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Stability Indicating Hplc Method For Simultaneous Estimation Of Lansoprazole And Domperidone In Pharmaceutical Preparations

Anup Barsagade*, Pruthviraj Meshram and Pragati Dongare

*Dr. Anup G. Barsagade
Assistant Professor Maharashtra Institute of Pharmacy, Gondwana University, Gadchiroli Armori Road, Bramhapuri – 441206, Maharashtra, INDIA. E-Mail: agbarsagade@gmail.com

Summary
A simple, precise, and accurate stability-indicating normal-phase HPLC method has been established for simultaneous estimation of Lansoprazole (LANS) and Domperidone (DOMP) in the bulk drug and dosage form. A Phenomenex C-18, 5 µm column having. 250 x 4.6 mm i.d. in isocratic mode with mobile phase containing 20 mM potassium dihydrogen phosphate: acetonitrile (60:40, v/v; pH 6.0) was used. The flow rate was 1.0 mL/min and quantitation was achieved with UV detection at 280 nm. Retention time of LANS and DOMP were 9.98 ± 0.5 min and 5.87 ± 0.5 min respectively. Validation of the method in accordance with ICH guidelines yielded good results for range, linearity, precision, accuracy, specificity, robustness and ruggedness. Response were a linear function of concentration of LANS over the range 3–90 µg mL^{-1} by peak area with correlation coefficient 0.999 and DOMP over the range 2-60 µg mL^{-1} by peak area with correlation coefficient 0.998. The limit of detection of LANS was 0.04 µg mL^{-1} for peak area and the limit of detection of DOMP was 0.19 µg mL^{-1} for peak area. Results from analysis of a commercial tablet formulation were 99.99 ± 0.1249 % and 99.36 ± 0.0196 % by peak area for LANS and DOMP respectively. Recoveries were 99.87 ± 0.8513 % and 100.17 ± 0.9762 % by peak area for LANS and DOMP respectively. The conditions used also enabled separation and detection of degradation products from acidic, basic, neutral, oxidation stress. No degradation products were obtained after photo and dry heat stress condition.

Key Words: HPLC Lansoprazole Domperidone Degradant Validation

1 Introduction

Lansoprazole (LANS) 2-({[3-methyl-4-(2, 2, 2-trifluoroethoxy)pyridin-2-yl]methane}sulfinyl)-1H-1,3-benzodiazole [Figure 1] is a proton pump inhibitor

which inhibits stomach acid production. Domperidone (DOMP) 5-chloro-1-{1-[3-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)propyl]piperidin-4-yl}-2,3-dihydro-1H-1,3-benzodiazol-2-one [Figure 2] is a specific blocker of dopamine receptors. Domperidone is given in order to relieve nausea and vomiting. [1-3]

Literature survey revealed Estimation of LANS and DOMP by UV Spectroscopy in tablet and capsules alone [4-7], in combination with each other [8] and with other drugs [9-14], HPLC in alone [15-24], in combination with each other [25-27] and with other drugs [28-33] and HPTLC in combination with each other [34] and with other drugs [35-36] has been reported. The reported HPLC method is only suitable for of simultaneous estimation of LANS and DOMP in the bulk drug and dosage form in presence of their degradation products.

In this manuscript we describe a simple, specific, rapid, precise and accurate stability-indicating HPLC method which is useful for analysis of LANS and DOMP and its degradation products in pharmaceutical preparations on the basis of peak area.

2 Experimental

2.1 Chemicals, Reagents and Solutions

Pharmaceutical grade Lansoprazole and Domperidone were procured as a gift samples from Zydus Cadila Healthcare Ltd., Ahmedabad and VAMA Pharma, Nagpur (India), LEEDOM-15 a capsule formulation, obtained commercially.

Acetonitrile HPLC grade, potassium dihydrogen phosphate, hydrochloric acid, sodium hydroxide and hydrogen peroxide 30% of analytical grade were used throughout the work.

To prepare standard solution, 15.0 mg LANS, accurately weighed and 10.0 mg of DOMP were dissolved in small amount of mobile phase and the volume was made up to 10.0 mL with the same solvent. Hundred microliter of resulting solution was diluted to 10.0 mL with mobile phase to furnish a solution of concentration 15 μg mL^{-1} and 10 μg mL^{-1} of LANS and DOMP respectively.

