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Research Article

Rapid Liquid Chromatographic Method for Quantification and Dissolution of Naproxen and Esomeprazole in Tablet Dosage Form

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ABSTRACT
In the present study, a new reverse phase high performance liquid chromatography method for the quantification and dissolution determination of naproxen and esomeprazole in tablet formulation has been developed and validated. Naproxen and esomeprazole in samples were analyzed by using the reversed-phase column Phenemonex Luna C_{18} (150x4.6 mm, 5µm) and the mobile phase consisting of pH:7.0 phosphate buffer and acetonitrile (50:50, v:v) at the constant flow rate (0.5ml/min) with a UV detection at 300 nm. In the assay validation a good linear relationship was observed for naproxen and esomeprazole in the concentration ranges of 0.1-0.7 mg/ml and 0.004-0.028 mg/ml respectively. The correlation coefficient for naproxen was found to be 1.0000 and that for esomeprazole was 0.9996. In the dissolution validation a good linear relationship was observed for naproxen and esomeprazole in the concentration ranges of 0.05-0.35 mg/ml and 0.002-0.014 mg/ml respectively. The correlation coefficient for naproxen was found to be 1.0000 and that for esomeprazole was 0.9996. The liquid chromatographic method can be applied to the routine quality control analysis of determination of naproxen and esomeprazole in tablet dosage form.
Keywords: Naproxen, esomeprazole, liquid chromatography

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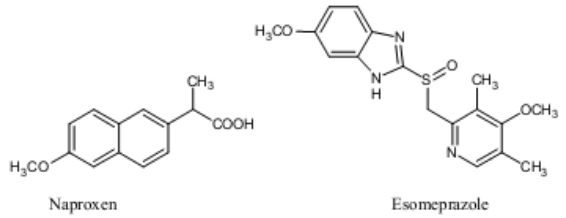
INTRODUCTION
Naproxen is a potent antiinflammatory and analgesic agent. The drug has demonstrated a variety of biologic actions, including stabilization of lysosomal membranes, but most of its therapeutic activity is probably mediated through prostaglandin synthesis inhibition. The linkage between inhibition of prostaglandin synthesis and relief of dysmenorrhea has been documented in clinical studiesi. It is used to treat firmness which is caused by conditions like ache which ranges from low level to mid level,fever, inflammation and osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, injure, menstrual cramps and tendinitis. It works by reducing mediators causing ache and inflammation in body (1-6). Administration of naproxen as the sodium salt, however, permits more rapid absorption from the gastrointestinal tract. In either form, the drug is essentially completely absorbed. Its metabolic half-life averages 13 hours. The metabolism of naproxen is quite simple: it is excreted almost entirely in the urine as the native molecule, its oxidative 6-desmethyl metabolite and their respective conjugates. Naproxen is an acidic drug that is highly bound to plasma albumin. It may thus be expected to displace and transiently increase the tissue availability of other protein-bound drugs. In practice, however, potential interactions with both warfarin and tolbutamide have been evaluated and do not appear to be of clinical significance. Naproxen has a high therapeutic index and a shallow dose-response curve, so the effect of other drugs on its pharmacokinetics is

not likely to have a large clinical impact. Naproxen is available in 250 mg, 375 mg and 500 mg tablets and is generally administered in therapeutic doses of 500-1000 mg per day with dosing intervals of 8-12 hours.

Naproxen like other NSAIDs may cause gastrointestinal disease (7). Therefore Naproxen is used in combination with proton pump inhibitors like other NSAID drugs. Taking into account all these, esomeprazole which can be prescribed with naproxen is a proton pump inhibitor. Rather than use a single form would be quite easy to use two tablets separately (8).

Esomeprazole is a proton pump inhibitor which is used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome. Esomeprazol is esomeprazole's S-isomery and it reduces gastric acid secretion by it's original effect mechanism. Esomeprazole reduces acid secretion through inhibition of ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. Esomeprazole is a competitive inhibitor of the enzymes CYP2C19 and CYP2C9, and may therefore interact with drugs that depend on them for metabolism, such as diazepam and warfarin. The drug is rapidly cleared from the body, largely by urinary excretion of pharmacologically-inactive metabolites such as 5-hydroxymethylesomeprazole and 5-carboxyesomeprazole (9-12). With an appropriate antibiotics combination,esomeprazole is used to treat Helicobacter pylori eradication and duodenum ulcer related with Helicobacter pylor and used to prevent relapses of peptic ulcer related with Helicobacter pylori (13).



