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Significance of Stress degradation study in the Stability indicating Analytical Technique development of Metoprolol, Ramipril and Lercanidipine

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ABSTRACT
Generally forced degradation/stress testing is used to generate the samples for stability-indicating assay methods. Forced degradation/stress testing is defined as "the stability testing of drug substance and drug product under conditions exceeding those used for accelerated stability testing". Degradation can be achieved by exposing the drug, for extended period of time, to extremes of pH (HCl or NaOH solutions of different strengths), at elevated temperature, to hydrogen peroxide at room temperature, to UV light, and to dry heat (in an oven) to achieve degradation to an extent of 5–20%.
The aim of the present work was to implement experimental design strategy in forced degradation experimentation and to arrive at optimum degradation conditions. For the same, metoprolol, ramipriland lercanidipinewere selected as a model drug. The percentage of degradation and standard deviation were 93.86% and 2.6882 – 9.7747 for MPS, 75.56% and 2.1122 – 12.4967 for RPL and 62.15% and 0.4397 – 3.0721 for LCH found. Stability data obtained in degradation study were found within acceptable limit.
Keywords: LercanidipineHCl, Ramipril, Metoprolol Succinate, degradation study, ICH guidelines

I. INTRODUCTION:

Generally forced degradation/stress testing is used to generate the samples for stability-indicating assay methods. Forced degradation/stress testing is defined as "the stability testing of drug substance and drug product under conditions exceeding those used for accelerated stability testing"[1].

Degradation can be achieved by exposing the drug, for extended period of time, to extremes of pH (HCl or NaOH solutions of different strengths), at elevated temperature, to hydrogen peroxide at room temperature, to UV light, and to dry heat (in an oven) to achieve degradation to an extent of 5–20%[1].

Forced degradation is a process of degradation of drug products and drug substances at conditions more severe than accelerated conditions[2]. Forced degradation studies helps to analyze the stability of drug samples in pharmaceutical industries, chemical stability of molecules effect on safety and efficacy of products[3].

Forced degradation helps to develop and validate stability indicating methods as per ICH guidelines. And also helps to propose shelf life of product without real time stability information. Degradation products or process related impurities arejustified [4].
International Conference on Harmonization (ICH) guidelinesmakes it mandatory to perform forced degradation study of drugs. Various ICH guidelines are applicable to forced degradation studies are[5, 6] –

a. ICH Q1A : Stability testing of new drug substances and products,
b. ICH Q1B : Photo stability testing of new drug substances and products,
c. ICH Q2B: Validation of analytical procedures: Methodology.

ICH Q1A (Stress Testing): The directions are to inspect the results of temperature, oxidation, PH range & photolysis.
ICH Q1B:this advices approach to assessing the photo stability of drug substances.
ICH Q2B: It advices the validation of analytical methods.[5, 6]

Degradation conditions:

1) **Hydrolysis:**The decomposition of a chemical compound by reaction with water is called hydrolysis.

International Journal of Pharmaceutical Research and Applications
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2) **Oxidation:** An electron transfer mechanism occurs in the oxidative degradation of drug substance. For oxidative forced degradation, hydrogen peroxide (H2O2) is broadly used.
3) **Photolytic:** Photo stability studies are performed to produced primary degradants of drug substance by exposure to UV or fluorescent conditions.
4) **Thermal:** Thermal degradation (e.g., dry heat and wet heat) should be carried at more strenuous conditions than recommended ICH Q1A accelerated testing conditions. Thermal degradation study is carried out at 40 - 80°C.
5) **Acidic and Alkaline:** In acidic and basic hydrolysis the catalysis of ionisable functional groups present in the molecules occurs. Forced degradation of a drug substance occurs when the drug interact with acid and base[5, 6]

Objectives of stress degradation study:

- To establish degradation pathway of drug substances and drug products.
- To elucidate the structure of degradation product.
- To determine the intrinsic stability of a drug substance in formulation.
- To understand the chemical properties of drug molecules.
- To generate more stable formulations.
- To solve stability related problems.

Drug Profile:

Metoprolol succinate(MPS)is a beta blocker; used in the treatment of hypertension, angina and to reduce myocardial infarction[7, 8]. Chemically it is (RS)-1-(Isopropylamino)-3-[p-(2-Methoxyethyl) phenoxy]-2-propan-2-ol succinate[9, 10].

