Supplementary Materials:

Carvedilol Microemulsion-Loaded Oleogel: Development and Validation of HPLC Method, Identification of three Degradation Products, and Toxicity Prediction

Table 1S. Summary of some trials for the HPLC development method

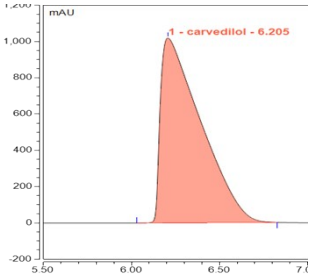
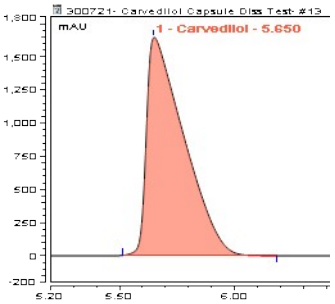
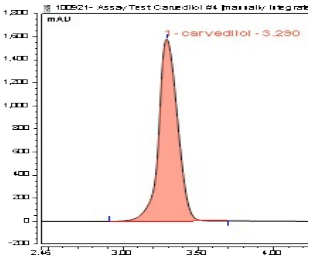
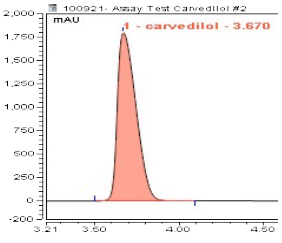
Mobile phase	Column	R_t (min)	Asymmetry	Theoretical Plates	Representative Chromatograms	Notes
(0.005M KH_2PO_4: MeCN) (450:550), adjust pH 3.0	Hypersil C18 (250×4.6) mm, 5µm	6.21	3.7	3273		Tailing peak
(0.005M KH_2PO_4: MeCN) (600:400), adjust to pH 3.0	Ace C18 (250×4.6) mm, 5µm	5.65	2.79	4962		Tailing peak
(Buffer 0.015M pH 2.70: MeCN) (550:450)	Phenomenx Luna C18 (250×4.6) mm, 5 µm	3.29	1.02	3734		Optimum peak (Ideal peak)
	Ace C18 (250×4.6) mm, 5µm	3.67	1.06	14808		

Table 2S. Summary of all trials to select the solvent and method of sample preparation for CARV-MEOG

Solvent	Method of Preparation			Assay (%)
	Sonication time (min)	Stirring time (min)	Centrifugation time (min)	
Mobile phase	15	-	10 at 4000 rpm	85.0
0.1 M HCl (A dilution was done using the mobile phase)	30	-	-	76.7
MeOH	15	-	10 at 4000 rpm	82.7
Mobile phase	30	-	10 at 4000 rpm	84.9
			-	85.3
(0.015M KH_2PO_4 pH 2.70: MeOH) (55: 45)	30	-	-	81.6
(0.1 M HCl: MeOH) (1: 9) (0.01 mg/ml) add 20 ml MeOH	15 min, then add diluent, 15 min	30	15 at 3500 rpm	77.2
	15 min add diluent then 15 min	30	-	78.6
(Water: MeOH) (25:75)	30 min	-	-	73.4
(0.1 M HCl: MeOH) (1: 9) for (0.5 g) 0.125 mg/ml	15 min add diluent then 15 min	30	15 at 3500 rpm	77.3
	15 min add diluent then 15 min	30	-	76.7
Mobile phase	-	Heat at 40 °C with stirring for 20	-	84.0
(0.1 M HCl: EthOH) (1: 9), dissolve with 10 ml EthOH	-	Heat at 40 °C with stirring for 20	-	62.0
10 ml THF then EthOH	-	Heat at 40 °C with stirring for 20	-	68.0
0.1 M HCl	-	Heat at 40 °C with stirring for 20	-	77.4
(0.1 M HCl: MeCN) (1: 9)	Adding 10 ml of MeCN and sonicating for 15 min, followed by adding the diluent and sonicating for another 15 min. Then stirring for 30 min.			69.1
(0.1 M HCl: MeOH) (1: 9)	Adding 20 ml of MeOH and sonicating for 15 min, followed by adding the diluent and sonicating for another 30 min. Then stirring for 45 min.			65.6
(0.1 M HCl: MeOH) (3:7)	Adding 20 ml of MeOH and sonicating for 20 min, followed by adding the diluent and sonicating for another 20 min. Then stirring for 45 min.			68.6
Mobile phase	Sonicate for 20 min then complete volume with diluent, then transfer the solution to prep tubes and mixing for 45 min at 5000 rpm using Distek prep engine instrument.			69.3
(0.1 M HCl: MeOH) (1: 9)				71.0
(0.1 M HCl: MeCN) (1: 9)	Add 5 ml Chloroform, stirring for 10 min with heating at 40 °C, sonication for 10 min with heating at 40 °C, interchangeable between them to accomplish 40 min.			65.8
(1.0 M HCl: MeCN) (1: 9)	Stirring for 10 min with heating at 40 °C, sonication for 10 min with heating at 40 °C, interchangeable between them to accomplish 40 min.			67.2

Table 3S. Summary of all trials to select the best solvent and method of sample preparation for carvedilol conventional oleogel formula

Solvent	Method of Preparation	%Assay
Mobile phase	Stir using a magnetic stirrer for 10 min, heating at 40 °C°C, then sonicate for 10 min. The whole time for the preparation was 40 min, which was used interchangeably between them.	89.9
Acetonitrile		93.5
10ml THF then MeOH		89.0
Methanol		90.2
Acetonitrile	Sonication for 30 min, then stirring using a magnetic stirrer for another 30 min	91.1
(0.1 M HCl: MeCN) (1: 9)	Adding 10 ml of MeCN and sonicating for 15min, followed by adding the diluent and sonicating for another 15 min. Then stirring for 30 min.	95.7
(0.1 M HCl: MeOH) (1: 9)	Adding 10 ml of MeOH and sonicating for 15min, followed by adding the diluent and sonicating for another 15 min. Then stirring for 30 min.	96.5
(0.1 M HCl: MeOH) (1: 9)	Adding 20 ml of MeOH and sonicating for 15min, followed by adding the diluent and sonicating for another 30 min. Then stirring for 45 min.	89.0
(0.1 M HCl: MeOH) (3:7)	Adding 20 ml of MeOH and sonicating for 20 min, followed by adding the diluent and sonicating for another 20 min. Then stirring for 45 min.	95.2
Mobile phase	Sonicate for 20 min, then complete the volume with diluent. Transfer the solution to prep tubes and mix for 45 min at 5000 rpm using the Distek PrepEngine instrument.	96.3
(0.1 M HCl: MeOH) (1: 9)		94.7
(0.1 M HCl: MeOH) (1: 9)	Add 5 ml Chloroform, stirring for 10 min with heating at 40 °C, sonication for 10 min with heating at 40 °C, and then interchange between them to accomplish 40 min	94.5
(1.0 M HCl: MeCN) (1: 9)	stirring for 10 min with heating at 40 °C, sonication for 10 min with heating at 40 °C, and then alternating between them to accomplish 40 min	97.3

Table 4S. Summary results for the investigated formula of CARV-MEOG

Name of formula	Assay (%)
Carvedilol: Transcutol	98.9
Carvedilol: Tween 20	96.7
CARV-MEOG without tween 20	94.8
CARV-MEOG without transcutol	100.0

Table 5S. Results of system suitability for assay test

Concentration (mg/ml)	0.0250			
Injection Number	**R_t (min)**	**Standard Area**	**Asymmetry (EP)**	**Number of Plates (USP)**
1	3.48	23.823	1.0	11481
2	3.47	23.781	1.0	11357
3	3.47	23.831	1.0	11310
4	3.46	23.857	1.0	11321
5	3.46	23.863	1.0	11259
6	3.46	23.868	1.0	11265
7	3.46	23.790	1.0	11265
8	3.45	23.871	1.0	11233
9	3.45	23.888	1.0	11278
10	3.45	23.900	1.0	11253
Average	**3.46**	**23.847**	**1.0**	**11302**
RSD%	**-**	**0.17**	**-**	**-**

Table 6S. Results of system suitability for dissolution test

Concentration (mg/ml)	0.0280			
Injection Number	**R_t (min)**	**Standard Area**	**Asymmetry (EP)**	**Number of Plates (USP)**
1	3.37	188.815	1.2	5744
2	3.37	188.540	1.2	5748
3	3.37	188.452	1.2	5752
4	3.37	188.400	1.2	5756
5	3.36	188.299	1.2	5756
6	3.36	188.615	1.2	5746
7	3.36	188.547	1.2	5744
8	3.36	188.292	1.2	5755
9	3.36	188.143	1.2	5761
10	3.36	188.143	1.2	5760
Average	**3.36**	**188.425**	**1.2**	**5752**
RSD%	**-**	**0.11**	**-**	**-**

Table 7S. Summary for linearity test results for assay test over the range (0.013-0.030) mg/ml

Level (%)	Concentration (mg/ml)	Area	RSD%	Average
50	0.013	11.198	0.062	11.205
		11.211		
		11.207		
80	0.020	17.938	0.026	17.939
		17.935		
		17.944		
90	0.023	20.057	0.036	20.051
		20.053		
		20.043		
100	0.025	22.445	0.027	22.438
		22.435		
		22.434		
110	0.028	24.660	0.041	24.668
		24.680		
		24.666		
120	0.030	26.715	0.078	26.703
		26.715		
		26.679		

Table 8S. Summary of the results of the linearity test for the assay test from the calibration curve equation

Assay Test						
Level (%)	**50**	**80**	**90**	**100**	**110**	**120**
Concentration (mg/ml)	0.013	0.020	0.023	0.025	0.028	0.030
Area[(1)]	11.205	17.939	20.051	22.438	24.668	26.703
Parameter		**Acceptance criteria**			**Result**	
Y- Intercept at target concentration		NMT 5.0%			0.443	
coefficient of determination (R^2)		≥ 0.999			1	
Y-Intercept		-			0.099	
Slope		-			887.11	

[(1)] The area is the average of three replicate injections.

Table 9S. Summary of the results of the linearity test for dissolution test over the range (0.00021-0.034) mg/ml

Level (%)	Concentration (mg/ml)	Area	RSD%	Average
1	0.00021	2.185	0.104	2.183
		2.181		
		2.182		
10	0.003	25.934	0.029	25.926
		25.924		
		25.920		
20	0.006	51.651	0.023	51.644
		51.651		
		51.631		
30	0.008	77.144	0.020	77.134
		77.142		
		77.116		
50	0.014	123.441	0.049	123.375
		123.365		
		123.321		
80	0.022	190.304	0.017	190.293
		190.257		
		190.319		
100	0.028	222.222	0.021	222.170
		222.157		
		222.130		
120	0.034	252.297	0.052	252.149
		252.108		
		252.043		

Table 10S. Summary of the results of the linearity test for the dissolution test from the calibration curve equation

Dissolution Test								
Level (%)	**1**	**10**	**20**	**30**	**50**	**80**	**100**	**120**
Concentration (mg/ml)	0.00021	0.003	0.006	0.008	0.014	0.022	0.028	0.034
Area[(1)]	2.183	25.926	51.644	77.134	123.375	190.293	222.17	252.149
Parameter				**Acceptance criteria**			**Result**	
Y- Intercept at target concentration				NMT 5.0%			3.9	
coefficient of determination (R^2)				≥ 0.98			0.99	
Y-Intercept				-			8.7009	
Slope				-			7590	

[(1)] The area is the average of three replicate injections.

Table 11S. The results of the precision test

Concentration of STD (mg/ml)		0.025	**Area of STD**	23.5627
Sample #	**weight of sample (mg)**	**Concentration (mg/ml)**	**Area**	**Assay (%)**
1	106.05	0.0265	24.8985	99.7
2	102.73	0.0257	24.4789	101.1
3	106.78	0.0267	25.1159	99.8
4	102.56	0.0256	24.1966	100.3
5	102.37	0.0256	24.0690	99.8
6	103.12	0.0258	24.0712	99.0
Average of Assay (6 samples) (%)				**99.9**
RSD (%)				0.69

Table 12S. The results of ruggedness test

Concentration of STD (mg/ml)		0.025	**Area of STD**	23.7438
Sample #	**weight of sample (mg)**	**Concentration (mg/ml)**	**Area**	**Assay (%)**
1	98.4	0.0266	24.8169	98.2
2	101.1	0.0261	25.0638	101.1
3	100.5	0.0258	24.5858	100.7
4	102.0	0.0266	25.7964	102.1
5	100.7	0.0264	25.2886	100.9
6	100.1	0.0252	24.0093	100.3
Average of Assay (6 samples) (%)				**100.5**
RSD (%)				**1.2**

Table 13S. Summary for the results of precision and ruggedness tests

Sample number	**Results for Precision (%)**	**Results for Ruggedness (%)**
1	99.7	98.2
2	101.1	101.1
3	99.8	100.7
4	100.3	102.1
5	99.8	100.9
6	99.0	100.3
RSD (%)	0.70	1.2
Average of 6 samples (%)	**100.0**	**100.5**
Average of 12 Samples (%)	**100.3**	
RSD% between two analyses	**1.0**	

Table 14S. Results of the precision test for the dissolution test

Time (h)	Release (%)							
	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	Average (% Release)	RSD (%)
0.5	14.5	14.8	16.0	17.1	17.5	16.0	16.0	6.8
1	20.7	21.1	23.0	23.8	23.7	25.7	23.0	7.4
2	28.3	29.9	31.9	33.5	33.5	35.7	32.1	7.6
4	39.7	41.4	44.4	46.3	46.9	44.4	43.9	5.8
6	50.7	50.9	52.9	55.0	56.9	61.4	54.6	6.8
8	60.0	60.4	59.7	62.2	65.7	67.9	62.7	5.0
10	71.0	73.1	73.7	74.6	76.9	77.5	74.5	3.0
12	80.6	83.3	83.0	84.0	83.7	82.8	82.9	1.3
16	92.7	95.3	98.0	93.9	98.5	95.3	95.6	2.2
18	97.2	97.5	97.5	96.5	97.4	95.5	96.9	0.8
20	95.8	98.9	99.2	98.0	99.6	99.3	98.5	1.3
22	98.8	100.3	101.3	100.1	101.2	100.5	100.4	0.8
24	103.9	101.6	102.1	99.0	100.2	103.5	101.7	1.7

Table 15S. Results of the ruggedness test for dissolution test

Time (h)	Release (%)							
	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	Average (% Release)	RSD (%)
0.5	15.4	15.4	15.4	18.6	18.2	18.2	16.9	9.6
1	21.6	21.6	21.3	25.7	25.7	25.7	23.6	9.8
2	28.5	28.5	28.3	32.5	32.5	32.5	30.5	7.3
4	46.7	36.7	43.4	46.8	43.4	43.4	43.4	8.5
6	47.4	46.8	46.4	54.7	56.5	53.1	50.8	8.8
8	57.8	56.5	55.3	59.4	62.4	59.7	58.5	4.3
10	69.8	68.8	67.6	67.8	69.2	73.6	69.5	3.2
12	82.3	82.2	82.2	80.5	83.8	84.4	82.6	1.7
16	89.3	89.2	87.2	87.4	86.4	86.1	87.6	1.6
18	89.0	93.0	93.8	93.9	92.7	88.0	91.7	2.8
20	93.0	93.9	93.9	95.6	96.3	93.1	94.3	1.4
22	95.0	95.0	95.0	97.9	98.8	96.7	96.4	1.7
24	99.3	99.2	103.8	100.7	98.8	98.7	100.1	2.0

Table 16S. Summary of the results between precision and ruggedness

Time (h)	Release (%)			Acceptance Criteria	RSD (%)
	Average of Precision	Average of Ruggedness	Average (for 12 samples)		
0.5	16	16.9	16.4	RSD ≤ 10% at time points %Release <85.0%	8.5
1	23	23.6	23.3		8.6
2	32.1	30.5	31.3		8.0
4	43.9	43.4	43.6		7.1
6	54.6	50.8	52.7		8.5
8	62.7	58.5	60.6		5.9
10	74.5	69.5	72		4.7
12	82.9	82.6	82.7		1.5
16	95.6	87.6	91.6	RSD ≤ 5% at time points %Release ≥ 85.0%	5.0
18	96.9	91.7	94.3		3.5
20	98.5	94.3	96.4		2.6
22	100.4	96.4	98.4		2.4
24	101.7	100.1	100.9		2.0

Table 17S. Summary results of accuracy test for assay test over a concentration range (0.0125-0.030) mg/ml

Acceptance Criteria	Individual Recovery for each preparation within level (%)		**97.0% - 103.0%**	Average recovery for each level (%)		**98.0% - 102.0%**
Concentration of CARV STD (mg/ml)		0.025	**Average Area of Carvedilol STD**			22.2558
Level (%)	**Concentration of CARV (mg/ml)**	**Concentration of Excipient (mg/ml)**	**Area**	**Recovery (%)**	**RSD (%)**	**Average (%)**
50	0.0125	0.957	10.951	98.9	0.13	99.0
	0.0125	0.978	11.041	99.2		
	0.0130	0.988	11.400	99.0		
80	0.0199	0.963	17.471	98.8	0.18	98.8
	0.0200	0.990	17.563	98.6		
	0.0204	1.008	17.968	99.0		
100	0.0250	0.969	21.925	98.9	0.15	99.1
	0.0247	0.971	21.779	99.2		
	0.0252	1.006	22.205	99.1		
120	0.0303	0.980	26.537	98.7	0.13	98.6
	0.0301	1.011	26.426	98.7		
	0.0301	0.997	26.365	98.5		

Table 18S. Summary results of accuracy test for dissolution test over a concentration range (0.0028-0.0334) mg/ml

Acceptance Criteria	Individual Recovery for each preparation within level (%)		**95.0% - 105.0%**	Average recovery for each level (%)		**95.0% - 105.0%**
Concentration of Carvedilol STD (mg/ml)		0.028	**Average Area of Carvedilol STD**			242.366
Level (%)	**Concentration of Carvedilol (mg/ml)**	**Concentration of Excipient (mg/ml)**	**Area**	**Recovery (%)**	**RSD (%)**	**Average (%)**
10	0.0028	1.086	24.266	100.1	1.9	102.3
	0.0028	1.098	25.127	103.7		
	0.0028	1.083	25.020	103.2		
30	0.0083	1.085	72.817	101.3	1.1	102.6
	0.0083	1.086	74.129	103.2		
	0.0083	1.082	74.305	103.4		
50	0.0138	1.085	120.799	101.1	0.65	101.7
	0.0138	1.073	122.364	102.4		
	0.0138	1.097	121.462	101.7		
80	0.0221	1.113	190.026	99.3	0.46	99.8
	0.0222	1.087	192.598	100.2		
	0.0222	1.099	192.168	100.0		
100	0.0277	1.113	239.527	99.9	0.66	100.3
	0.0278	1.08	243.262	101.1		
	0.0278	1.126	240.590	100.0		
120	0.0332	1.101	277.884	96.7	0.20	96.8
	0.0334	1.107	280.547	97.0		
	0.0333	1.114	278.759	96.7		

Table 19S. Results of filter compatibility test for STD and Sample of assay and dissolution tests

Acceptance Criteria		Recovery (%): 98.0% - 102.0%			
Test Name		Assay test		Dissolution test	
Type of filter	Discard volume (ml)	Recovery (%) STD	Recovery (%) Sample	Recovery (%) STD	Recovery (%) Sample
Nylon	4	99.9	99.6	47.7	63.3
	8	99.7	99.9	93.9	98.3
	15	NS[1]	NS[1]	99.9	99.1
Glass fiber	4	99.2	100.1	100.3	97.3
	8	99.2	100.2	100.6	98.3
	15	NS[1]	NS[1]	100.8	99.0
PTFE	4	99.3	99.8	NS[1]	NS[1]
	8	99.2	100.1	NS[1]	NS[1]
PVDF	4	98.9	100.0	NS[1]	NS[1]
	8	98.9	100.0	NS[1]	NS[1]
RC	4	99.7	100.0	NS[1]	NS[1]
	8	99.9	100.0	NS[1]	NS[1]

[1] Not Studied

Table 20S. Summary of the results of SOAS for STD and sample solutions at RT and 5 °C for assay and dissolution tests

Acceptance Criteria		Recovery (%): 98.0% - 102.0%			
Test Name		Assay test		Dissolution test	
No. of Days	Condition	% Recovery		Recovery (%)	
		STD	Sample	STD	Sample
1 Day	Fridge	100.2%	100.5%	100.6	99.4
	RT	101.0%	100.6%	**105.3**	**96.6**
2 Days	Fridge	100.9%	101.1%	**101.9**	**98.5**
	RT	**102.2%**	**102.1%**	-	-
3 Days	Fridge	100.6%	99.2%	-	-
4 Days	Fridge	101.0%	101.3%	-	-
5 Days	Fridge	100.7%	100.5%	-	-
6 Days	**Fridge**	**101.3%**	**100.5%**	-	-

Table 21S. Summary of results for system suitability test using aged mobile phase

Test Name		Stability of mobile phase	
Standard concentration (mg/ml)		0.025	
Parameters	Acceptance Criteria	Average	RSD%
R_t (min)	-	3.55	-
Standard Area	RSD: Not more than 2.0%	23.44	0.04
Asymmetry (EP)	0.8-1.8	0.91	-
Number of Plates (USP)	Not less than 2000	13544	-

Table 22S. Summary of results of system suitability and the deference between samples in normal system with samples for each parameter changed

Changed Parameters	R_t (min)	Asymmetry (EP)	Number of Plates (USP)	RSD[(1)] (%)	RSD[(2)] (%)
Normal	**3.39**	**0.90**	**12449**	**0.05**	-
Change Column (Ace C18 (250*4.6) mm, 5µm)	3.48	1.06	14808	0.03	0.37
Increase Flow Rate to 1.40 ml/min	2.92	0.87	11126	0.13	0.34
Decrease flow rate to 1.0 ml/min	4.21	1.12	7772	0.21	0.82
Wavelength minus (238nm)	3.39	0.89	12103	0.12	0.37
Wavelength plus (242nm)	3.39	0.88	12095	0.05	0.41
Raise column oven to 40 °C	3.33	0.87	11767	0.04	0.45
Minimize column oven to 30 °C	3.45	0.91	12201	0.08	0.52
Decrease time preparation of sample	3.39	0.88	11982	0.03	1.44
Decrease pH of Buffer for mobile phase to 2.5	3.51	0.91	13906	0.03	0.47
Increase pH of Buffer for mobile phase to 2.9	3.54	0.93	13502	0.05	0.47
Organic solvent increase with 5%	3.27	1.20	6247	0.05	0.42
Organic solvent reduced by 5%	4.06	1.08	7075	0.03	0.42

[(1)] The RSD% was calculated for the standard system suitability for each parameter. Acceptance criteria: as in system suitability test.

