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Stability Indicating RP- HPLC Method for the Determination of Niacin and Lovastatin In Bulk Drug and Tablet Formulation

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ABSTRACT

A new simple, rapid, precise, accurate and specific stability indicating method has been developed for the simultaneous estimation of Niacin (NIA) and Lovastatin (LOVA) in tablet dosage form. A chromatographic column used for separation was (250*4.6mm i.d., 5 mm) C_{18} (Hyperchrome ODS-BP).The mobile phase was 0.02M Disodium hydrogen Phosphate buffer:Acetonitrile (75:25, pH-5) and UV detection of effluent at 237nm.The flow rate was 1ml/min. The retention times of Niacin and Lovastatin were 3.29 min and 4.75 min, respectively. The range of Linearity for Niacin and Lovastatin were 125-325µg/ml and 5-25 µg/ml respectively**.** The recoveries of Niacin and Lovastatin were found to be in the range of 99.91-100.42 % and 100.03-100.41% respectively. The optimized RP-HPLC method proved to be specific, accurate and robust for the estimation of Niacin and Lovastatin in tablet dosage form. Stability testing study includes the acid hydrolysis, base hydrolysis, oxidation, thermal degradation, and photolysis.

Keywords: Niacin, Lovastatin, RP-HPLC Method

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INTRODUCTION

Hyperlipidemia is an excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called hyperlipoproteinemia. Hyperlipidemia, in general, can be divided into two subcategories: Hypercholesterolemia in which there is a high level of cholesterol. Hypertriglyceridemia in which there is a high level of triglycerides, the most common form of fat.Millions of patients worldwide now receive statins for hypercholesterolemia. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase enzyme and reduce plasma LDL. Statin is main group of drugs which is used for the treatment of hypercholesterolemia.

Niacin is chemically 3-pyridinecarboxylic acid. Niacin, a B vitamin, has long been used to increase high-density lipoprotein (HDL), or the "good," cholesterol. HDL cholesterol helps sweep up low-density lipoprotein (LDL), or the "bad," cholesterol, in bloodstream. The ability of nicotinic acid to strongly increase the plasma concentration of high-density lipoprotein (HDL) cholesterol has in recent years led to an increased interest in the pharmacological potential of nicotinic acid. There is increasing evidence that nicotinic acid alone or in addition to LDL cholesterol-lowering drugs can reduce the progression of atherosclerosis and reduce the risk of cardiovascular events.

Lovastatin is chemically [1 S -[1α(R*),3α,7β,8β(2 S*,4 S*), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2 methylbutanoate. Lovastatin is a lactone that is readily hydrolyzed in vivo to the corresponding β- hydroxyacid, a potent inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early and rate limiting step step in the biosynthetic pathway for cholesterol.

A thorough literature survey revealed that numerous analytical methods such as LC-MS/MS analytical method for estimation of Niacin in human plasma, capillary electrophoresis and high performance liquid chromatography: acid extraction method for estimation of Niacin in food. Analytical methods reported for quantitative determination of Niacin in combination with other drugs in pharmaceutical formulations are Spectrophotometry, HPLC,Stability indicating HPLC,HPTLC, liquid chromatographic tandem mass spectrometric. Some methods reported for the estimation of Lovastatin alone include reverse phase HPLC , HPLC stability-indicating method. Many analytical methods for Lovastatin in combination with other drugs including spectroscopic,HPLC-UV, liquid chromatography–electrospray ionization tandem mass

spectrometry,Liquid Chromatographic Method in Human plasma. Simultaneous determination of lovastatin and niacin in tablet by first and third derivative Spectrophotometry. In present article, reversed phase HPLC-Stability Indicating method was developed for the separation of Niacin and Lovastatin in tablet dosage form.

