Original Article

RP-HPLC Accelerated Degradation Method Development and Validation for Determination of Amlodipine and Atorvastatin in Combination Dosage Form of Tablet

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ABSTRACT

Aim: The Cost effective, Accurate, Precise Accelerated degradation method has been developed for determination of Atorvastatin and Amlodipine in combination dosage form of tablet and validated as directed by ICH guidelines. **Objectives:** To develop and validate analytical method which can be easily adoptable in frequent analysis of Amlodipine and Atorvastatin combinations in the laboratories. **Materials and Methods:** The 0.02 M potassium dihydrogen phosphate: acetonitrile: methanol (30:10:60 v/v/v) was used as mobile phase and pH 4 adjusted using ortho phosphoric acid at flow rate 1.0 ml/min. The column used for method development was Octadecylsilane-C_{18} (5 μm, 25 cm $\times$ 4.6mm, i. d.). The peaks obtained in the chromatogram were well resoluted. The scanning wavelength used was 244 nm with PDA detector. **Results:** The linearity for both the drugs was found between 05 - 30 μg/ml for both drugs with regression coefficient equation 0.995 and 0.999 at retention time 8.32 min and 11.09 min for Amlodipine and Atorvastatin respectively. The results obtained were statistically validated as directed by ICH guidelines and was found satisfactory. **Conclusion:** The developed and validated method was found to be very specific, accurate and precise. It can be utilized for routine analysis of combined dosage form of Amlodipine and Atorvastatin in the laboratory.

Key words: Amlodipine, Atorvastatin, RP-HPLC, ICH Guidelines, PDA Detector, Validation.

INTRODUCTION

Amlodipine[1,2] is calcium channel blocker used for hypertension in adults and in case of children's above 6 years. The angina (chest pain) and coronary artery disease also can be treated with this drug. Atorvastatin,[3,4] HMG-CoA reeducates inhibitors (statins) used to reduce low-density lipoprotein (LDL) cholesterol and triglycerides and are responsible for increasing high-density lipoprotein (HDL) cholesterol in the blood. The chemical structures of both the drugs are shown in Figure 1. This combination is a unique one used to reduce hypertension and high cholesterol in the body which gives patient compliance.

As per the literature survey Amlodipine single or in combined dosage form with Metoprolol,[5] Telmisartan,[6] Valsartan,[7] Hydrochlorothiazide,[8] Losartan,[9] Olmesartan,[10] Chlorthalidone,[11] and Atorvastatin[12,13] was estimated. In the same way Atorvastatin in single form or in combined dosage form with Ezetimibe,[14] Ramipril,[15] Aspirin,[16] Fenofibrate,[17] Clopidogrel,[18] Rosuvastatin[19] and Atenolol[20] was estimated by using HPLC, HPTLC and UV-Visible Spectrophotometer. Although HPLC methods are available for estimation of Amlodipine and Atorvastatin there is still scope for development of accelerated

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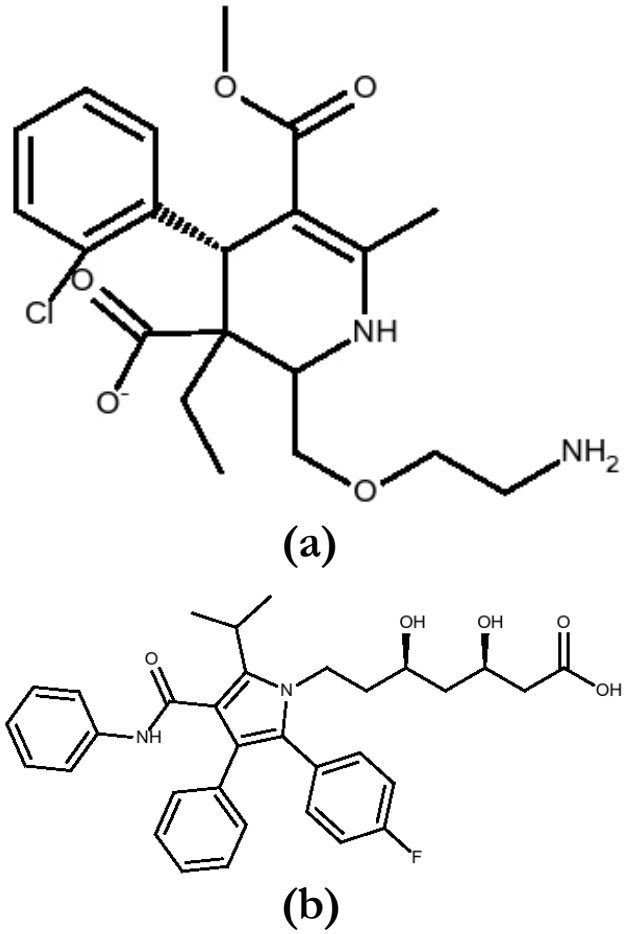