[(2)] The RSD% was calculated for the % Amount of carvedilol with normal system (samples in normal system with samples for each changed parameter). Acceptance criteria: RSD ≤ 2.0%.

Table 23S. Summary of results for acidic hydrolysis of CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	%Area of CARV after degradation	% Degradation of Carvedilol	Peak Match
0.1 M HCl at RT , 1 h	No degradation			100.0	0.0	1000
0.1 M HCl at 70 °C, 1 h	No degradation			100.0	0.0	1000
1M HCl at RT, 1 h	No degradation			100.0	0.0	1000
1 M HCl at 70 °C, 1 h	No degradation			100.0	0.0	1000
0.1 M HCl at 70 °C, 24 h	3.0	0.9	0.27	99.2	0.8	986
	5.5	1.6	0.06			
	7.4	2.2	0.04			
	7.9	2.4	0.09			
	13.0	3.9	0.54			
0.5 M HCl at 70 °C, 24 h	2.9	0.9	0.39	99.0	1.0	989
	3.1	0.9	0.12			
	4.2	1.2	0.41			
	7.9	2.3	0.20			
1.0 M HCl at 70 °C, 24 h	3.0	0.9	0.29	99.0	1.0	986
	3.1	0.9	0.03			
	4.2	1.3	0.69			
	7.9	2.3	0.13			
2.0 M HCl at 70 °C, 24 h	1.8	0.5	0.19	98.5	1.5	991
	2.9	0.9	0.28			
	4.2	1.2	1.13			
	5.2	1.6	0.18			
1 M HCl at RT, 8 h	No degradation			100.0	0.0	997
1 M HCl at 85 °C, 8 h	2.1	0.6	0.14	99.1	0.9	974
	2.2	0.7	0.12			
	2.4	0.7	0.10			
	2.9	0.9	0.21			
	4.0	1.2	0.31			
2 M HCl at RT, 6 h	No degradation			100.0	0.0	989
2 M HCl at 85 °C, 6 h	7.1	2.1	0.16	99.4	0.6	1000
4 M HCl at RT, 4 h	1.7	0.5	0.25	98.8	1.2	997
	1.7	0.5	0.26			
	4.1	1.2	0.62			
4 M HCl at 85 °C, 4 h	7.2	2.1	0.18	99.3	0.7	1000
6 M HCl at 85 °C, 1 h	1.7	0.5	0.09	99.5	0.5	988
	1.7	0.5	0.11			
	2.1	0.6	0.07			
	4.2	1.2	0.07			
	7.3	2.2	0.04			

Table 24S. Summary of results for acidic hydrolysis of CARV.

Stress Condition	Rt for Impurity (min)	RRT of Impurity	% Impurity	% Area of CARV after degradation	% Degradation of CARV	Peak Match
0.1 M HCl at RT , 1 h	No degradation			100	0.0	1000
0.1 M HCl at 70 °C, 1 h	No degradation			100	0.0	1000
1M HCl at RT, 1 h	No degradation			100	0.0	1000
1 M HCl at 70 °C, 1 h	No degradation			100	0.0	1000
0.1 M HCl at 70 °C, 24 h	1.8	0.6	0.01	99.9	0.1	986
	2.2	0.7	0.03			
	2.8	0.9	0.03			
	4.4	1.4	0.00			
0.5 M HCl at 70 °C, 24 h	2.1	0.6	0.02	99.9	0.1	985
	3.0	0.9	0.10			
1.0 M HCl at 70 °C, 24 h	2.8	0.9	0.03	99.8	0.2	986
	6.7	0.5	0.06			
	11.7	0.4	0.05			
2.0 M HCl at 70 °C, 24 h	6.7	2.1	0.14	99.8	0.2	987
	11.7	3.6	0.05			
1 M HCl at RT, 8 h	No degradation			97.3	2.7	977
1 M HCl at 85 °C, 8 h	3.0	0.9	0.05	99.7	0.3	973
	7.2	2.2	0.25			
2 M HCl at RT, 6 h	No degradation			100.0	0.0	989
2 M HCl at 85 °C, 6 h	7.2	2.1	0.21	99.6	0.4	998
4 M HCl at RT, 4 h	No degradation			100.0	0.0	976
4 M HCl at 85 °C, 4 h	3.0	0.9	0.06	98.8	1.2	987
	3.2	1.0	0.10			
	7.2	2.1	0.48			
	21.0	6.2	0.27			
6 M HCl at 85 °C, 1 h	1.7	0.5	0.05	97.3	2.7	997
	1.8	0.5	0.02			
	2.0	0.6	0.08			
	2.3	0.6	0.02			
	3.3	0.9	0.02			
	7.3	2.1	0.09			
	14.3	4.1	1.36			

Table 25S. Summary of results for acidic hydrolysis of excipient components.

Stress Condition	Rt for Impurity (min)	Rt of Carvedilol (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
0.1 M HCl at RT , 1 h	No degradation				N.A	N.A
0.1 M HCl at 70 °C, 1 h	No degradation				N.A	N.A
1M HCl at RT, 1 h	1.86	-	0.53	1.47	N.A	N.A
1 M HCl at 70 °C, 1 h	1.863	-	0.53	1.53	N.A	N.A
0.1 M HCl at 70 °C, 24 h	No degradation products				N.A	N.A
0.5 M HCl at 70 °C, 24 h	No degradation products				N.A	N.A
1.0 M HCl at 70 °C, 24 h	No degradation products				N.A	N.A
2.0 M HCl at 70 °C, 24 h	No degradation products				N.A	N.A
1 M HCl at RT, 8 h	No degradation products				N.A	N.A
1 M HCl at 85 °C, 8 h	No degradation products				N.A	N.A
2 M HCl at RT, 6 h	No degradation products				N.A	N.A
2 M HCl at 85 °C, 6 h	No degradation products				N.A	N.A
4 M HCl at RT, 4 h	No degradation products				N.A	N.A
4 M HCl at 85 °C, 4 h	No degradation products				N.A	N.A
6 M HCl at 85 °C, 1 h	No degradation products				N.A	N.A

Table 26S. Summary of results for basic hydrolysis of CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
1 M NaOH at RT, 8 h	13.93	4.24	2.62	4.7	977
1 M NaOH at 85 °C, 8 h	1.98	0.60	0.82	26.6	988
	12.33	3.71	0.22		
	13.93	4.19	5.58		
2 M NaOH at RT, 6 h	1.98	0.60	0.72	17.2	984
	2.28	0.69	0.27		
	12.36	3.72	0.21		
	13.93	4.20	7.03		
2 M NaOH at 85 °C, 6 h	1.98	0.59	0.73	36.4	993
	2.28	0.68	0.26		
	12.33	3.68	0.15		
	13.94	4.15	5.45		
4 M NaOH at RT, 4 h	1.98	0.59	0.46	44.2	996
	2.29	0.68	0.48		
	13.93	4.14	3.85		
4 M NaOH at 85 °C, 4 h	1.98	0.59	0.45	50.6	997
	2.29	0.68	0.57		
	13.94	4.14	2.91		
6 M NaOH at 85 °C, 1 h	1.95	0.58	0.59	17.4	987
	2.28	0.68	0.58		
	12.36	3.67	0.15		
	13.97	4.14	1.52		
1 M NaOH at 85 °C, 14 h	2.00	0.56	1.09	86.4	995
	2.30	0.65	0.17		
	4.13	1.16	0.33		
	4.79	1.35	0.14		
	7.43	2.09	0.13		
	15.08	4.24	11.74		

Table 27S. Summary of results for basic hydrolysis of carvedilol.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
1 M NaOH at RT, 9 h	13.94	4.26	1.44	1.5	971
1 M NaOH at 85 °C, 9 h	2.28	0.69	0.21	13.0	978
	13.94	4.23	11.95		
2 M NaOH at RT, 6 h	1.99	0.60	0.14	14.7	986
	13.94	4.21	1.56		
2 M NaOH at 85 °C, 6 h	1.99	0.60	0.87	5.1	980
	13.95	4.22	7.89		
4 M NaOH at RT, 4 h	1.98	0.60	0.13	1.3	972
	4.35	1.32	0.14		
	13.95	4.24	0.20		
4 M NaOH at 85 °C, 4 h	1.98	0.60	0.77	19.1	965
	2.31	0.70	0.89		
	13.96	4.25	2.16		
6 M NaOH at 85 °C, 1 h	1.86	0.53	2.06	27.2	996
	13.98	4.01	1.09		
1 M NaOH at 85 °C, 14 h	2.00	0.55	1.03	80.41	994
	2.30	0.64	0.28		
	4.22	1.17	0.16		
	5.49	1.52	0.04		
	15.06	4.17	18.08		

Table 28S. Summary of results for basic hydrolysis of excipients.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
1 M NaOH at RT, 9 h	No Degradation			N.A	N.A
1 M NaOH at 85 °C, 9 h	1.98	0.55	0.29	N.A	N.A
	2.27	0.63	0.05		
2 M NaOH at RT, 6 h	1.98	0.55	0.06	N.A	N.A
2 M NaOH at 85 °C, 6 h	1.98	0.55	0.04	N.A	N.A
4 M NaOH at RT, 4 h	1.98	0.55	0.05	N.A	N.A
	3.48	0.97	0.02		
4 M NaOH at 85 °C, 4 h	1.98	0.55	0.05	N.A	N.A
	3.48	0.97	0.01		

Table 29S. Summary of results for neutral hydrolysis for CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Area of CARV after degradation	% Degradation of CARV	Peak Match
H_2O at 85 °C, for 4 h	2.127	0.6	0.1	98.9	1.1	974
	12.614	3.8	0.5			
H_2O at 85 °C, for 8 h	2.119	0.6	0.2	99.2	0.8	978
	12.625	3.8	0.7			
H_2O at 85 °C, for 24 h	0.63	0.2	0.2	98.6	1.4	996
	1.17	0.3	0.3			
	1.56	0.5	0.1			
	2.12	0.6	0.1			
	3.68	1.1	0.6			
	4.13	1.2	0.1			

Table 30S. Summary of results for neutral hydrolysis for CARV.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Area of CARV after degradation	% Degradation of CARV	Peak Match
H_2O at 85 °C, for 4 h	No degradation			98.9	0.0	975
H_2O at 85 °C, for 8 h	No degradation			100.0	0.0	990
H_2O at 85 °C, for 24 h	No degradation			100.0	0.0	991

Table 31S. Summary of results for neutral hydrolysis for excipient.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
H_2O at 85 °C, for 4 h	No degradation				-
H_2O at 85 °C, for 8 h	No degradation				-
H_2O at 85 °C, for 24 h	No degradation				-

Table 32S. Summary of results for oxidation of CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
35%H_2O_2, 30 min	4.49	1.29	0.58	27.8	989
	4.68	1.35	1.23		
	9.22	2.66	0.85		
	11.40	3.52	2.23		
35% H_2O_2, for 6 h	2.96	0.85	1.32	15.2	977
	4.64	1.33	0.58		
	4.85	1.39	3.81		
	10.04	2.88	0.62		
30% H_2O_2, for 8 h	2.95	0.85	0.30	12.1	989
	4.62	1.33	0.93		
	4.81	1.38	0.86		
	11.35	3.26	0.69		
35% H_2O_2, for 8 h	2.98	0.86	0.99	8.2	978
	4.65	1.34	0.54		
	4.87	1.40	1.57		
	10.05	2.89	0.58		
30% H_2O_2, for 24 h	2.96	0.85	1.41	20.1	981
	4.65	1.33	1.41		
	4.86	1.40	3.40		

	10.04	2.89	0.83		
35% H_2O_2, for 24 h	2.95	0.85	1.06	23.7	939
	4.62	1.33	2.40		
	4.82	1.38	2.99		
	9.91	2.85	0.65		

Table 33S. Summary of results for oxidation of carvedilol.

Stress Condition	Rt for Impurity	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
3% H_2O_2- 3 h and 30 min	4.98	1.48	0.71	11.0	985
	11.92	3.55	7.13		
35%H_2O_2, 30 min	4.99	1.49	7.95	25.9	992
	11.92	3.55	4.21		
30% H_2O_2, for 8 h	4.68	1.39	0.40	33.2	985
	4.89	1.46	14.87		
	7.18	2.14	0.82		
35% H_2O_2, for 8 h	4.68	1.39	0.57	32.2	981
	4.89	1.45	12.64		
	7.17	2.13	0.78		
	8.66	2.58	1.70		
	9.16	2.73	1.55		
35% H_2O_2, for 6 h	4.68	1.39	0.39	29.3	974
	4.89	1.46	12.28		
	8.67	2.58	1.39		
	9.16	2.73	1.28		
	10.16	3.02	0.85		
30% H_2O_2, for 24 h	2.98	0.89	1.07	40.5	989
	4.68	1.39	0.76		
	4.89	1.46	16.50		
	7.17	2.13	1.76		
	8.67	2.58	2.99		
	9.16	2.73	2.71		
35% H_2O_2, for 24 h	2.73	0.81	0.54	46.6	992
	2.95	0.88	1.50		
	4.82	1.43	27.24		

	7.04	2.10	1.89		
	9.903	2.95	0.36		
	16.443	4.89	0.77		
	22.19	6.60	0.44		

Table 34S4. Summary of the results for the oxidation of excipient.

Stress Condition	Rt for Impurity	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
0.1% H_2O_2 for 1 h	No Degradation			NA	NA
3% H_2O_2 for 3 h	No Degradation			NA	NA
3% H_2O_2- 3 h-30 min	No Degradation			NA	NA
35% H_2O_2 for 6 h	No Degradation			NA	NA
30% H_2O_2 for 8 h	No Degradation			NA	NA
35% H_2O_2 for 8 h	No Degradation			NA	NA
30% H_2O_2 for 24 h	No Degradation			NA	NA
35% H_2O_2 for 24 h	No Degradation			NA	NA

Table 35S. Summary of the results for the thermal degradation of CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
150 °C, for 1 h	13.22	3.86	2.88	17.6	996
85 °C, for 24 h	12.30	3.67	1.76	11.7	997
120 °C, for 2 days	13.20	3.78	2.39	32.2	1000
120 °C, for 3 days	13.36	3.70	17.81	69.3	1000
120 °C, for 4 days	11.80	3.70	2.25	60.8	1000

Table 36S. Summary of the results of the thermal degradation of carvedilol.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
85 °C, for 24 h	3.92	1.2	0.23	14.2	991
	5.24	1.6	0.14		
120 °C, for 4 days	2.95	0.9	0.50	13.4	984
	6.82	2.1	0.41		

	11.26	3.4	0.59		
	11.79	3.6	0.57		
	13.32	4.0	0.38		

Table 37S. Summary of the results for the thermal degradation of excipient.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
85 °C, for 24 h	3.45	1.03	0.06	N.A	N.A
	4.70	1.40	0.14		
	6.39	1.91	0.14		
120 °C, for 4 days	3.45	1.02	0.06	N.A	N.A
	4.59	1.36	0.05		
	6.19	1.84	0.04		

Table 38S. Summary of the results for the photodegradation for CARV-MEOG.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
Sun light for 1 week	2.08	0.63	0.29	11.9	988
	3.997	1.21	0.07		
	6.86	2.07	0.15		
	11.89	3.58	6.20		

Table 39S. Summary of the results for the photodegradation of carvedilol.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
Sun light for 1 week	No Degradation			NA	NA

Table 40S. Summary of the results for the photodegradation of excipients.

Stress Condition	Rt for Impurity (min)	RRT	% Impurity	% Degradation of Carvedilol	Peak Match
Sunlight for 1 week	3.45	1.04	0.02	N.A	N.A
	4.60	1.39	0.02		
	6.20	1.87	0.01		

Table 41S. Summary of results of Air degradation for CARV-MEOG, carvedilol, and excipients

CARV-MEOG					
Stress Condition	**Rt for Impurity (min)**	**RRT**	**% Impurity**	**% Degradation of CARV**	**Peak Match**
Keep at RT with solvent for 24 h	No degradation			0.0	989
Keep at RT without solvent for 24 h	No degradation			0.0	985
CARV Raw material					
Stress Condition	**Rt for Impurity (min)**	**RRT**	**% Impurity**	**% Degradation of CARV**	**Peak Match**
Keep at RT with Solvent for 24 h	No degradation			0.0	986
Keep at RT without Solvent for 24 h	No degradation			0.0	989
Excipient					
Stress Condition	**Rt for Impurity (min)**	**RRT**	**% Impurity**	**% Degradation of CARV**	**Peak Match**
Keep at RT with Solvent for 24 h	No degradation				-
Keep at RT without Solvent for 24 h	No degradation				-

List of Figures:

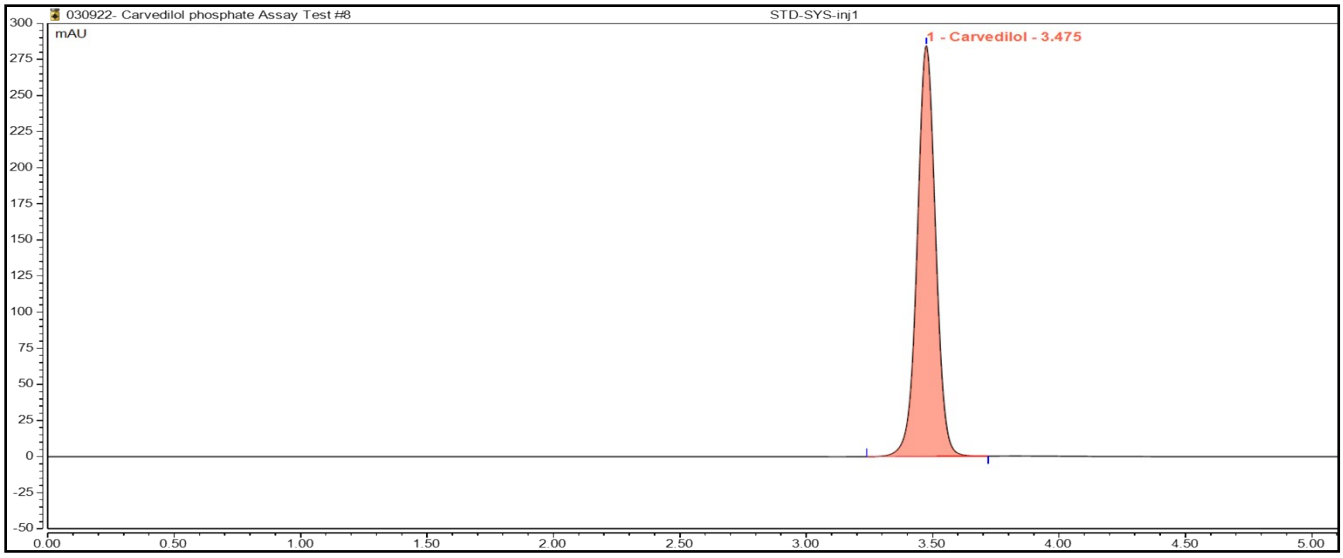


Figure 1S. A representative chromatogram for system suitability of the assay test.

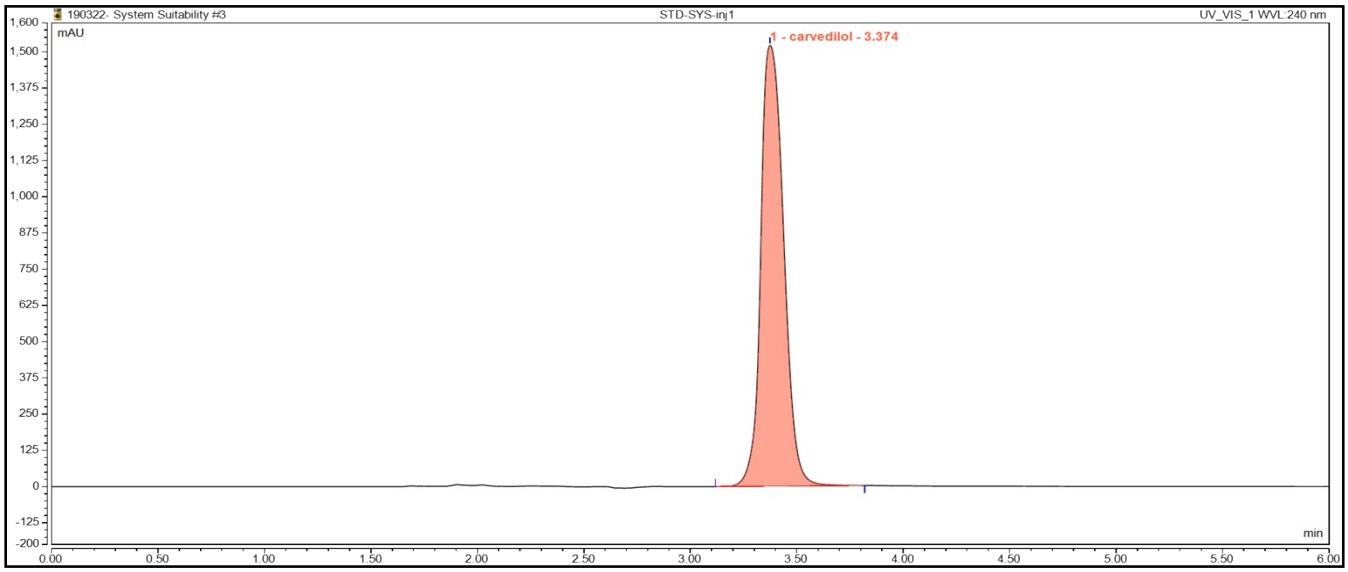


Figure 2S. A representative chromatogram for system suitability of the dissolution test.