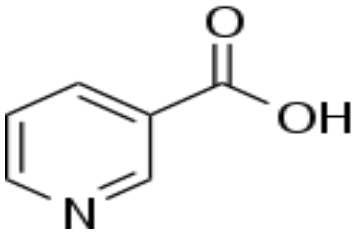

Figure.1: Chemical structure of Niacin

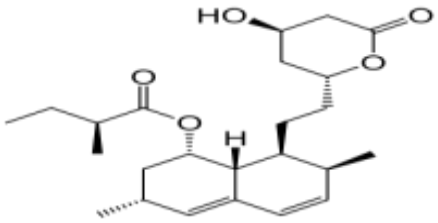

Figure.2: Chemical structure of Lovastatin

MATERIALS AND METHODS

Chemicals and Reagents

Niacin as a free gift sample was obtained from Vihita Chem Private Ltd, Ankleshwar and Lovastatin as a gift sample was obtained from Sterling Biotech Ltd, Vadodara.Marketed formulation having brand name Advicor [Niacin (500 mg) and Lovastatin (20 mg)] were procured from local market. HPLC grade Acetonitrile, Water and Methanol (RFCL Ltd., New Delhi) used. Di Sodium Hydrogen phosphate and Orthophosphoric acid (OPA) were of AR grade.

Buffer preparation

Disodium hydrogen phosphate(0.02M) was weighed 2.81gm and taken into a 1000 ml volumetric flask,800 ml water was added and dissolved. The pH 5.0 was adjusted with (1%) Orthophosphoric acid. Finally Volume was adjusted to 1000ml with water. It was filtered through 0.45 µm nylon membrane filter and degassed.

METHOD

Wavelength detection

Accurately weighed 250mg Niacin and 10 mg of Lovastatin in 100 ml volumetric flask ,diluted up to the mark with 100 ml of Acetonitrile, sonicated for 5 min and filtered through 0.45 µm nylon membrane filter. Pipette out 1 mL of the above solution and dilute to 10 mL with Acetonitrile in 10 mL volumetric flask and scanned between 200-400 nm by UV spectroscopy (Figure. 3).

Chromatographic conditions

The drug shows good absorbance at 237nm, which was selected as wavelength for further analysis at a Flow rate of 1mL/min and run time was 10 min. The injection volume was 20 µL

for estimation.

Standard preparation

Accurately weighed 250 mg of Niacin and 10 mg of Lovastatin and transferred into a 100 mL volumetric flask and make up to the volume with diluent. Pipette out 1 ml of the above solution is diluted 10 ml with mobile phase to get the final concentration of 250 µg/ml of Niacin and 10 µg/ml. A representative chromatogram of the standard was shown in Figure.4.

Sample preparation

Twenty tablets were weighed and powdered. The tablet powder equivalent to 500 mg of Niacin and 20 mg of Lovastatin was transferred in to a 100 ml volumetric flask, dissolved and diluted up to mark with solvent mixture Mobile phase. The solution was sonicating for 5 minutes. The solution was filtered through Whatman filter paper no. 41 and first few drops of filtrate were discarded. An aliquot of 5 ml of this solution was diluted to 100ml with Mobile phase. The resulting solution contained 250 (µg/ml) Niacin and 10 (µg/ml) lovastatin. A representative chromatogram of the sample was shown in the Figure.5 and Table 1.

Evaluation of System Suitability

System Suitability was performed by injecting five replicate injections of standard solutions of Niacin and Lovastatin at 100% & measured retention time, theoretical plates and tailing factor. The column efficiency was determined was found to be more than 2000 USP plate count, USP Tailing for the same peak is not more than 2.0 and % RSD of six injection of the standard solution is not more than 2.0%. The chromatogram was shown in Fig. 6 and Table 2.

ANALYTICAL METHOD VALIDATION (ICH, 2005)

Specificity

Placebo solution was prepared and injected in to the HPLC system following the test conditions; the chromatogram was recorded and measure the responses of the peaks. They were noted for any interference of the excipient at the retention time of drugs. (Figure.7).

Linearity

The linearity of the HPLC method was established for Niacin and Lovastatin solutions ranging from 125-625 µg/ml for Niacin and 5-25 µg/ml for Lovastatin. The values obtained for the correlation coefficients were 0.9999 for NIA and 0.9991 for LOVA,

Accuracy

The percentage Recovery studies were carried out at three different levels of 80%, 100% and 120% of standard solution in triplicate in each level. Known amounts of standard solutions of NIA (200, 250 and 300µg/ml) and LOVA (8, 10 and 12 µg/ml) were added to prequantified

sample solutions of tablet dosage forms. The percentage recoveries of Niacin and Lovastatin for RP-HPLC method was in the range of 99.91-100.42%and 100.03-100.41% respectively. (Figure 8 and Table 3).

