lansoprazole

Flow rate modification			
No. of Injection	**Retention Time (min)**		**Retention Time (min)**
	Flow Rate = 0.8 ml/min	**Flow Rate = 1.2 ml min**	**Flow Rate = 1 ml/ min**
1	9.029	6.1	7.309
2	9.04	6.09	7.319
3	9.03	6.1	7.32
4	9.032	6.101	7.329
5	9.028	6.103	7.321
6	9.033	6.09	7.318
Mean of Rt	9.032	6.097	7.319
RSD %	0.048	0.094	0.0875

Table (11): Wave length modification of Lansoprazole

Wave length modification			
No. of Injection	**Peak Area**		**Peak Area (without modification)**
	λ=283 nm	λ=287 nm	λ=285 nm
1	1046741	939184	1037506
2	1047732	947653	1053249
3	1039896	924456	1046741
4	1051127	948432	1026130
5	1048729	946510	1044657
6	1045526	939962	1038876
Mean of Peaks' Area	1046625.167	941032.8333	1041193.167
RSD %	0.363	0.959	0.894

As shown in **Table (10)** and **Table (11)**, the slight changes in the method parameter do not affect the analysis. The same procedure was applied for OMP and ESOMP, and all results showed that the slight changes in the method parameter do not affect the analysis.

- **LOD and LOQ**[17,18]

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantified as an exact value. The quantification limit of an individual analytical procedure is the lowest amount of analyte in a

sample which can be quantitatively determined with suitable precision and accuracy. The quantification limit is a parameter of quantitative assays for low levels of compounds in sample matrices and is used particularly for the determination of impurities and/or degradation products. LOD and LOQ have been calculated using the following formulas:

$$Limit\ of\ Detection\ (LOD) = \frac{3.3\ x\ SR}{b}$$

$$Limit\ of\ Quantitation\ (LOQ) = \frac{10\ xSR}{b}$$

LOD_{LNS} = 0.34 ppm, LOQ_{LNS} = 1.039 ppm.

LOD_{OMP} = 0.12 ppm, LOQ_{OMP} = 0.982 ppm.

LOD_{ESOMP} = 0.145 ppm, LOQ_{ESOMP} = 0.995 ppm. [9,10]

- **Specificity** [17,18]

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradation products, matrix, etc. A standard solution of LNS, OMP and ESOMP was exposed to different kinds of degradation (acid, base, heat, and oxidation). **Figures (10), (11), (12), (13), (14), (15), (16), (17), (18), (19), (20),** and **(21)** show the results for studying the specificity of the three compounds.

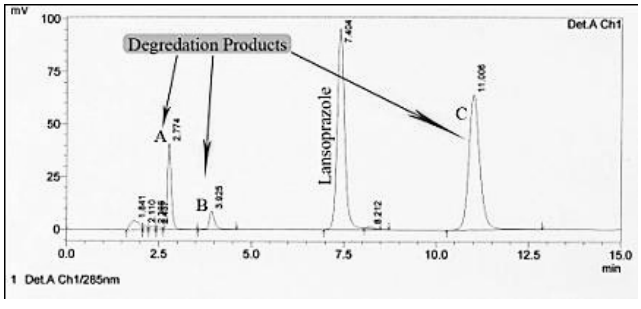

Figure (10): Acidic degradation of Lansoprazole

The peak of Lansoprazole is completely separated from the peaks of degradation products

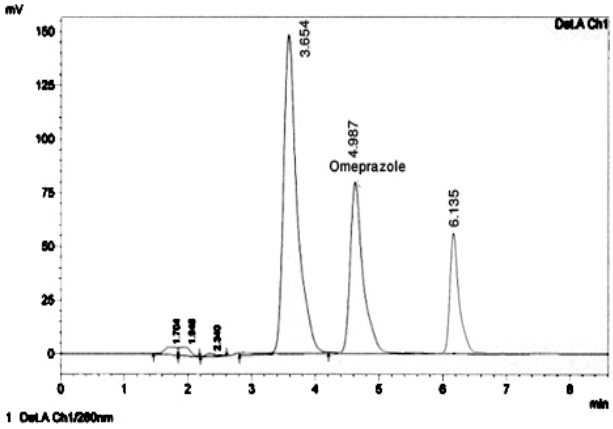

Figure (11): Acidic degradation of Omeprazole

The peak of Omeprazole is completely separated from the peaks of degradation products

