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Forced Degradation and Solution Stability Studies of Pheniramine API Drug

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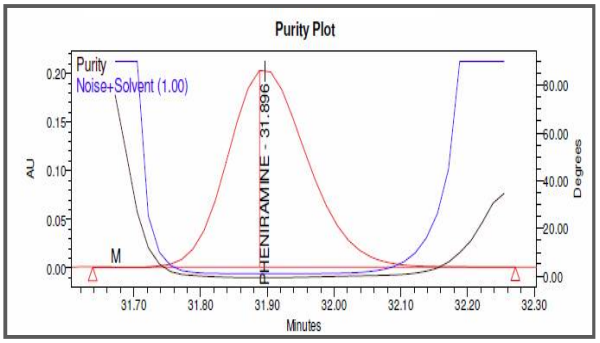
ABSTRACT

Pheniramine API drug were analyzed by forced degradation method using high performance liquid chromatography method was developed and validated. Two impurities in the Pheniramine API drug was identified. The separation was achieved on HPLC Columns (C-104) and (C-118) analytical column (250 mm × 4.6 mm i.d., 5.0 µm) using acetonitrile, methanol in the ratio 50:50 v/v as mobile phase and at a flow rate of 1.0 mL min^{-1}. Acid degradation (5N HCl) RT was 31.943, base degradation (5N NaOH) for impurity RT was 30.813 and for drug it was 31.911. Peroxide degradation (30% H_2O_2) RT was 31.896, reduction degradation (10% Sodium bisulphate) for impurity RT was 30.846 and for drug it was 31.878. Hydrolysis degradation for impurity RT was 30.856 and for drug it was 31.901. Thermal degradation (105°C/72 h) for impurity RT was 30.844 and for drug it was 31.969. Humidity degradation (25°C/92% RH for 72 h) for impurity RT was 30.611 and for drug it was 31.640. Photolytic degradation (1.2 Million lux hours) for impurity RT was 31.109 and for drug it was 32.262. The developed and validated method was successfully applied for the quantitative analysis Pheniramine API drug. The solution stability of spiked was studied.

Graphical Abstract



Chromatogram and Peak Purity of Peroxide degradation

Keywords: HPLC Techniques, Solubility Stability, Acid and Base Degradation, thermal, Peroxide Degradation.

INTRODUCTION

Pheniramine (trade name Avil,) is an antihistamine [1] with anticholinergic [2] properties used to treat allergic conditions such as hay fever or urticaria [3]. It has relatively strong sedative effects, and may sometimes be used off-label as an over-the-counter sleeping pill in a similar manner to other sedating antihistamines such as diphenhydramine [4]. Pheniramine is also commonly found in eye drops used for the treatment of allergic conjunctivitis [5]. HPLC is an essential illustrative instrument in evaluating drug item control. HPLC policies must to have the capacity to independent, recognize, and evaluate the different drug related degradants that can shape on capacity or assembling, in addition to identify and evaluate any drug related degradations that might be presented among curve [6]. Constrained degradation contemplates (synthetic and physical anxiety testing) of new substance elements and drug items are basic to help create and exhibit the specificity of such steadiness demonstrating techniques. Notwithstanding showing specificity, constrained impurities studies can be utilized to decide the degradation pathways and degradation results of the APIs that could frame among capacity and encourage plan advancement, assembling and bundling. Methodology for the readiness of particular degradation items required for policy validation regularly rise up out of these examinations. For promoting applications, current FDA and ICH [7-8] direction prescribes incorporation of the outcomes, including chromatograms of focused on tests, demonstration of the dependability showing nature of the expository policies and the degradation pathways of the API in strong state, arrangement and drug item [9].

The compound structures of critical impurities items and the related methodology for their confinement and additionally portrayal are likewise anticipated that would be incorporated into the documenting. The test convention for performing constrained impurities studies will rely upon the normal fixings and definition included in light of the fact that the science of each compound is unique. When all is said in done an objective of roughly 10% degradation of the API among constrained impurities, or presentation to vitality in slight overabundance of what is ordinarily utilized as a part of quickened stockpiling is prescribed. Along these lines, the "thinking pessimistically" impurities items can be examined. The accompanying will give a few recommendations to performing constrained impurities contemplates in light of accessible direction from the ICH and FDA [10]. Constrained impurities consider are irreplaceable in the improvement of steadiness demonstrating and degradants checking techniques as a major aspect of validation convention.