Precision

Precision was measured in terms of repeatability of application and measurement. Repeatability of standard application (system precision) was carried out using six replicates of the sample injection (100 µg/ml). Repeatability of sample measurement (method precision) was carried out in six different sample preparations from the same homogenous blend of the marketed sample (100 µg/ml). The percentage RSD for repeatability of standard preparation was 1.16 % where as the %RSD for repeatability of the sample preparation was 0.02 %. This shows that the precision of the method is satisfactory as percentage RSD is not more than 2 % the chromatogram was shown in (Figure.9, 10 and Table 4).

Robustness

The robustness of the proposed method was determined by analysis of aliquots from homogenous lots by differing physical parameters like flow rate and wave length which may differ but their responses were still within the specified limits. (Table 5).

Limit of detection (LOD) and Limit of quantification (LOQ)

LOD values for NIA and LOVA were found to be 4.67 µg/mL and 0.46 µg/mL, respectively. LOQ values for NIA and LOVA were found to be 15.62 µg/mL and 1.54 µg/mL, respectively These data showed that the method was sensitive enough for the determination of NIA and LOVA. (Table 6).

Forced Degradation study of NIA & LOVA

Niacin (250mg) and Lovastatin (10mg) were accurately weighed and transferred to a separate 100 ml volumetric flask, dissolved in sufficient quantity of mobile phase buffer(0.02mNa_2HPO_4,pH5.0). **Acetonitrile** (75:25v/v)and then diluted to the mark with Mobile phase. (The solution contains 2500 µg/ml of Niacin and 100 µg/ml of Lovastatin). The final solution was labeled as Standard Solutions for Degradation. Twenty tablets were weighed and powdered.The tablet powder equivalent to 500 mg of Niacin and 20 mg of Lovastatin was transferred to a 100 ml volumetric flask, dissolved and diluted up to mark with solvent mixture Mobile phase.The solution was sonicated for 5 minutes. The solution was filtered through Whatman filter paper no. 41 and first few drops of filtrate were discarded. An aliquot (5 ml of this solution was diluted to 100ml with Mobile phase. The resulting solution contained 250 (µg/ml) Niacin and 10 (µg/ml) lovastatin.

Acidic Hydrolysis-

1 ml of forced degradation standard stock solution and sample solution were transferred in to 10 ml of volumetric flask. 2 ml of 0.1 M HCl solution was added and mixed well. The volumetric flasks were refluxed at 70°C for 2 hrs. After time period the content was cooled to ambient temperature. The above solutions were neutralized with 2 ml of 0.1 M NaOH solution and then diluted the volume with diluents. (Table.7).

Base degradation:

1 ml of forced degradation standard stock solution and sample solution were transferred in to separate 10 ml of volumetric flasks. 2 ml of 0.1 M NaOH solution was added and mixed well. The volumetric flasks were refluxed at 70°C for 2 hrs. After time period the content was cooled to ambient temperature. The above solution was neutralized with 2 ml of 0.1 M HCL solution and then diluted the volume with diluents. (Table.8)

Oxidation Degradation

1 ml of forced degradation standard stock solution and sample solution were transferred in to separate 10 ml of volumetric flasks. 2 ml 3% H_2O_2 was added and refluxed the volumetric flasks for 2 hrs at 70°C, after time period content was cooled to ambient temperature and diluted to volume with diluents. (Table.9)

Thermal Degradation

1 ml of forced degradation standard stock solution and sample solution were transferred in to separate 10 ml of volumetric flasks. The volumetric flasks were stored in oven at 105°C for 2 hrs. After time period the content was cooled to ambient temperature and diluted to volume with diluents. (Table.10)

Photo degradation

1 ml of forced degradation standard stock solution and sample solution were transferred in to separate 10 ml of volumetric flasks and exposed to Sun light for 2 hrs. (Table.11)

RESULTS AND DISCUSSION

For conventional determination of Nia and lOVA several Mobile phase composition were tried.most efficient resolution and peak symmetry for Niacin and Lovastatin were achieved with the mobile phase composed of 0.02mM Disodium Hydrogen phosphate buffer (Na_2HPO_4) pH5.0:Acetonitrile (75:25,v/v). Quantification of the drugs was performed at 237 nm using chromatographic conditions like Hyperchrome ODS-BP(250*4.6mm) C18 Column,1ml/min flow rate,20 10 µL injection,10 min run time.