Ramipril (RPL) is a highly lipophilic, long acting ACE inhibitor[7]. RPL is chemically (2S,3aS,6aS)-1-[(S)-2-[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino] propanoyl] octahydrocyclopenta [b] pyrrole – 2 - carboxylic acid[9, 10].

Lercanidipine Hydrochloride (LCH) is a dihydropyridine calcium channel blocker with actions similar to those of nifedipine[7]. It is used in the treatment of hypertension. Chemically lercanidipine is 1,4 dihydro-2,6 dimethyl-4(3-nitrophenyl)-3-5-pyridinedicarboxylic acid-3-[2[(3,3 diphenyl propyl)methyl amino]-1,1 dimethyl ethyl] 5 methyl ester[9, 10].

Metoprolol succinate and Ramiprilare official in IP[11] and BP[12]. The chemical structure of drug molecule is shown in Fig No 1.

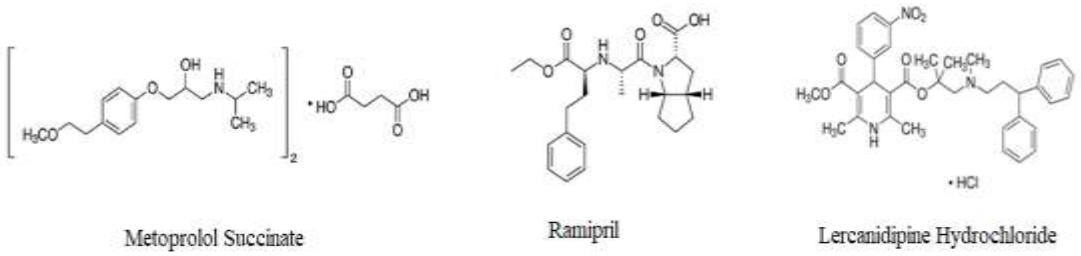

Fig No 1: Chemical structure of Drug Molecule

II. MATERIALS AND METHOD:

Instrumentation:

Analysis was performed with a Shimadzu Double beam UV - Visible spectrophotometer (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was utilised for weighing and for degassing the solutions Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

Chemicals:

Pharmaceutically pure samples of metoprolol succinate was procured from Lupin Pharmaceutical Limited (Maharashtra, India), Lercanidipine AND Ramipril were procured as a gift samples from Swapnaroop Pharmaceutical Aurangabad (Maharashtra, India) and the commercial formulationswere procured from local market. NaOH(AR grade), HCl(AR grade),

International Journal of Pharmaceutical Research and Applications
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H_2O_2(AR grade), Ethanol, methanolAR grade were utilized.

III. EXPERIMENTAL METHOD:

1) Stress degradation study of Metoprolol succinate[13] :

Solubility study and solvent selection of drug

Solubility of the MPS was determined by weighing 10 mg of drug and dissolving in 10 ml solvent at room temp i. e. 27±1°C; and the different solvents like distilled water, methanol, ethanol, HCL, NaOH were used for study. It was found that MPS was freely soluble in distilled watertheresultsaretabulated in table 1.In the present piece of research work distilled water was usedas a solvent.

Preparation of Stock solution (1)

Standard stock solution of metoprolol succinate was prepared by dissolving 50mg of drug in distilled water into 100 ml volumetric flask and making up the volume to 100ml to get 500µg/ml. Further solution was degassed by sonicating for 10 mins.

Preparation of Secondary stock solution (2)

From the stock solution (1) pipette out 5ml and was transferred into 50ml volumetric flask. The volume was made up to the mark with distilled water to get a solution having conc50 µg/ml.

Preparation of standard solutions for Linearity study

From stock solution (2) 1ml, 2ml, 3ml, 4ml, 5ml and 6ml solution was pipette out in six clean and dry test tubes and further the volume was made up to 10 ml with distilled water to get the concentrations of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml and 30µg/ml respectively.All these solutions were scanned in spectrum mode of UV-VIS spectrophotometer in the wavelength region from 400 nm to 200 nm. The absorbance was recorded at λ_{max}i.e. 221.5 nm and shown in Table No1. Calibration graph was plotted in Microsoft office excel tool and used for concdetermination of samples.