Constrained impurities think about additionally give priceless understanding an investigative degradation items, pathways of drug substances and items. Despite the fact that the ICH and FDA direction archives require the consideration of these investigations in Phase-III of the administrative accommodation process, it is unequivocally prescribed these investigations be begun as right on time as conceivable to have the capacity to give important data that can be utilized to survey the characteristic solidness of a drug, and to enhance definitions and the assembling procedure. Given that no particular arrangement of conditions will be material to all drug substances and items, the pharmaceutical researcher must to guarantee the stretch conditions are reliable with item deterioration under ordinary assembling, stockpiling, and proposed utilize conditions. Prescribed concern factors incorporate to low and high pH, raise temperature, photolysis and oxidation. Care must to be taken to stay away from under pushing or, then again unduly finished focusing on the drug substance or item, for this may prompt atypical and non-agent comes about. A degradation level of around 10% of the drug substance must to be ideal for policy enhancement. We are discussed the force degradation and solution stability studies of pharmaceutical drugs.

MATERIALS AND METHODS

The standard bulk drug (API) of Pheniramine was obtained from Supriya Lifescience Limited, Mumbai. The chemical was used for this research by HPLC grade, where other chemicals were high purity with analytical grades. All the chemicals were purchased from Sigma Aldrich.

Apparatus and Chromatographic Conditions: Equipments were used for the validation studies such as HPLC System: SLL/QC/29, 57, Waters 2695 Separation Module, Waters UV and 996 PDA, Empower 2.0 and 3.0 Software, Balance (SLL/QC/50), HPLC Columns (C-104) and (C-118), Photo Stability Chamber (SLL/QC/74) and Hot air oven (SLL/QC/24).

RESULTS AND DISCUSSION

Acid Degradation (5N HCl): In 20 mL flask add pre-weighted 20 mg of sample was added then 5 mL of diluents and sonicated to dissolve. 5N HCl of 5 mL was heated at 70°C for three hours in water bath then flask was allowed to cool at room temperature. Then 5ml of 5N NaOH was added to neutralize solution.

Table 1. Peak Result of Acid degradation

S.No	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.943	20368059	132338	1.741

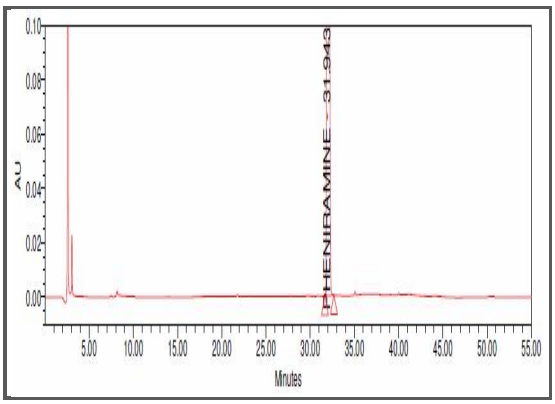


Figure 1 Peak Result of Acid degradation

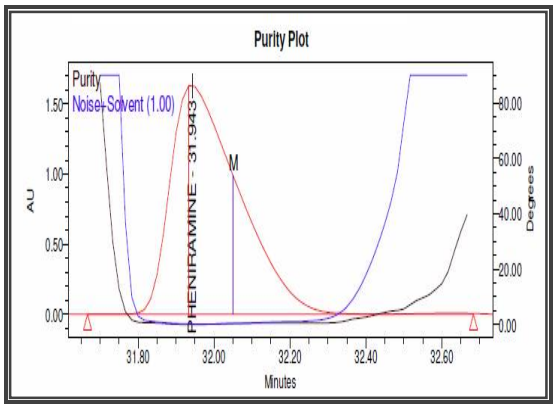


Figure 2. Chromatogram of Acid degradation.

Base Degradation (5N NaOH): Weighed accurately 20 mg of the sample in a 20 mL volumetric flask, added 5 mL of diluents and sonicated to dissolve. Further 5ml of 5N NaOH and heated at 70°C for 3 h on a water bath. Removed the flask from the water bath allowed the flask to cool to room temperature. Further 5mL of 5N HCl is add to neutralize the solution. Cooled to room temperature and diluted to volume with diluent and mixed [11].

Table 2. Peak Results of Alkali degradation

S.No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		21.653	5232	0.03		142859	1.149
2	Impurity-B	30.813	1810	0.01	31.976	62811	1.454
3	Pheniramine	31.911	20306849	99.87	3.134	129414	1.746
4		34.992	12751	0.06	10.237	362873	0.979
5		37.621	2298	0.01	10.616	386536	0.930
6		40.070	3725	0.02	9.900	470503	1.020

Table 3. Peak Results Acid degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.911	20306849	129414	1.746