2.2 Forced Degradation of Lansoprazole and Domperidone (Stress Studies)

Stress studies were performed to determine the effect of a wide range of pH, heat, oxidizing, and photolytic conditions on LANS and DOMP. LANS (15 mg) was weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, LANS (30 mg) was weighed in round bottom flask and dissolved in 20 mL 0.1 M aqueous sodium hydroxide and were kept at 80°C. For neutral degradation, 30 mg of LANS was weighed in round bottom flask and dissolve in 20 ml of distilled water. The solutions were heated under reflux on a water bath at 60°C. For oxidative degradation, 15 mg LANS was dissolved in 10 mL 1% H_2O_2 (1.5 mg mL^{-1}) in volumetric flask and kept in dark at

room temperature. For photo degradation, LANS was evenly spread in a thin layer in a covered Petri dish and exposed to sunlight. The same amount of sample was placed in a Petri dish for thermal degradation at 60 °C.

Similarly, DOMP (10 mg) was weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, DOMP (20 mg) was weighed in round bottom flask and dissolved in 20 mL 0.1 M aqueous sodium hydroxide and were kept at 80°C. For neutral degradation, 20 mg of DOMP was weighed in round bottom flask and dissolve in 20 ml of distilled water. The solutions were heated under reflux on a water bath at 60°C. For oxidative degradation, 10 mg DOMP was suspended in 10 mL 1% H_2O_2 (1 mg mL^{-1}) in volumetric flask and kept in dark at room temperature. For photo degradation, DOMP was evenly spread in a thin layer in a covered Petri dish and exposed to sunlight. The same amount of sample was placed in a Petri dish for thermal degradation at 60 °C.

For drug-drug interaction study LANS (15 mg) and DOMP (10 gm) were weighed, mix and transfer into 10 mL volumetric flasks. LANS (15 mg) and DOMP (10 mg) were weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, LANS (30 mg) and DOMP (20 mg) were weighed in round bottom flask and dissolved in 20 mL 0.1 M aqueous sodium hydroxide and were kept at 80°C. For neutral degradation, LANS (30 mg) and DOMP (20 mg) were weighed in round bottom flask and dissolve in 20 ml of distilled water. The solutions were heated under reflux on a water bath at 60°C. For oxidative degradation, LANS (15 mg) and DOMP (10 mg) were suspended in 10 mL 1% H_2O_2 in volumetric flask and kept in dark at room temperature. For photo degradation, LANS and DOMP were mixed and evenly spread in a thin layer in a covered petri dish and exposed to sunlight. The same amount of sample mixture was placed in a petri dish for thermal degradation at 60 °C.

Samples of the solutions used for acidic, alkaline and neutral hydrolysis were withdrawn periodically and stored under refrigeration. To compare the effect of H_2O_2 sample (2 mL) were withdrawn periodically and stored under refrigeration. In thermal and photo degradation studies, samples were withdrawn periodically and dissolved in 10 mL mobile phase to furnish concentrations of 1.5 mg mL^{-1} and 1.0 mg mL^{-1} of LANS and DOMP respectively. From the solutions obtained 100 µL was withdrawn by pipette, transferred to a 10-mL volumetric flask, and diluted to volume with mobile phase to furnish a solution of concentration 15 µg mL^{-1} and 10 µg mL^{-1} of LANS and DOMP respectively.

2.3 Chromatography

Chromatographic measurements were made on Shimadzu LC-20AB prominence model which consisted of Shimadzu SPD-20A prominence PDA detector, Shimadzu DGU-20A3 prominence degasser and Rheodyne injector 7725 I with 20 µl loop. The

system was controlled through personal computer using chromatographic software (LC Solution).

Chromatographic separations were performed on Phenomenex C-18, 5 µm column having 250 x 4.6 mm i.d. The flow rate was 1.0 mL/min and quantitation was achieved with UV detection at 280 nm. The injection volume of the sample was 20 µL and the total run time was 30 min. The HPLC system was used in an air conditioned laboratory atmosphere (25 ± 2)

Initially, pure drugs solution was chromatographed using single solvents to ascertain the movement of the drug. Use of mobile phase containing 20 mM potassium dihydrogen phosphate: acetonitrile (60:40, v/v; pH 6) gives well separated, sharp, symmetrical peaks of drugs and separation of degradation products from drugs as well. Retention time of LANS and DOMP were 9.98 ± 0.5 min and 5.87 ± 0.5 min respectively. Typical HPLC chromatogram (obtained at 280 nm) obtained from standard solution is shown in **Figure 3.**