Table No 1: Absorbance of standard solutions of MPS in Linearity study

Sr. No.	Concentration (µg/ml)	Absorbance (Å) at wavelength 221.5 nm
1	5 µg/ml	0.1721
2	10 µg/ml	0.3359
3	15 µg/ml	0.4963
4	20 µg/ml	0.6298
5	25 µg/ml	0.7820
6	30 µg/ml	0.9121

Acid Stress degradation

For this study 3ml of stock solution (1) of MPS and 6ml of 0.5N HCL was transferred into 10ml volumetric flask and the volume was made up to the mark with water. The volumetric flask was kept at normal condition for 6 hours. After time interval 1ml, 2ml of solution was pipette out from this flask, and diluted with water in order to make the volume up to 25ml into 25 ml volumetric flask to achieve the expected concentration (6µg/ml, 12µg/ml). The absorbance of both the solutions was measured against blank (prepared without the drug).

Alkaline Stress degradation

To 3ml of stock solution (1) of MPS, 1ml of 0.1N NaOH was added into 10ml volumetric flask and volume was made up to the mark with water. Volumetric flask was kept at room temp for 6 hours. After time interval completion 1ml, 2ml of solution was pipette out, and diluted with water in order to make the volume up to 25ml into 25 ml volumetric flask to attain desired concentration (6µg/ml, 12µg/ml).The solutions were scanned in the wavelength region and absorbances were recorded.

Stressdegradation under thermal condition

From the stock solution (2) of MPS aliquots of solution was diluted to25 ml into 25ml volumetric flask to achieve the appropriate concentration (6µg/ml, 8µg/ml). Further the solutions were kept in hot air oven (dry heat) at 50°C for 6 hours. Then absorbance was recorded at 221.5 nm.

Stress degradation under oxidative condition

International Journal of Pharmaceutical Research and Applications
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To 1ml of the stock solution (2) of MPS, 1ml of Hydrogen peroxide was added into 10ml volumetric flask and the volume was made up to the mark with distilled water. The volumetric flask was then kept at room temperature for 6 hours. Similarly blank solution was prepared by diluting 1 ml of hydrogen peroxide to 10 ml and was kept for 6 hours. Then the absorbance was recorded.

Stress degradation study under photolytic condition

The2 mlMPS from stock (2) was diluted with distilled water to make volume of 10ml to get 10 µg/ml concentrations. Then this solution was exposed under sunlight for 6 hours; absorbance was recorded.

2) Stress of degradation study of Ramipril[14, 15]

Solubility study and solvent selection of drug

Solubility of drug was determined by weighing 10 mg of drug and dissolving in 10 ml solvent at room temp i. e. at 27±1°C. Pure drug was dissolved in various solvents like distilled water, NaOH, HCL etc. It wasfound that Ramipril was freely soluble in alkaline i. e. NaOH solution. Hence for the present study alkaline solution (NaOH)was used as a solvent.

Preparation of Stock solution (1)

Standard stock solution of RPL was prepared by dissolving 50mg of drug in 0.05N NaOHand making up the volume to 100ml into 100 ml clean and dry volumetric flask to getconc500µg/ml.

Preparation of stock solution (2)

From the stock solution (1) 5 ml solution was pipette out and placed into 50ml volumetric flask. The volume was made up to the mark with 0.05 N NaOH to obtain the conc 50µg/ml stock solution (2).

Preparations of the standard solutions for Linearity study

Similar procedure was followed as mentioned under linearity study of MPS. Series of standard

Solutions were obtained by diluting the aliquots of stock solution (2) to get conc 5µg/ml,

10µg/ml, 15µg/ml, 20µg/ml and 25µg/ml.All the solutions were scanned on the

Spectrophotometer and obtained absorbances at 215 nm were tabulated in following Table No 2. Calibration graph was obtained in the Microsoft offices excel and used for conc determination of samples in the degradation study.