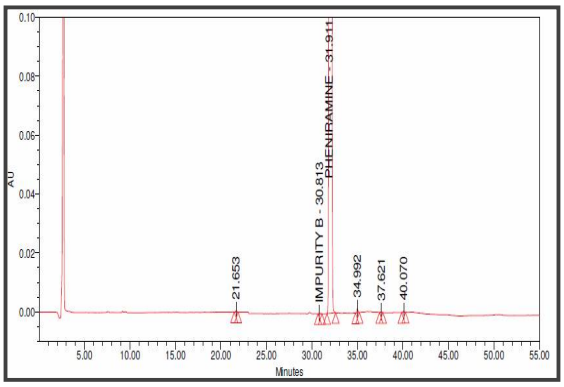


Figure 3. Peak Results of Alkali degradation

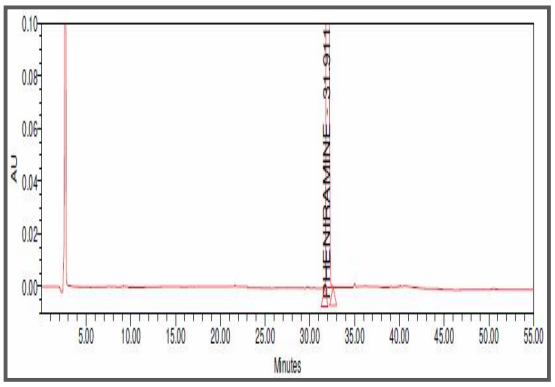


Figure 4. Chromatogram of Alkali degradation

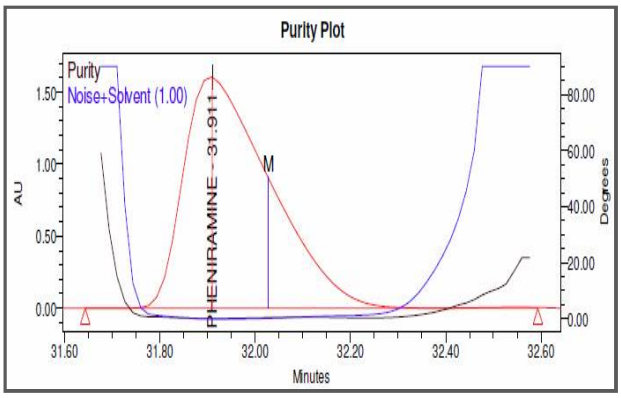


Figure 5. Chromatogram and Peak Purity of Alkali degradation.

Peroxide Degradation (30% H_2O_2): 20 mg of sample was dissolved in 20 mL volumetric flask then 5 mL of diluents was added to dissolve it. Further 5 mL of 30% v/v H_2O_2 was added and heated at 70°C for 3 h on a water bath after three hours the flask was cooled to room temperature.

Table 4. Peak Results Peroxide degradation

S.No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1	Pheniramine	31.896	1707145	100	--	329906	1.163

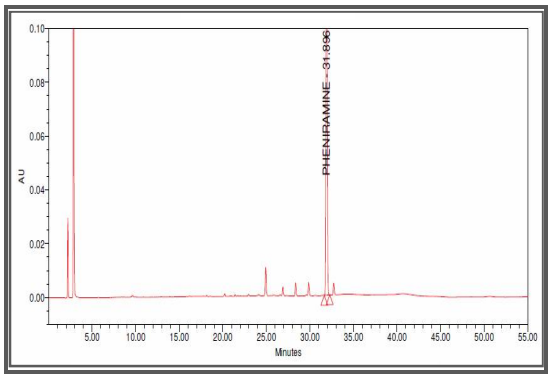


Figure 6 Peak Results of Peroxide degradation

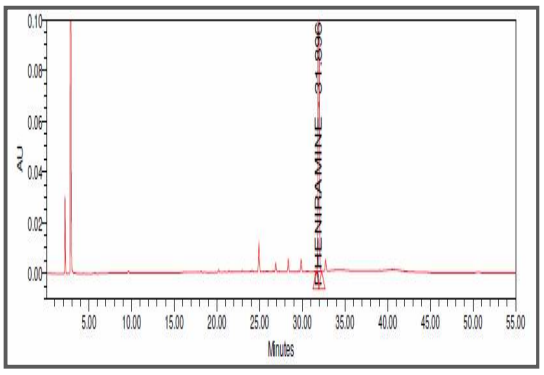


Figure 7. Chromatogram of Peroxide degradation-diluted.