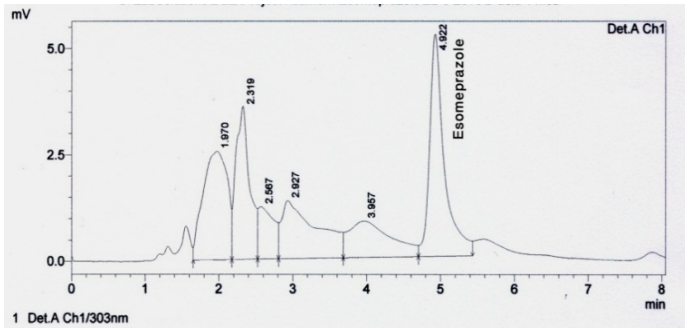

Figure (12): Acidic degradation of Esomeprazole

The peak of Esomeprazole is completely separated from the peaks of degradation products

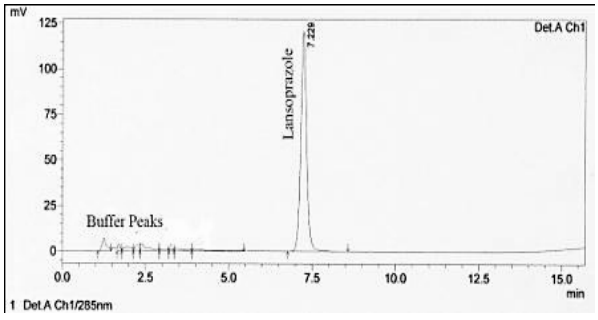

Figure (13): Basic degradation of Lansoprazole

Lansoprazole under the effect of basic solutions shows no degradation

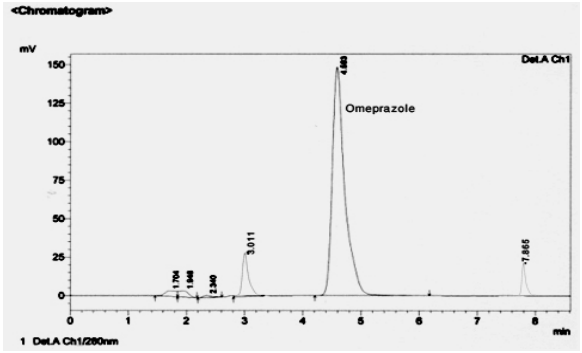

Figure (14): Basic degradation of Omeprazole

Omeprazole under the effect of basic solutions shows no degradation

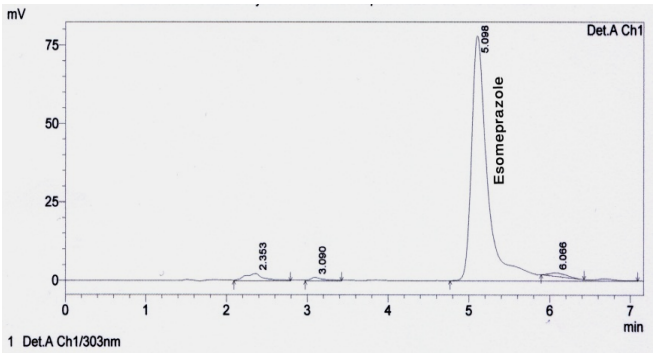

Figure (15): Basic degradation of Esomeprazole

Esomeprazole under the effect of basic solutions shows no degradation

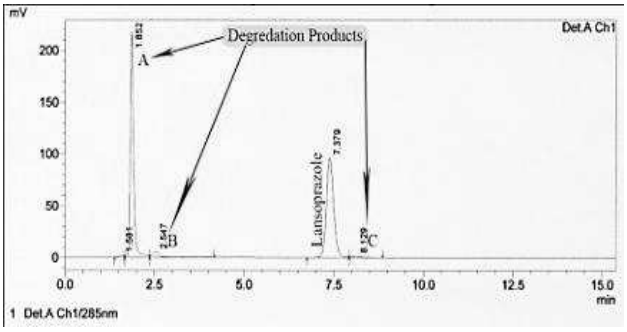

Figure (16): Degradation of Lansoprazole under H_2O_2

