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Forced Degradation Study Of Lansoprazole And Domperidone By Hptlc

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Summary
A simple, precise, and accurate stability-indicating normal-phase HPTLC method has been established for simultaneous estimation of Lansoprazole (LAN) and Domperidone (DOM) in the bulk drug and dosage form. Chromatography was performed on silica gel $60F_{254}$ with toluene: methanol 8:2 (v/v) as mobile phase. Densitometric quantification was performed at 295 nm by reflectance scanning. The R_F value of DOM and LAN were 0.34 ± 0.03 and 0.50 ± 0.03 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 LAN over the range 375–3000 ng/band by peak area with correlation coefficient 0.99693 and DOM over the range 250–2000 ng/band by peak area with correlation coefficient 0.99372. The limit of detection of LAN was 1.70 ng per band for peak area and the limit of detection of DOM was 4.06 ng per band for peak area. Results from analysis of a commercial tablet formulation were 100.62 ± 0.0357 % and 100.00 ± 0.0388 % by peak area for LAN and DOM respectively. Recoveries were 100.06 ± 0.4690 % and 99.66 ± 0.2482 % by peak area for LAN and DOM 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: HPTLC, Lansoprazole, Domperidone, Degradant, Validation

Introduction

Lansoprazole (LAN) 2-({[3-methyl-4-(2, 2, 2-trifluoroethoxy)pyridin-2-yl]methane}sulfinyl)-1H-1,3-benzodiazole [Fig. 1] is a proton pump inhibitor which inhibits stomach acid production. Domperidone (DOM) 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 [Fig. 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 LAN and DOM by UV Spectroscopy in tablet and capsules single [4-7] and in combination with other drugs [8-14], HPLC in single [15-24] and in combination with other drugs [25-33] and HPTLC in combination with other drugs [34-36] has been reported. The proposed HPTLC method is suitable for simultaneous estimation of LAN and DOM 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 HPTLC method which is useful for analysis of LAN and DOM and its degradation products in pharmaceutical preparations on the basis of peak area.

Experimental

Chemicals, Reagents and Solutions

Pharmaceutical grade lansoprazole and domperidone were procured as a gift samples from Zydus Cadila Healthcare Ltd., Ahmadabad, Guj, (India) and VAMA Pharma, Nagpur, MS, (India), LEEDOM-15 a capsule formulation were obtained commercially.

Toluene, methanol, hydrochloric acid, sodium hydroxide and hydrogen peroxide 30% of analytical grade were used throughout the work.

To prepare standard solution, 15.0 mg LAN, accurately weighed and 10.0 mg of DOM standard stock solution were added and the volume was made up to 10.0 mL with the same solvent. One milliliter of resulting solution was diluted to 10.0 mL with methanol to furnish a solution of concentration 150 μg mL^{-1} and 100 μg mL^{-1} of LAN and DOM respectively.

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 LAN and DOM. LAN (15 mg) was weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, LAN (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 LAN 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 LAN 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, LAN 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, DOM (10 mg) was weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, DOM (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 DOM 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 DOM 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, DOM 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 LAN (15 mg) and DOM (10 gm) were weighed, mix and transfer into 10 mL volumetric flasks. LAN (15 mg) and DOM (10 mg) were weighed into 10 mL volumetric flasks and dissolved in 10 mL 0.01 M aqueous hydrochloric acid, For alkaline hydrolysis, LAN (30 mg) and DOM (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, LAN (30 mg) and DOM (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, LAN (15 mg) and DOM (10 mg) were suspended in 10 mL 1% H_2O_2 in volumetric flask and kept in dark at room temperature. For photo degradation, LAN and DOM 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 methanol to furnish concentrations of 1.5 mg mL^{-1} and 1.0 mg mL^{-1} of LAN and DOM respectively. From the solutions obtained 1 mL was withdrawn by pipette, transferred to a 10-mL volumetric flask, and diluted to volume with methanol to furnish a solution of concentration 150 µg mL^{-1} and 100 µg mL^{-1} of LAN and DOM respectively.