Table 5. Peak Results of Peroxide degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.896	1707145	329906	1.163

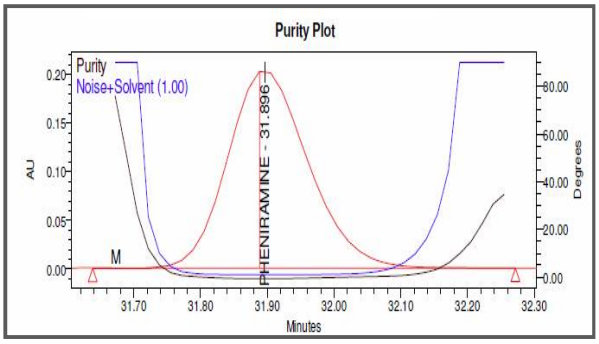


Figure 8. Chromatogram and Peak Purity of Peroxide degradation

Reduction Degradation (10% Sodium Bisulphate): 100 mg of sample was dissolved in 100 mL volumetric flask. Then 5 mL of 10% w/v sodium Bisulphate was added and heated at 70°C for 3 h on a water bath after completing three hours the flask was allowed to cool at room temperature [12].

Table 6. Peak Results Reduction degradation

S.No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		3.286	1734	0.01		9577	1.147
2		21.734	4544	0.02	97.304	136250	0.996
3	Impurity-B	30.846	2374	0.01	28.306	97774	0.963
4	Pheniramine	31.878	19120998	99.86	2.782	140990	1.694
5		34.961	11748	0.06	10.608	353784	0.991
6		37.567	2221	0.01	9.777	245630	1.042
7		39.987	3437	0.02	9.211	500916	0.892

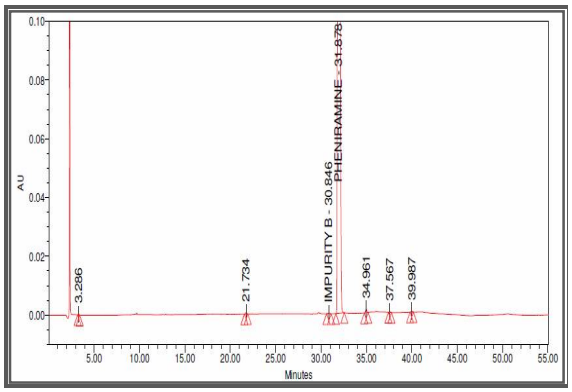


Figure 9. Peak Results Reduction degradation

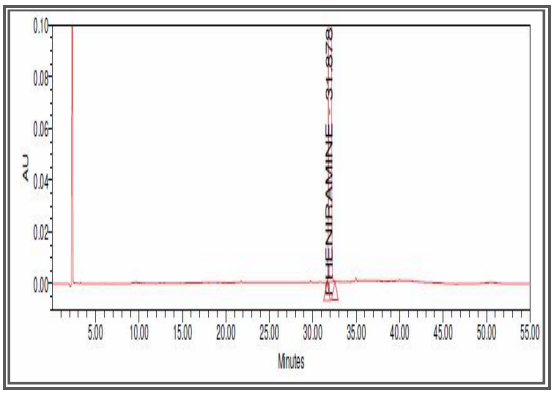


Figure 10. Chromatogram of Reduction degradation

Table 7. Peak Results of Reduction degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.878	19120998	140990	1.694

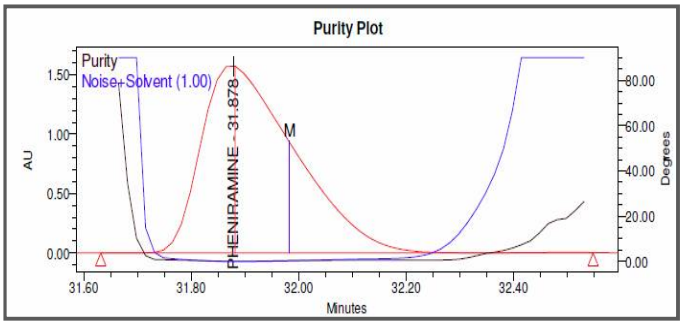


Figure 11. Chromatogram and Peak Purity of Reduction degradation.

Hydrolysis Degradation: Weighed accurately 20 mg of the sample in a 20 mL volumetric flask, further 10 mL of water and sonicated to disperse to dissolve and heated at 70°C for 3 h on a water bath. Removed flask from water bath, allowed flask to cool at room temperature and diluted to volume by diluent and mixed.