Then samples obtained from forced degradation were then chromatographed with the same mobile phase and it was found that chromatogram obtained after acidic hydrolysis gave four degradation products of LANS at 3.85 ± 0.5 min (LDP-1), 10.72 ± 0.5 min (LDP-2), 18.34 ± 0.05 min (LDP-3) and 25.61± 0.5 min (LDP-4), alkaline hydrolysis gave degradation product of LANS at 13.46 ± 0.5 min (LDP-5), Neutral Hydrolysis gave three degradation products of LANS at 3.82 ± 0.5 min (LDP-6), 9.74 ± 0.5 min (LDP-7) and 25.94± 0.5 min (LDP-8), Oxidation gave degradation product of LANS at 13.32 ± 0.5 min (LDP-9) [Figure 4]. No degradation products were obtained after photo and heat stress condition. No degradation product of DOMP was found when same stress conditions applied alone or in combination with LANS.

2.4 Preparation of Sample Solution for Assay

Twenty capsule's pellets were weighed and finely powdered. An accurately weighed amount of pellets powder equivalent to 15 mg of LANS and 10 mg of DOMP was transfered into a 10-mL volumetric flask containing little mobile phase. The flask contents were sonicated for 10 min to make the contents homogeneous. This solution was then diluted up to the mark with mobile phase. The resultant solution was filtered through 0.2 µm membrane filter. Hundred microlitre of filtrate was transfered to a 10 mL volumetric flask and then volume was made up to the mark with mobile phase to furnish a sample solution containing 15 µg mL^{-1} of LANS and 10 µg mL^{-1} of DOMP. Six replicate homogenous sample solutions were prepared in a similar manner.

3 Results and Discussion

3.1 HPLC Method Development and Optimization

Isocratic reversed phase HPLC with 20 mM potassium dihydrogen phosphate: acetonitrile (60:40, v/v; pH 6) as mobile phase enabled satisfactory baseline resolution of the both API and all degradation products with reasonably acceptable retention times for the purpose of quantification. Retention times were 9.98 ± 0.5 min and 5.87 ± 0.5 min for LANS and DOMP respectively. LANS gave at 3.85 ± 0.5 min (LDP-1), 10.72 ± 0.5 min (LDP-2), 18.34 ± 0.05 min (LDP-3) and 25.61± 0.5 min (LDP-4) for acidic hydrolysis, 13.46 ± 0.5 min (LDP-5) for base hydrolysis, 3.82 ± 0.5 min (LDP-6), 9.74 ± 0.5 min (LDP-7) and 25.94± 0.5 min (LDP-8) for neutral hydrolysis and 13.32 ± 0.5 min (LDP-9) for oxidation degradation. No degradation products of LANS and DOMP were obtained after photo and dry heat stress condition. No degradation product of DOMP was found when same stress conditions applied alone or in combination with LANS.

3.2 Validation of the Method

As recommended in ICH guidelines [37, 38] all validation was performed during development of the procedure. The proposed method was validated for linearity, precision, accuracy, specificity, limits of detection and quantification, ruggedness, and robustness. Linearity was established by least-squares linear regression analysis of the calibration data. Calibration plots were linear over the concentration range 2-60 μg mL^{-1} by area for DOMP and 3-90 μg mL^{-1} by area for LANS. Peak areas were plotted against the respective concentrations and linear regression analysis performed on the resulting curves. Equation for the calibration plots of LANS was Y= 1E+06X - 38481, for peak area. Correlation coefficient was 0.999 for peak area. Equation for the calibration plots of DOMP was Y= 54740X – 20510, for peak area. Correlation coefficient was 0.998 for peak area. The limits of detection (LOD) and quantification (LOQ) were calculated from the standard deviation of the response and the slope of calibration plot. LOD and LOQ were established, in accordance with ICH definitions, by use of the equations LOD = 3.3σ/S and LOQ = 10σ/S, where σ is the standard deviation of the regression line and S is the slope of the calibration plot. The LOQ of LANS for which precision and accuracy were satisfactory was 0.12 μg mL^{-1} for peak area and LOD was 0.04 μg mL^{-1} for peak area. The LOQ of DOMP for which precision and accuracy were satisfactory was 0.58 μg mL^{-1} for peak area and LOD was 0.19 μg mL^{-1} for peak area.

Method, system and intermediate precision data are summarized in Table 1. Method precision was investigated by injecting extracts from six tablet samples (n = 6) in triplicate. Intermediate precision (inter-day and intra-day) was investigated by injecting three samples (n = 3) in triplicate.