Figure 1: Chemical Structure of (a) Amlodipine and (b) Atorvastatin.

degradation analytical method using HPLC which gives more accurate and precise results for different chromatographic conditions.

Hence here the attempt is done to develop and validate RP-HPLC method where Amlodipine and Atorvastatin are estimated in combined tablet dosage form under different accelerated degraded conditions such as Acid, Base, Oxidative and Thermal and Photolytic degradation. The results obtained for this method are found to be in the specific limit as per directives of ICH guidelines.[21-24]

MATERIALS AND METHODS

Reagents and Chemicals

Amlodipine and Atorvastatin standard API were procured from IPCA Laboratories, Mumbai, India. The tablets were purchased from retail of BITTOR AM, Glenmark, Mumbai containing concentration of Amlodipine 5.0 mg and Atorvastatin 10 mg make in each tablet. The solvents obtained were Methanol, Acetonitrile were procured from E-Merck (India) Ltd, Pune of HPLC grade. The HPLC grade water was prepared by double distillation process in the laboratories.

Instruments Used

The method was developed on RP-HPLC of make Agilent Technologies Limited. The HPLC column used was C_{18} (150 mm × 4.6 mm, 5.0 µ) with loop injector having injection volume 20µl. The both drugs were scanned at 250 nm with PDA detector.

Mobile Phase

The optimized mobile phase was 0.02 M potassium dihydrogen phosphate: acetonitrile: methanol (30:10:60, v/v/v) adjusted to pH 4 using ortho phosphoric acid with flow rate 1.0 ml/min.

Preparation of Standard Solutions

The standard stock solutions of 1000 µg/ml concentration were prepared. Both the APIs weighed accurately about 100 mg and taken in 100 ml volumetric flask. The volume is made up with optimized mobile phase. The working stock solutions of 100 µg/ml concentration were prepared by pipetting out in 10 ml stock in100 ml volumetric flask and volume is obtained with optimized mobile phase.

Linearity Study

The linearity obtained for Amlodipine and Atorvastatin were prepared in the concentration range of 05 - 30 µg/ml. Three repeated determinations for all concentrations were used for preparation of calibration curve. The injection volume used was 20µl.

Validation of Proposed Method

The validation obtained was carried out as per guidelines of ICH. The parameters used for validation of the analytical methods are Accuracy, Precision, Intraday and Interday Precision,

Repeatability, Robustness, Sensitivity, Specificity, Selectivity, Ruggedness and System Suitability Test.

Analysis of Pharmaceutical Formulation

The twenty tablets of BITTOR AM, Glenmark Ltd, India, containing concentration of Amlodipine 5.0 mg and Atorvastatin 10.0 mg per tablet make weighed, average weight is obtained and the tablets are finely powdered. AML and ATV powder equivalent to 100 mg was separately weighed, taken in 100 ml volumetric flask and mobile phase is added to make up the volume. This solution is sonicated for 30 min and filtered using 0.45 µm filters to separate excipients. The standard solution concentration of 10µg/ml of AML and ATV was determined.