Naproxen Esomeprazole

Figure 1: Molecular structure of naproxen and esomeprazole

Combination of both naproxen and esomeprazolis used for the treatment indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to diminish the risk of developing gastric ulcers by the usage of NSAID alone. Literature survey revealed that, a few simultaneous determinations available for naproxen and esomeprazolein pharmaceutical formulations by RP-HPLC method (14-16). A successful attempt was made to develop accurate, precise and sensitive developed method is simple, rapid, selective, less expensive and less time consuming. The purpose of present study was to develop and validate RP-HPLC methods for simultaneous estimation of naproxen and esomeprazol in their combined tablet dosage form.

MATERIALS AND METHODS

Assay Method of Naproxen and Esomeprazole

Apparatus:

The Chromatographic analysis was performed on a Waters HPLC system with a DAD dedector system using a Phenomenex Luna C_{18} 150x4.6 mm, 5µm column. Mettler Toledo sevenmulti pH-meter connected to Mettler Toledo inlab Rutin Pro pH electrode was used for pH measurements.

Chromatographic Conditions

In the present study, the use of the reversed phase column Phenemonex Luna C 18 150x4.6 mm, 5µm and the mobile phase consisting of pH:7.0 phosphate buffer and acetonitrile (50:50, v:v) at the constant flow rate (0.5ml/min) with a UV detection at 300 nm were found to be optimal chromatographic conditions for the HPLC separation and determination of naproxen and esomeprazole in samples. The chromatographic separation was performed at the column temperature, 25°C.

The Phosphate Buffer Solution (pH:7.0) was prepared by dissolving 1.4 g of dipotassium hydrogen phosphate in distillated water in 1000 ml calibrated flask. pH of the solution was adjusted with phosphoric acid.

Analysis Procedure of Sample

The enteric coated tablets containing naproxen and esomeprazole pulverized in a mortar. An amount of tablets powder equivalent to 500 mg naproxen or 20 mg esomeprazole was transferred 100 ml volumetric flask and dissolved mobile phase. Sample solution was sonicated for 15 min and 5 ml of sample solution was transferred 50 ml volumetric flask and was completed with mobile phase. Sample solution was shaken and filtrated by using a 0.45µm PTFE filter. The chromatogram of the resulting solution was recorded under the above mentioned chromatographic conditions. Naproxen and esomeprazole in enteric coated tablet samples was determined by using the calculated regression equation.

Dissolution study

Chromatographic Conditions

In the present study; chromatographic conditions of dissolution analysis are the same chromatographic conditions of assay described aboved. Unlike the analysis quantity determination column temperature of 40 °C.

Dissolution Conditions

For acid phase**;** calibrated dissolution vessel was filled with 0.1 N HCI dissolution medium. The temperature of the dissolution medium was adjusted to 37°C. Enteric coated tablets were dissolved for 2 hours with the pedals at 100 rpm in the 0.1 N HCl dissolution medium. Any deformation of the enteric coating after 2 hours was observed.

For base phase**;** calibrated dissolution vessel was filled with pH:6.8 phosphate buffer dissolution medium. The temperature of the dissolution medium was adjusted to 37°C. Samples which taken from the acid medium were dissolved for 45 minutes with the pedals at 100 rpm in pH:6.8 phosphate buffer medium.

0.1 N HCI Buffer: was prepared by dissolving 8.3 ml hydrochloric acid in distillated water in 1000 ml calibrated flash.

pH:6.8 Phosphate Buffer Solution: was prepared by dissolving 35,4 g of disodium hydrogen phosphate and 13,2 g potasium dihydrogen phosphate in distillated water in 1000 ml calibrated flask. pH of the solution was adjusted with phosphoric acid.

Analysis Procedure of Sample

In the present study, in terms of the dissolution samples were dissolved as described above. After 45 minutes from the dissolution media 10 ml sample solution was diluted with 5 ml to 10 ml of mobile phase. Sample solution was shaken and filtrated by using a 0.45µm PTFE filter. The chromatogram of the resulting solution was recorded under the above mentioned chromatographic conditions. Naproxen and esomeprazole in enteric coated tablet samples was determined by using the calculated regression equation.