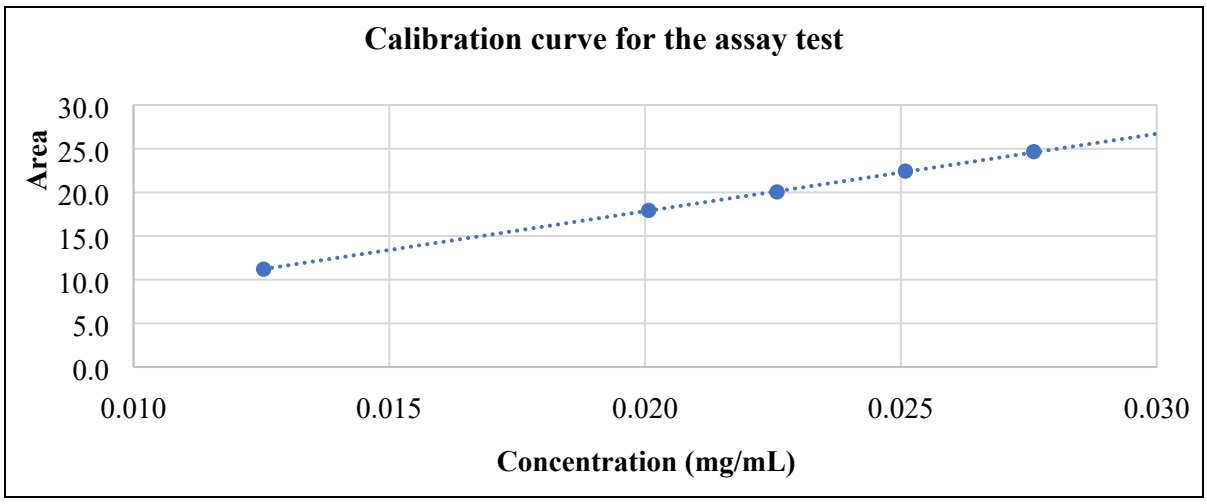


Figure 3S. Calibration curve for linearity test of assay test.

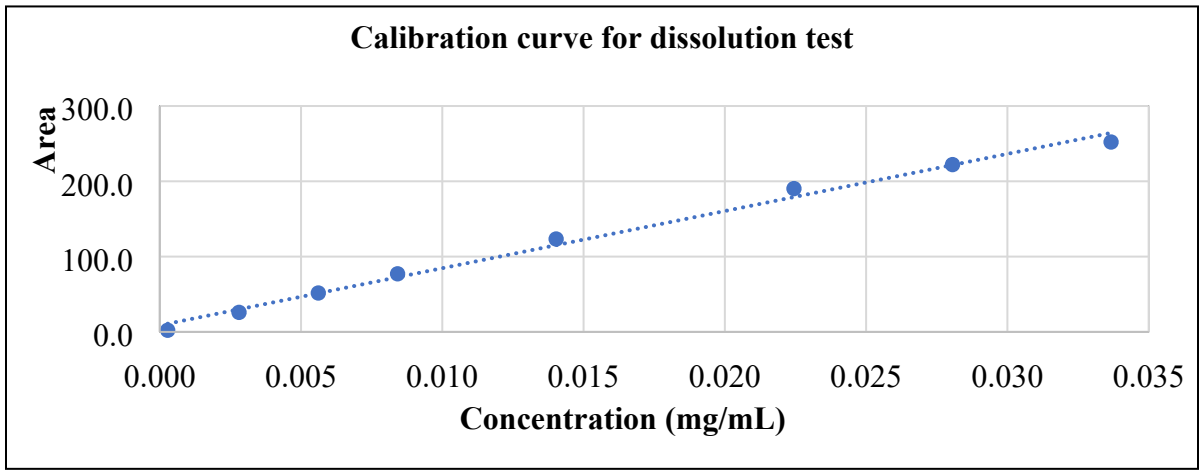


Figure 4S. Calibration curve for linearity test of dissolution test.

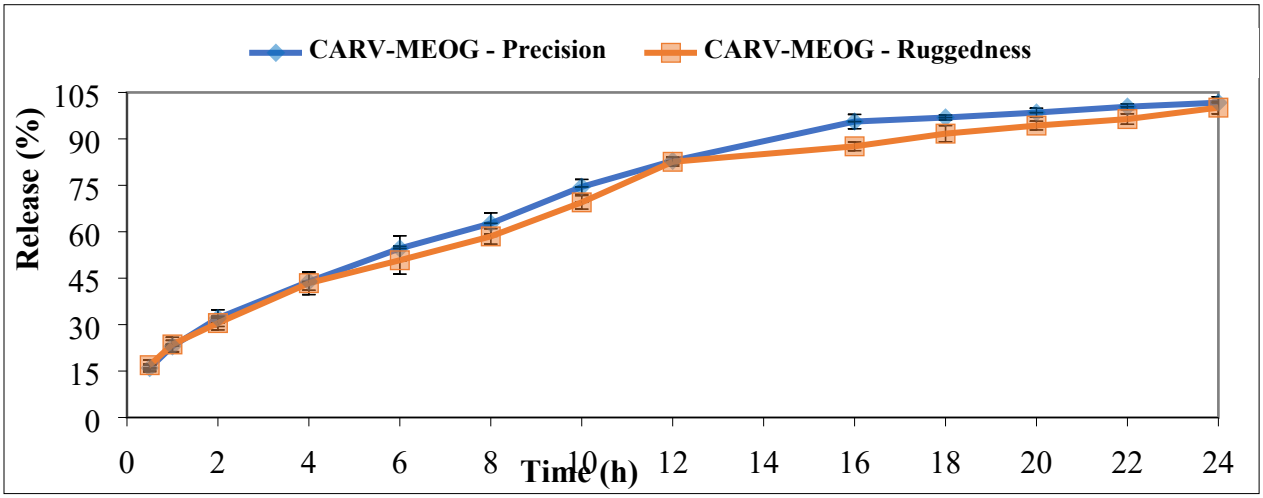
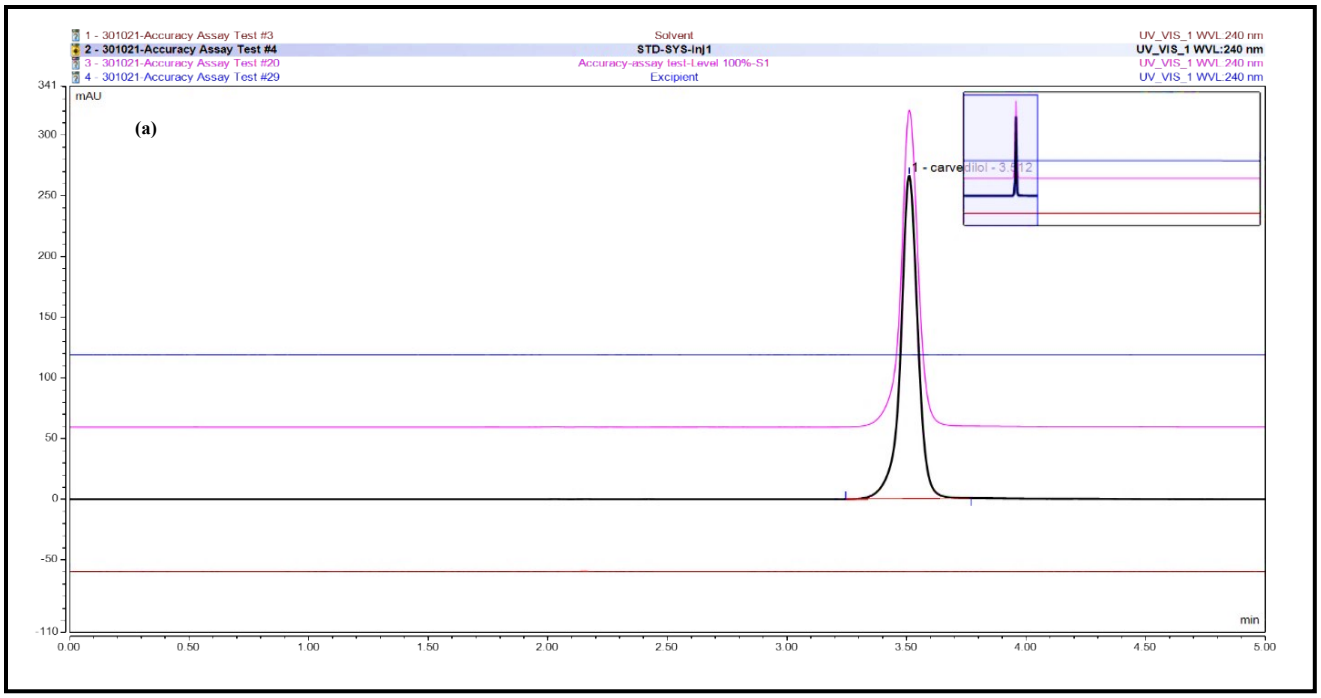


Figure 5S. A plot between precision and ruggedness.



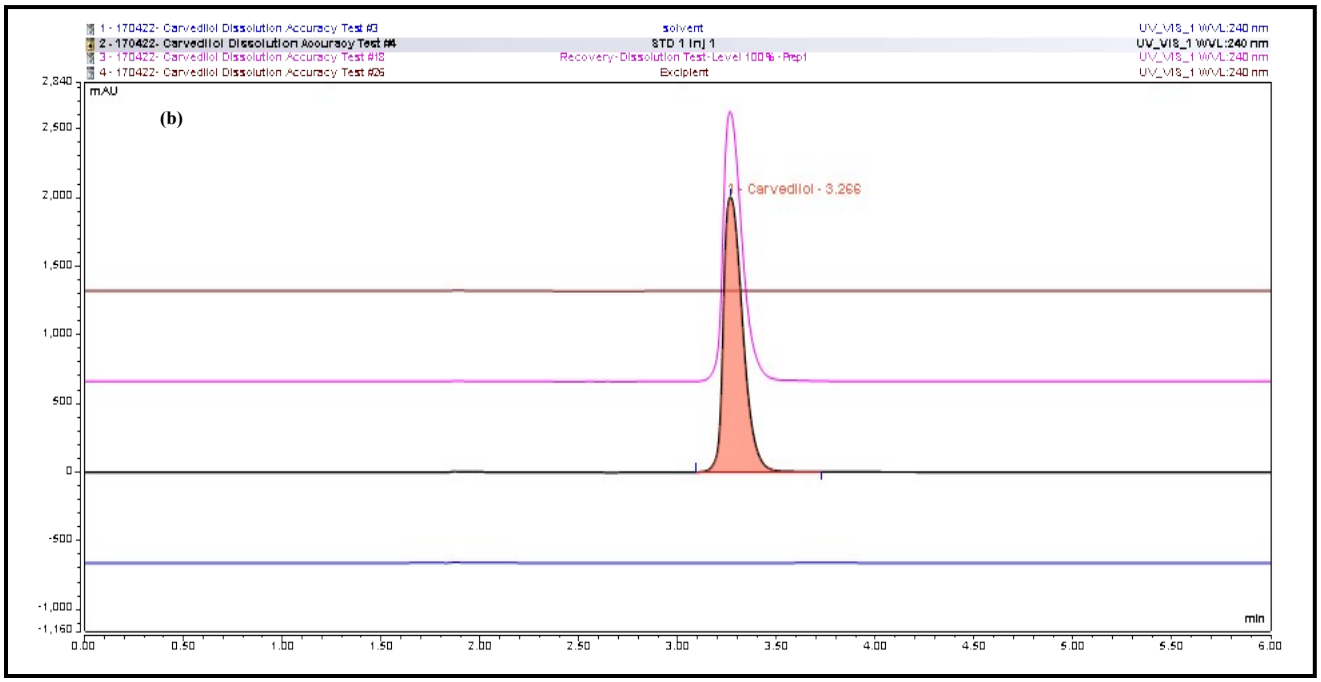


Figure 6S. Overlay chromatogram for solvent, standard, sample, and excipients: a- assay test, b- dissolution test.

Forced Degradation Study – Chromatograms (CARV Raw material)

Acid Hydrolysis:

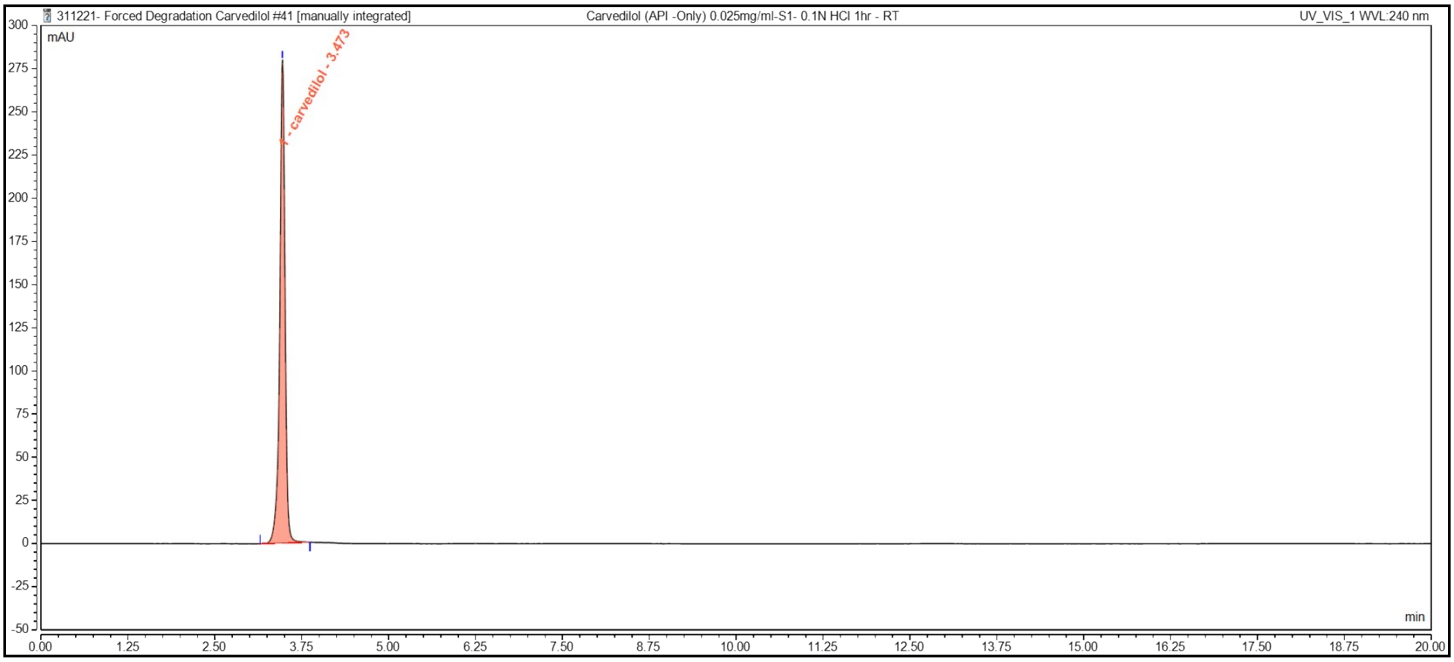


Figure 7S. HPLC Chromatogram of acid hydrolysis of CARV, 0.1 M HCl for 1 h at RT.

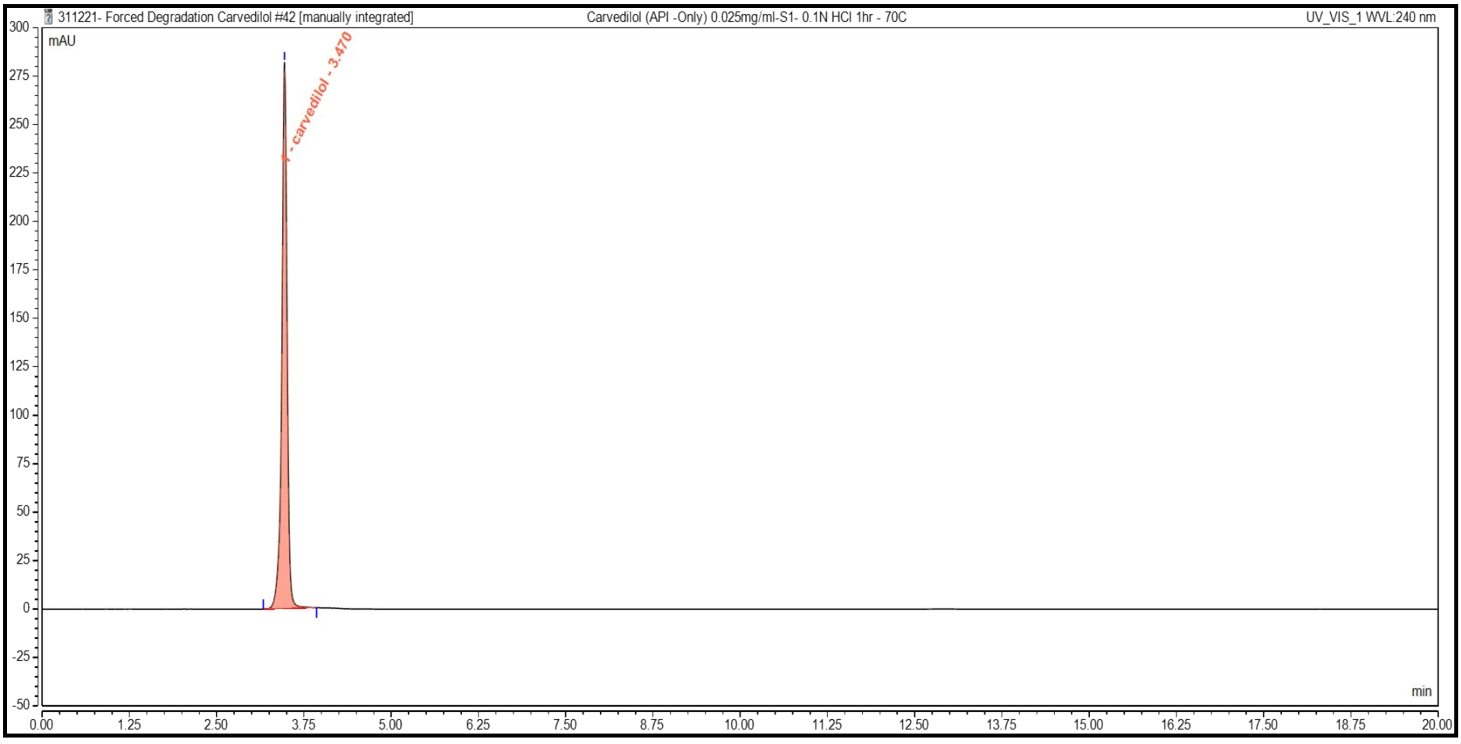


Figure 8S. HPLC Chromatogram of acid hydrolysis of CARV, 0.1 M HCl for 1 h at 70 ℃.

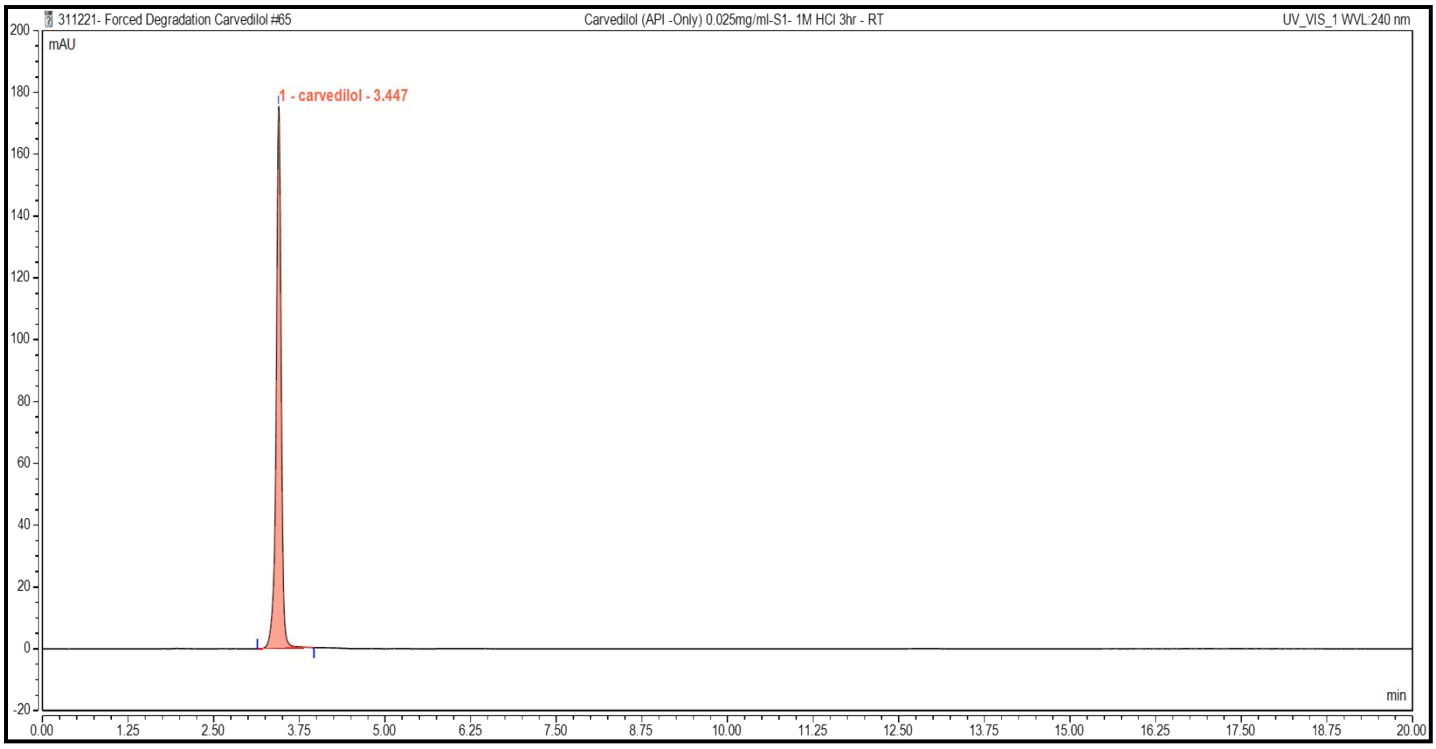


Figure 9S. HPLC Chromatogram of acid hydrolysis of CARV, 1.0 M HCl for 3 h at RT.