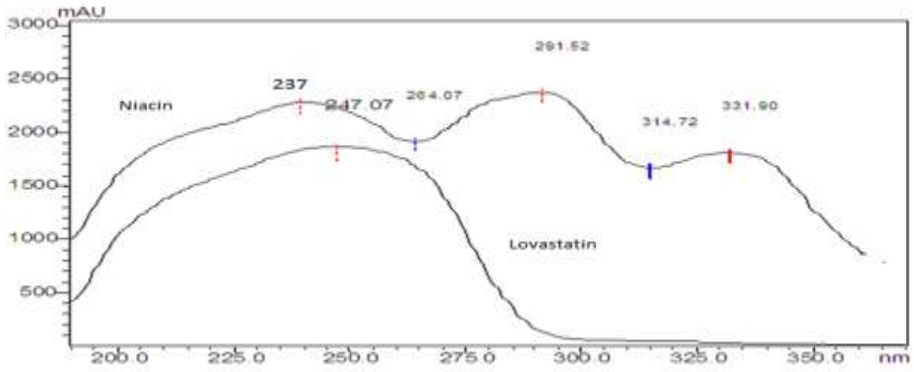

Figure. 3: UV Absorbance spectra

Retention time for NIA and LOVA were 3.260 and 4.707 respectively. The results of the system suitability tests assure the adequacy of the proposed HPLC Method for routine analysis of NIA and LOVA. Figure. 6 and Table 2.The instrumental precision gave 0.375 and 0.674 %RSD for NIA and LOVA respectively. Specificity of the method was checked by injecting the placebo solution, no peaks were found at the retention time of NIA and LOVA.