Optimization of Chromatographic Conditions

The optimized mobile phase 0.02 M potassium dihydrogen phosphate: acetonitrile: methanol (30:10:60, v/v/v) adjusted to pH 4 using ortho phosphoric acid at a flow rate of 1.0 ml/min was used for good resolution of AML and ATV. The Octadecyl Silane-C_{18} column (5 µm, 25 cm × 4.6mm i. d.) was used as stationary phase. The scanning of both the drugs was observed at 250 nm. The retention time for AML and ATV was found to be 8.32 min and 11.12 min respectively as shown in Figure 3. The calibration curves for both the drugs are as the Figure 2 respectively for Amlodipine and Atorvastatin.

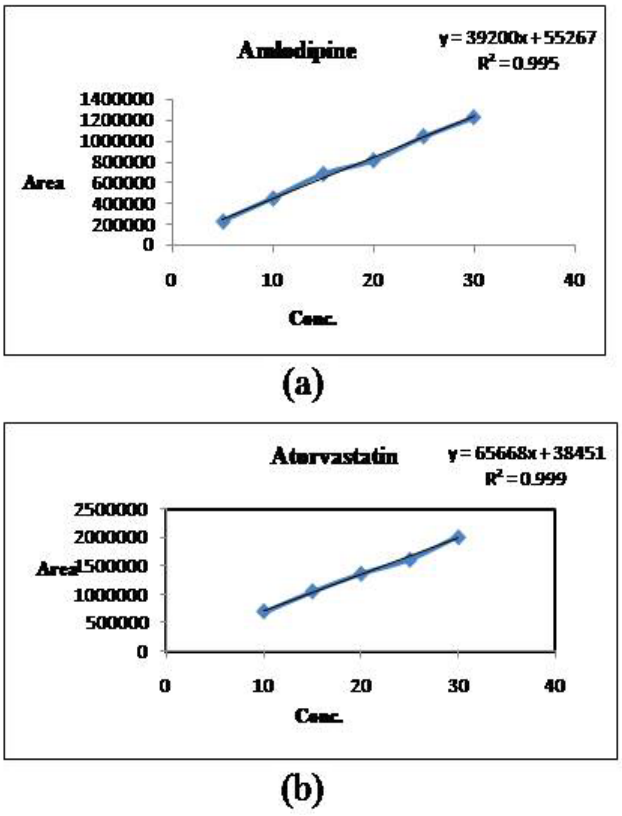

Figure 2: Calibration Curve of (a) Amlodipine and (b) Atorvastatin.

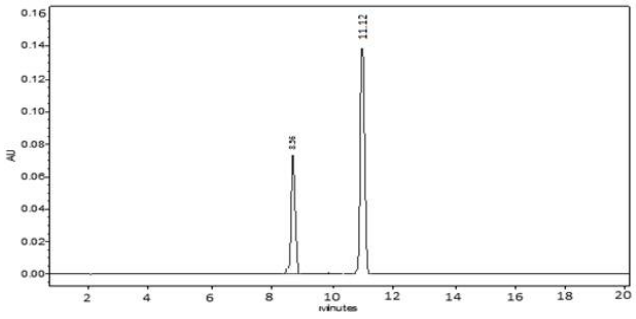

Figure 3: Chromatogram of Standard Amlodipine and Atorvastatin.

Linearity Study

Linearity was obtained by studying different concentrations and their absorbance. The linearity obtained for Amlodipine and Atorvastatin were found in the range of 5 - 30 µg/ml with equation y = 39200x + 55267 with regression R^2 = 0.995 and y = 65668x + 38451 with regression R^2 = 0.999 respectively as given in Figure 2 and results are as per Table 1.

RESULTS AND DISCUSSION

Study of Validation Parameters of Accelerated Degradation analytical method

Accuracy

Accuracy is checked by studying recovery in triplet at 50%, 100% and 150% levels of concentration. The standard concentration of AML and ATV were added in known amount of samples and then contents are determined. The % recovery at these levels were obtained as 100.04 - 100.70% for AML and 98.94–99.55 % for ATV and results Table 2.