Chromatography

Chromatography was performed on 10 cm × 20 cm HPTLC plates coated with silica gel 60 F_{254}. Before use plates were washed with AR-grade methanol and activated at 115°C for 30 min. Samples (5 µL) were applied to the plates as bands 5 mm wide and 3 mm apart by use of a CAMAG Linomat IV automatic sample applicator equipped with a Hamilton syringe. The application rate was 5 s μL^{-1}.

Initially, pure drugs solution was chromatographed using single solvents to ascertain the movement of the drug. Use of toluene: methanol 8:2 (v/v) as mobile phase gives well separated peaks of drugs and separation of degradation products from drugs as well. The R_F value of DOM and LAN were found to be 0.34 ± 0.03 and

0.50 ± 0.03 respectively. Typical HPTLC densitogram (295 nm) was obtained from standard solution is shown in Fig. 3.

Then samples obtained from forced degradation were then chromatographed with the same mobile phase and it was found that densitogram obtained after acidic hydrolysis gave four degradation products of LAN at R_F value0.13 ± 0.03 (LDP-I), 0.27 ± 0.03 (LDP-II), 0.40 ± 0.03 (LDP-III) and 0.60 ± 0.03 (LDP-IV), alkaline hydrolysis gave degradation product of LAN at R_F values 0.44 ± 0.03 (LDP-V), Neutral Hydrolysis gave three degradation products of LAN at R_F values 0.15 ± 0.03 (LDP-VI), 0.22 ± 0.03 (LDP-VII) and 0.43 ± 0.03 (LDP-VIII), Oxidation gave degradation product of LAN at R_F values 0.19 ± 0.03 (LDP-IX) [Fig. 4]. No degradation products were obtained after photo and heat stress condition. No degradation product of DOM was found when same stress conditions applied alone or in combination with LAN. Toluene: methanol 8:2 (v/v) was therefore used as mobile phase and resulted in sharp, well defined, symmetrical peaks with no fronting when scanning was performed at 295 nm. There was no interference from common excipients present in the tablets. Linear ascending development to a distance of 180 mm was performed in a 20 cm × 20 cm CAMAG twin-trough chamber. Before the insertion of the plate, the chamber was saturated with mobile phase vapour for 10 min at room temperature and after the insertion of plate again saturated for 10 min. After development the plate was removed and dried with hot air drier. Densitometric scanning was performed at 295 nm with a CAMAG TLC Scanner III in reflectance–absorbance mode controlled by CATS 4 software (version 1.4.1; CAMAG) resident in the system. The slit dimensions were 4.00 mm × 0.45 mm and the scanning speed 20 mm s^{-1}. The radiation source was a deuterium lamp emitting continuous UV radiation between 190 and 360 nm. The amounts of the compounds chromatographed were determined from the intensity of diffusely reflected light.

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 LAN and 10 mg of DOM was transferred into a 10-mL volumetric flask. Then 5 mL of methanol was added in it. The flask contents were sonicated for 10 min to make the contents homogeneous. This solution was then diluted up to the mark with methanol. The resultant solution was filtered through Whatman Grade I filter paper. One millilitre of filtrate was transferred to a 10 mL volumetric flask and then volume was made up to the mark with methanol to furnish a sample solution containing 150 µg mL^{-1} of LAN and 100 µg mL^{-1} of DOM. Six replicate homogenous sample solutions were prepared in a similar manner.

Results and Discussion

HPTLC Method Development and Optimization

Normal phase HPTLC with toluene: methanol 8:2 (v/v) as mobile phase enabled satisfactory baseline resolution of the both API and all degradation products with reasonably acceptable R_F values for the purpose of quantification. R_F values were 0.34 ± 0.03 and 0.50 ± 0.03 for DOM and LAN respectively, 0.13 ± 0.03 (LDP-I), 0.27 ± 0.03 (LDP-II), 0.40 ± 0.03 (LDP-III) and 0.60 ± 0.03 (LDP-IV) for acidic hydrolysis, 0.44 ± 0.03 (LDP-V) for alkaline hydrolysis, 0.15 ± 0.03 (LDP-VI), 0.22 ± 0.03 (LDP-VII) and 0.43 ± 0.03 (LDP-VIII) for neutral hydrolysis, 0.19 ± 0.03 (LDP-IX) for oxidation degradation. No degradation products of LAN and DOM were obtained after photo and dry heat stress condition. No degradation product of DOM was found when same stress conditions applied alone or in combination with LAN.