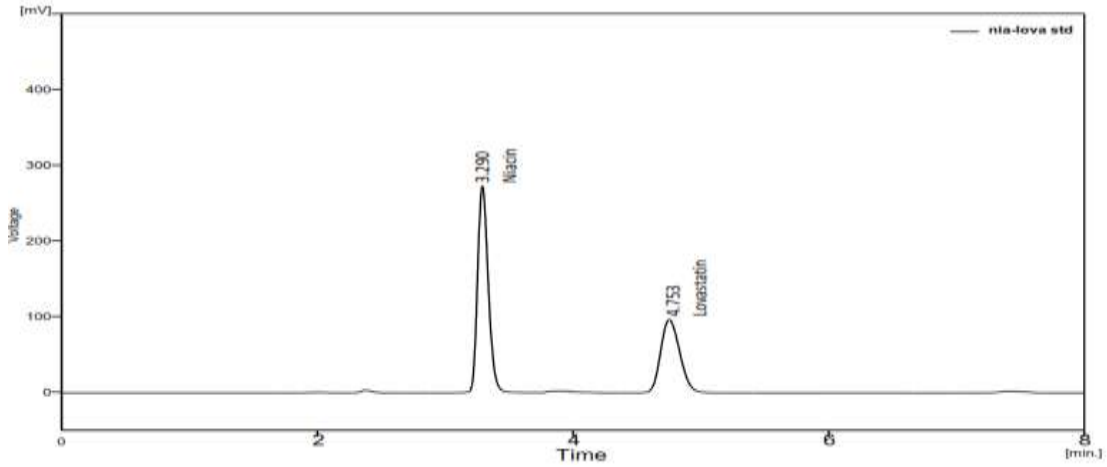

Figure.4: Standard chromatogram

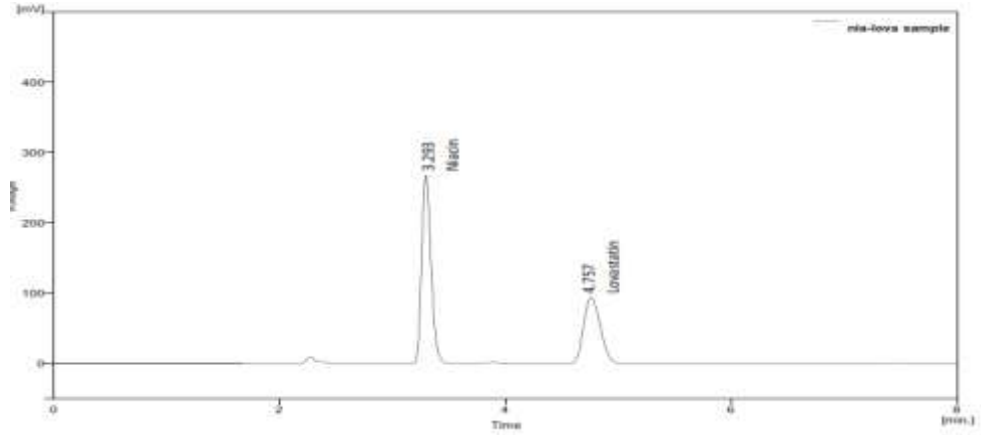

Figure.5: Test chromatogram

Table 1: Analysis of marketed formulations

Niacin			**Lovastatin**		
Labelled Claim(mg)	**Amt found**	**% Purity**	**Labelled Claim(mg)**	**Amt found**	**%Purity**
500	493	98.68	20	19.85	99.25
	497.2	99.44		19.98	99.9
	491	98.2		19.74	98.7
	495.4	99.08		19.78	98.9
	494.3	98.85		19.66	98.3
Mean	494.176	98.85	**Mean**	19.8	99.01
SD	2.352	0.462	SD	0.121	0.605
% CV	0.475	0.467	**% CV**	0.611	0.611

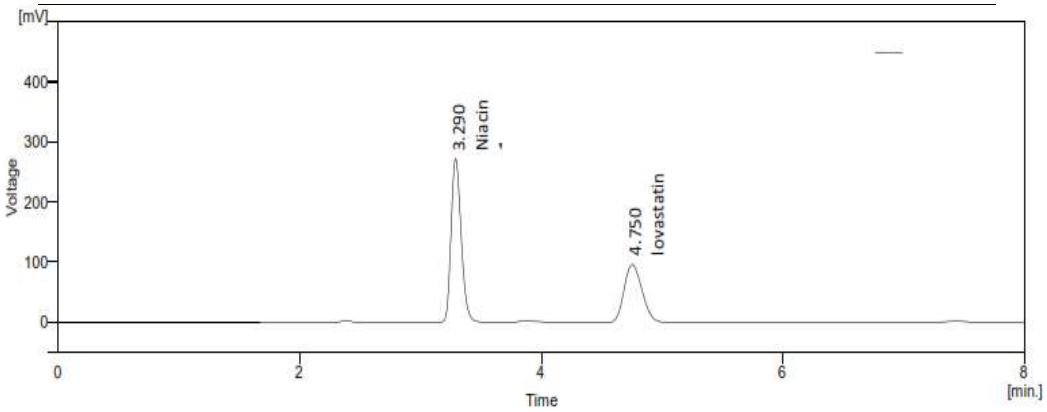

Figure.6: System Suitability Chromatogram

Table 2: System suitability study

Parameter	**Niacin (MEAN ± SD)**	**Lovastatin (MEAN ± SD)**
Retention time (min)	3.29 ±0.0025	4.756 ± 0.0035
Theoretical plates	7003 ± 114.32	4506.33± 6.50
Tailing factor	1.39± 0.06	1.31 ±0.0025
Resolution	6.68±0.065	

Linear correlation was obtained between peak areas and concentrations of NIA and LOVA having. The calibration curve was linear over the concentration range of 125-625 µg/ml for niacin and 5-25 µg/ml for Lovastatin. The correlation coefficient in both cases were found to be 0.9999 and 0.9991 respectively. Intermediate Precision was done by changing the analyst, column, with the same chromatographic conditions and the obtained results were within the limits. The robustness of the proposed method was determined by analysis of aliquots from homogenous lots by differing physical parameters like mobile phase flow rate and wave length which may differ but the responses were still within the specified limits. The percentage

recoveries of Niacin and Lovastatin was in the range of 99.91-100.42%and 100.03-100.41% respectively.