Precision

The six independent sample preparations of a single sample were used for studying precision. In this type intra-day and inter-day precision was performed. These studies were validated statistically by obtaining relative standard deviation (% RSD) which was found less than 2 %. The results of precision are as Table 3 and 4.

Sensitivity

The LOQ and LOD is determined for both the drugs. LOD was obtained 0.0958 µg/ml and 0.1263 µg/ml and LOQ was determined 0.2904 µg/ml and 0.3828 µg/ml respectively for AML and ATV. The results are as Table 5.

Specificity and Selectivity

Signal to noise ratio is null in specificity and selectivity in this analytical method.

Table 1: Linearity for Amlodipine and Atorvastatin.

Amlodipine		Atorvastatin	
Concentration (µg/ml)	Mean peak area ± SD (n = 3)	Concentration (µg/ml)	Mean peak area ± SD (n = 3)
5	231562	05	3628441
10	452154	10	6985200
15	684315	15	1055986
20	813524	20	1365899
25	1042573	25	1615245
30	1223467	30	2014785

Table 2: Recovery Study of Amlodipine and Atorvastatin.

	Level of recovery Study	Initial amount (µg/ml)	Amount added (µg/ml)	Amount recovered (µg/ml)	S.D. (n = 3)	% Recovery	% RSD
AML	50%	10	5	14.98	100.17	0.2687	0.2682
	100%	10	10	20.00	100.04	0.5167	0.5164
	150%	10	15	25.10	100.70	0.4350	0.4320
ATV	50%	10	5	14.93	99.55	0.4312	0.4331
	100%	10	10	19.78	98.94	0.1706	0.1724
	150%	10	15	24.82	99.31	0.0799	0.0804

Table 3: The Precision of the AML and ATV.

	Initial amount (µg/ml)	Amount recovered (µg/ml)	Mean (%)	S.D. (n = 3)	% Recovery	% RSD
AML	10	9.97	99.76	0.1850	0.1855	0.1855
ATV	10	9.92	99.27	0.9755	0.9827	0.9827

Table 4: Precision Study Intraday and Interday.

	Intra-day					Inter-day			
	Conc. (µg/ml)	Amt. recovered (µg/ml)	Mean (µg/ml)	RSD	% RSD	Amt. recovered (µg/ml)	S.D. (*n* = 3)	RSD	% RSD
AML	10.0	9.98	99.84	0.2471	0.2475	09.97	99.73	0.4374	0.4385
ATV	10.0	9.96	99.63	0.5725	0.5746	10.00	100.02	0.2028	0.2028

Table 5: LOD and LOQ values of the analyte.

Analyte	S.D. (n=3)	LOD (µg/ml)	LOQ (µg/ml)
AML	1138.62	0.0958	0.2904
ATV	2444.19	0.1263	0.3828

Table 6: System Suitability Parameters.

Sr. No.	System Suitability Parameters	Amlodipine	Atorvastatin
1.	Retention time(min)	8.37	11.18
2.	No. of Theoretical Plates	4156	3852
3.	Tailing Factor	1.34	1.16

System Suitability Parameters

The system suitability parameters are observed for both the drugs and given as shown in the Table 6.

Ruggedness

The standard sample solutions of both APIs were prepared for study of ruggedness and analyzed by two persons which states that method was rugged and can be applied to estimate these drugs as Table 7.

Robustness

The robustness was performed on three different conditions for which results are obtained and validated by SD and RSD found in the specified range. The method was found robust and it can be applied on different instruments as Table 8 and 9 respectively for Amlodipine and Atorvastatin.

Analysis of Pharmaceutical Formulation

The analysis for combination was performed and the label claim of the tablet formulation was determined and found in the range. The assay is found to be in the limit as Table 10.