Accuracy data for the assay after analysis of the compound are summarized in Table 2. The accuracy of the method was determined on the basis of recovery studies performed by standard addition at different levels (80, 100, and 120%) of the label claim, in triplicate. A known amount of powder standard was added to

samples of tablet powder, which was then mixed, extracted, and subsequently diluted to volume with AR-grade methanol, to yield the required concentration of drug. Specificity studies were conducted by attempting deliberate degradation of tablet samples by exposure for 10 min. at room temperature to the acidic (0.01N HCl) stress condition, 24 hr in oven at 50°C for alkaline (0.1 N NaOH) stress condition, 1 hr at room temperature for oxidation (1% H_2O_2) stress condition and UV irradiation at 366 nm. The results showed in Table 3. Ruggedness was assessed out for different elapsed times (intraday and inter-day). The results (Table 1) showed the method is rugged under these conditions. Robustness was studied by varying the detection wavelength by ± 2.0 nm, mobile phase composition (± 2.0 mL of acetonitrile) and pH of mobile phase (± 0.2). The results are listed in Table 4.

4 Conclusion

The method enables simple, precise, and accurate analysis of Lansoprazole and Domperidone and its degradation products in the bulk drug and pharmaceutical preparations. It was validated for precision, accuracy, specificity, ruggedness, and robustness. The method can therefore be used for routine quality-control analysis of Lansoprazole and Domperidone in combined dosage forms.

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Table 1 System, method, and intermediate precision data

Validation Parameters		**LANS**			**DOMP**		
		Mean	**SD[±]**	**RSD [%]**	**Mean**	**SD[±]**	**RSD [%]**
System Precision [a)]		16326738	27898.184	0.1700	5463833	2124.776	0.038
Method Precision [a)]		99.99%	0.1249	0.1249	99.36%	0.0196	0.0197
Intermediate precision	**Interday** [b)]	100.08%	0.0208	0.0207	100.35%	0.0929	0.0925
	Intraday [b)]	100.12%	0.0472	0.0471	100.37%	0.0854	0.0851
	Different Analyst [b)]	100.44%	0.0264	0.0263	99.55%	0.0611	0.0613

a) Mean from six analyses (n =6)
b) Mean from 3 analyses (n =3)

n = Number of samples, SD = standard deviation; RSD = relative standard deviation

Table 2 Accuracy data

LANS	**Level [%]**	**Wt. of sample (mg)**	**Wt. of drug(mg)**	**Amount of standard added (mg)**	**Calculated Wt. Of drug (mg)**	**[%] Recovery**

	80	258.4	15.0	12.0	12.11	100.91
		258.2	14.98	12.1	12.1	100.00
		258.3	14.99	12.1	12.1	100.00
	100	258.4	15.00	15.1	14.87	98.47
		258.4	15.00	15.0	14.86	99.06
		258.3	14.99	15.0	14.84	98.93
	120	258.2	14.98	18.1	18.21	100.60
		258.2	14.98	18.0	18.08	100.44
		258.3	14.99	18.0	18.08	100.44
	Mean ±SD					99.87±0.8513
	RSD [%]					0.8523
DOMP	**Level [%]**	**Wt. Of sample (mg)**	**Wt. of drug(mg)**	**Amount of standard added(mg)**	**Calculated Wt. Of drug (mg)**	**[%]Recovery**
	80	258.4	10.0	8.1	8.16	100.74
		258.2	9.99	8.0	8.16	102.00
		258.3	9.99	8.1	8.16	100.74
	100	258.4	10.0	10.0	9.94	99.40
		258.4	10.0	10.1	9.99	98.91
		258.4	10.0	10.1	10.00	99.00
	120	258.2	9.99	12.0	12.04	100.33
		258.2	9.99	12.0	12.02	100.16
		258.3	9.99	12.0	12.0	100.33
	Mean ±SD					100.17±0.9762
	RSD [%]					0.9744

Table 3 Specificity data

Formulation		Normal	Acid	Alkali	Oxide	Heat	UV
LEEDOM-15	**LANS**	99.87	81.92	94.91	94.34	99.14	99.81
	DOMP	99.57	99.44	99.65	99.67	99.40	99.56