RESULTS AND DISCUSSION

Assay

In this investigation chromatographic separation and quantitative analysis result of naproxen and esomeprazole in samples were observed by using the reversed-phase column Phenemonex Luna C 18 (150x4.6 mm, 5µm) and the mobile phase consisting of pH: 7.0 phosphate buffer and acetonitrile (50:50, v:v) at the constant flow rate (0.5ml/min) with a UV detection at 300 nm. The chromatogram for naproxen and esomeprazole and its sample was obtained by using the above chromatographic conditions. Figure 2 and 3 shows the chromatograms of naproxen and esomeprazole and blank.

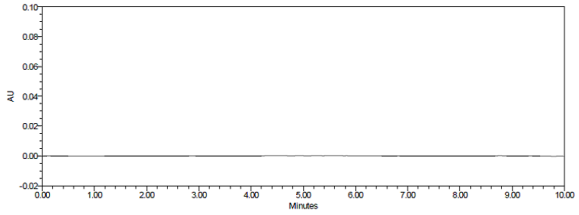


Figure 2: Chromatogram of blank

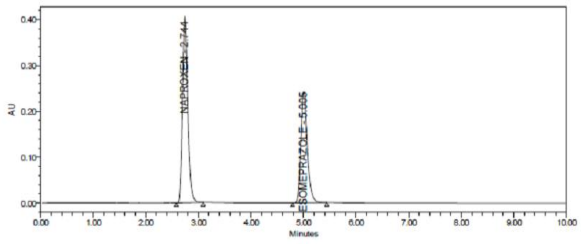


Figure 3: Chromatogram of naproxen and esomeprazole

In the above described chromatographic conditions, the retention time for naproxen was obtained as 2.7 min and esomeprazole was obtained as 5.0 min as shown in Figure 3.

The calibration graph for esomeprazole in the concentration range of 0.004-0.028 mg/ml and for naproxen in the concentration range of 0.1-0.7 mg/ml was calculated by using chromatographic areas obtained at the dedection, 300 nm. Figure 4 and 5 indicates the calibraiton graph with correlation 0.9996 for esmoprazole and 1.0000 for naproxen. As it can be seen from these figures, good linearity and correlation coefficient were reported.

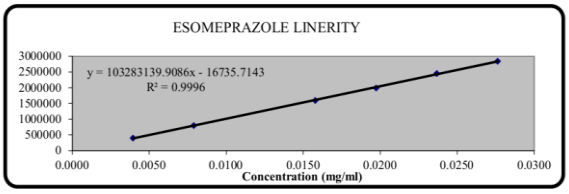


Figure 4: Calibration curve for esomeprazole in the concentration range 0.004-0.028 mg/ml

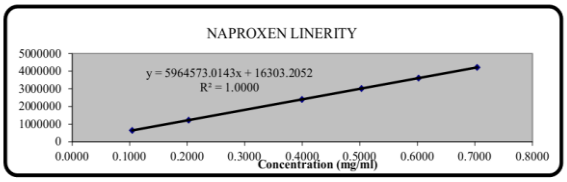


Figure 5: Calibration curve for naproxen in the concentration range 0.1-0.7 mg/ml

For the method validation, the HPLC method was applied to the analysis of the samples

containing esomeprazole and naproxen. System suitability of assay was given in Table 1.

In the recovery studies, the percent mean recovery and relative standard deviation were found as %99.78, %100.04and %0.42, %0.39.(Table 2 and 3) The applied HPLC approach was successfully applied to the quality control and quantitative estimation of esomeprazole and naproxen in a developed enteric coated formulation. The applied HPLC method was used for the quantiative determination of esomeprazole and naproxen in a developed enteric coated formulation. Analysis results of the related drug were presented in Table 4.