Forced Degradation Study

Amlodipine and Atorvastatin weighed 25 mg seperayely taken in 25 ml volumetric flask and distilled water was added to make up the volume giving concentration 1000µg/ml. For combined dosage form the tablets are weighed equivalent to 25 mg of larger concentration of drug in dosage form and taken in 25 ml volumetric flask and distilled water was added to make up the volume.

Table 7: The ruggedness of the Amlodipine and Atorvastatin.

	Analyst 1					Analyst 2			
	Conc.	Amt. recovered (µg/ml)	Mean (n = 3)	SD	RSD	Amt. recovered (µg/ml)	Mean (n = 3)	SD	RSD
AML	10.0	9.96	99.61	0.3581	0.3594	9.93	99.34	0.6346	0.6388
ATV	10.0	10.01	100.14	0.2066	0.2063	10.02	100.27	0.4060	0.4049

Table 8: Robustness of Amlodipine.

Sr. No.	Parameter	Change Level	Retention Time (min)	Peak Area (*n*=3)	Mean (%)	SD	RSD
1.	Flow Rate (1.0 ml/min)	0.8ml/min	8.20	446616	99.837	0.1551	0.1554
		1.0 ml/min	8.25	447167	99.97	0.2984	0.2985
		1.2ml/min	8.31	444533	99.30	0.9049	0.9112
2.	Mobile Phase (±10%v/v)	25:05:55	8.20	447369	100.02	0.2662	0.2661
		30:10:60	8.32	446952	99.91	0.1406	0.1407
		35:15:65	8.21	445124	99.45	0.4126	0.4149
3.	Temperature (±5°C)	25	8.25	446738	99.86	0.1446	0.1448
		30	8.30	446966	99.92	0.3731	0.3734
		35	8.31	446912	99.90	0.1504	0.1506

Table 9: Robustness of Atorvastatin.

Sr. No.	Parameter	Change Level	Retention Time (min)	Peak Area (n=3)	Mean (%)	SD	RSD
1.	Flow Rate (1.0 ml/min)	0.8ml/min	5.12	713718	100.31	0.5524	0.5506
		1.0 ml/min	5.01	713023	100.20	0.3520	0.3512
		1.2ml/min	5.10	714291	100.40	0.6252	0.6227
2.	Mobile Phase (±10%v/v)	25:05:55	5.23	716298	100.71	0.4143	0.4113
		30:10:60	5.14	716027	100.67	0.4505	0.4475
		35:15:65	5.20	715818	100.64	0.3593	0.3570
3.	Temperature (±5°C)	25	5.31	714649	100.45	0.0804	0.0801
		30	5.22	716352	100.72	0.3136	0.3113
		35	5.31	722214	100.85	0.8679	0.8605

Table 10: Analysis of tablet Formulation.

	Label claim (mg)	Amount found (mg)	Mean (%)	S.D. (n = 3)	RSD
AML.	5.0	4.97	99.47	0.3809	0.3829
ATV.	10.00	10.02	100.02	0.2874	0.2873

Degradation studies were obtainedby pipetting out specific ml of working stock solution seperately depending on the standard concentration required for analysis.

Acid Degradation Studies

In the standard working solution 5 ml 0.5 M HCl is added. This acidic solution is refluxed at 70°C for 01 hr and 40 min on water bath. The refluxed solutions are neutralised with addition of 5.0 ml 0.5 M NaOH in 10 ml volumetric flask and methanol was added to make up the volume. The chromatogram for acid degradation studies for individual drug API and in combined dosage form are obtained and studied. The Chromatograme for the same are as shown in the Figure 4 for Amlodipine and Atorvastatin and combination of both the drugs.