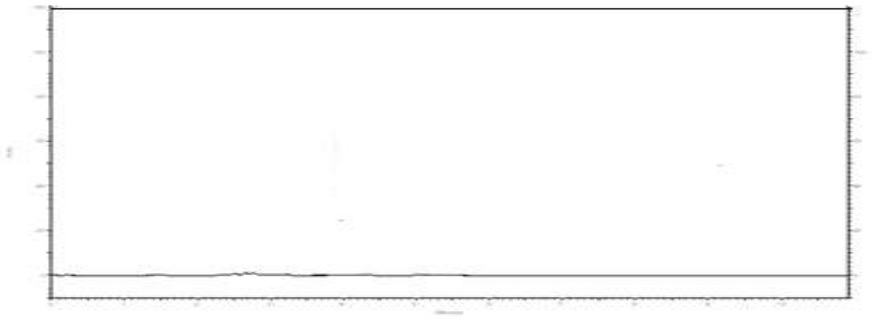

Figure.7: Placebo (Specificity) Chromatogram

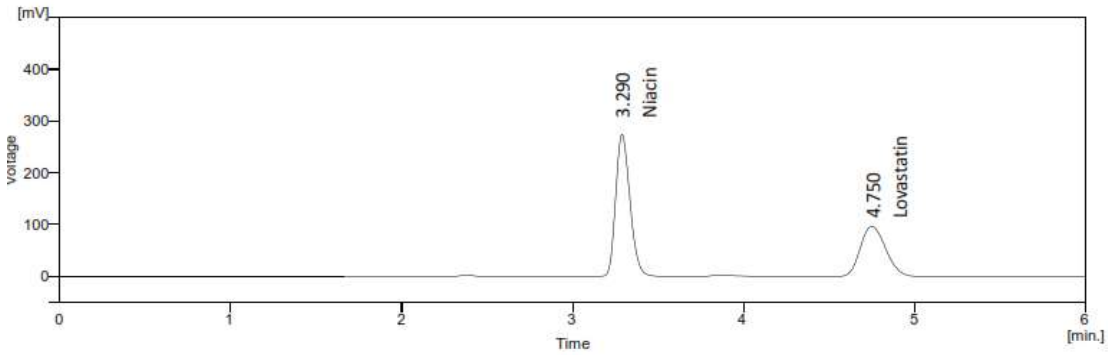

Figure.8 : Accuracy Chromatogram

Table 3: Accuracy study

Amount OF Niacin (µg/ml)	% OF STD Niacin Added	Amount Found	% Recovery (Mean ± SD)	Amount OF Lovastatin (µg/ml)	% OF STD Lovastatin ADDED	Amount Found	% Recovery (MEAN ±SD)
250	80	200.47		10	80	8.03	
		201.57	100.34±0.39			8.07	100.04±1.190
		200.03				7.89	
	100	252.23			100	10.10	
		250.47	99.91±1.14			10.03	100.03±1.245
		246.64				9.86	
	120	302.97			120	12.13	
		299.18	100.42±0.64			11.98	100.41±0.661
		301.68				12.02	