Table 4 Robustness

Condition		LANS		DOMP	
		By peak area*		By peak area*	
		Amount estimated [%] ± SD	RSD [%]	Amount estimated [%] ± SD	RSD [%]
Change in wavelength (280±2 nm)	**278 nm**	99.80 ± 0.0264	0.0265	99.97 ± 0.0888	0.0889
	282 nm	99.75 ± 0.0152	0.0153	99.65 ± 0.1778	0.1784
Change in mobile phase composition (±2 ml)	**20mM pot dihydr. phos. :acn 58:42 (v/v)**	99.93 ± 0.0321	0.0321	99.65 ± 0.0692	0.0695
	20mM pot dihydr. phos. :acn 62:38 (v/v)	99.85 ± 0.0251	0.0252	99.99 ± 0.0450	0.0450
Change in mobile phase pH (6.0±0.2)	**6.2**	99.93 ± 0.0351	0.0351	99.74 ± 0.0793	0.0795
	5.8	99.93 ± 0.0057	0.0057	99.8 ± 0.0360	0.0361

* Each value is a mean of three observations.

Figure 1 Chemical structure of Lansoprazole

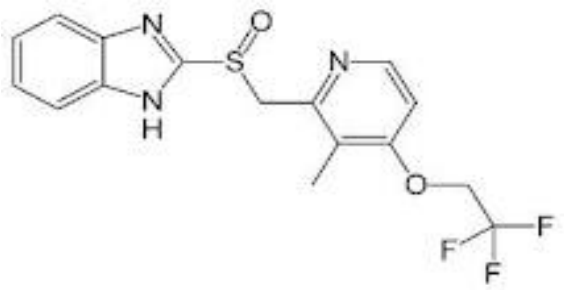


Figure 2 Chemical structure of Domperidone

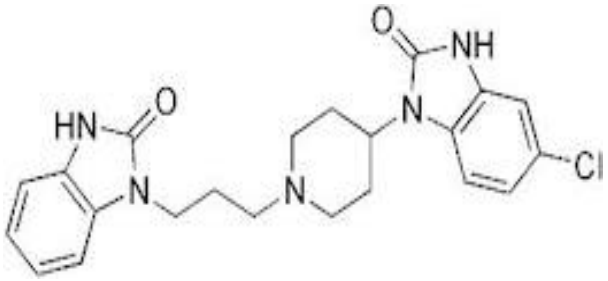
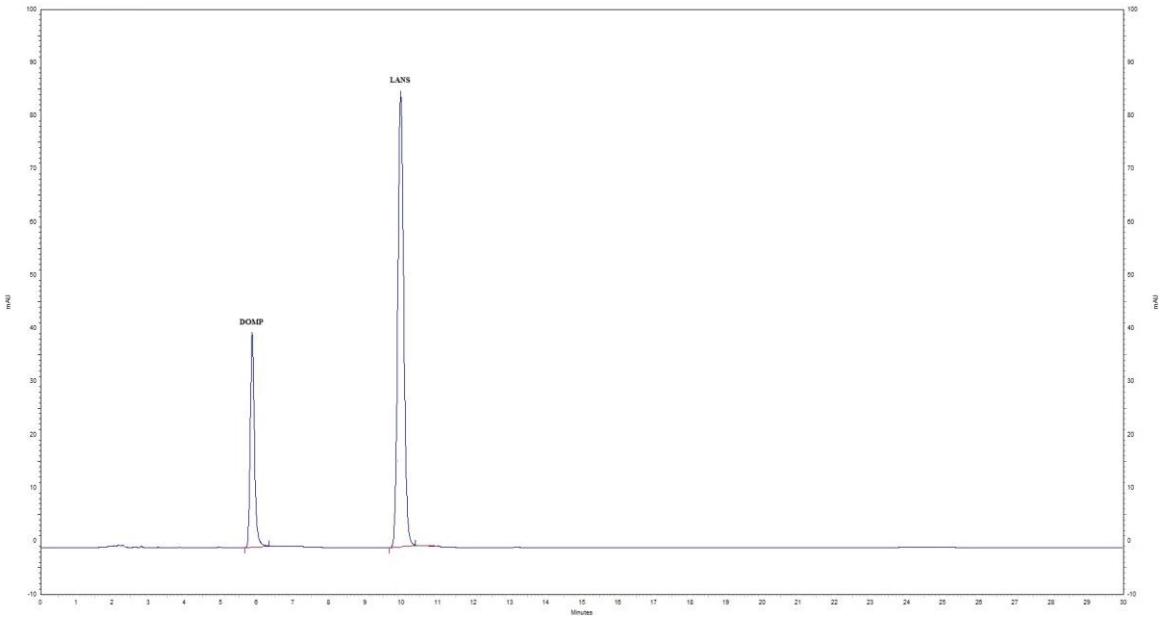