Base Degradation Studies

In the standard working solution 5 ml 0.5 M NaOH is added. This basic solution is refluxed at 70°C for 01 hr and 40 min on water bath. The refluxed solutions are neutralised with addition of 5.0 ml 0.5 M HCl in 10 ml volumetric flask and methanol was added to make up the volume. The chromatogram for base degradation studies

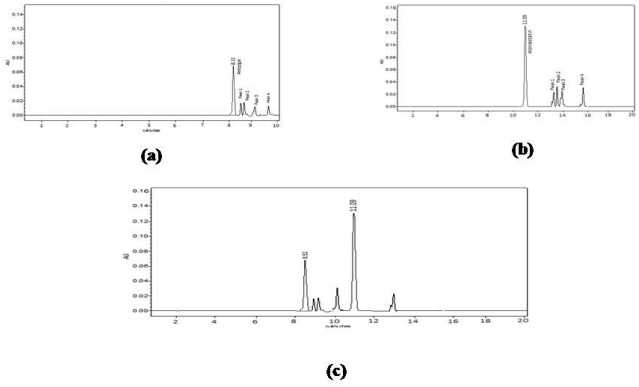

Figure 4: Acid Degradation of (a) Amlodipine and (b) Atorvastatin (c) Amlodipine and Atorvastatin Tablet.

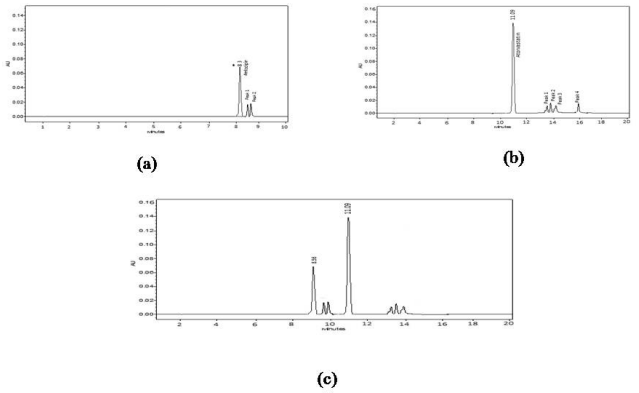

Figure 5: Base Degradation of (a) Amlodipine and (b) Atorvastatin (c) Amlodipine and Atorvastatin Tablet.

for individual drugs API and in combined dosage form are obtained and studied. The Chromatograme for the same are as shown in the Figure 5 for Amlodipine and Atorvastatin and combination of both the drugs.

Oxidative Degradation Studies

In the standard working solution Hydrogen Peroxide 5 ml 3.0 % is added. This solution is refluxed at 70°C for 01 hr and 40 min on water bath. The refluxed solutions area added in 10 ml volumetric flask and methanol was added to make up the volume. The chromatogramfor oxidative degradation studies for individual drugs API and in combined dosage form are obtained. The Chromatograme for the same are as the Figure 6 for Amlodipine and Atorvastatin and combination of both the drugs.

Thermal Degradation Studies

In the standard working solution distilled water 5 ml is added. The solution is refluxed at 70°C for 1 hr and 40 min. on water bath. The refluxed solution is added in 10 ml volumetric flask and methanol was added to make up the volume. The chromatogram for thermal degradation studies for individual drugs API and in combined dosage

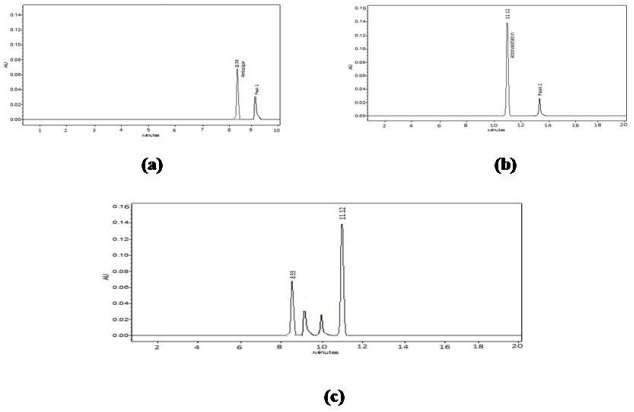

Figure 6: Oxidative Degradation of (a) Amlodipine and (b) Atorvastatin (c) Amlodipine and Atorvastatin Tablet.