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 375-3000 ng by area for LAN and 250-2000 ng by area for DOM. Peak areas were plotted against the respective concentrations and linear regression analysis performed on the resulting curves. Equation for the calibration plots of LAN was Y= 5670 + 8.339 X, for peak area. Correlation coefficient was 0.99693 for peak area. Equation for the calibration plots of DOM was Y= 1047+ 6.198 X, for peak area. Correlation coefficient was 0.99372 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 = $3.3\sigma/S$ and LOQ = $10\sigma/S$, where σ is the standard deviation of the regression line and S is the slope of the calibration plot. The LOQ of LAN for which precision and accuracy were satisfactory was 5.18 ng per band for peak area and LOD was 1.70 ng per band for peak area. The LOQ of DOM for which precision and accuracy were satisfactory was 12.32 ng per band for peak area and LOD was 4.06 ng per band for peak area.

Method, system and intermediate precision data are summarized in Table I. 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 III. Ruggedness was assessed out for different elapsed times (intraday and inter-day). The results (Table I) showed the method is rugged under these conditions. Robustness was studied by varying the detection wavelength by ± 2.0 nm, mobile phase composition (± 0.2 ml of methanol) and saturation time by ± 5 min. The results are listed in Table IV.

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 as per ICH guidelines. The method can therefore be used for routine quality-control analysis of lansoprazole and domperidone in combined dosage forms.

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Table I System, method, and intermediate precision data

Validation Parameters		**LAN**			**DOM**		
		Mean	**SD[±]**	**RSD [%]**	**Mean**	**SD[±]**	**RSD [%]**
System Precision [a)]		11920.76	15.4795	0.1298	4032.34	31.8198	0.7891
Method Precision [a)]		100.62%	0.0357	0.0355	100.00%	0.0388	0.0388
Intermediate precision	**Interday** [b)]	99.90%	0.0457	0.0458	100.90%	0.0882	0.0874
	Intraday [b)]	99.97%	0.0893	0.0893	100.42%	0.1521	0.1515
	Different Analyst [b)]	100.76%	0.0450	0.0447	99.88%	0.0744	0.0745

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 II Accuracy data

	Level [%]	Wt. of sample (mg)	Wt. of drug(mg)	Amount of standard added (mg)	Calculated Wt. Of drug (mg)	[%] Recovery
LAN	80	258.1	14.98	12.2	12.29	100.73
		258.2	14.98	12.0	12.08	100.66
		258.0	14.97	12.1	12.16	100.49
	100	258.4	15.00	15.0	15.01	100.06
		258.3	14.99	15.1	15.09	99.93
		258.0	14.97	15.1	15.08	99.86
	120	258.2	14.98	18.1	18.00	99.44
		258.2	14.98	18.0	17.99	99.94
		258.4	15.0	18.1	18.01	99.50
	Mean ±SD					100.06±0.4693
	RSD [%]					0.4690
	Level [%]	**Wt. Of sample (mg)**	**Wt. of drug(mg)**	**Amount of standard added(mg)**	**Calculated Wt. Of drug (mg)**	**[%]Recovery**
DOM	80	258.1	9.98	8.1	8.05	99.38
		258.2	9.99	8.1	8.06	99.50
		258.0	9.98	8.0	7.96	99.50
	100	258.4	10.0	10.1	10.08	99.80
		258.3	9.99	10.1	10.09	99.90
		258.0	9.98	10.1	10.07	99.70
	120	258.2	9.99	12.0	12.02	100.16
		258.2	9.99	12.1	12.04	99.50
		258.4	10.0	12.1	12.05	99.58
	Mean ±SD					99.66±0.2474
	RSD [%]					0.2482

Table III Specificity data

Formulation		Normal	Acid	Alkali	Oxide	Heat	UV
LEEDOM-15	**LAN**	99.94	81.99	95.15	95.33	99.91	99.97
	DOM	100.69	100.83	100.87	100.78	100.74	100.85