Parameters	Acceptance Criteria	Naproxen	Esomeprazole
Retention Time	-	2.7	5.0
RSD of Replicate Injections	Not more than %2.0	0.3	0.4
Symmetry Factor	Not more than 2.0	1.2	1.3
Teorical Plate	More than 2500	3794	8382
Resolution	More than 2.0	-	11.4
Purity Angle	Purity Criteria (Purity Angle<Purity Threshold)	0.063	0.035
Purity Threshold	Purity Criteria (Purity Angle<Purity Threshold)	0.247	0.218

Table 1: System suitability of assay

NO	Sample (%, w/w)	Recovery (%)
1	80	100,37
2	80	100,29
3	80	100,07
4	100	99,23
5	100	99,34
6	100	99,30
7	120	99,81
8	120	99,85
9	120	99,75
	Mean	99,78
	SD	0,42
	RSD	0,42

Table 2. Recovery result for esomeprazole obtained by HPLC method

NO	Sample (%, w/w)	Recovery (%)
1	80	99,87
2	80	99,82
3	80	99,73
4	100	99,76
5	100	99,73
6	100	99,82
7	120	100,53
8	120	100,50
9	120	100,63
	Mean	100,04
	SD	0,39
	RSD	0,39

Table 3. Recovery result for naproxen obtained by HPLC method.

NO	Sample of Esomeprazole (%, mg/mg)	Sample of Naproxen (%, mg/mg)
1	100,3	99,9
2	100,4	99,9
3	99,9	99,6
4	99,8	99,4
5	100,4	100,0
6	100,2	99,8
Mean	100,1	99,7
SD	0,27	0,23
RSD	0,27	0,23

Table 4. Sample analysis results obtained by HPLC method

Dissolution

In this investigation, chromatographic separation and dissolution analysis result of naproxen and esomeprazole in samples were observed by using the reversed-phase column Phenemonex Luna C 18 (150x4.6 mm, 5µm) and the mobile phase consisting of pH:7.0 phosphate buffer and acetonitrile (50:50, v:v) at the constant flow rate (0.5ml/min) with a UV detection at 300 nm. Column temperature was at 40°C. The samples were dissolved in 1000 ml 0.1 N HCl acid medium at 100 rpm with pedals. Any deformation of the enteric coating after 2 hours was observed. Samples which taken from the acid medium were dissolved for 45 minutes with the pedals at 100 rpm in 1000 ml pH:6.8 phosphate buffer medium. After 45 minutes from the dissolution media 10 ml sample solution was diluted with 5 ml to 10 ml of mobile phase. Sample solution was shaken and filtrated by using a 0.45µm PTFE filter. The chromatogram of the resulting solution was recorded under the above mentioned chromatographic conditions. Figure 6 and 7 shows the chromatograms of Naproxen and esomeprazole and dissolution buffer.

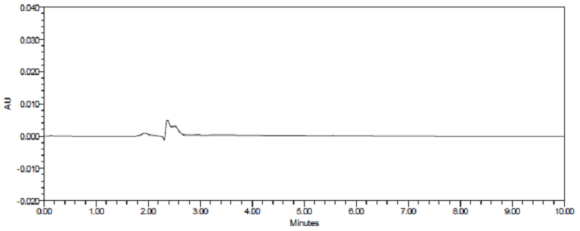


Figure 6: Chromatogram of 6.8 phosphate buffer

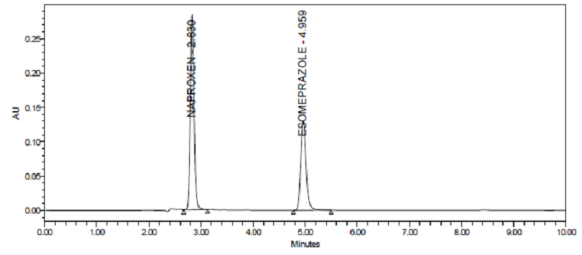


Figure 7: Chromatogram of naproxen and esomeprazole dissolution

In the above described chromatographic conditions, the retention time for naproxen was obtained as 2.8 min and esomeprazole was obtained as 5.0 min as shown in Figure 8.

The calibration graph for esomeprazole in the concentration range of 0.002-0.014 mg/ml and for naproxen in the concentration range of 0.05-0.35 mg/ml was calculated by using chromatographic areas obtained at the dedection, 300 nm. Figure 8 and 9 indicates the calibraiton graph with correlation 0.9996 for esmoprazole and 1.0000 for naproxen. As it can be seen from these figures, good linearity and correlation coefficient were reported.