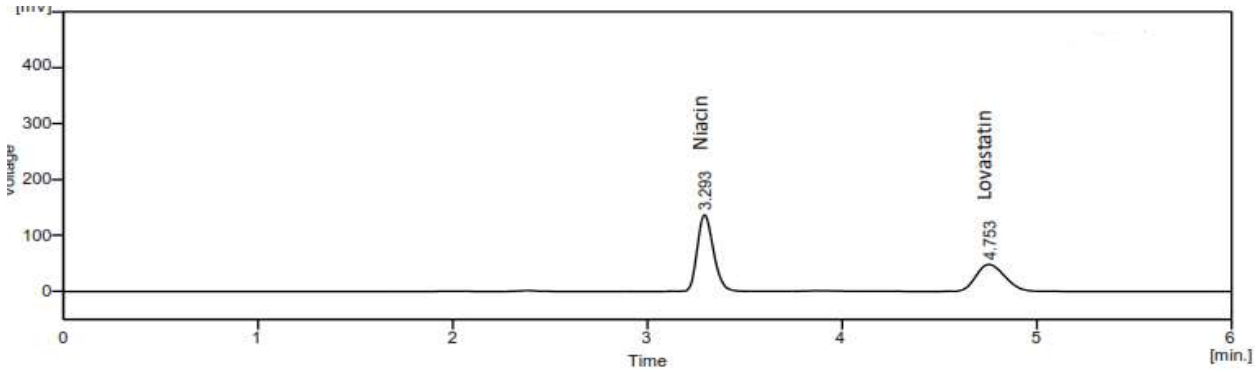

Figure. 9: Precision Chromatogram

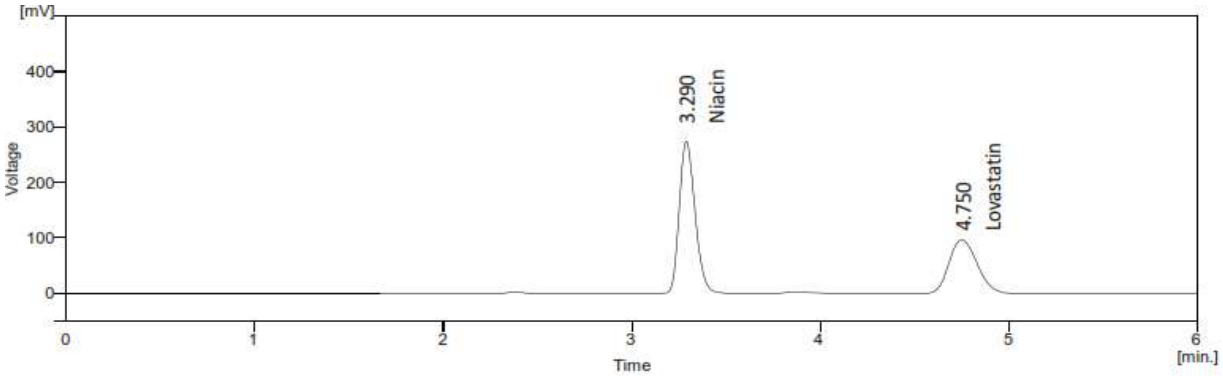

Figure. 10: Intermediate Precision Chromatogram

Table 4: Precision study

conc. OF Niacin(µg/ml)	Area	Conc. OF Lovastatin (µg/ml)	Area
375	1579.26	15	993.36
	1574.25		996.50
	1580.01		989.22
	1575.31		981.11
	1582.15		999.12
	1578.14		997.33
MEAN	1578.18	**MEAN**	992.77
SD	2.96	**SD**	6.69
% CV	0.37	**% CV**	0.67

Table 5: Robustness study

System suitability parameters (Variations)	%RSD of peak area response		Mean tailing factor (n=3)		Mean retention time in min.(n=3)	
	NIA	**LOVA**	**NIA**	**LOVA**	**NIA**	**LOVA**
Organic Phase **+2**-2	1.546	1.174	1.381	1.316	3.28	4.73
	1.49	1.25	1.397	1.307	3.28	4.73
Changein pH +2-2	1.40	1.41	1.381	1.316	3.28	4.73
	1.308	1.246	1.381	1.3o7	3.27	4.72
Changeinflow +2-2	1.108	1.082	1.30	1.33	3.12	4.50
	0.85	0.78	1.409	1.328	3.45	4.98

LOD values for NIA and LOVA were found to be 4.67 µg/mL and 0.46 µg/mL, respectively. LOQ values for NIA and LOVA were found to be 15.62 µg/mL and 1.54 µg/mL, respectively. Table 6

Table 6: LOD and LOQ

Conc of Niacin (µg/ml)	Mean Area ± SD (n=5)	% CV	Conc of Lovastatin (µg/ml)	Mean Area ± SD (n=5)	% CV
125	791.860± 3.096	0.399	5	495.898±3.126	0.681
250	1188.892± 2.333	0.196	10	749.151±5.104	0.681
375	1578.198± 3.314	0.209	15	990.626±1.629	0.164
500	1957.721± 4.130	0. 210	20	1203.299±6.952	0. 577
625	2368.658±6.274	0.264	25	1490.799±3.797	0.254

In Stability indicating method both the drugs subjected to acid and alkali hydrolysis, chemical oxidation, Thermal degradation and Photo degradation conditions. The peaks of the degradation products were well resolved from the drug peaks.