Figure 3 Chromatogram of Lansoprazole and Domperidone combination



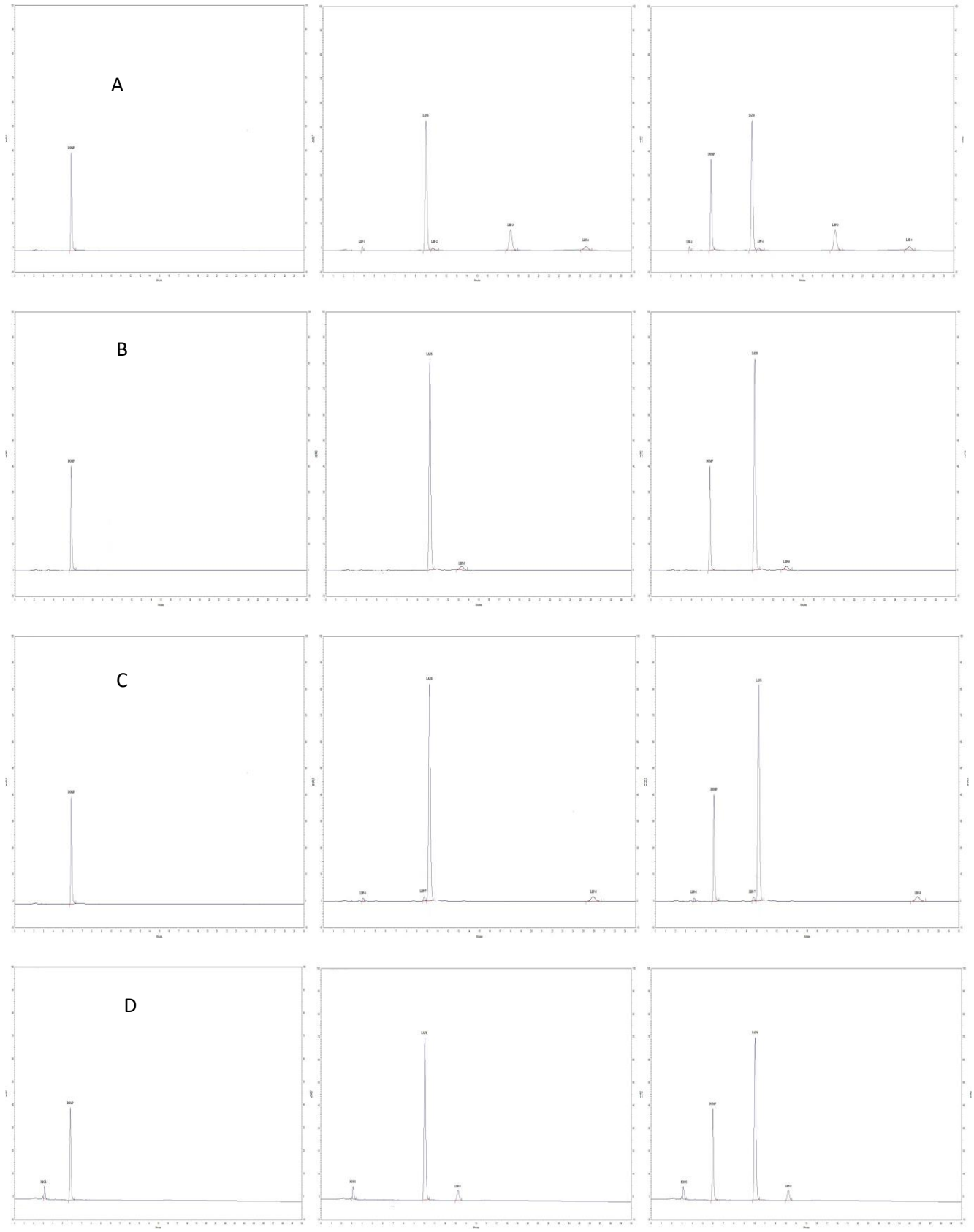


Figure 4: Results from forced degradation of Lansoprazole, Domperidone and Lansoprazole-Domperidone Mixture in A) 0.01 N HCL, 10 min. at room temperature, B) 0.1 N NaOH, 1hr. at 80°C, C) Neutral hydrolysis, 30 min. at 60°C, D) 1% H_2O_2, 1 hr. at room temperature