The peak of Lansoprazole is completely separated from the peaks of degradation products

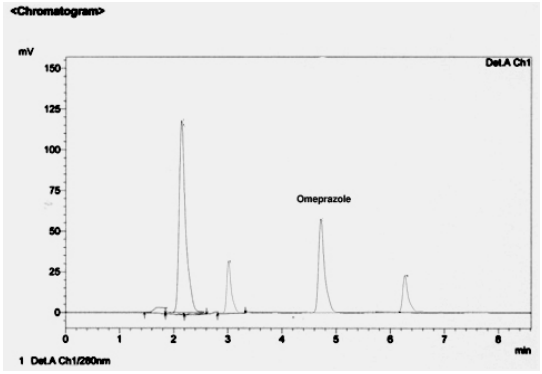

Figure (17): Degradation of Omeprazole under H_2O_2

The peak of Omeprazole is completely separated from the peaks of degradation products

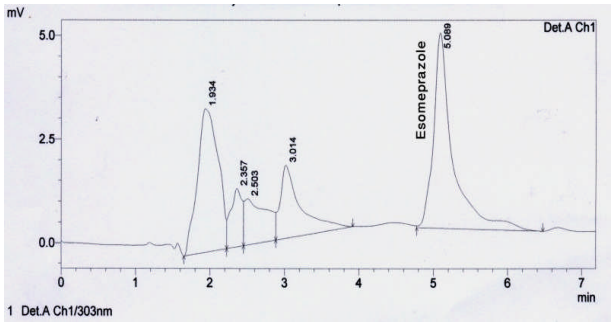

Figure (18): Degradation of Esomeprazole under H_2O_2

The peak of Esomeprazole is completely separated from the peaks of degradation products

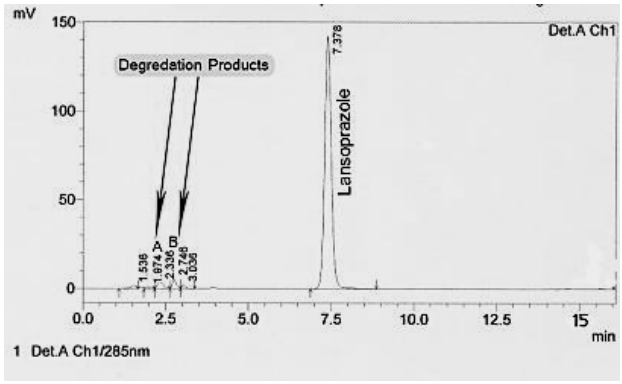

Figure (19): Heat Degradation of Lansoprazole

The peak of Lansoprazole is completely separated from the peaks of degradation products

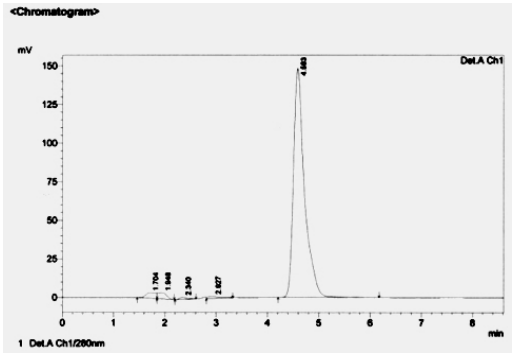

Figure (20): Heat Degradation of Omeprazole

The peak of Omeprazole is completely separated from the peaks of degradation products