Table No 2: Absorbance of standard solutions of RPL in Linearity study

Sr. No.	Concentration (µg/ml)	Absorbance (Å) at 215 nm
1	5 µg/ml	0.2317
2	10 µg/ml	0.4581
3	15 µg/ml	0.6842
4	20 µg/ml	0.8769
5	25 µg/ml	1.0842

Stress degradation under acidic condition

2 ml of stock solution (2) of RPL was transferred into 10 ml volumetric flask and 6ml of 0.5N

HCL was added. Then the volumetric flask was kept at laboratory condition for 6 hours. After time interval completion volume was made up to 10ml with 0.05N NaOH. The absorbance was measured.

Stress degradation under thermal condition

From the stock solution (2) of RPL dilutions were preparedin 10ml volumetric flask to achieve the appropriate concentration (10µ/ml, 15µg/ml). Thenthese solutions were kept in hot air oven at 50°C for 6 hours. Then was recorded the absorbance.

Stress degradation under oxidative condition

To 1ml of the stock solution (2) of RPL, 1ml of Hydrogen peroxide was added into 10ml of volumetric flask. The volumetric flask was kept at laboratory conditions for 6 hours; and the volume was made up to the mark with 0.05 N NaOH. Also For the blank preparation 1ml of Hydrogen peroxide was kept at room temp for 6 hours and volume was made to 10 ml into 10 ml volumetric flask. Then the absorbance was record.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1837-1846 www.ijprajournal.com ISSN: 2249-7781

3) Stress of degradation study of Lercanidipine Hydrochloride

Solubility and solvent selection of drug

Also solubility study of the drug LCH was carried out at27±1°C. Pure drug 10 mg was weighed and dissolved in 10 ml solvent. For solubility puposedifferent solvents like water, NaOH, HCL, ethanol and methanol were used. It was found that LCH was freely soluble in ethanol; hence it is used in the present investigational study.

Preparation of stock solution (1)

Standard stock solution of LCH was prepared by dissolving 50mg of drug with ethanol into 100 ml volumetric flask and volume was made up to 100ml to get conc500µg/ml.

Preparation of stock solution (2)

Aliquotes of the stock solution (1) 5 ml was pipette out and transferred into 50 ml volumetric flask and the volume was made up to the mark i. e. 50 ml with ethanol to obtain a solution having conc50 µg/ml.

Preparations of the standard solutions for Linearity study

Aliquotes of the stock solution (2) 0.4ml, 0.8ml, 1.2ml, 1.6ml and 2ml solutions was pipette out in five different 10 ml volumetric flask and made the volume up to 10ml with ethanol to obtain the accurate concentration 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml respectively. Absorbance of all the solutions were measured at 219.5 nm maximum wavelength (found after scanning in spectrum mode) Table No 3. Calibration graph was generated by plotting conc against absorbance in Microsoft office excel and used for conc determination of samples of degradation study.

Table No 3: Absorbance of standard solutions of LCH in Linearity study

Sr. No.	Concentration (µg/ml)	Absorbance (Å) at 219.5 nm
1	2 µg/ml	0.2262
2	4 µg/ml	0.3524
3	6 µg/ml	0.5035
4	8 µg/ml	0.4901
5	10 µg/ml	0.6332

Stress degradation under acidic condition

3ml of stock solution (1) of LCH was pipette out into 10 ml volumetric flask to this 6ml of 0.5 N HCL was added; the volumetric flask was kept atlaboratory condition for 6 hours. Further volume was made up to the mark with ethanol. After time interval, 1ml, 2ml, of solution was further diluted with ethanol in order to make the volume up to 25ml to achieve the appropriate concentration (6µg/ml, 12µg/ml). Then absorbance was recorded.

Stress degradation under alkaline condition

To 3ml of stock solution (1) of LCH, 1ml of 0.1N NaOH was added in 10ml volumetric flask and made up the volume to the mark with ethanol. Volumetric flask was kept at laboratory condition for 6 hours. After time interval 1ml, 2ml of solution was pipette out and diluted with ethanol into 25 ml volumetric flask to 25 ml in order to obtain the appropriate concentration (6µg/ml, 12µg/ml). The absorbance was recorded.

Stress degradation under oxidative condition

To 1ml of stock solution (2) of LCH, 1ml of hydrogen peroxide added into 10ml volumetric flask and the volume was made up to the mark with ethanol. The volumetric flask was then kept at room temperature for 6 hours. For the blank 1ml of hydrogen peroxide diluted to 10 ml was kept at room temp for 6 hours. Then the absorbance was recorded.