Table 8. Peak results hydrolysis degradation

S.No	Name	RT	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		9.596	1408	1.01		90484	0.801
2		21.709	4483	0.02	65.929	146298	0.872
3	Impurity-B	30.856	1850	0.01	30.986	190885	0.846
4	Pheniramine	31.901	19209012	99.88	2.950	136726	1.713
5		35.028	11769	0.06	10.601	357224	1.016
6		40.148	3627	0.02	21.076	461686	0.997

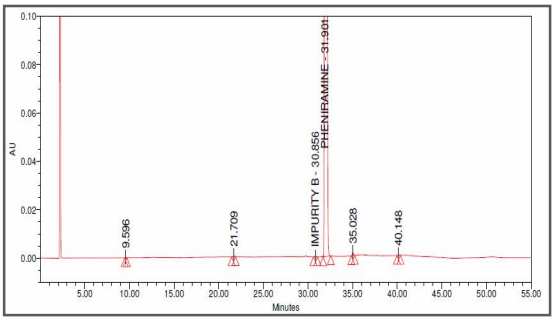


Figure 12. Peak results hydrolysis degradation

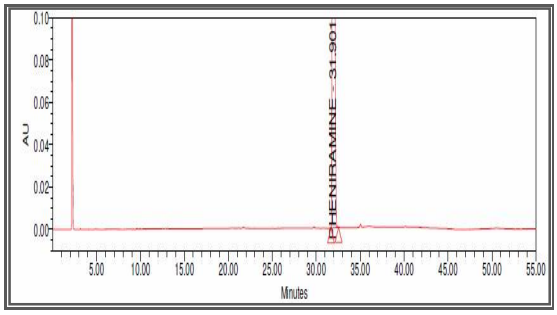


Figure 13. Chromatogram of hydrolysis degradation

Table 9. Peak results hydrolysis degradation

S.No	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.901	19209012	136726	1.713

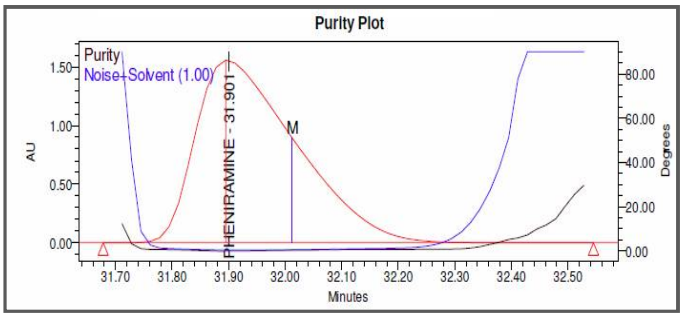


Figure 14. Chromatogram and Peak Purity of Hydrolysis degradation.

Thermal Degradation (105°C/72 h): Sample was exposed at 80°C for 72 h and analyzed to exposed sample[13].

Table 10. Peak Results Thermal degradation

S.No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		9.600	1280	0.01		99267	1.120
2		21.755	2169	0.01	72.435	178260	0.660
3	Impurity-B	30.844	2352	0.01	31.767	135502	1.046
4	Pheniramine	31.969	18692314	99.86	3.151	133733	1.713
5		35.099	14432	0.08	10.558	366034	1.030
6		37.774	1723	0.01	9.299	301670	1.110
7		40.252	4078	0.02	8.563	438127	0.974

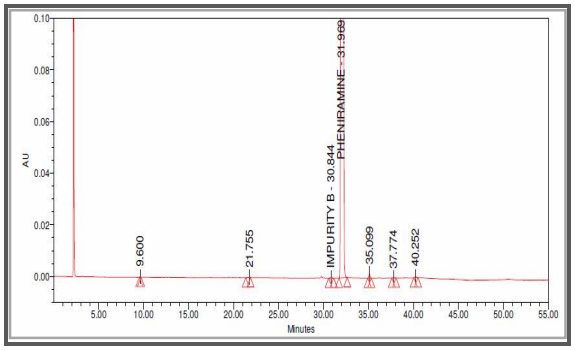


Figure 15. Peak Results Thermal degradation

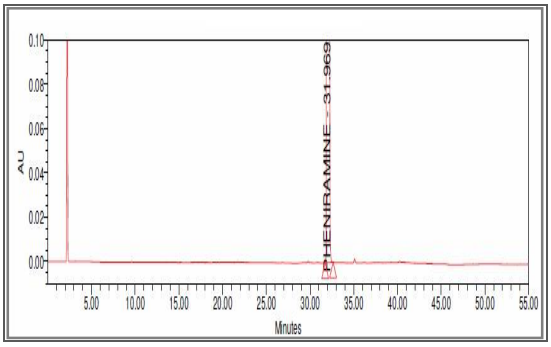


Figure 16. Chromatogram of Thermal degradation

Table 11. Peak Results Thermal degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.969	18692314	133733	1.713

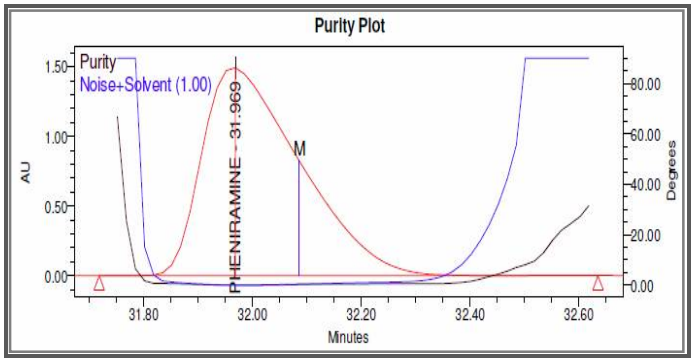


Figure 17. Chromatogram and Peak Purity of Thermal degradation.