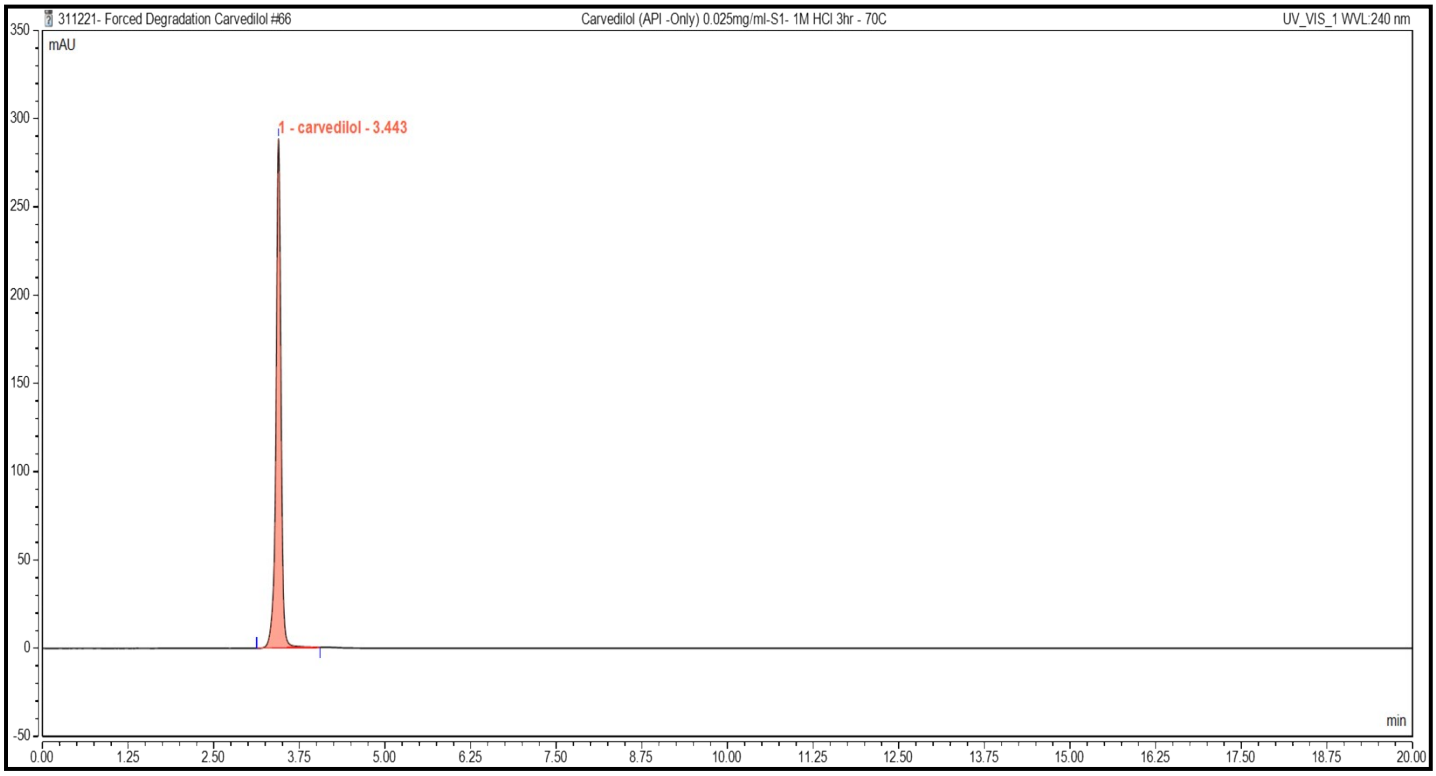


Figure 10S. HPLC Chromatogram of acid hydrolysis of CARV, 1.0 M HCl for 3 h at 70 ℃.

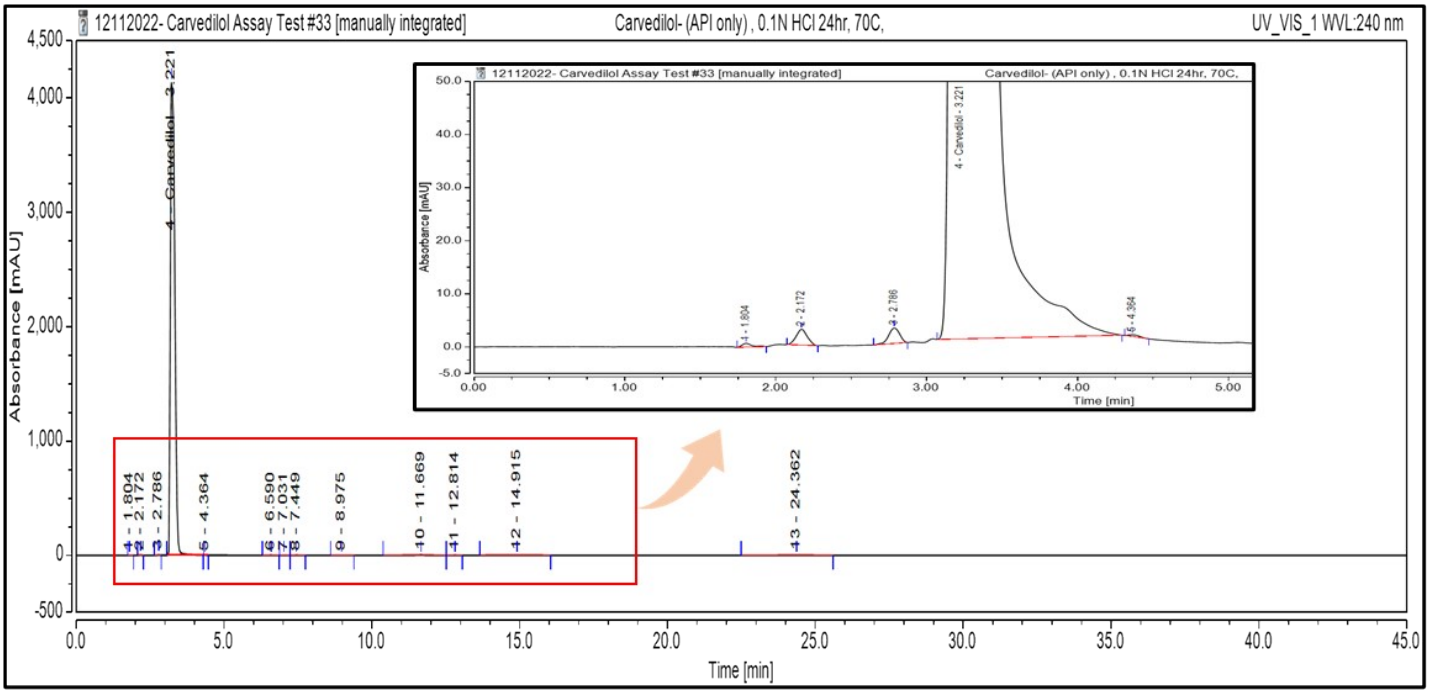


Figure 11S. HPLC chromatogram of acid hydrolysis of CARV, 0.1 M HCl for 24 h at 70 ℃.

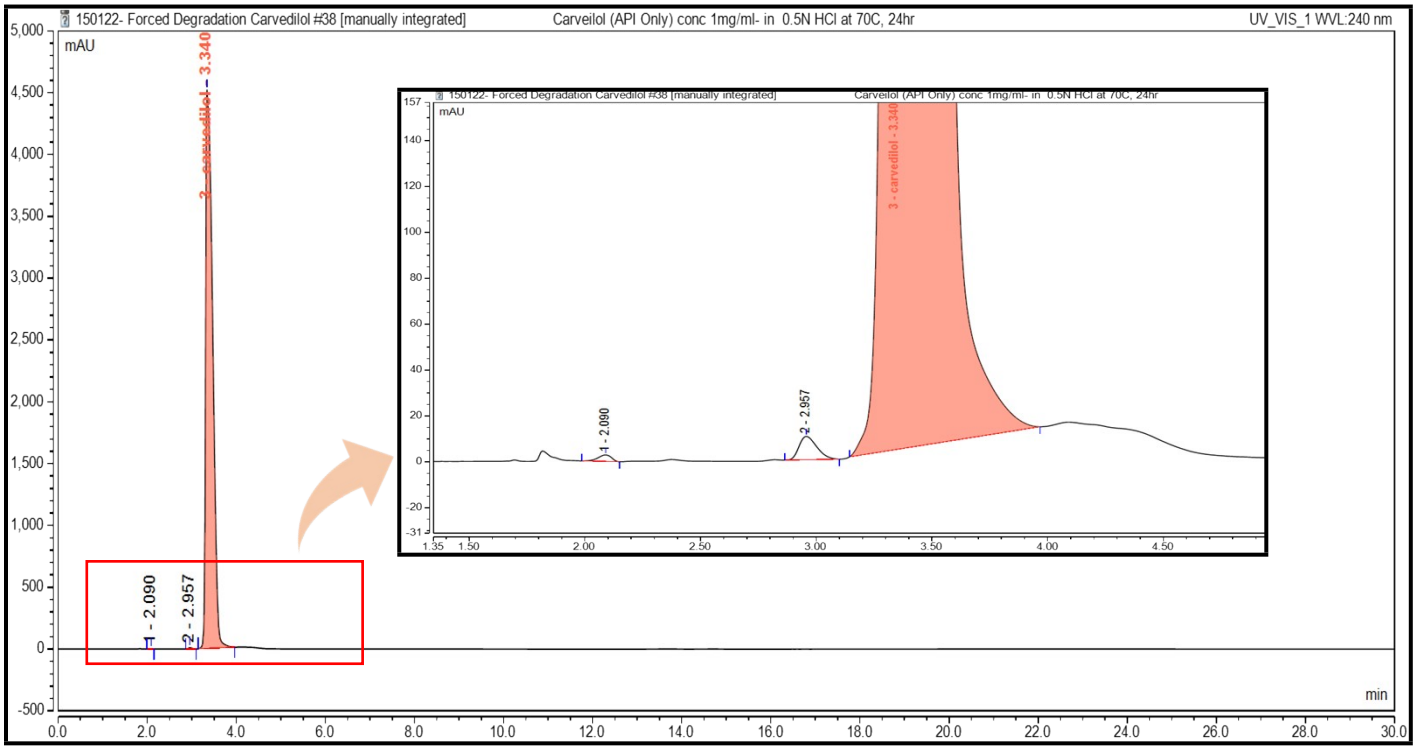


Figure 12S. HPLC chromatogram of acid hydrolysis of CARV, 0.5 M HCl for 24 h at 70 ℃.

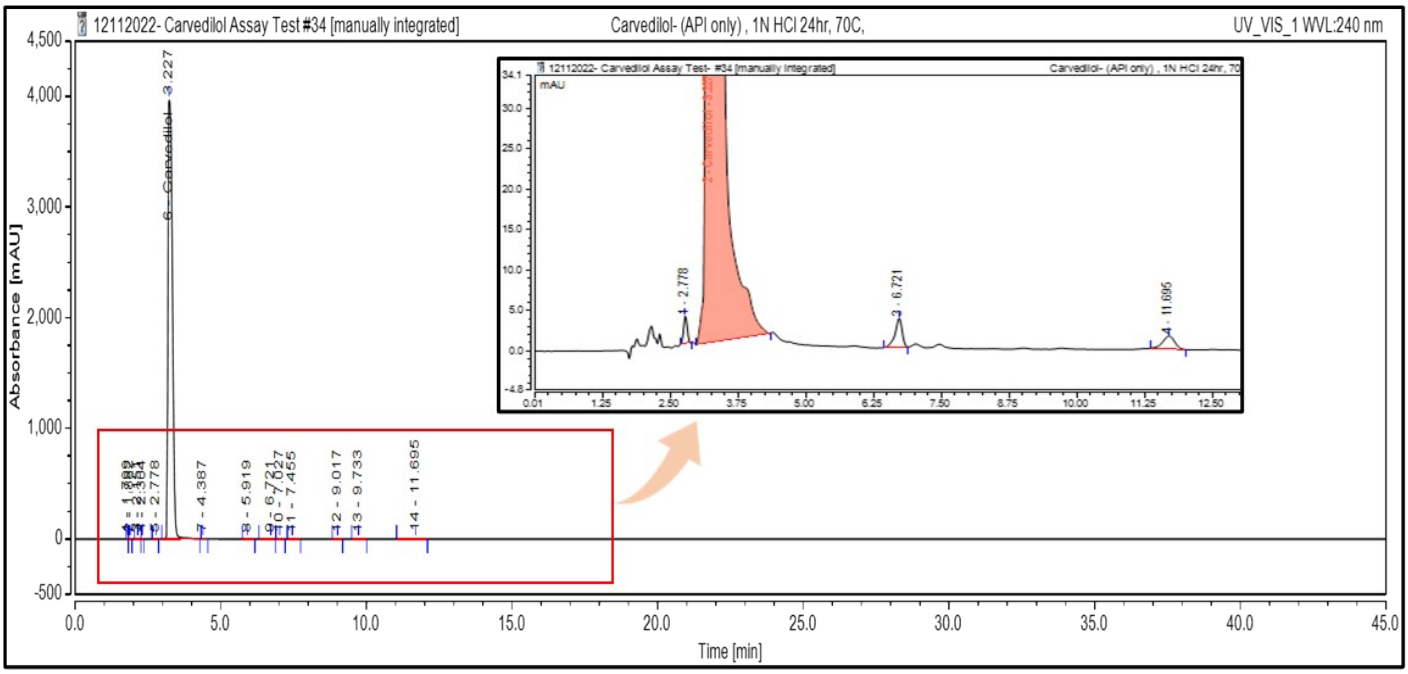


Figure 13S. HPLC chromatogram of acid hydrolysis of CARV, 1.0 M HCl for 24 h at 70 °C.

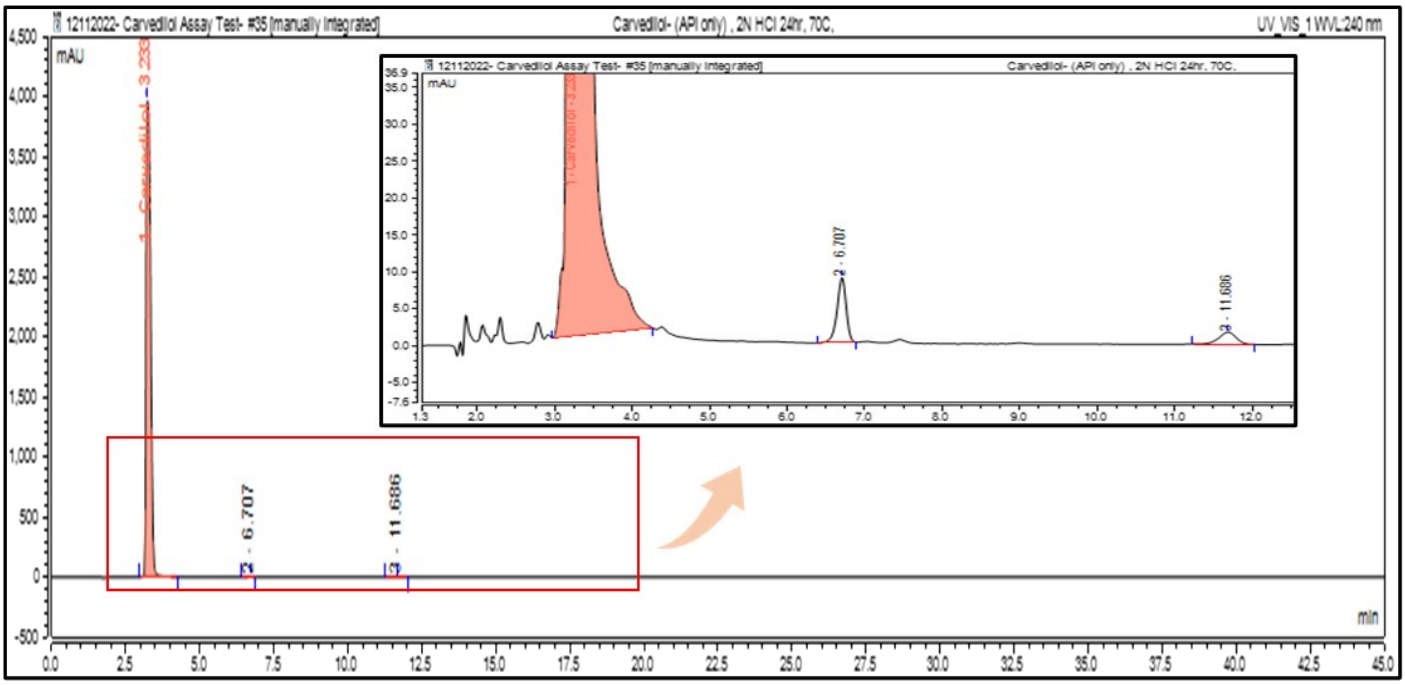


Figure 14S. HPLC chromatogram of acid hydrolysis of CARV, 2.0 M HCl for 24 h at 70 °C.

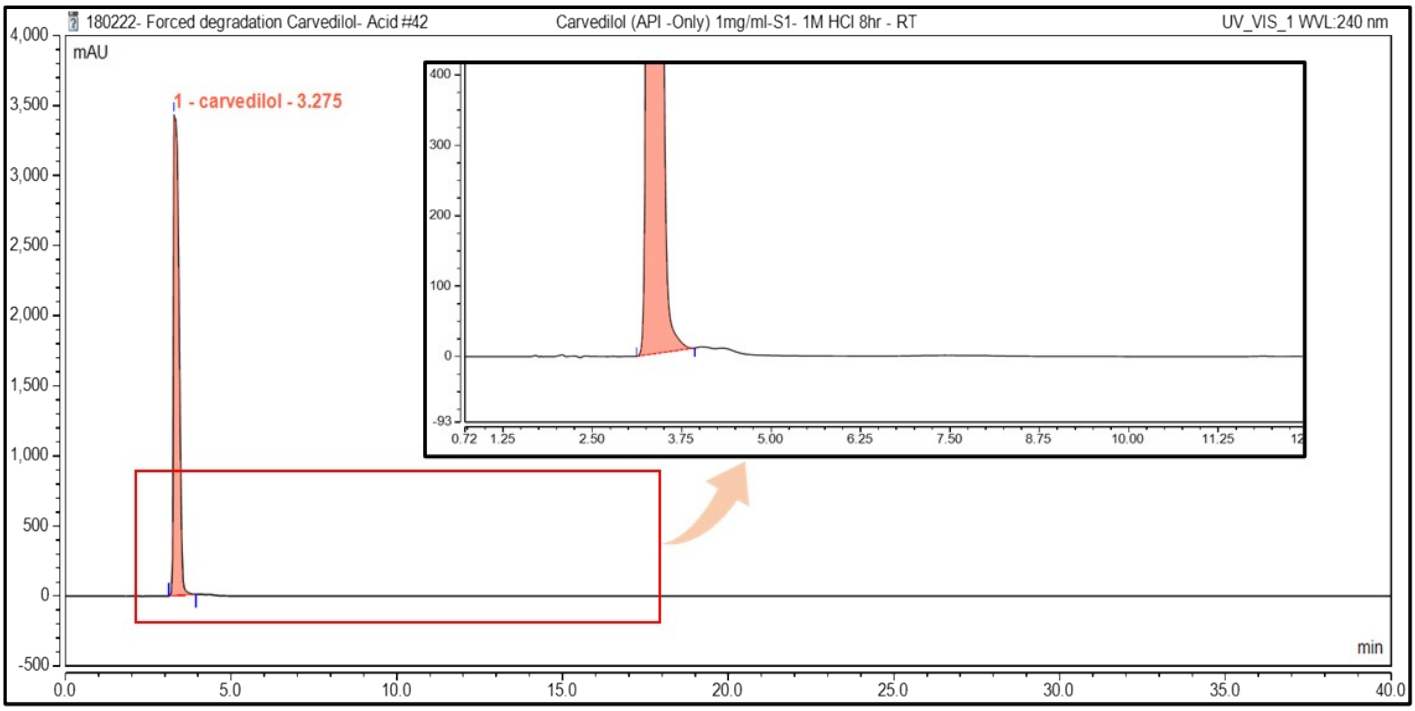


Figure 15S. HPLC chromatogram of acid hydrolysis of CARV, 1.0 M HCl for 8 h at RT.

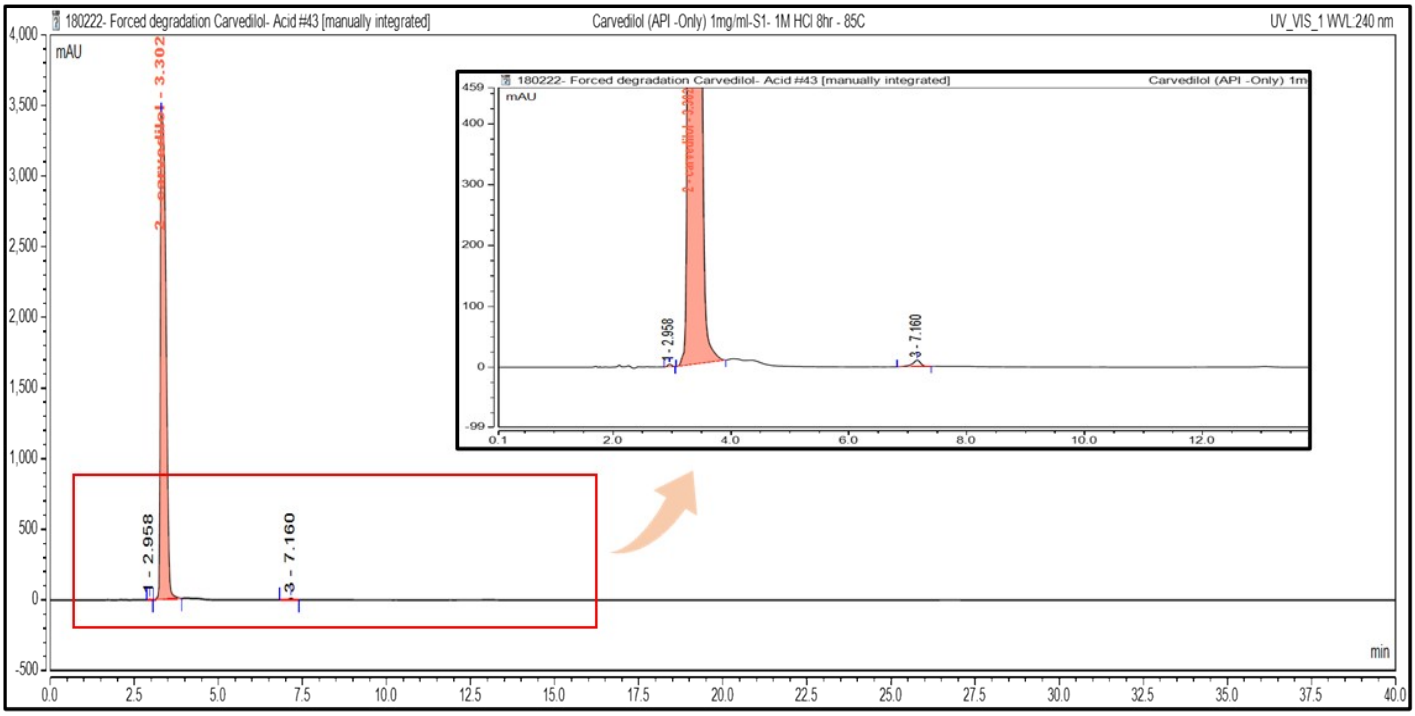


Figure 16S. HPLC chromatogram of acid hydrolysis of CARV, 1.0 M HCl for 8 h at 85 °C.