Stress degradation under photolytic condition

The 0.5 ml from stock solution (2) was diluted with ethanol to make volume of 10ml to obtain conc 5µg/ml. Then this sample was exposed under sunlight for 6 hours. And was recorded the absorbance.

IV. RESULT AND DISCUSSION:

The purpose of the degradation studies is to examine those changes, to get a shelf life for the drug product and to recommend storage conditions, which will be applicable to all forthcoming batches of the tested drug product manufactured and packaged under similar circumstances.

International Journal of Pharmaceutical Research and Applications
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Solubility study results

All three drug entity was studied for solubility and obtained inference was tabulated in Table No 4.

Table No 4: Results of solubility studies of drug

Sr. No.	Solvent	Solubility status		
		LercanidipineHCl	**Ramipril**	**Metoprolol succinate**
1	Ethanol	Soluble	Soluble	Sparingly soluble
2	NaOH	Insoluble	Freely soluble	soluble
3	HCL	Insoluble	Sparingly soluble	Sparinglysoluble
4	Distilled water	Insoluble	Sparingly soluble	Freely soluble

Calibration graph of drug

Linearity andthe beers law limit were studied Fig No 2 and 3 for these three drugs, and obtained calibration graph was employed to calculate the conc of prepared sample solutions. The obtained calibration graph Fig No4was studied with parameters like linear regression equation, slope and r^2valueare given in following Table No 5.