Humidity Degradation (25°C/ 92% RH for 72 h): Sample was exposed at 25°C /92% RH for 72 h and analyzed to exposed sample.

Table 12. Peak results Humidity degradation

S.No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		21.689	4577	0.02		128171	0.793
2	Impurity-B	30.611	1625	0.01	29.477	78603	0.890
3	Pheniramine	31.640	18979239	99.88	2.958	143959	1.671
4		34.749	11440	0.06	10.800	362490	1.069
5		37.368	2037	0.01	9.911	241199	1.052
6		39.835	3736	0.02	9.154	436276	1.021

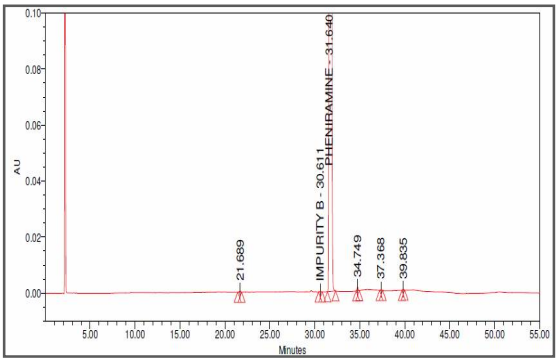


Figure 18. Peak results Humidity degradation

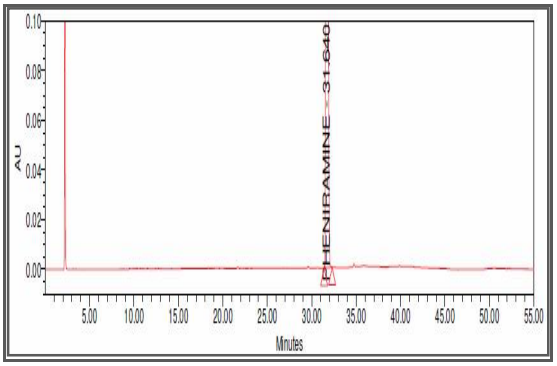


Figure 19. Chromatogram of Humidity degradation

Table 13. Peak results Humidity degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	31.640	18979239	143959	1.671

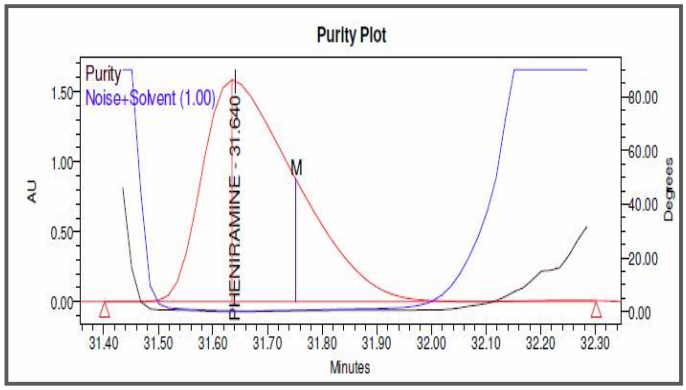


Figure 20. Chromatogram and Peak Purity of Humidity degradation

Photolytic Degradation (1.2 Million lux hours): Sample was exposed to 1.2 Million lux hours of light and analyzed to exposed sample.

Table 14. Peak results Photolytic degradation

S. No.	Name	R Time	Area	% Area	Usp Resolution	Usp Plate count	Usp Tailing
1		3.190	31247	0.23		7904	1.210
2		9.803	1136	0.01	49.708	104479	0.972
3		21.057	3323	0.02	62.067	124135	0.959
4		22.004	1406	0.01	4.075	157371	0.898
5	Impurity-B	30.065	7277	0.05	27.577	102851	0.956
6	Pheniramine	31.109	3009	0.02	2.597	86695	0.986
7		32.262	13721122	99.55	3.072	392337	1.558
8		35.282	10268	0.07	11.255	392337	1.053
9		37.863	1260	0.01	9.610	125364	0.766
10		40.309	1260	0.01	9.610	125364	0.766