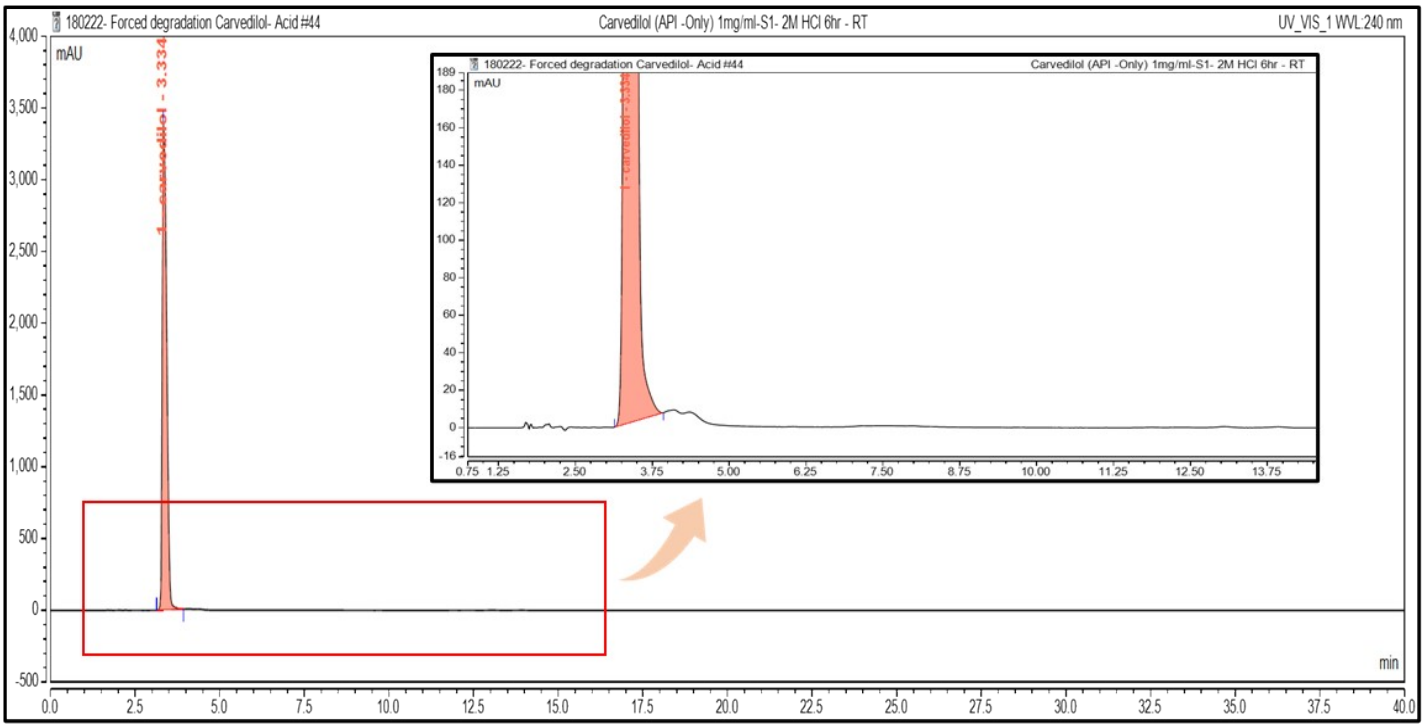


Figure 17S. HPLC chromatogram of acid hydrolysis of CARV, 2.0 M HCl for 6 h at RT.

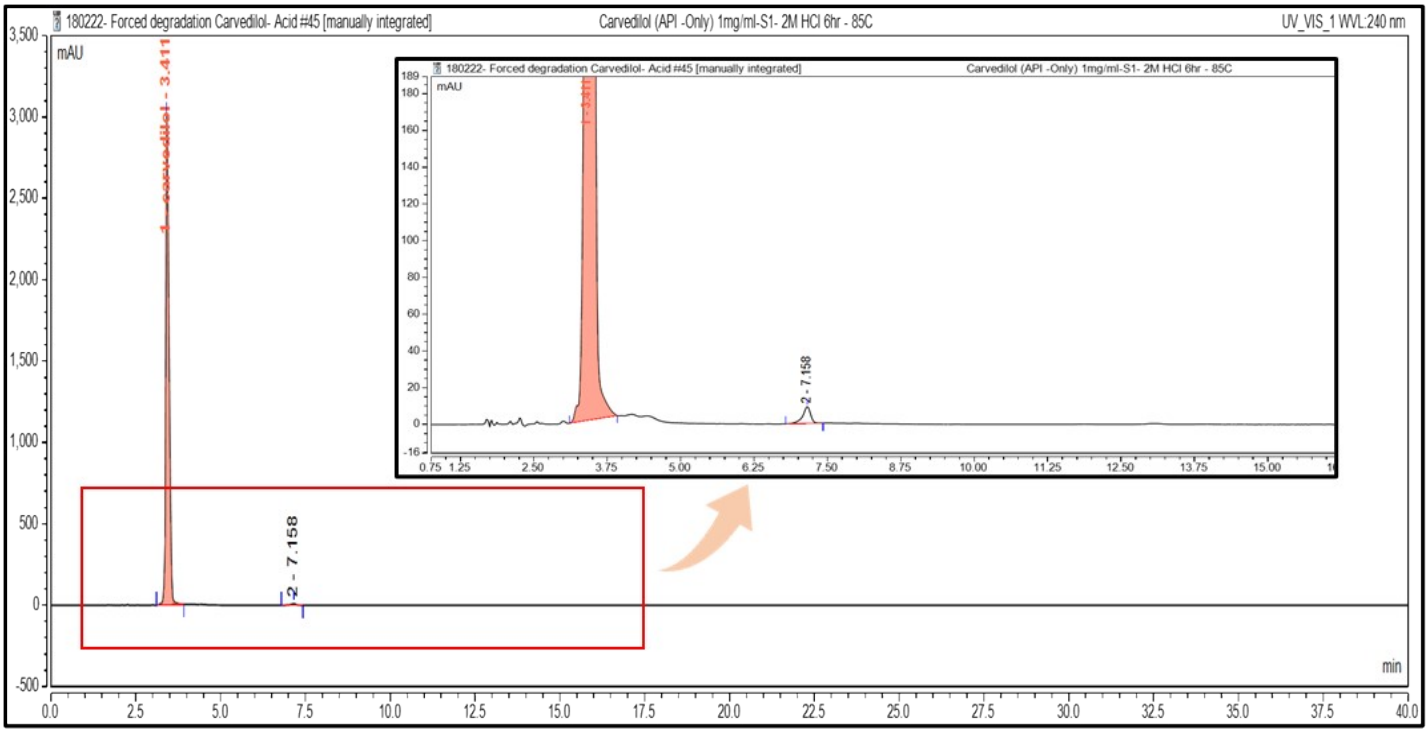


Figure 18S. HPLC chromatogram of acid hydrolysis of CARV, 2.0 M HCl for 6 h at 85 °C.

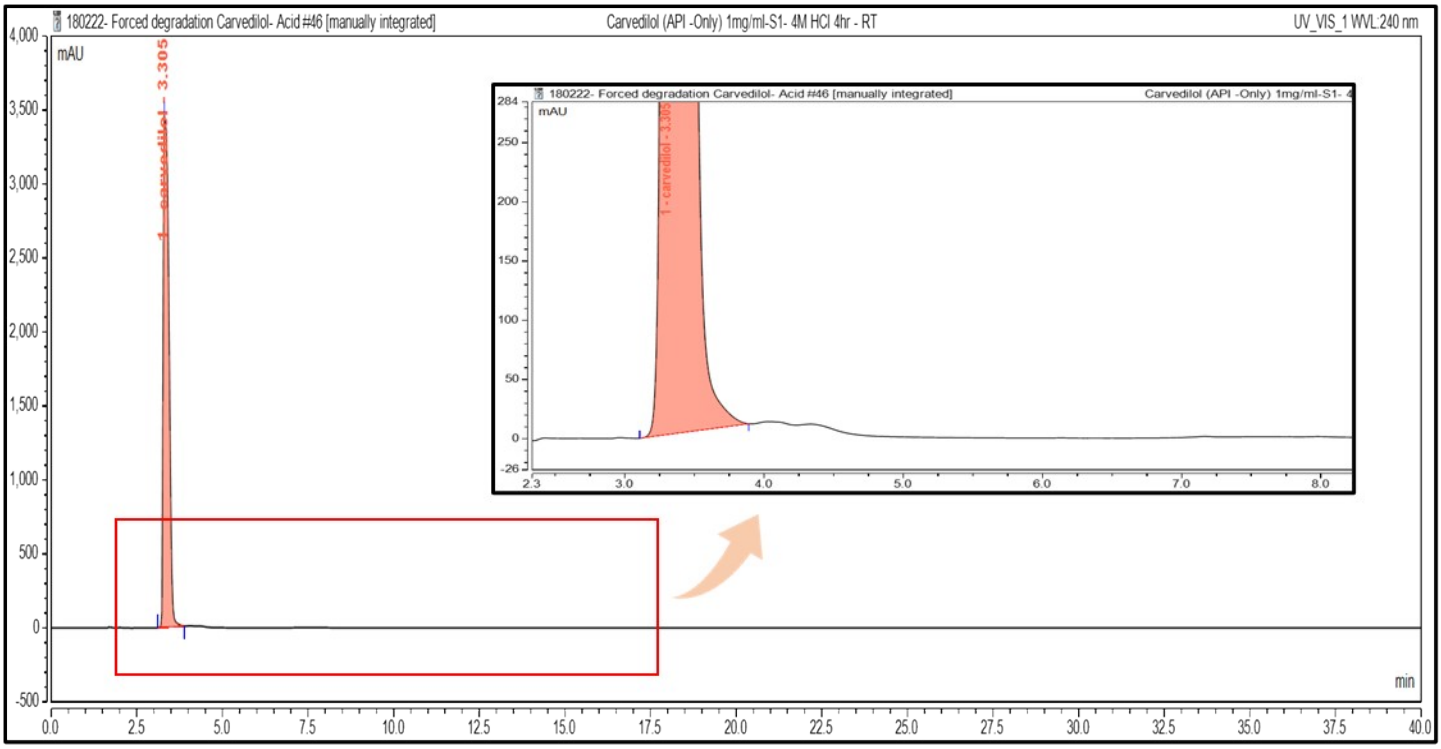


Figure 19S. HPLC chromatogram of acid hydrolysis of CARV, 4.0 M HCl for 4 h at RT.

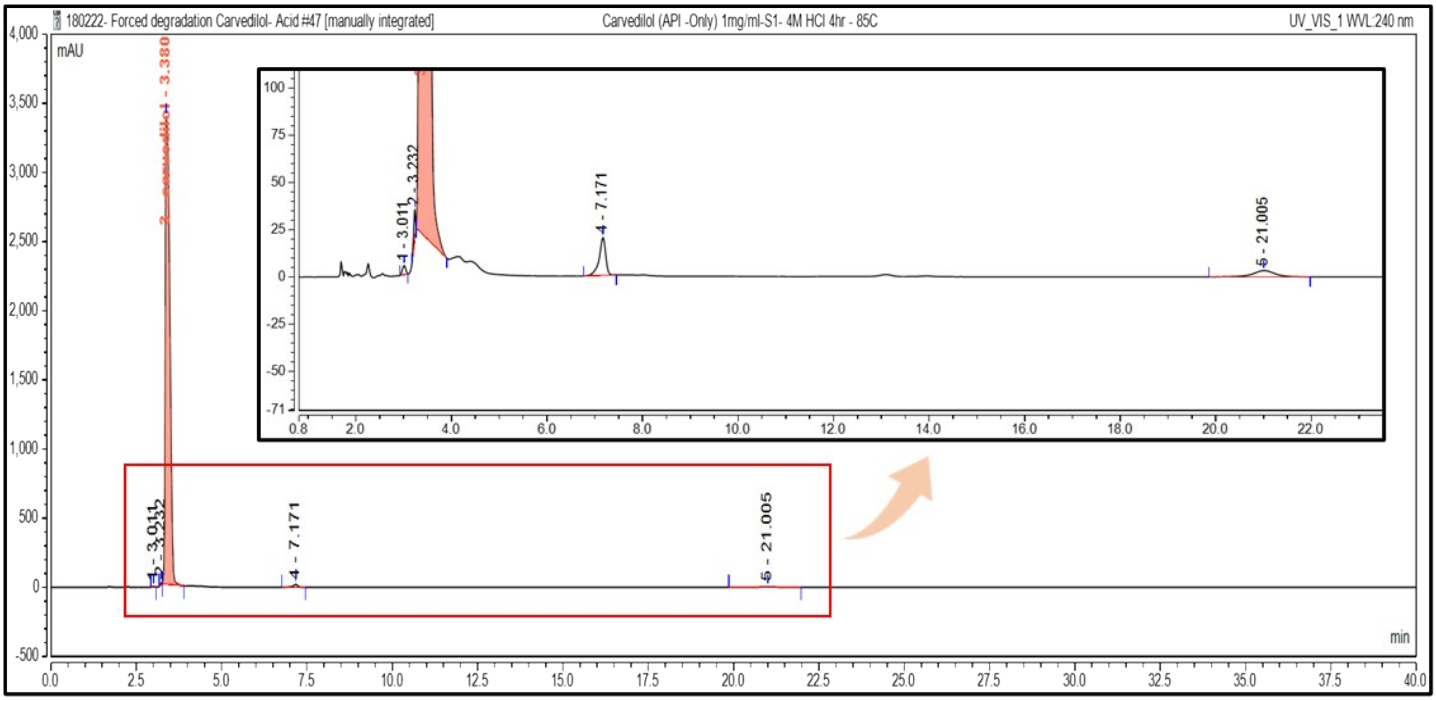


Figure 20S. HPLC chromatogram of acid hydrolysis of CARV, 4.0 M HCl for 4 h at 85 °C.

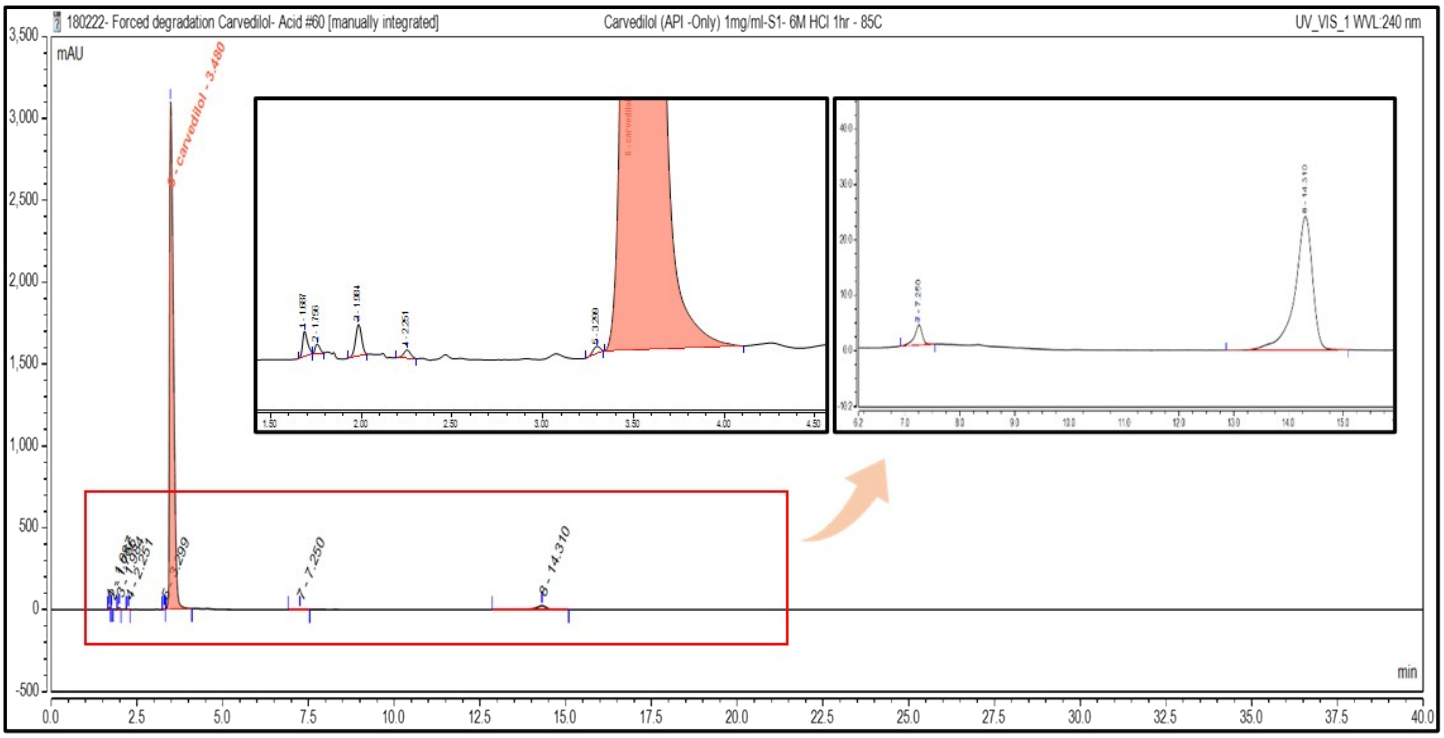


Figure 21S. HPLC chromatogram of acid hydrolysis of CARV, 6.0 M HCl for 1 h at 85 °C.

CARV-MEOG - Acid Hydrolysis:

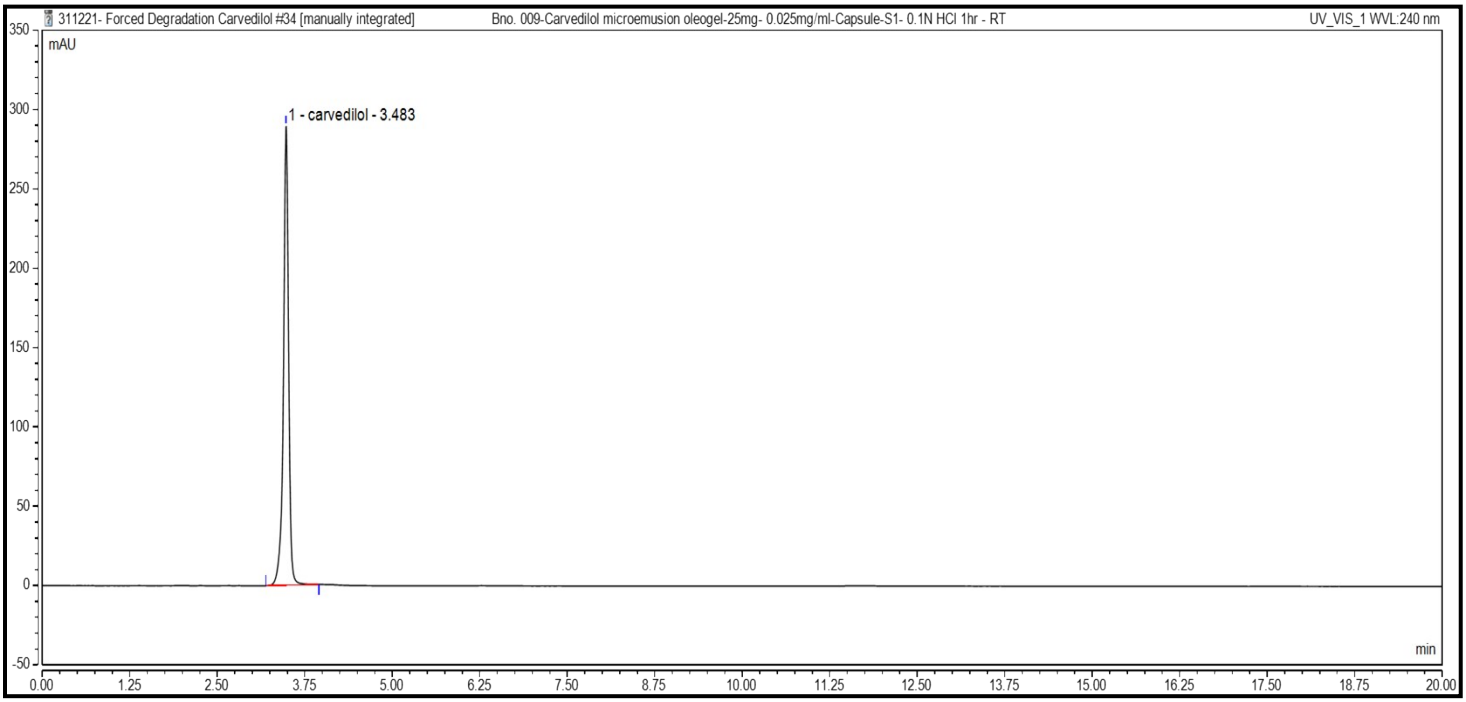


Figure 22S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 0.1 M HCl for 1 h at RT.