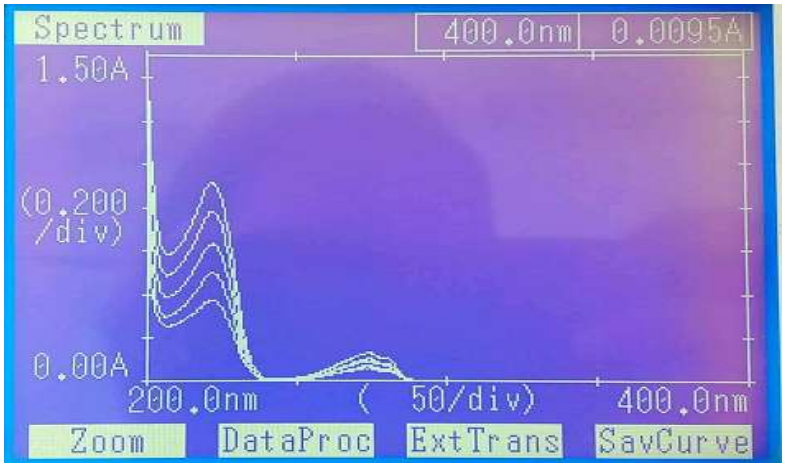

Fig No 2: Overlay UV spectra of MPS in linearity study

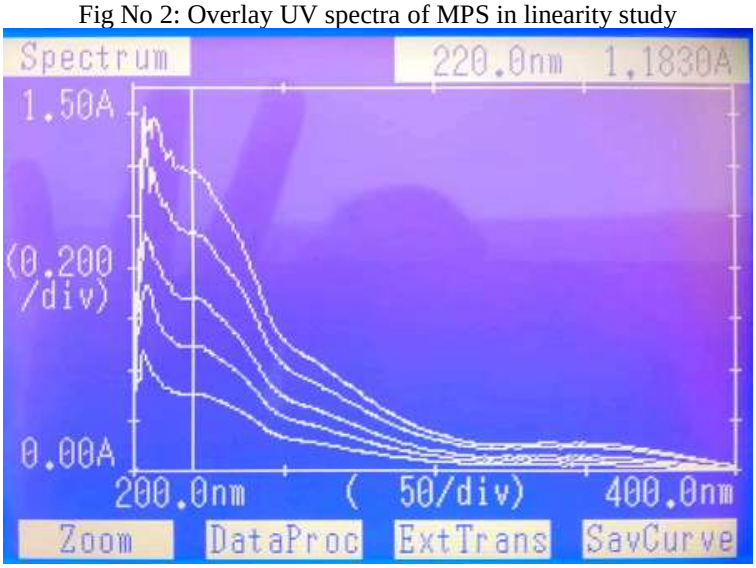

Fig No 3: Overlay UV spectra of LCH in linearity study

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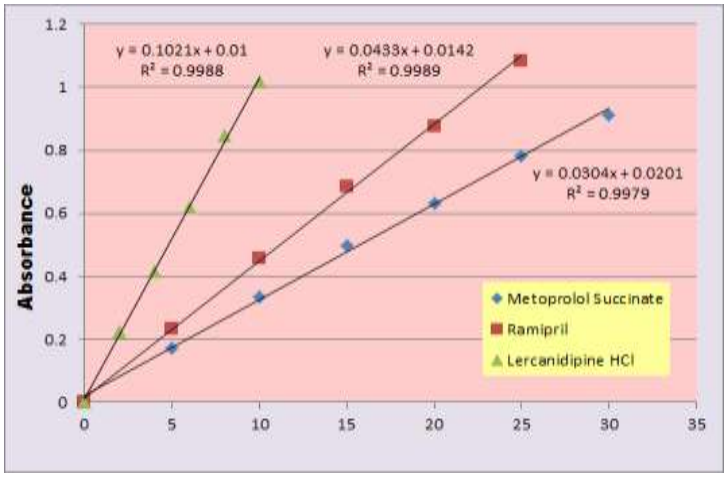

Fig No 4: Calibration graph of MPS, RPL and LCH

Table No 5: Linearity data results of MPS, RPL and LCH

Parameters	MPS	RPL	LCH
Detection wavelength	221.5 nm	215 nm	219.5 nm
Beer's law limit (µg/ml)	5 -30	5 - 25	2-10
Correlation coefficient (r)	0.9979	0.9989	0.9988
Regression equation (y = mx + c)	Y=0.0304X +0.0201	Y=0.0433X+ 0.0142	Y=0.1021X+0.01
Slope (b)	0.0304	0.0433	0.1021
Intercept (a)	0.0201	0.0142	0.01

Degradation study of Metoprolol succinate

UV spectra obtained in photostability study shown in Fig No 5 and Obtained data in stress degradation study were further studied by SD and RSD, to comprehend the methods precision. Various stresses of degradation exposed to MPS were affected; and decrease the drug down to 93.93 % was found in acid stress shown in Table No 6.

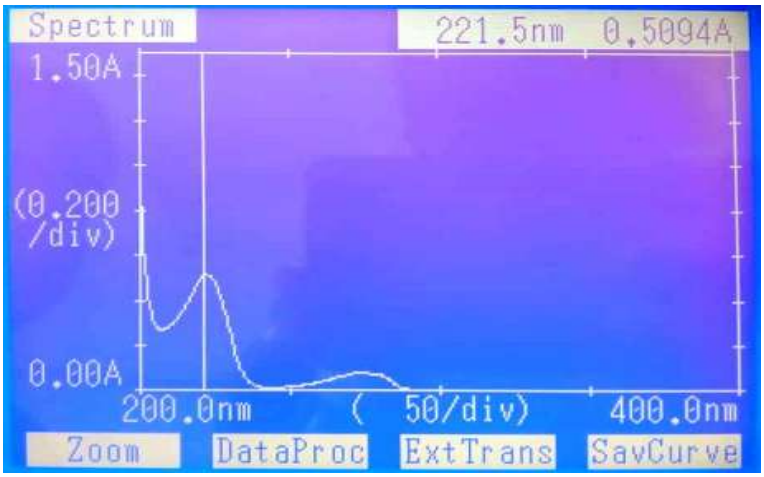

Fig No 5: UV spectra of photo stability study of MPS

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1837-1846 www.ijprajournal.com ISSN: 2249-7781

Table No 6: Results of stress degradation studies of MPS

. Sr No	Stress study	Conc of solution µg/ml	% of degradation found mean*	SD	% RSD
1	Acid	6	93.93	4.2875	4.5645
		12	+ 106.48	2.9440	2.7648
2	Alkali	6	+ 101.1	2.6882	2.6589
		12	95.33	5.9488	6.2402
3	Thermal	25	+ 114.66	9.7747	8.5249
		30	+ 114.26	4.6312	4.0532
4	Oxidative	5	93.86	4.6341	4.9372
5	Photolytic	10	+ 106.5	3.5001	3.2863

Degradation study of Ramipril

Obtained graph in thermal degradation study is shown in Fig No 6.Stress degradation data in RPL were found towards border line of acceptable limit, and calculated data are tabulated in Table No 7.