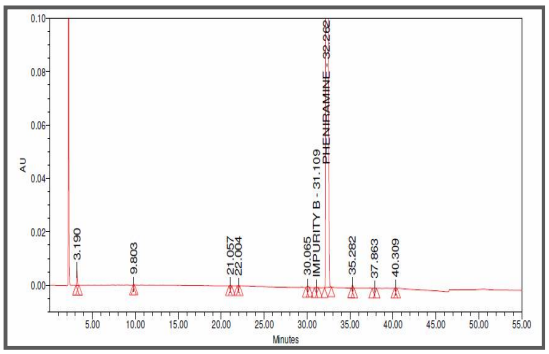


Figure 21. Peak results Photolytic degradation

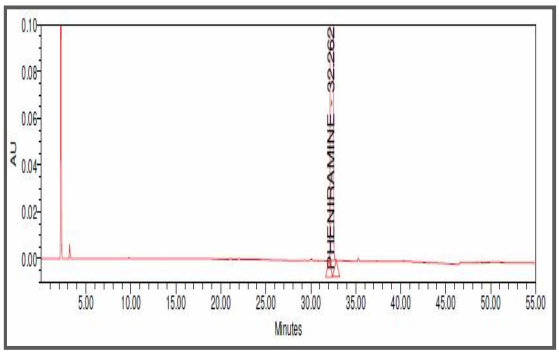


Figure 22. Chromatogram of Photolytic degradation

Table 15. Peak Results Photolytic degradation

S.No.	Name	R Time	Area	Usp Plate count	Usp Tailing
1	Pheniramine	32.262	13721122	181870	1.558

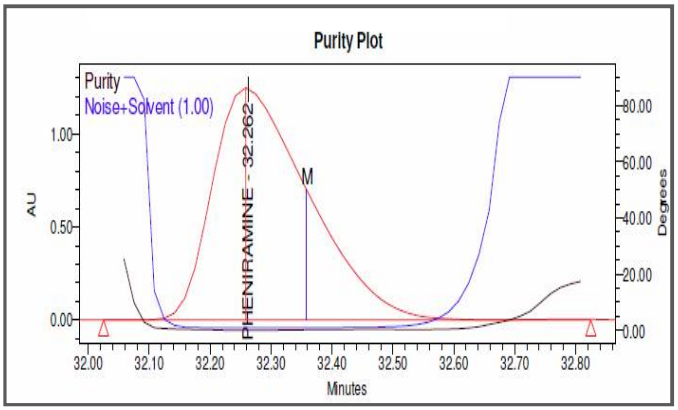


Figure 23. Chromatogram and Peak Purity of Photolytic degradation.

Table 16. Forced degradation studies (Pheniramine)

S. No.	Experiment	Degradation Condition	Purity Angle	Purity 'Threshold'
1	Control	--	0.298	1.028
2	Acid Degradation	5mL, 5N HCl/ 70°C/3h	0.283	1.024
3	Base Degradation	5mL, 5N NaOH/70°C/ 3h	0.284	1.018
4	Peroxide Degradation	5mL, 30% v/v/ 70°C/3h	0.046	1.117
5	Reduction Degradation	5mL,10% $NaHSO_4$/ 70°C/3h	0.261	1.021
6	Hydrolysis Degradation	5mL, Water/ 70° C/3h	0.276	1.022
7	Thermal Degradation	105 ° C/72 h	0.242	1.020
8	Humidity Degradation	25° C /92% RH/72 h	0.261	1.027
9	Photolytic Degradation	1.2 million lux hours	0.168	1.046

Acceptance Criteria: Pheniramine Peak is homogeneous; it does not show co- eluting peaks. The Peak purity for pheniramine peak and known Impurity Peaks must be good and it is validated. From the peak data of Pheniramine in every degradation sample shows that, the Pheniramine and all known impurities are homogeneous and it does not shows co-eluting peaks which indicating that, the method is validated and specific.

Table 17. Impurities in Forced degradation studies

S.No	Experiment	Degradation Condition	% Impurity-A	% Impurity-B	% highest Unspecified	% Total
1	Control	--	ND	ND	0.06	0.06
2	Acid Degradation	5mL, 5N HCl/ 70°C / 3h	0.01	ND	0.55	0.61
3	Base Degradation	5mL, 5N NaOH/ 70° C / 3h	0.01	ND	0.06	0.06
4	Peroxide Degradation	5mL, 30% v/v/ 70° C / 3h	0.04	ND	4.33	12.5
5	Reduction Degradation	5mL,10%$NaHSO_4$ /70°C / 3h	0.01	ND	0.06	0.06
6	Hydrolysis Degradation	5mL, Water/ 70° C / 3h	0.01	ND	0.06	0.06
7	Thermal Degradation	105 ° C / 72 h	0.01	ND	0.08	0.08
8	Humidity Degradation	25° C /92% RH/ 72 h	0.01	ND	0.06	0.06
9	Photolytic Degradation	1.2 million lux hours	0.02	ND	0.23	0.35

Stability in Analytical Solution: The solution stability is strength of standard and separated specimen arrangement (prepared to impart) from the example or lattice and dissected according to determined plan, and it must to be put away legitimately in room temperature and cooled condition contingent on dependability and standard arrangement [14-15]. The solution stability of the reference solution-B, the cumulative % RSD average value 3.19 for the Pheniramine and average value for Area 27491 and mean are 27539.