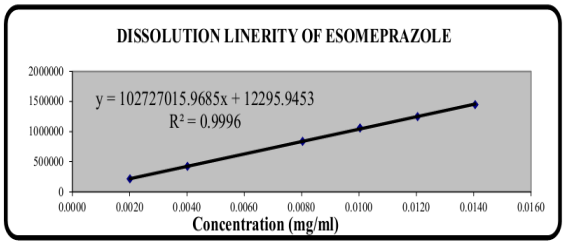


Figure 8: Calibration curve for esomeprazole in the concentration range 0.002-0.014 mg/ml

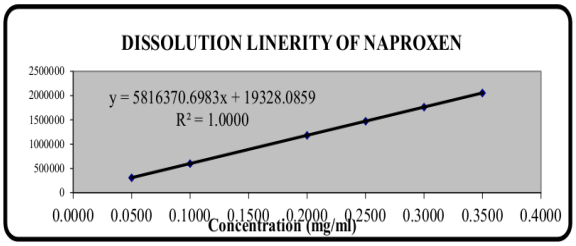


Figure 9: Calibration curve for naproxen in the concentration range 0.05-0.35 mg/m

For the method validation, the HPLC method was applied to the analysis of the samples containing esomeprazole and naproxen. System suitability of dissolution was presented in Table 5.

Parameters	Acceptance Criteria	Naproxen	Esomeprazole
Retention Time	-	2.7	5.0
RSD of Replicate Injections	Not more than %2.0	0.1	0.3
Symmetry Factor	Not more than 2.0	1.1	1.2
Teorical Plate	More than 2500	8368	12081
Resolution	More than 2.0	-	14.1
Purity Angle	Purity Criteria (Purity Angle<Purity Threshold)	0.063	0.033
Purity Threshold	Purity Criteria (Purity Angle<Purity Threshold)	0.246	0.215

Table 5: System Suitability of dissolution

In the recovery studies, the percent mean recovery and relative standard deviation were found as %100,1, %100.6 and %0.82, %0.22. (Table 6 and 7) The applied HPLC approach was successfully applied to the quality control and dissolution determinationof esomeprazole and naproxen in a developed enteric coated formulation.

NO	Sample (%, w/w)	Recovery (%)
1	50	100,29
2	50	100,47
3	50	101,53
4	80	98,95
5	80	99,01
6	80	99,20
7	100	100,70
8	100	100,65
9	100	100,76
10	120	99,37
11	120	100,15
12	120	100,56
	Mean	100,1
	SD	0,82
	RSD	0,82

Table 6: Recovery result for esomeprazole dissolution obtained by HPLC method

NO	Sample (%, w/w)	Recovery (%)
1	50	100,39
2	50	100,33
3	50	100,36
4	80	100,43
5	80	100,47
6	80	100,48
7	100	101,02
8	100	100,68
9	100	100,91
10	120	100,47
11	120	100,53
12	120	100,47
	Mean	100,6
	SD	0,22
	RSD	0,22

Table 7: Recovery result for naproxen dissolution obtained by HPLC method

The applied HPLC method was used for the dissolution determination of esomeprazole and naproxen in a developed enteric coated formulation. Analysis results of the related drug were presented in Table 8.

NO	Sample of Esomeprazole (%)	Sample of Naproxen (%)
1	86,8	95,8
2	86,7	96,0
3	86,9	96,1
4	86,6	96,1
5	86,7	95,0
6	85,6	95,0
Mean	86,6	95,7
SD	0,50	0,54
RSD	0,58	0,56

Table 8: Dissolution result of naproxen and esomeprazole

CONCLUSION

In this study, high performance liquid chromatgraphic methods (assay and dissolution) were developed for the routine quality control

analysis of determination of naproxen and esomeprazole in enteric coated tablet samples. For both molecules were provided high success for analysis of assay and the dissolution study.In the assay validation a good linear relationship was observed for naproxen and esomeprazole in the concentration ranges of 0.1-0.7 mg/ml and 0.004-0.028 mg/ml respectively. The correlation coefficient for naproxen was found to be 1.0000 and that for esomeprazole was 0.9996. In the dissolution validation a good linear relationship was observed for naproxen and esomeprazole in the concentration ranges of 0.05-0.35 mg/ml and 0.002-0.014 mg/ml respectively. The correlation coefficient for naproxen was found to be 1.0000 and that for esomeprazole was 0.9996.

Hence naproxen and esomeprazole can be single tablet formulation and the single tablet formulation can provide ease of use.

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