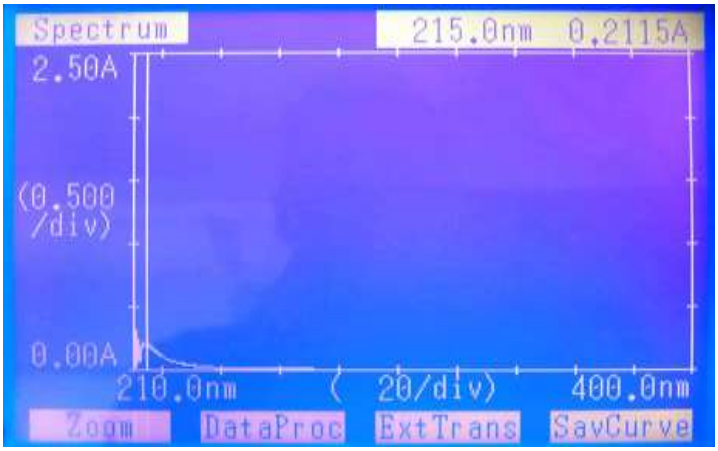

Fig No 6: Thermal degradationUV spectra of RPL

Table No 7: Results of stress degradation studies of RPL

Sr No	Stress study	Conc of solution µg/ml	% of degradation found mean*	SD	RSD
1	Acid	10	82.83	2.9425	3.5012
2	Thermal	10	84.10	2.1122	2.5121
		15	78.06	12.4967	16.2149
3	Oxidative	5	75.56	4.6251	6.1223

Degradation study of LercanidipineHCl

UV spectra obtained in acid degradation study is shown in Fig No 7.The percentage of degradation and SD calculated in validation of data Shown Table No 8were within acceptable limit, hence it indicates the stability of drug.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1837-1846 www.ijprajournal.com ISSN: 2249-7781

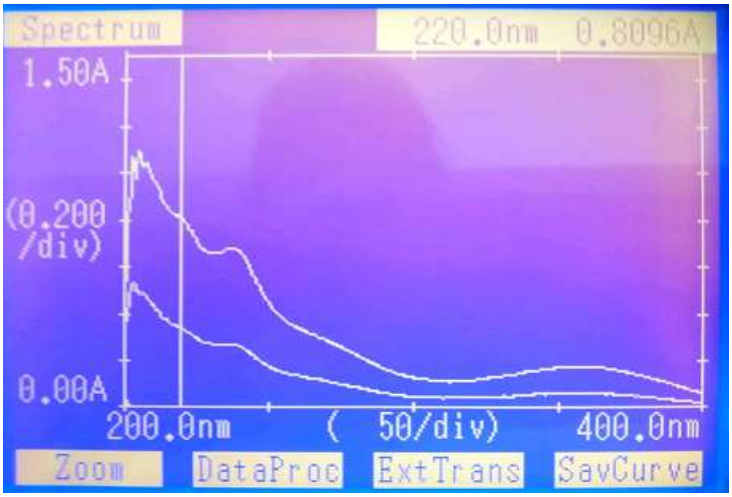

Fig No 7: Acid degradationUV spectra of LCH

Table No 8: Results of stress degradation studies of LCH

Sr No	Stress study	Conc of solution µg/ml	% of degradation found mean*	SD	RSD
1	Acid	6	64.56	2.7001	4.1901
		12	64.08	0.4397	0.6861
2	Alkali	6	65.24	1.7812	2.7302
		12	62.15	2.1252	3.4194
3	Oxidative	5	60.91	3.0721	5.0435
4	Photolytic	2.5	87.97	2.5013	2.8433

V. CONCLUSION

The stress degradation studies of these three drugs were carried out as per regulatory guidelines. Within acceptable range of the summarized data indicates stability of these drugs.

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Conflicts of Interest

The authors declared that they have no conflicts of interest.

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