Table 18. Solution Stability of Reference solution B

Reference Solution-B			
Pheniramine			
Time	Area	Mean	Cumulative % RSD
Initial	27167	--	--
1 h	27826	27497	1.69
2 h	28959	27984	3.24
8 h	27808	27940	2.67
11 h	25694	27491	4.34
14 h	27128	27430	3.93
17 h	27337	27417	3.59
20 h	27445	27421	3.33
23 h	26911	27364	3.18
26 h	27590	27387	3.01
29 h	28216	27462	2.99

Table 19. Solution Stability of Reference solution C

Reference solution -C							
Impurity-A				Impurity-B			
Time	Area	Mean	Cumulative %RSD	Time	Area	Mean	Cumulative %RSD
Initial	117767	--	--	1 h	30972	30715	1.19
1 h	114680	116224	1.88	2 h	30457	30578	1.14
2 h	117147	116531	1.40	6 h	30304	30570	0.94
6 h	119188	117196	1.61	9 h	30545	30656	1.03
9 h	115384	116833	1.56	12 h	31004	30654	0.92
12 h	114452	116436	1.63	15 h	30644	30833	1.74
15h	115378	116285	1.53	18 h	30903	30816	1.62
18 h	113948	115993	1.59	21 h	30695	30906	1.75
21 h	118213	116240	1.61	24 h	31628	31076	2.39
24 h	118303	116446	1.62	27 h	32609	31223	2.74
27 h	112677	116103	1.82	-	-	-	-

Table 20. Solution Stability of Spiked Solution

Time in hours	Impurity-A			Impurity-B			Unspecified		
	Area	Mean	RSD*	Area	Mean	RSD*	Area	Mean	RSD*
Initial	153827	--	--	53620	--	--	13137	--	--
1	153511	153669	0.15	53380	53500	0.32	13011	13074	0.68
2	154139	153826	0.20	55016	54005	1.64	13492	13123	1.54
3	154534	154003	0.28	48577	52648	5.33	13642	13215	1.95
4	152186	153639	0.38	48792	51877	5.75	13841	13301	1.99
5	154055	153709	0.53	48469	51309	5.86	13736	13353	2.27
6	153348	153657	0.49	49054	50987	5.64	14541	13422	2.25
7	154377	153747	0.49	49639	50818	5.32	13875	13462	3.37
8	154661	153849	0.50	48579	50570	5.22	14212	13582	3.24
9	155184	153982	0.54	49930	50506	4.94	14270	13611	3.34
10	155340	154109	0.58	49660	50429	4.72	13989	13666	3.42
11	155133	154195	0.59	50059	50398	4.51	14138	13916	3.31
12	154852	154245	0.57	50169	50380	4.32	14024	13737	3.27
13	154871	154290	0.56	50167	50384	4.15	13879	13766	3.08
14	155949	154400	0.61	50431	50378	4.00	14199	13783	3.00
15	156803	154551	0.79	50304	50450	3.91	13514	13789	3.16
16	156531	154667	0.82	51671	50451	3.79	14489	13813	3.17
17	157179	154806	0.83	50232	50475	3.68	14102	13842	3.21

*Cumulative % RSD

Acceptance Criteria: Cumulative % RSD values rare not more than 10%. The % Cumulative RSD is within limits. Therefore Impurities in sample solutions was stable for 47 h at room temperature.

APPLICATION

HPLC Method for the determination of related substances of pheniramine was accurate, simple, it is useful for the determination of pharmaceutical formulations.

CONCLUSIONS

The HPLC methods for the determination of pheniramine API drug, two unknown impurities were identified. The drug is validating by Force degradation method and solution stability. The Mean recovery for known Impurities is within limits. Therefore, the HPLC Method for the determination of related substances of pheniramine was accurate. Impurities in sample solutions are stable for 24 h at room temperature. Reference Solutions are stable up to 47 h. Pheniramine peak is homogeneous, it does not show co- eluting peaks. The peak purity for pheniramine peak and known Impurity Peaks must be good and it is validated. The peak data of Pheniramine in every degradation sample shows that, the pheniramine and all known impurities are homogeneous and it does not shows co-eluting peaks which indicating that, the method is validated and specific

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