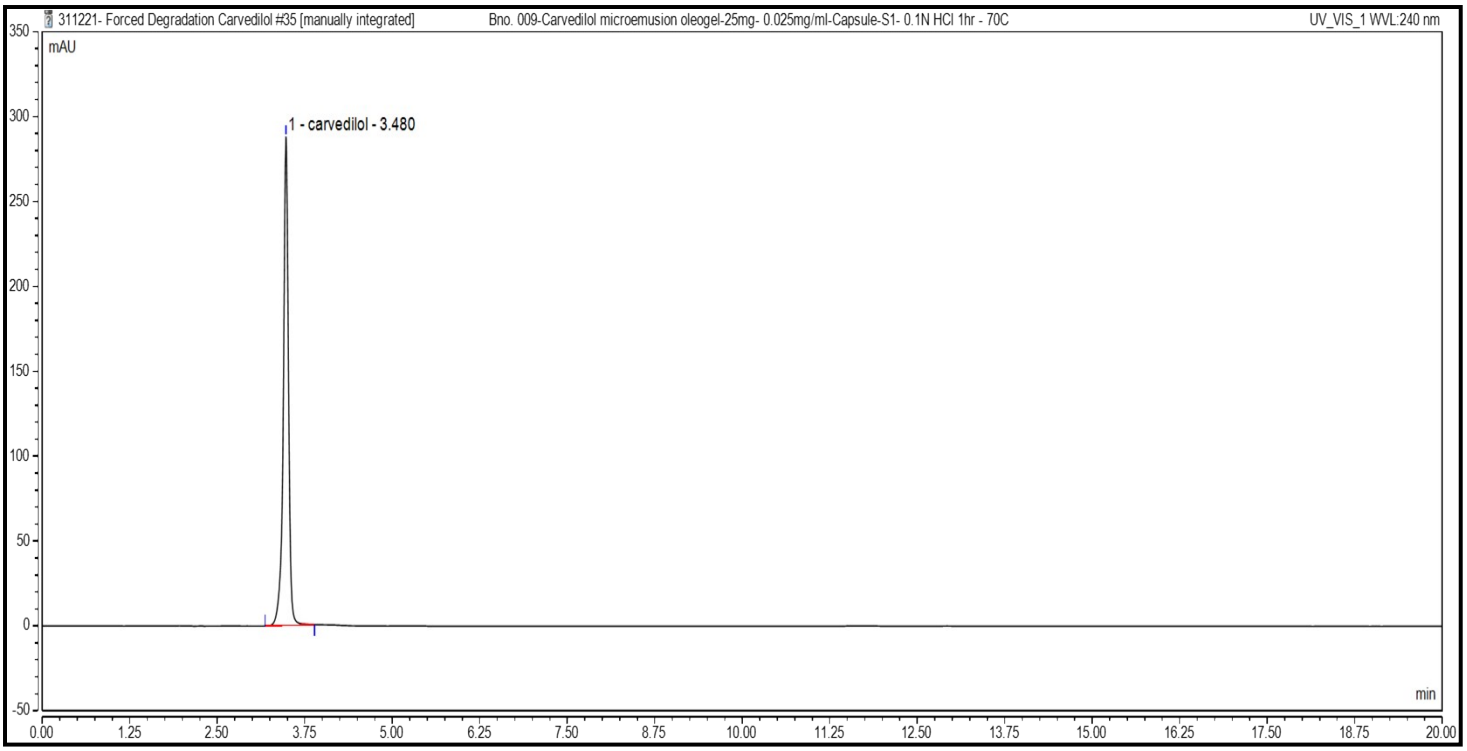


Figure 23S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 0.1 M HCl for 1 h at 70 °C.

Figure 24S. HPLC Chromatogram of acid hydrolysis of CARV-MEOG, 1.0 M HCl for 3 h at RT.
(Note: peak at retention time 1.860 min is related for the excipient degradation).

Figure 25S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 1.0 M HCl for 3 h at 70 °C.

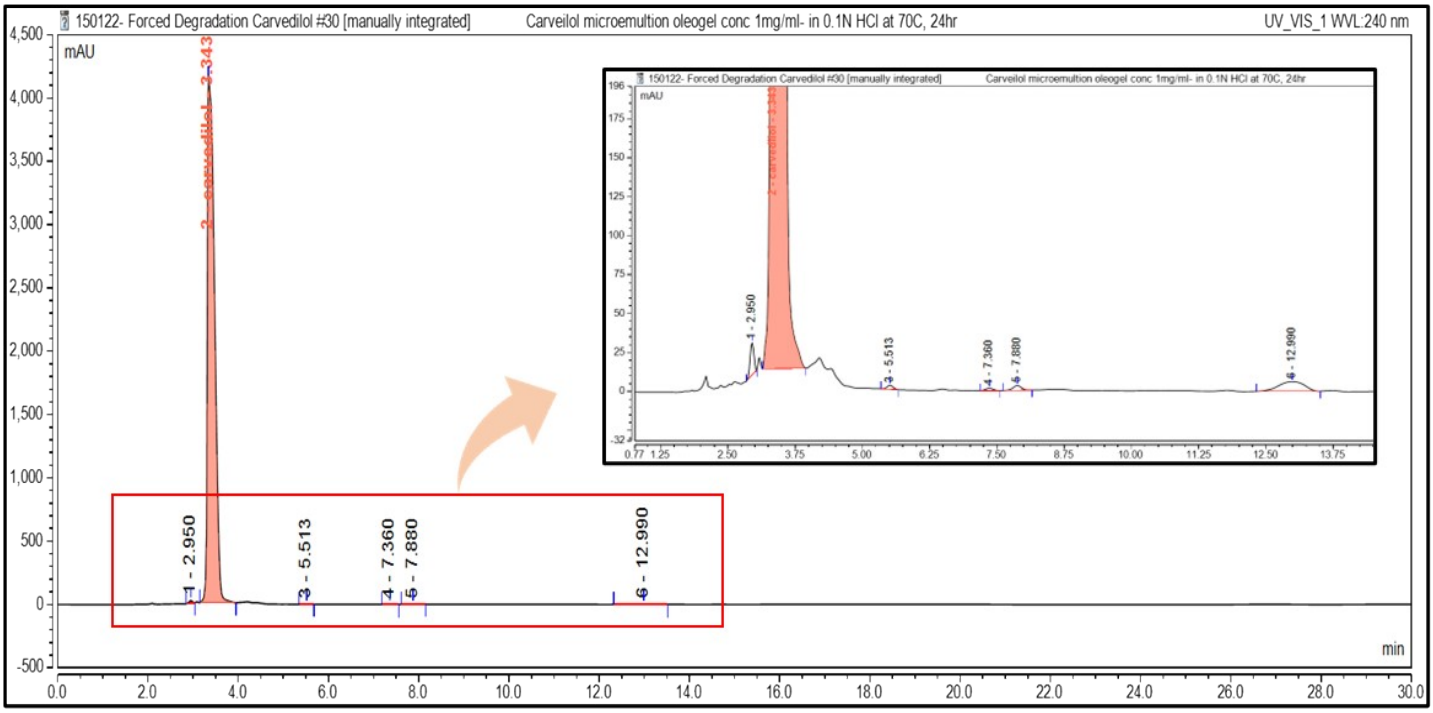


Figure 26S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 0.1 M HCl for 24 h at 70 °C.

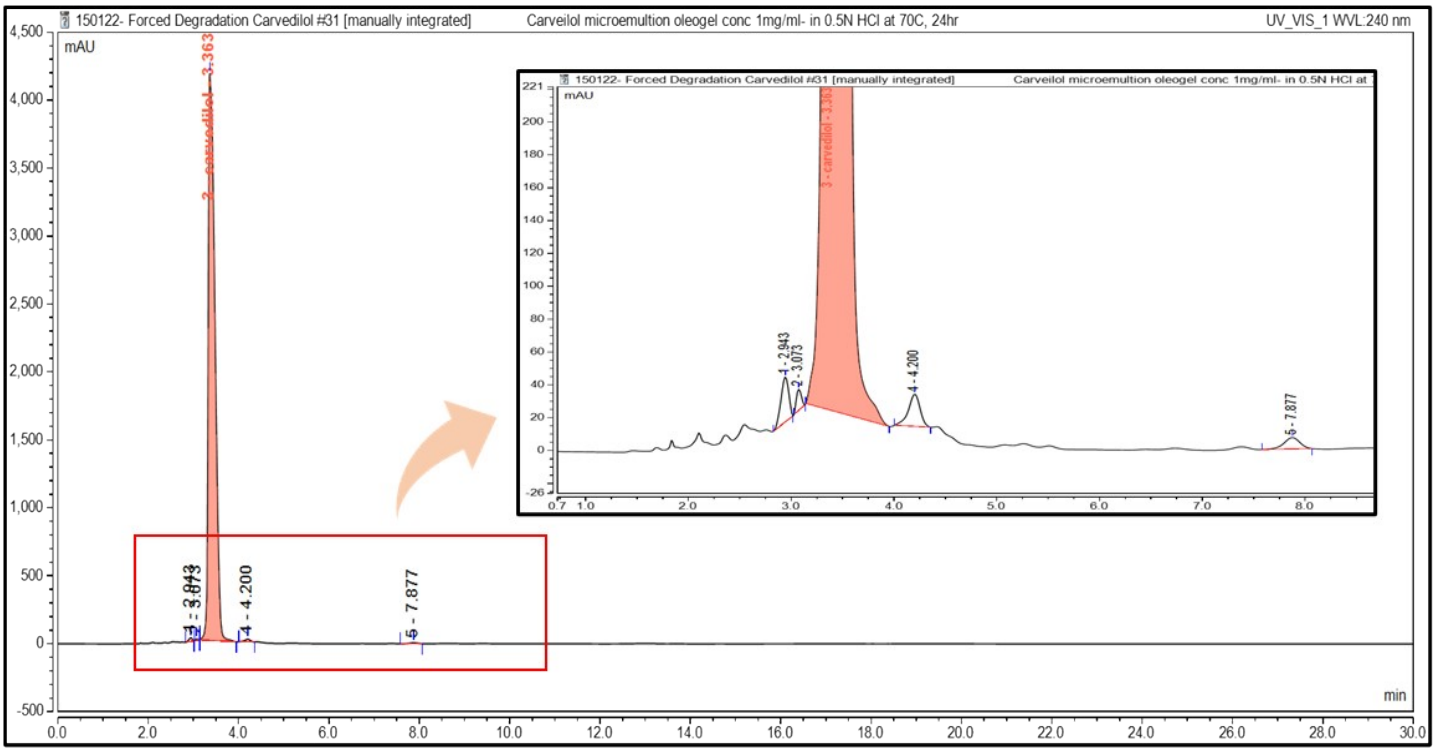


Figure 27S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 0.5 M HCl for 24 h at 70 °C.

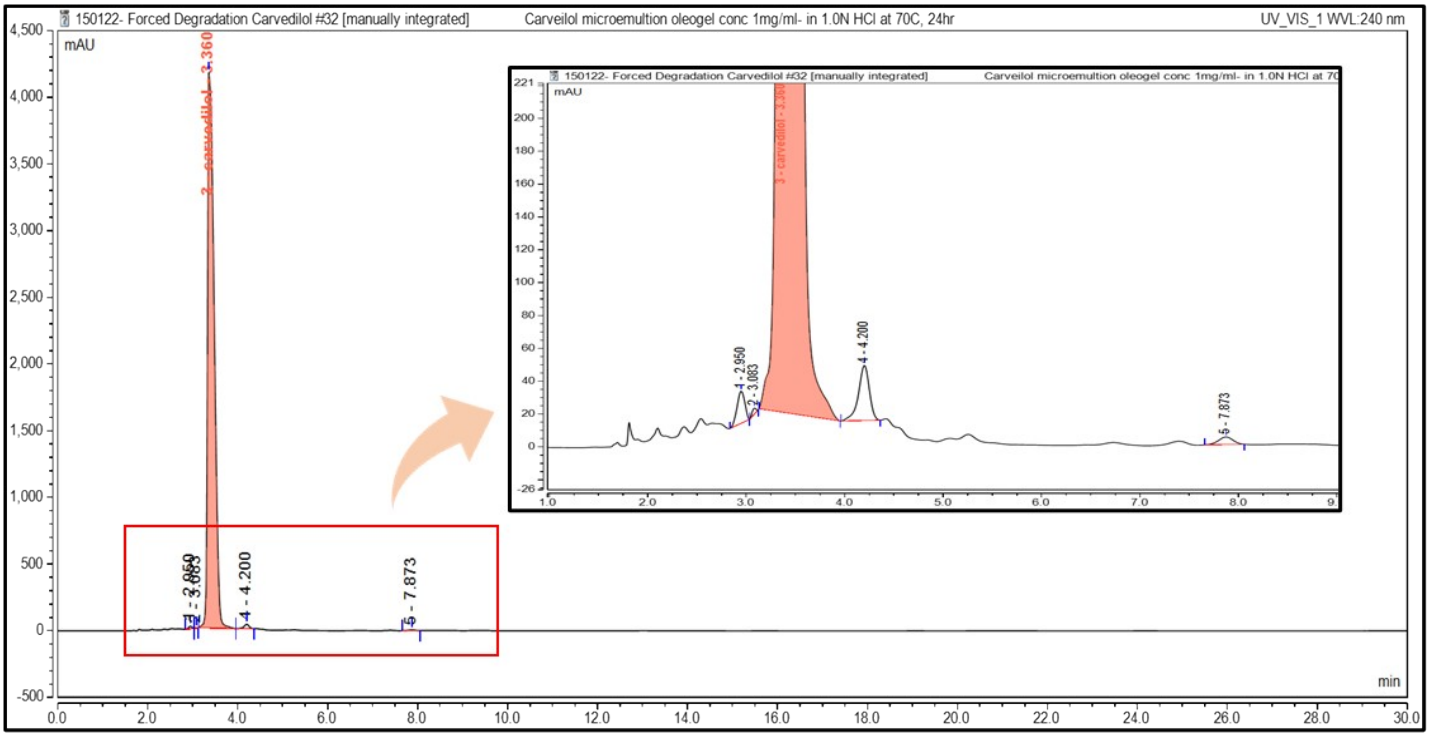


Figure 28S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 1.0 M HCl for 24 h at 70 °C.

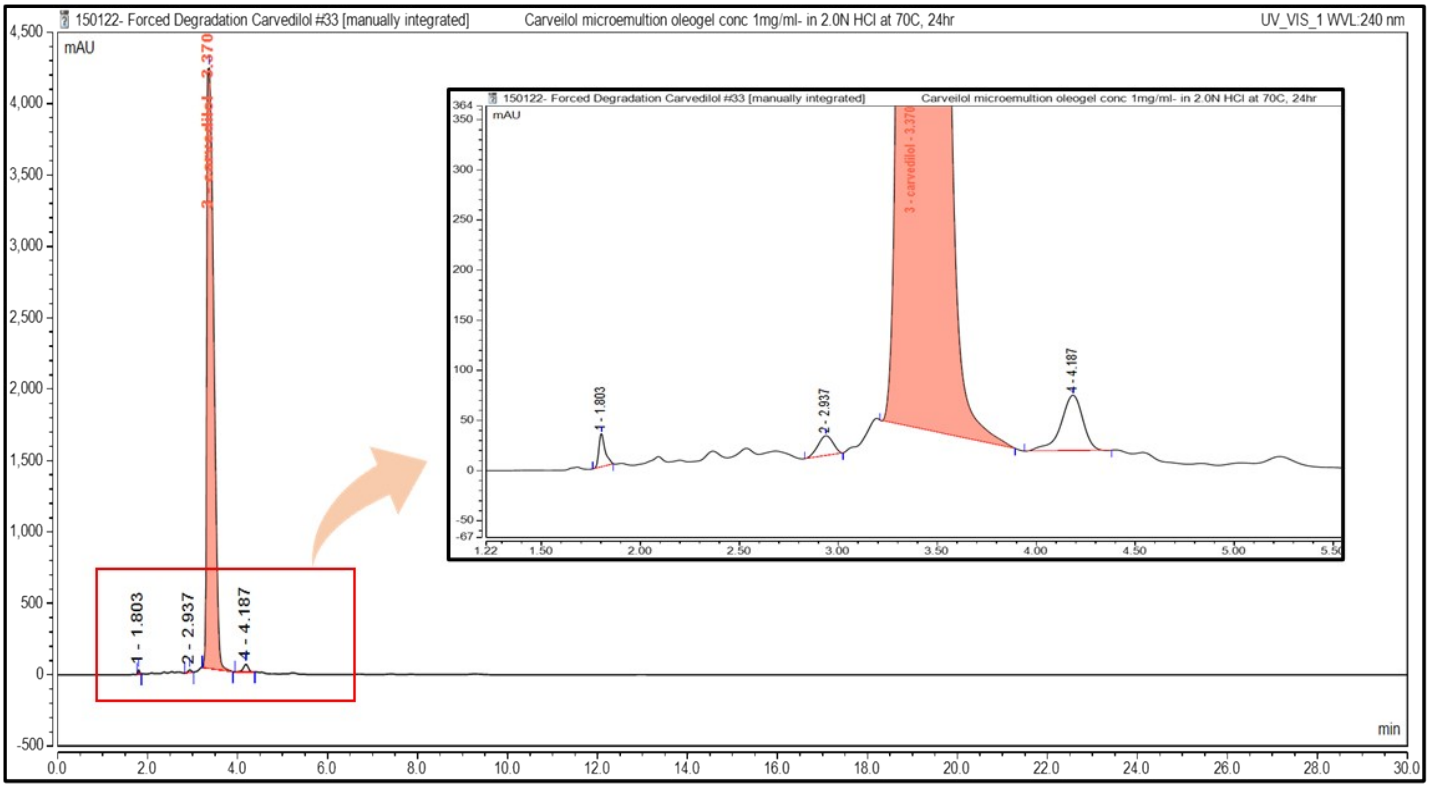


Figure 29S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 2.0 M HCl for 24 h at 70 °C.

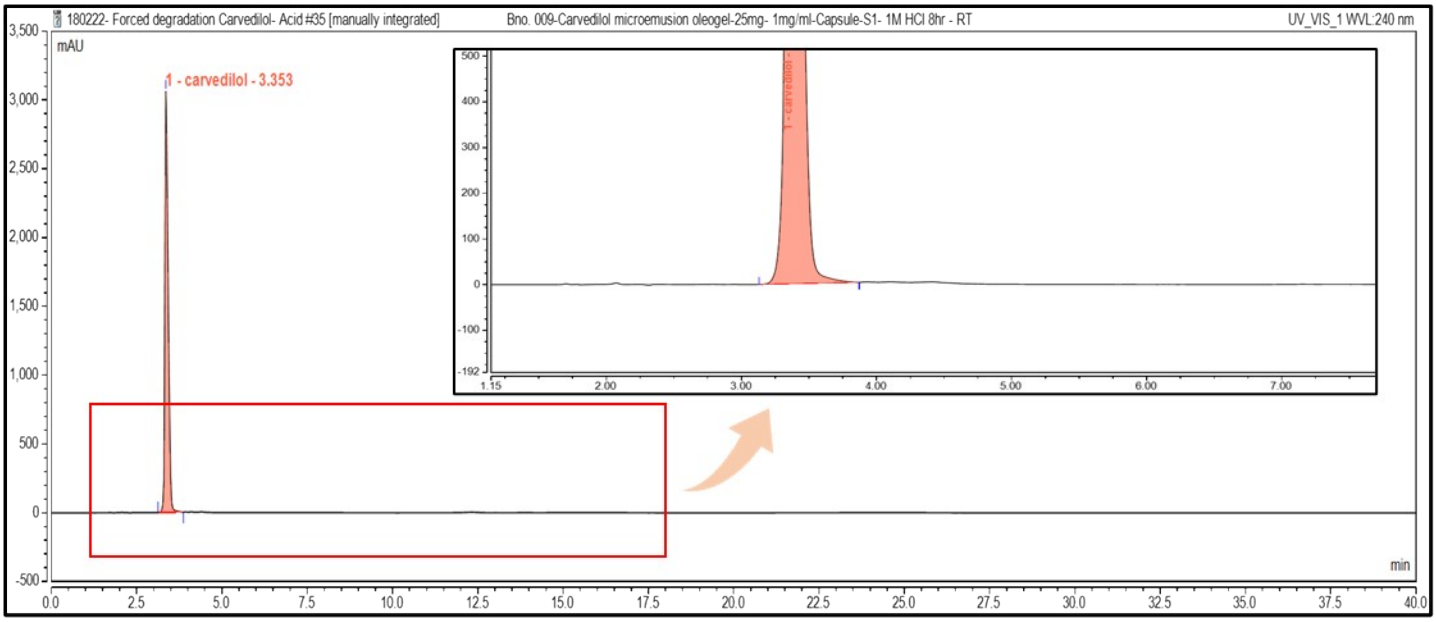


Figure 30S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 1.0 M HCl for 8 h at RT.