Table IV Robustness

Condition		LAN		DOM	
		By peak area*		By peak area*	
		Amount estimated [%] ± SD	RSD [%]	Amount estimated [%] ± SD	RSD [%]
Change in wavelength (295±2 nm)	293 nm	100.07 ± 0.0321	0.0321	99.94 ± 0.0700	0.0700
	297 nm	100.09 ± 0.0650	0.0650	99.80 ± 0.0802	0.0803
Change in mobile phase composition (±0.2 ml)	Toluene: methanol 8.2:1.8 (v/v)	100.00 ± 0.0264	0.0264	100.77 ± 0.0305	0.0303
	Toluene: methanol 7.8: 2.2 (v/v)	100.01 ± 0.0152	0.0152	100.86 ± 0.0458	0.0454
Change in saturation time (20±5min)	15 min	99.99 ± 0.0152	0.152	100.80 ± 0.0251	0.0249
	25 min	100.02 ± 0.0152	0.0152	100.96 ± 0.0513	0.0508

* Each value is a mean of three observations.

Fig. 1 Chemical structure of Lansoprazole

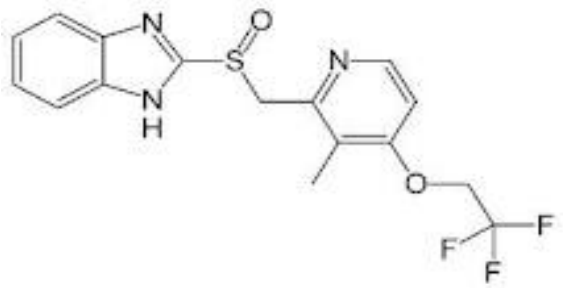


Fig. 2 Chemical structure of Domperidone

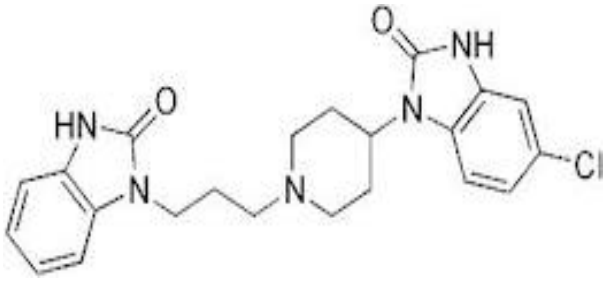
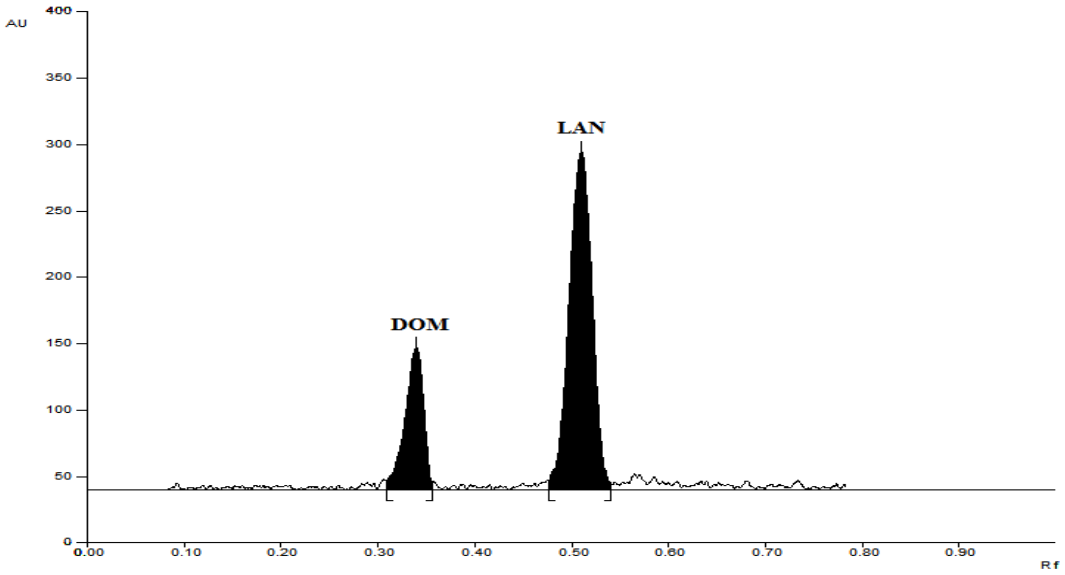