Table 7: Acid Degradation

Degradation Peaks	R.T	Area	Resolution	Theoretical plates	Tailing factor
1	1.987	1.919	-	2699	1.000
2	2.433	258.296	2.354	1845	1.484
3	2.633	52.158	0.917	2526	3.714
4	3.270	1375.418	3.458	6800	1.381
5	3.627	9.950	1.825	3901	0.893
6	3.817	37.885	0.664	2018	2.656
7	4.720	888.841	2.899	4443	1.289
8	5.163	56.540	1.597	5769	1.541
9	6.427	101.147	3.982	5028	1.313
10	7.370	20.832	2.775	8636	1.333
11	7.717	50.800	0.770	2799	2.173
12	9.233	74.199	2.338	2677	1.560

Table 8: Base Degradation

Degradation Peaks	R.T	Area	Resolution	Theoretical plates	Tailing factor
1	1.987	1.972	-	2510	0.967
2	2.467	351.622	2.456	1805	2.361
3	3.270	1362.254	4.110	6800	1.381
4	3.843	31.220	2.300	2046	2.765
5	4.720	866.152	2.814	4443	1.289
6	5.253	83.836	1.712	3822	1.404
7	6.363	180.306	2.375	1831	2.245
8	7.370	21.876	2.194	8336	1.564
9	9.137	84.984	3.427	2664	1.548

Table 9: Oxidation Degradation

Degradation Peaks	R.T	Area	Resolution	Theoretical plates	Tailing factor
1	1.987	1.946	-	2510	1.000
2	2.450	454.118	2.406	1871	2.625
3	3.270	1343.725	4.257	6800	1.381
4	3.537	21.423	0.914	1109	3.000
5	3.837	31.470	0.785	2039	3.400
6	4.340	130.891	1.709	4851	1.333
7	4.720	863.209	1.427	4443	1.289
8	5.603	64.805	3.150	6520	1.514
9	6.230	95.344	1.639	2617	1.579
10	7.370	20.697	2.834	8636	1.538
11	8.387	65.933	2.149	2846	2.255

Table 10: Thermal Degradation

Degradation Peaks	R.T	Area	Resolution	Theoretical plates	Tailing factor
1	3.553	2.663	-	5446	1.692
2	4.463	258.305	2.818	1552	1.320
3	5.260	12.786	1.863	2737	1.909
4	5.733	47.792	1.038	2023	1.241
5	6.407	181.870	1.862	7286	1.415
6	7.983	404.272	4.678	7295	1.420
7	9.047	78.533	2.391	4928	1.338
8	10.097	1428.857	2.131	7378	1.391
9	17.180	131.262	9.963	5214	1.290

Table 11: Photolytic Degradation

Degradation Peaks	R.T	Area	Resolution	Theoretical plates	Tailing factor
1	1.987	2.206	----------	2048	1.069
2	2.453	477.860	2.321	1876	2.625
3	2.947	19.938	1.759	1244	2.842
4	3.270	1386.08	1.327	7313	1.429
5	3.617	110.658	1.883	4517	1.357
6	3.837	31.137	0.769	1849	3.875
7	4.720	880.187	2.785	4626	1.351
8	5.247	157.888	1.603	3058	1.475
9	7.370	21.287	6.095	8636	1.564
10	11.860	32.814	10.639	8109	1.581

Table 12: Force degradation summary

Stress condition	Niacin			Lovastatin		
	Area	R.T	% Degradation	Area	R.T	% Degradation
As such	1570.315	3.290	-	988.22	4.753	-

Acid	1375.418	3.270	12.41133148	866.152	4.720	12.35231021
Base	1362.254	3.270	13.24963463	864.58	4.720	12.5113841
Oxidation	1343.725	3.270	14.42958897	863.209	4.720	12.65011839
Thermal	1327.862	3.270	15.43976845	833.303	4.720	15.67636761
Photolytic	1386.081	3.270	11.73229575	880.187	4.720	10.9320799

CONCLUSION

The proposed Stability Indicating RP-HPLC method was found to be accurate, specific and reproducible for the quantitative determination of NIA and LOVA. No co-eluting peaks with the main peaks and no interference from degradation products to main peak. The method shows linear response in stated range and is accurate and precise. The method was completely validated showing satisfactory data for all method-validated parameters tested. The developed method can be conveniently used as a Stability Indicating method for the determination of Niacin and Lovastatin in bulk drugs and pharmaceutical dosage form.

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