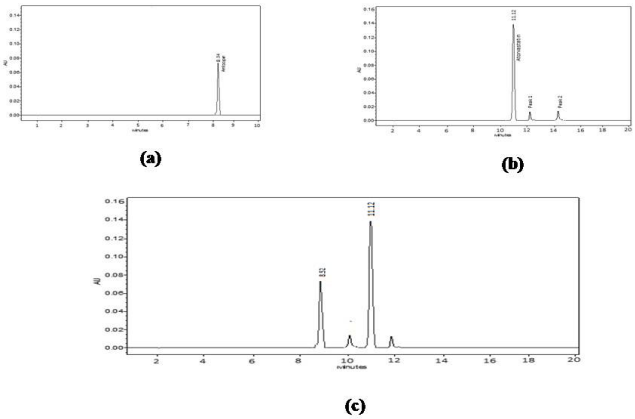

Figure 7: Thermal Degradation of (a) Amlodipine and (b) Atorvastatin (c) Amlodipine and Atorvastatin Tablet.

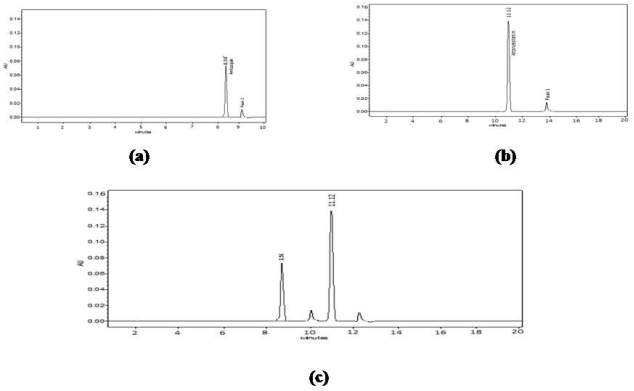

Figure 8: Photolytic Degradation of (a) Amlodipine and (b) Atorvastatin (c) Amlodipine and Atorvastatin Tablet.

form are obtained and studied. The Chromatograme for the same are as the Figure 7 for Amlodipine and Atorvastatin and combination of both the drugs.

Photolytic Degradation Studies

In the standard working solution ddistilled water 5 ml is added. This solution is kept under UV light for 24 hr. The solutions are added in 10 ml volumetric flask

Table 11: Forced Degradation Study for Amlodipine and Atorvastatin.

Analyte	API	Degradation Conditions	% Degradation	Retention time of Degradation Product (min)
Acid Degradation	AML	01 Hr 40 min 70°C	8.67, 8.65, 7.13, 5.96	8.90, 8.95, 9.24, 9.91
	ATV	01 Hr 40 min 70°C	3.02, 3.65, 2.64, 4.22	13.71, 13.91, 13.99, 15.95
Base Degradation	AML	01 Hr 40 min 70°C	7.78, 7.77	8.91, 8.99
	ATV	01 Hr 40 min 70°C	0.73, 0.45, 0.48, 0.86	13.72, 13.92, 14.05, 15.97
Oxidative Degradation	AML	01 Hr 40 min 70°C	18.25	9.15
	ATV	01 Hr 40 min 70°C	0.677	13.78
Thermal Degradation	AML	01 Hr 40 min 70°C	00	--
	ATV	01 Hr 40 min 70°C	0.77, 0.80	12.21, 14.29
Photolytic Degradation	AML	24 Hr	7.54	9.12
	ATV	24 Hr	0.677	13.78

Table 12: Forced Degradation Study for Amlodipine and Atorvastatin in tablet dosage form.