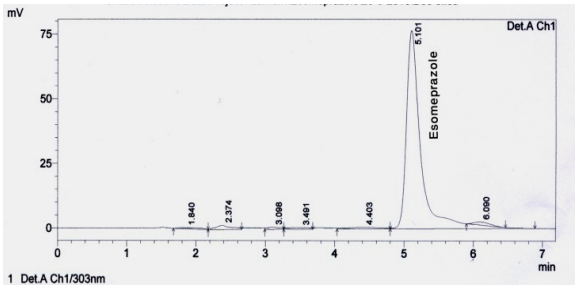

Figure (21): Heat Degradation of Esomeprazole

The peak of Esomeprazole is completely separated from the peaks of degradation products

- **System Suitability** [17,18]

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. System suitability parameters were calculated. **Table (12)** shows the results of system suitability.

Table (12): System Suitability

Acceptance Criteria	Value	Result
RSD% of Area ≤ 1	0.6899	Pass
RSD% of RT ≤ 1	0.1834	Pass
Asymmetry: 0.8-1.5	1.302	Pass
Plate Eff. 50 %> 2000	11458	Pass

CONCLUSION

HPLC with UV detector can be easily used to determine and quantify LNS, OMP, and ESOMP with fixed parameter. The parameters were the same RP-C_{18} Column, isocratic mobile phase (water: acetonitrile: TEA, 60:40:0.5, V/V/V), flow rate = 1 ml/min, but the wave lengths were 285, 280, 303 nm for LNS, OMP, and ESOMP, respectively. These parameters allowed the quantifying of each compound in its pharmaceutical dosage forms. The method was easy, precise, and economical for the determination and quantification of LNS, OMP, and ESOMP in-Process control, on finished products, and other pharmaceutical tests such as *In-Vitro* dissolution test.

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تطوير طريقة تحليلية سهلة و سريعة لبعض مثبطات مضخة البروتون بـاستعمال الكروماتوغرافيا السائلة عالية الأداء HPLC

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ملخـص

تم تطوير طريقة تحليلية بسيطة و نوعية و سريعة باستخدام الكروماتوغرافيا السائلة عالية الأداء لتحليل اللانسوبرازول و الأوميبرازول و الإيس أوميبرازول. استُخدِم في الطريقة جهاز HPLC مرتبط بكاشف الأشعة فوق البنفسجية و معايير ثابتة من عمود RP-C18 و طور متحرك مؤلف من (ماء: أسيتونتريل: تري إيتيل أمين بنسبة 60: 40: 0.5 ح/ح/ح عند pH=7 تم ضبطه بواسطة حمض الفوسفور) و معدل تدفق = 1 مل/دقيقة من أجل التحديد الكمي لكل مركب على حدة في مستحضره الصيدلاني. استخدمت نفس المعايير من أجل المركبات الثلاثة ما عدا طول الموجة حيث تم تعديله ليتناسب مع كل مركب فكانت الأطوال الموجية 285 نم و 280 نم و 303 نم لكل من اللانسوبرازول و الأوميبرازول و الإيس أوميبرازول على التوالي و كان زمن الاحتباس 7 د و 4.9 د و 5 د لكل من اللانسوبرازول و الأوميبرازول و الإيس أوميبرازول على التوالي، كما تم التحقق من صلاحية الطريقة فكانت كافة المعايير مقبولة النتائج. و بالتالي يمكن استخدام الطريقة كخيار سهل و فعال لتحليل اللانسوبرازول و الأوميبرازول و الإيس أوميبرازول خلال التحاليل الروتينية في المعامل الدوائية حيث مكنت الطريقة من معايرة كل من هذه المركبات الثلاثة باستخدام نفس المعايير و لا تتطلب سوى تغيير طول الموجة (الذي لا يستغرق أكثر من دقيقتين) ليتوافق مع كل مركب

الكلمات الدالة: لانسوبرازول، أوميبرازول، إيس أوميبرازول، الكروماتوغرافيا السائلة عالية الأداء، التحقق من صلاحية الطريقة.

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