Fig. 3 Densitogram of Lansoprazole and Domperidone combination



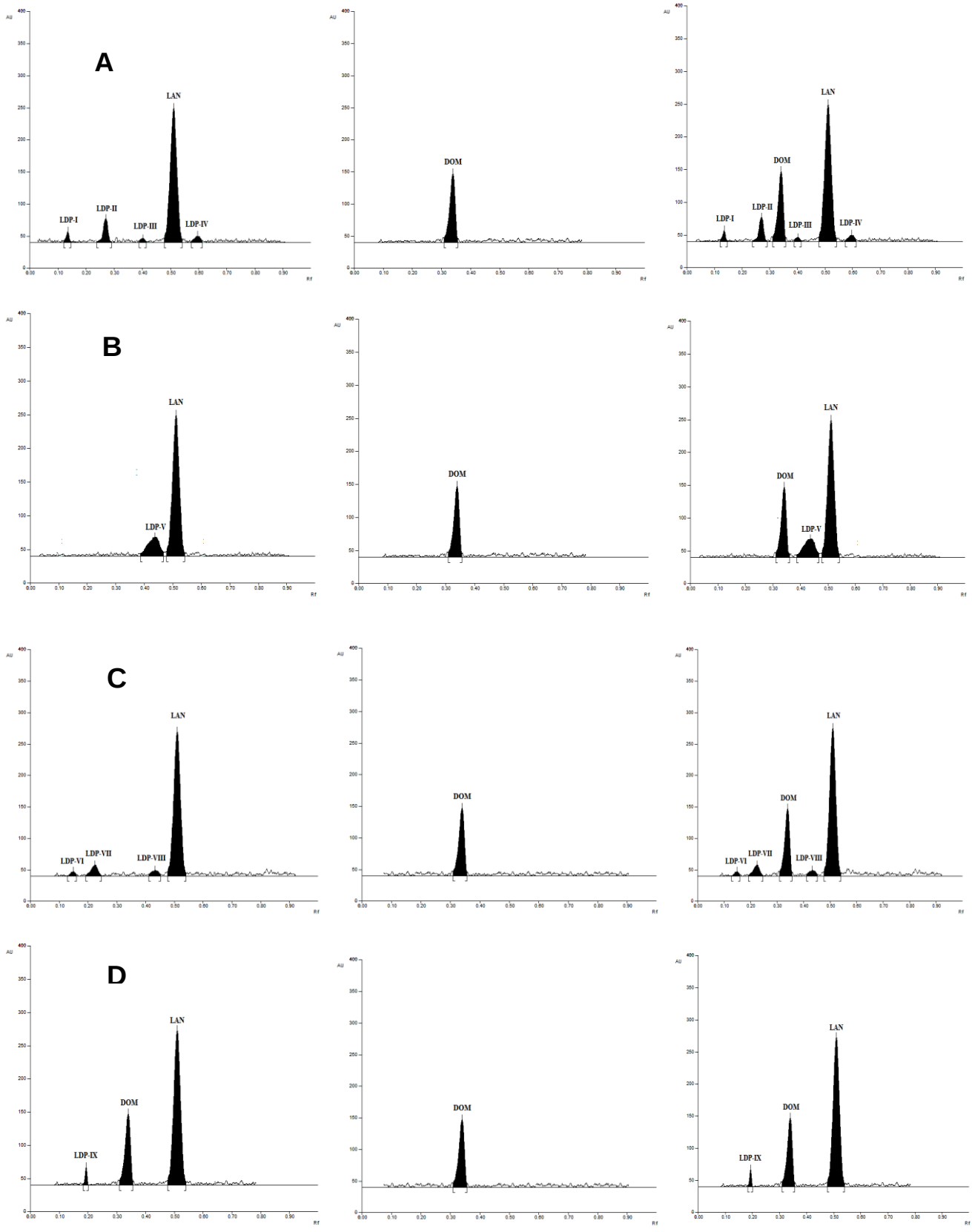


Fig. 4 **: Results from forced degradation of Lansoprazole, Domperidone and Lansoprazole-Domperidone Mixture in A) 0.01 N HCL, 10 min. at room temperature, B) 0.1 N NaOH, 1hr. at 80°C, C) Neutral hydrolysis, 30 min. at 60°C, D) 1% H_2O_2, 1 hr. at room temperature**