Analyte	Tab.	Degradation Conditions	% Degradation	Retention time of Degradation Product (min)
Acid Degradation	AML	01 Hr 40 min 70°C	3.01, 3.64, 2.64	8.40, 8.65, 10.15
	ATV	01 Hr 40 min 70°C	30.57	13
Base Degradation	AML	01 Hr 40 min 70°C	7.39, 7.48	9.9, 10.01
	ATV	01 Hr 40 min 70°C	0.86, 0.94, 0.78	13.00, 13.73, 14.00
Oxidative Degradation	AML	01 Hr 40 min 70°C	18.25, 17.93	9.01, 10.02
	ATS	01 Hr 40 min 70°C	00	00
Thermal Degradation	AML	01 Hr 40 min 70°C	2.17	10.16
	ATV	01 Hr 40 min 70°C	0.236	12.00
Photolytic Degradation	AML	24 Hr	7.54	10.02
	ATV	24 Hr	1.91	12.2

and methanol was added to make up the volume. The chromatogram for photolytic degradation studies for individual drugs API and in combined dosage form are obtained and studied. The Chromatograme for the same are as the Figure 8 for Amlodipine and Atorvastatin and combination of both the drugs.

Forced Degradation Studies

Forced degradation for different conditions were obtained and the results observed for individual and in combination form respectively. It is observed that in individual APIs the AML and ATV shows in acid, base and thermal good degradation response but for oxidative and for photolytic degradation it is average as Table 11.

Forced Degradation Study for Amlodipine and Atorvastatin in tablet dosage form

Forced degradation for different conditions was obtained and the results observed for individual and in combination form respectively. It is observed that in individual APIs the AML and ATV in acid, base and oxidative degradation good response but for thermal and photolytic degradation it is average as Table 12.

CONCLUSION

The accelerated degradation method was developed using RP-HPLC for estimation of Amlodipine and Atorvastatin in tablet dosage form. The peaks of chromatogram are well resoluted and sharp detected by PDA detector. The method is validated as per directives of ICH guidelines. Accelerated degradation studies were carried out under different conditions and degradation peaks were observed in chromatograms. The % degradation was determined by using area under curve as standard comparison method. It is found that Amlodipine gives degradation in Acidic, Basic, Oxidative and Photolytic conditions whereas Atorvastatin shows degradation in all conditions. The results conclude that developed method is specific, reliable, efficient and reproducible by using RP-HPLC. This method can be applied in the laboratories.

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CONFLICT OF INTEREST

There is no any conflict of interest regarding this Research Paper.

ABBREVIATIONS

RP-HPLC: Reverse Phase High Performance Chromatography; **AML:** Amlodipine; **ATV:** Atorvastatin; **LOD:** Limit of Detection; **LOQ:** Limit of Quantitation.

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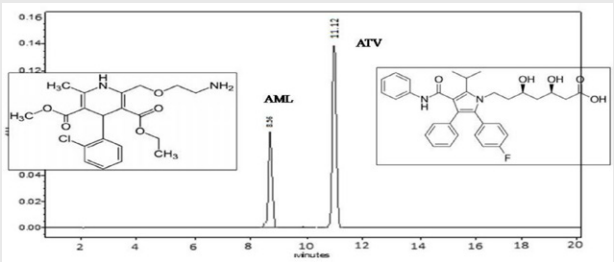
PICTORIAL ABSTRACT



Forced Degradation method development by RP-HPLC for AML and ATV

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SUMMARY

The research work in the paper presents the novel RP-HPLC accelerated degradation study for estimation of Amlodipine and Atorvastatin in combined dosage form. The mobile phase used for separation of both the drugs was 0.02 M potassium dihydrogen phosphate: acetonitrile: methanol (30:10:60, v/v/v) adjusted to pH 4 using ortho phosphoric acid with flow rate 1.0 ml/min. The Retension time for Amlodipine and Atorvastatin was found to be at 8.32 min and 11.09 min and respectively. The regression at linearity 5-30 μg/ml was R^2 = 0.995 and 0.999 for both drugs respectively. The method was validated as per ICH guidelines. The LOD were found to be 0.095 μg/ml and 0.290 μg/ml and LOQ 0.126 μg/ml and 0.3828 μg/ml. The results are validated as per ICH guidelines and confirmed by statistical data. The forced degradation studies under different conditions obtained and the results shows that the degradation is observed in Acidic, Basic Oxidative and Photolytic condition for Amlodipine and in Thermal condition it is found to be stable whereas the Atorvastatin shows degradation in all conditions.

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