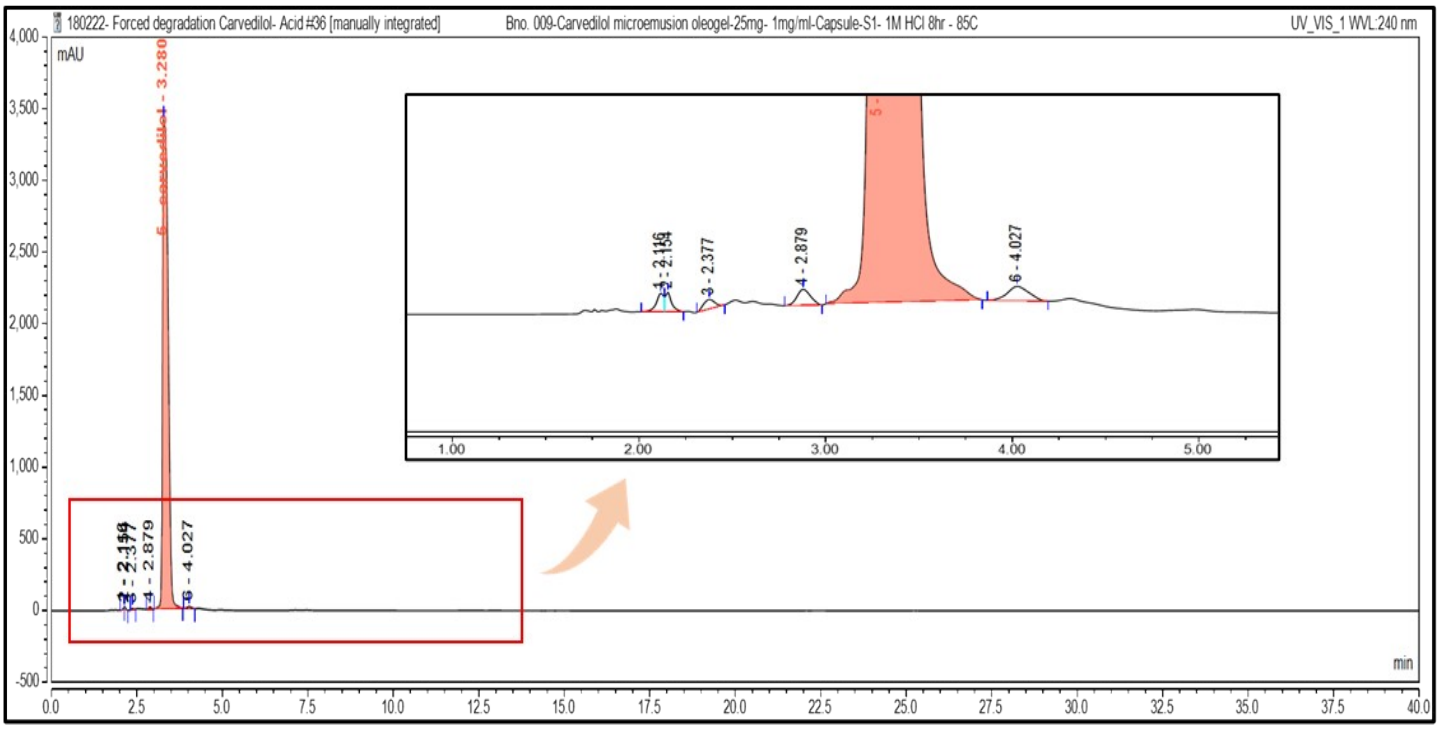


Figure 31S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 1.0 M HCl for 8 h at 85 °C.

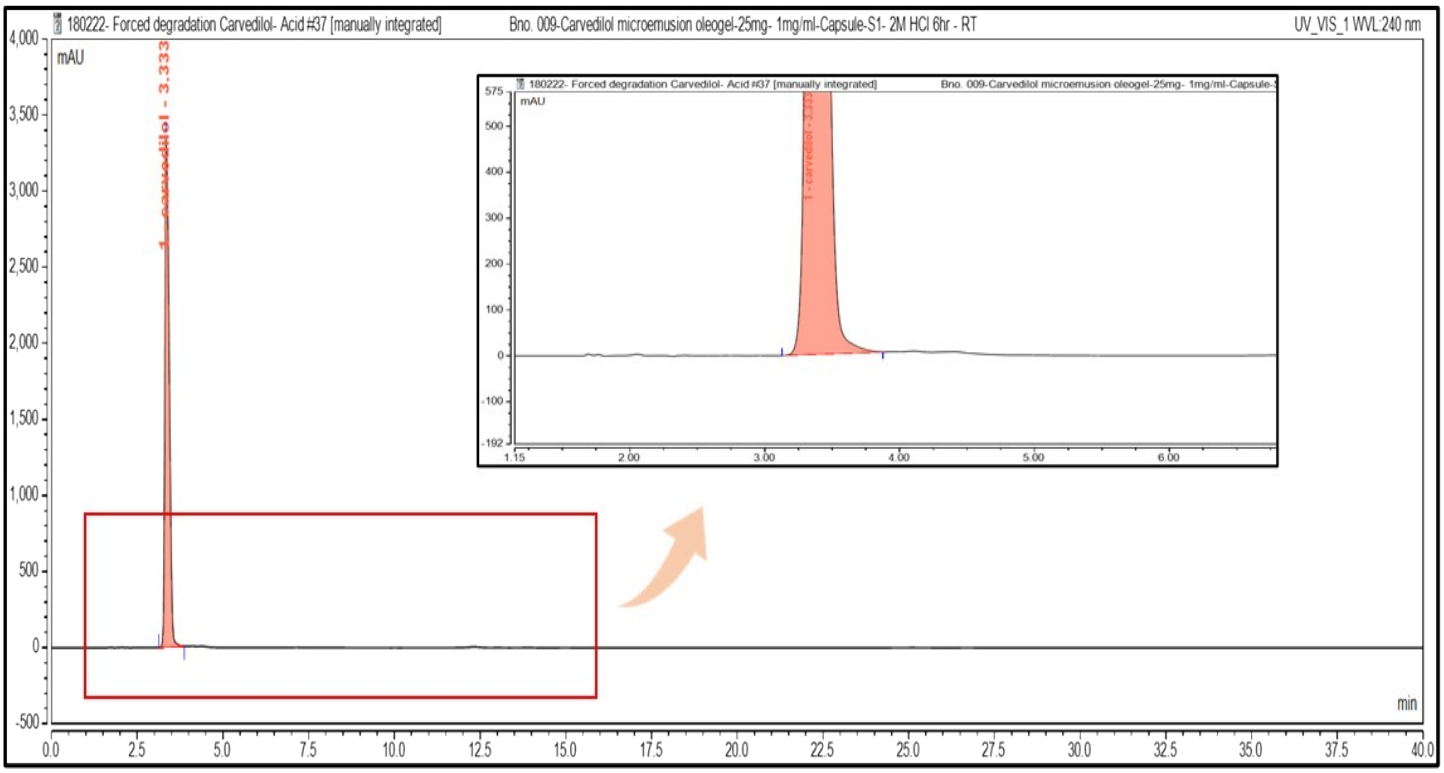


Figure 32S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 2.0 M HCl for 6 h at RT.

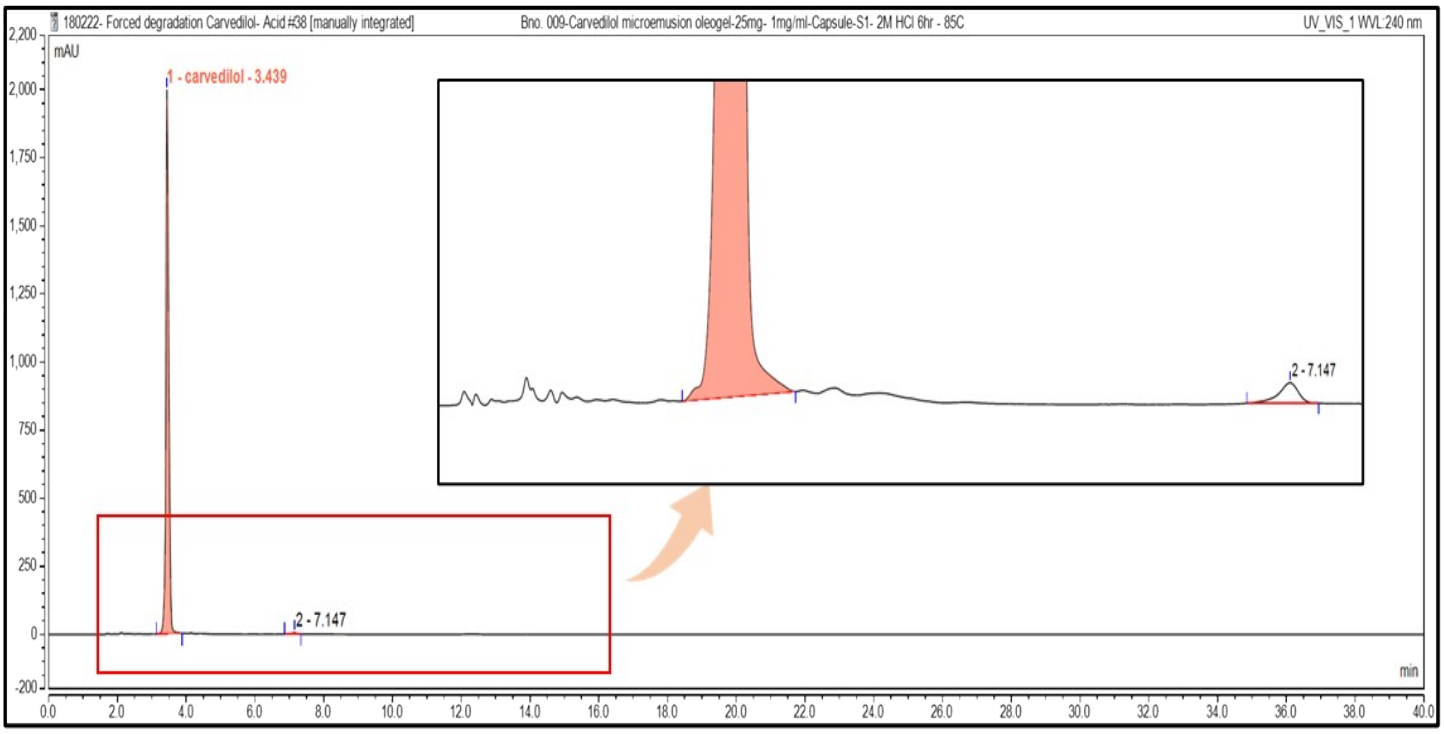


Figure 33S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 2.0 M HCl for 6 h at 85 ℃.

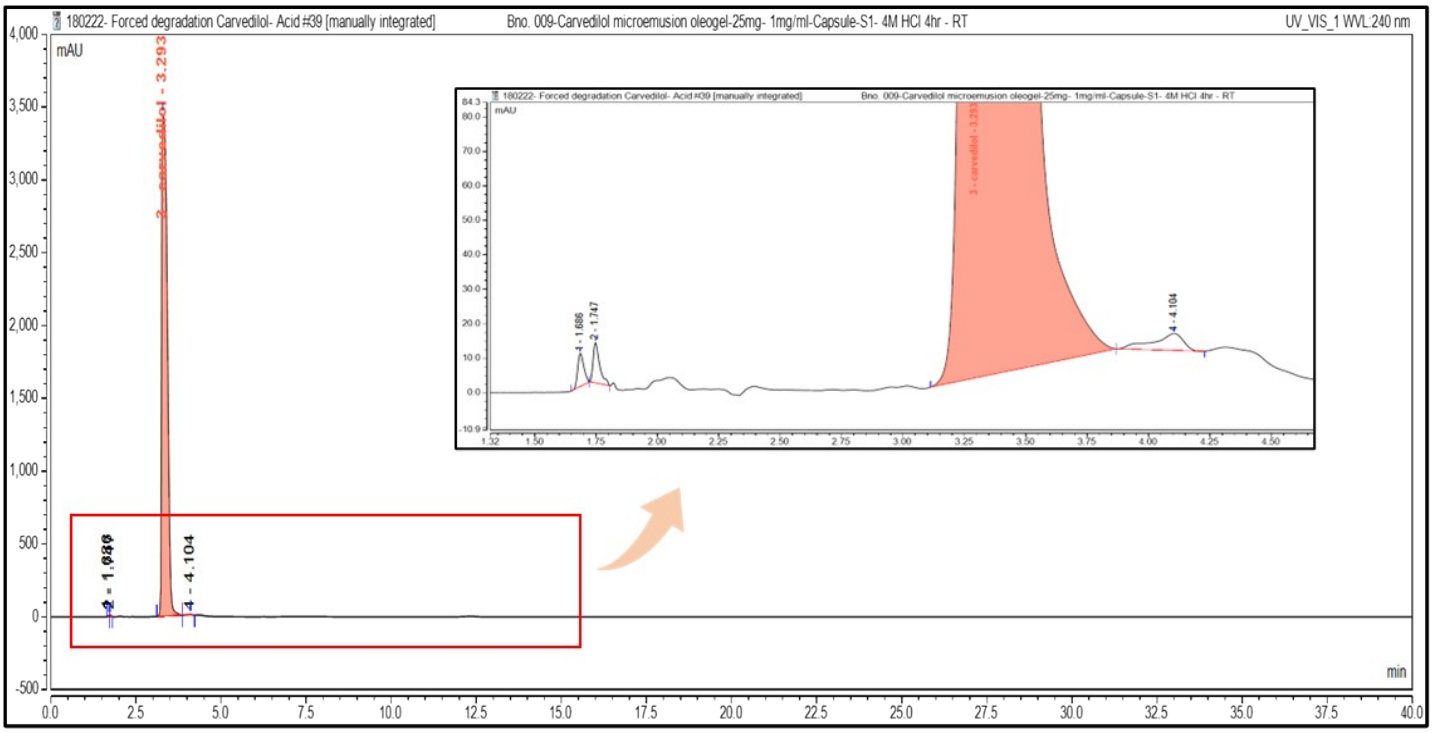


Figure 34S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 4.0 M HCl for 4 h at RT.

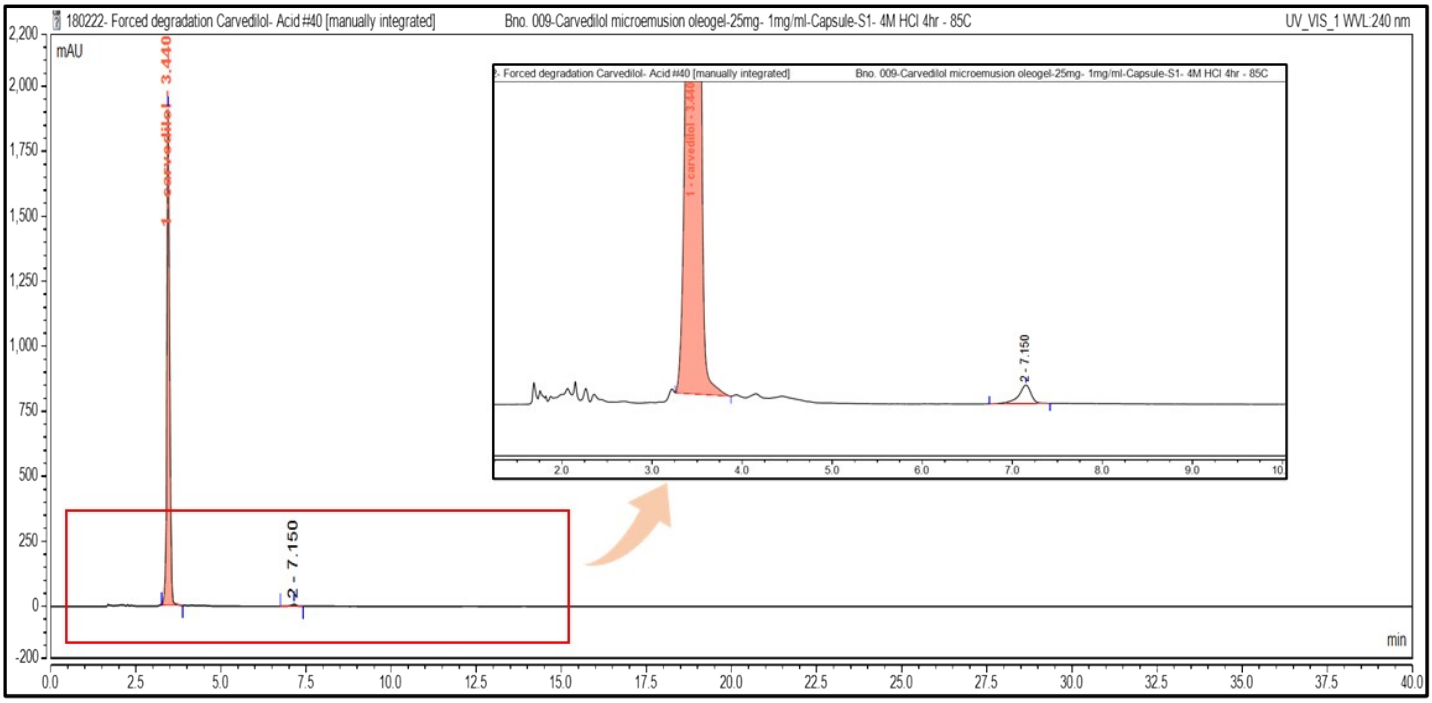


Figure 35S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 4.0 M HCl for 4 h at 85 ℃.

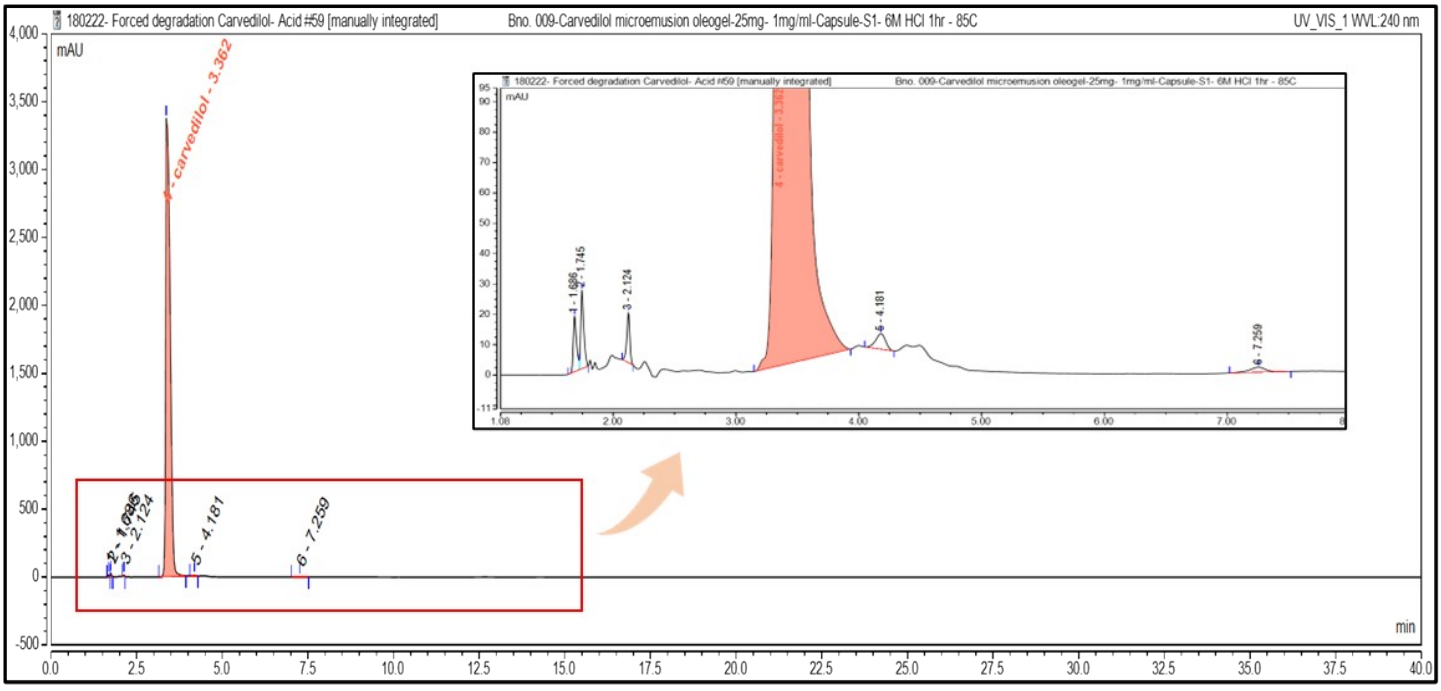


Figure 36S. HPLC chromatogram of acid hydrolysis of CARV-MEOG, 6.0 M HCl for 1 h at 85 ℃.

Excipient- Microemulsion Loaded Oleogel- Acid Hydrolysis:

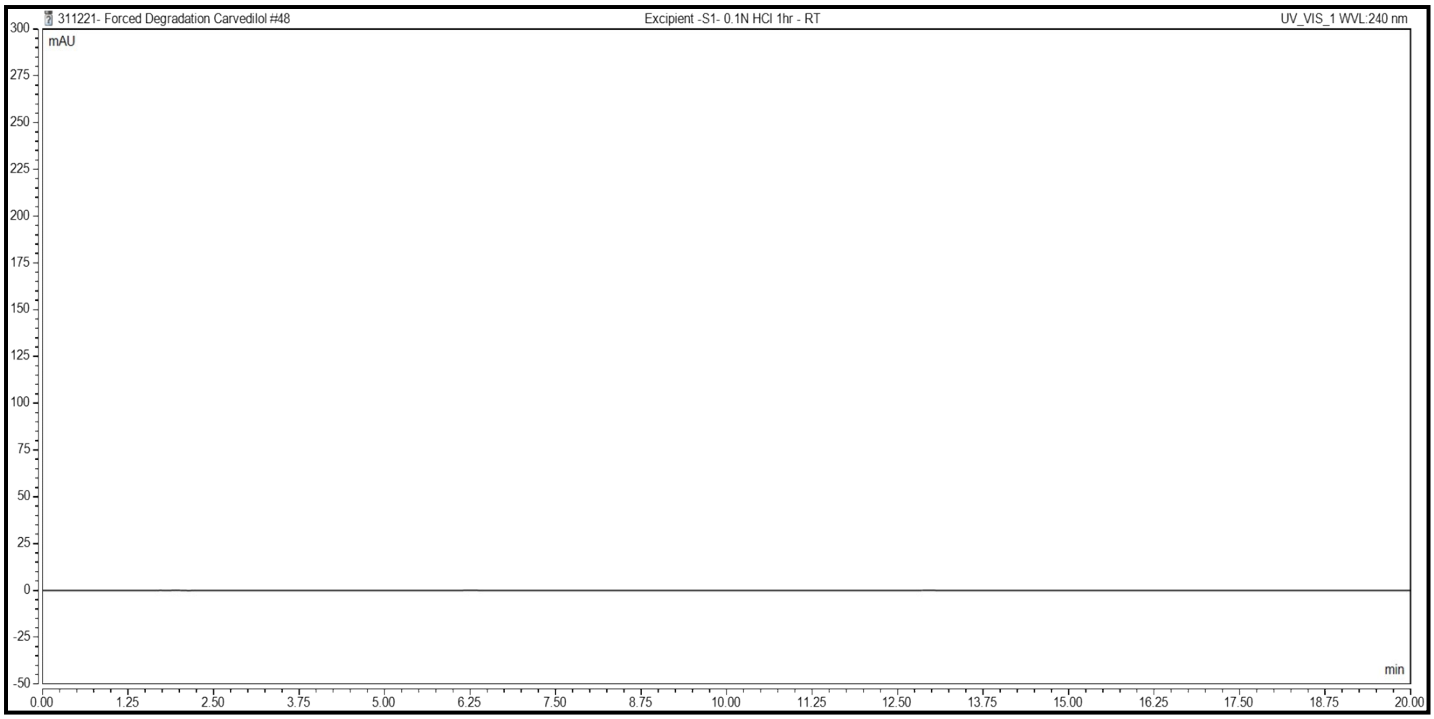


Figure 37S. HPLC chromatogram of acid hydrolysis of excipients, 0.1 M HCl for 1 h at RT.

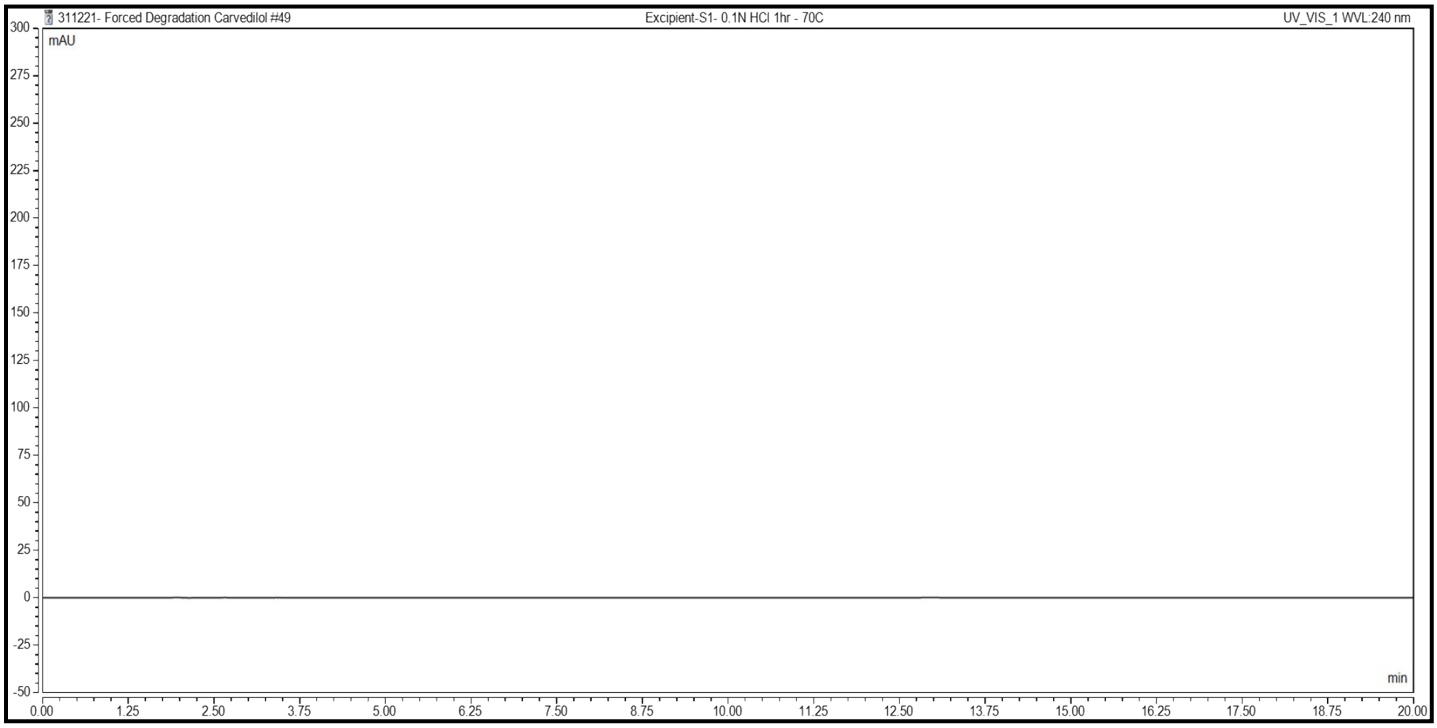


Figure 38S. HPLC chromatogram of acid hydrolysis of excipients, 0.1 M HCl for 1 h at 70 °C.

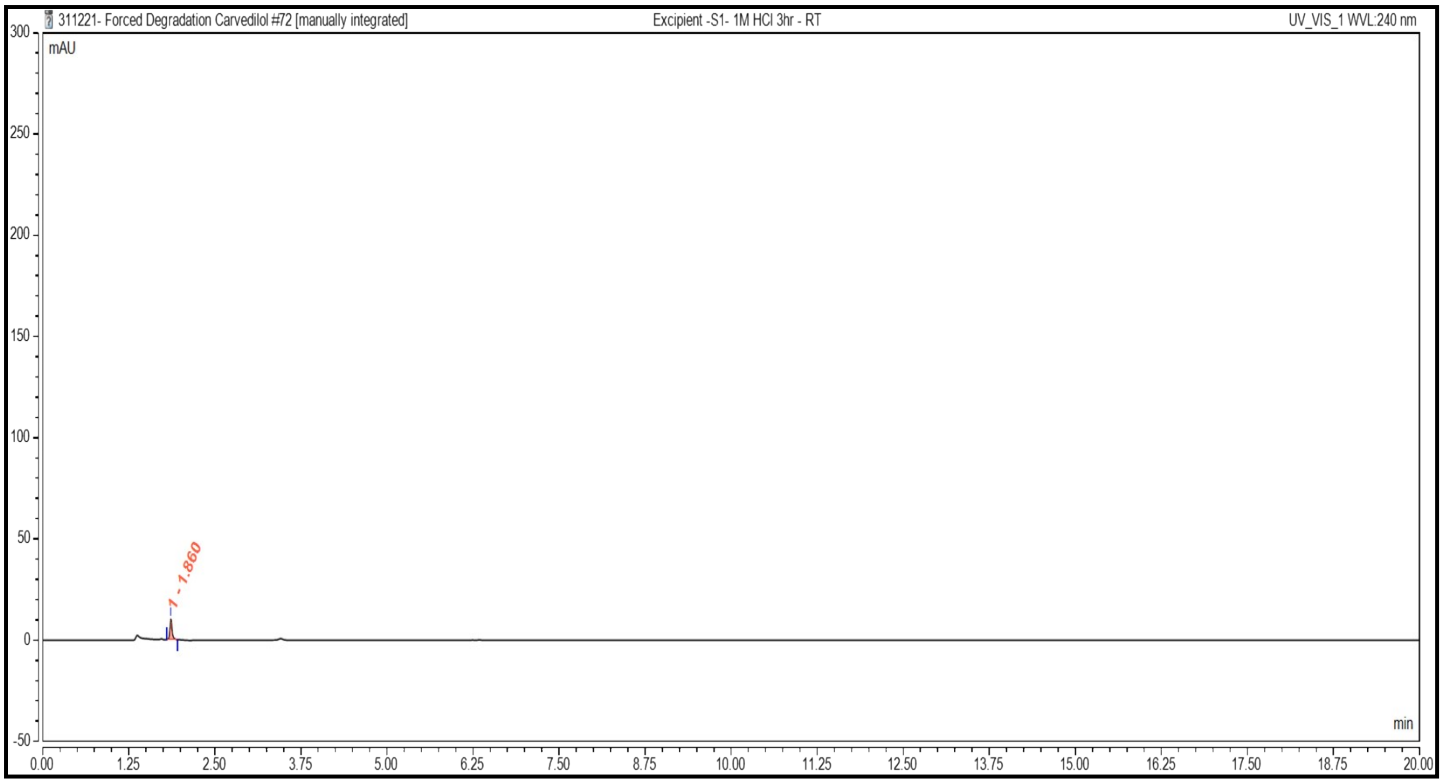


Figure 39S. HPLC chromatogram of acid hydrolysis of excipients, 1.0 M HCl for 3 h at RT.

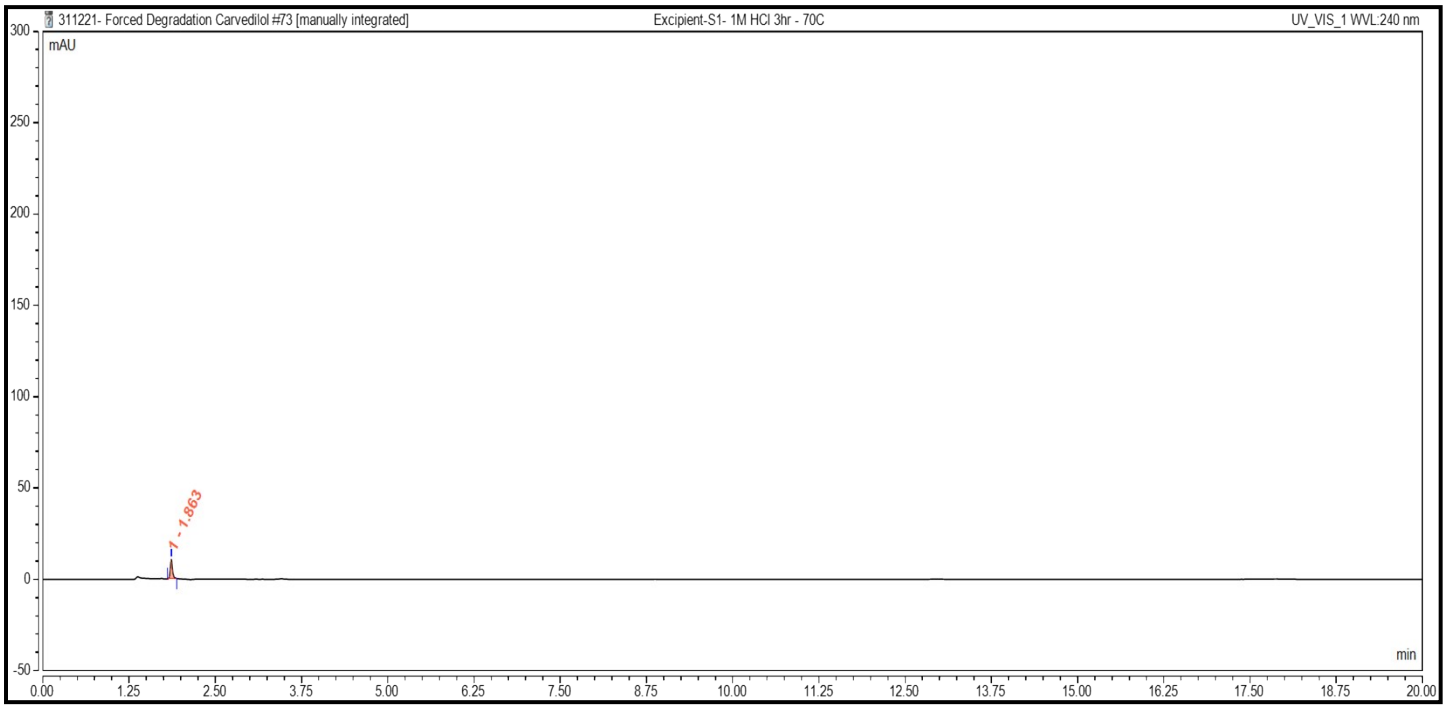


Figure 40S. HPLC chromatogram of acid hydrolysis of excipients, 1.0 M HCl for 3 h at 70 °C.

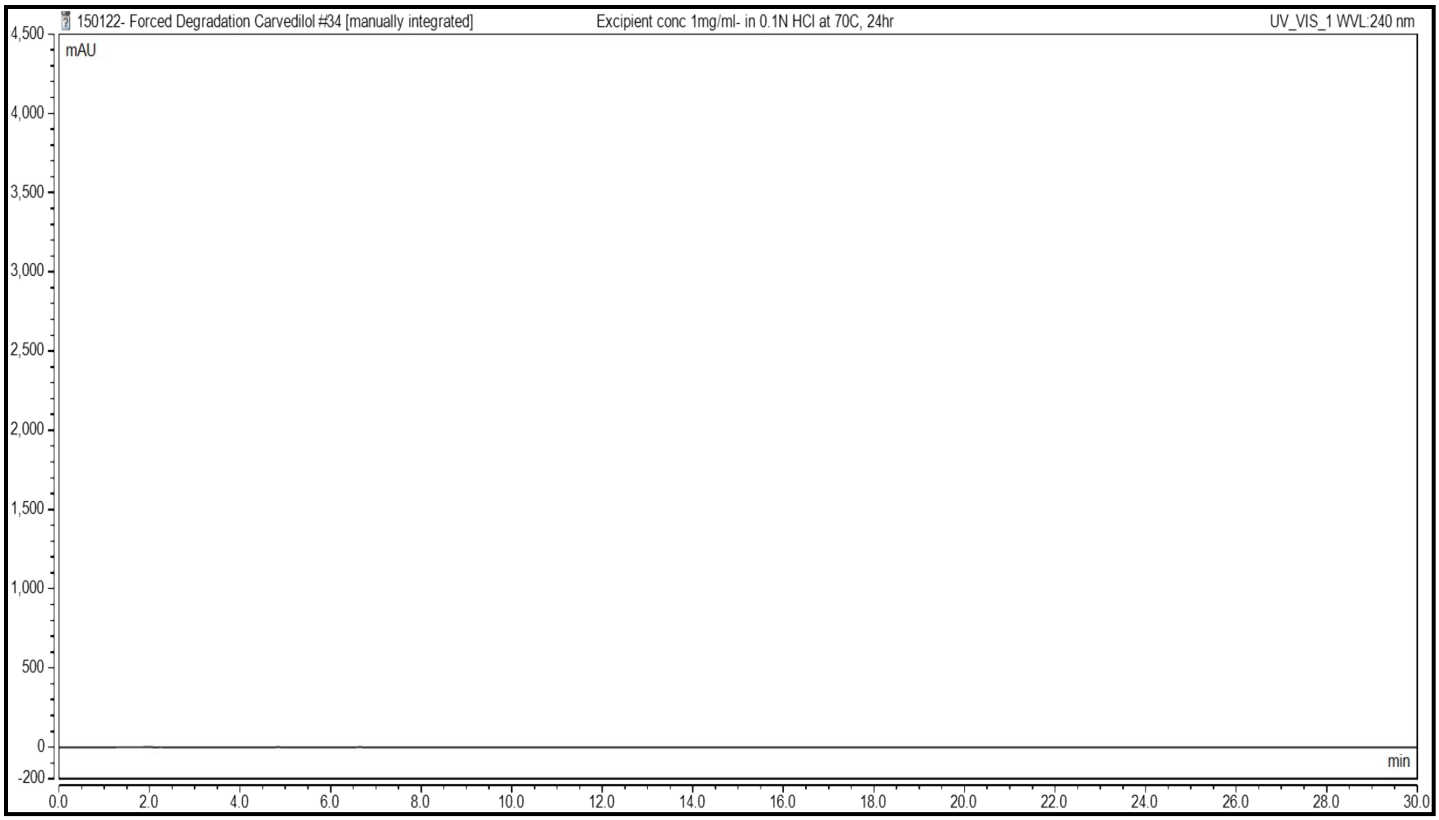


Figure 41S. HPLC chromatogram of acid hydrolysis of excipients, 0.1 M HCl for 24 h at 70 ℃.

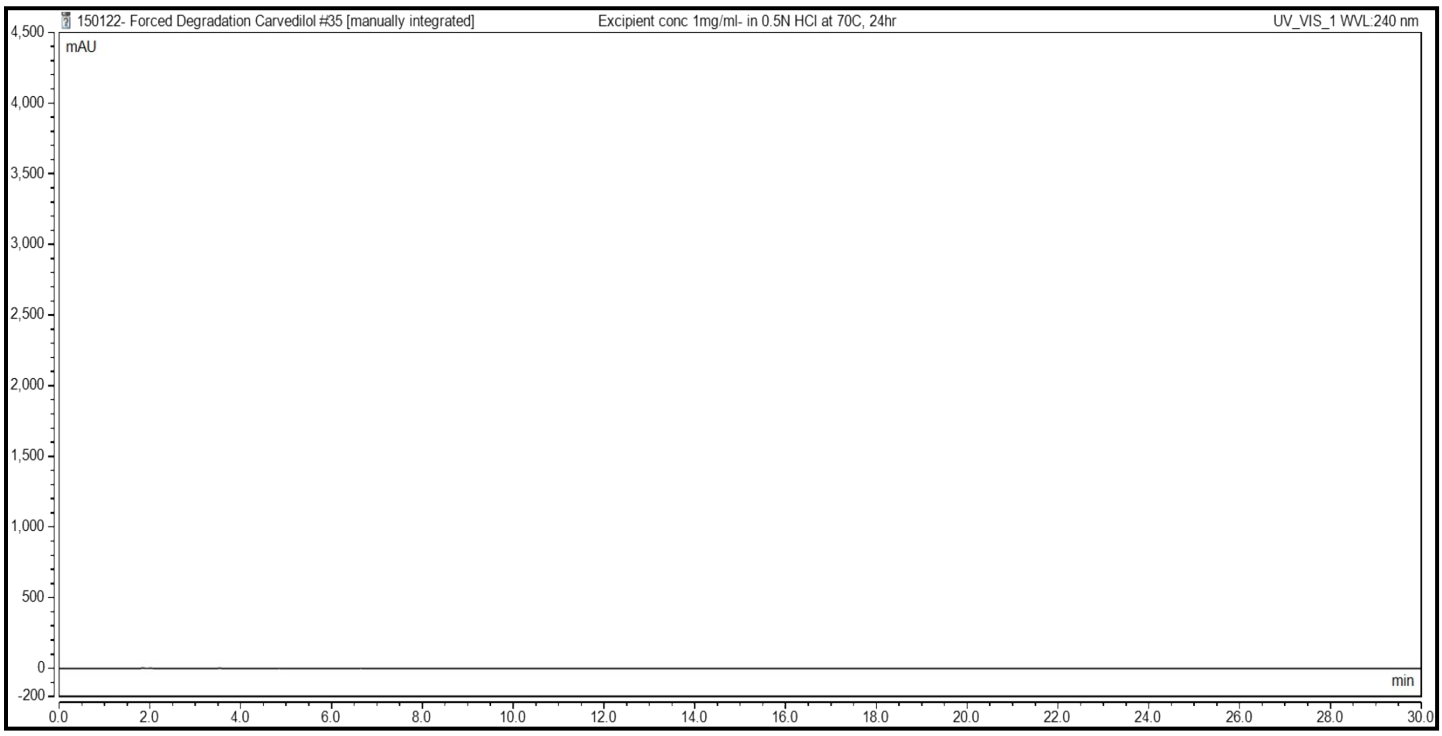


Figure 42S. HPLC chromatogram of acid hydrolysis of excipients, 0.5 M HCl for 24 h at 70 ℃.

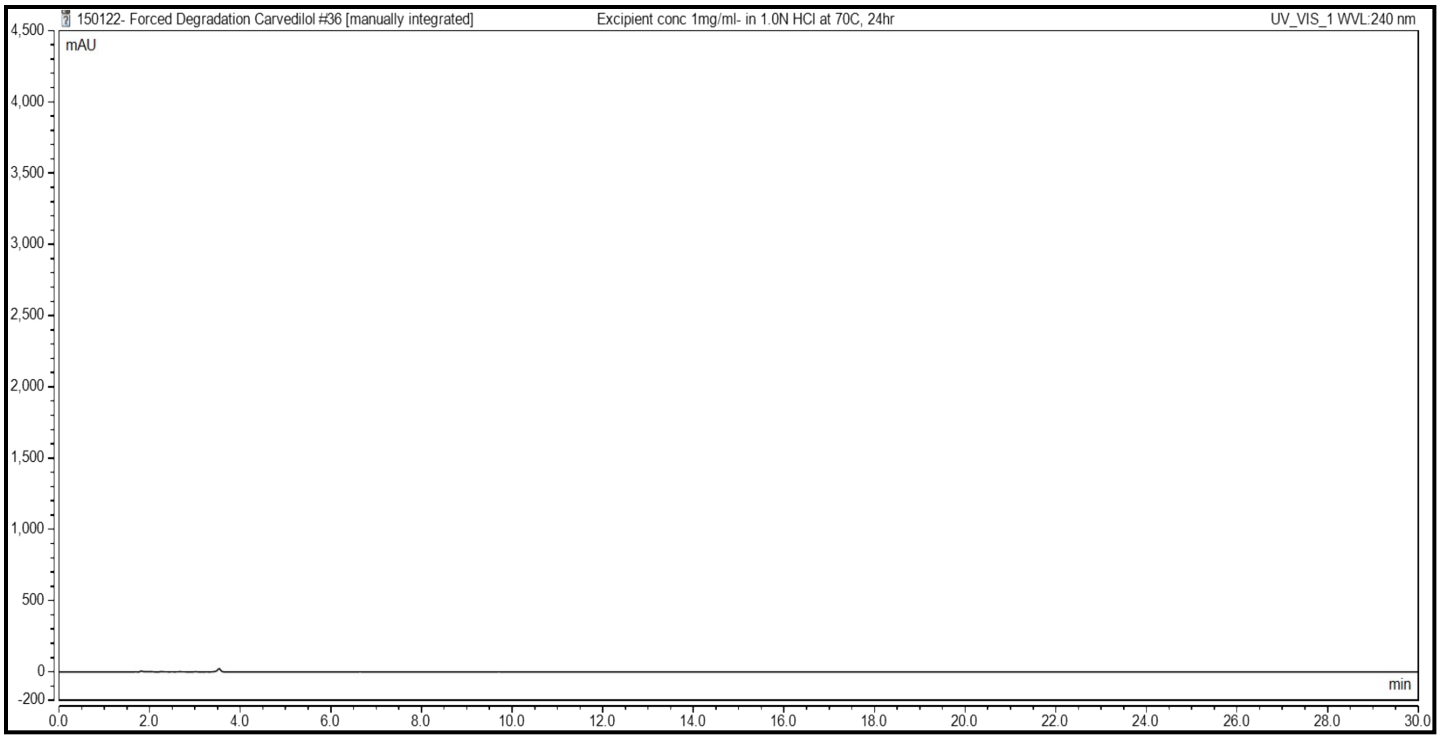


Figure 43S. HPLC chromatogram of acid hydrolysis of excipients, 1.0 M HCl for 24 h at 70 ℃.

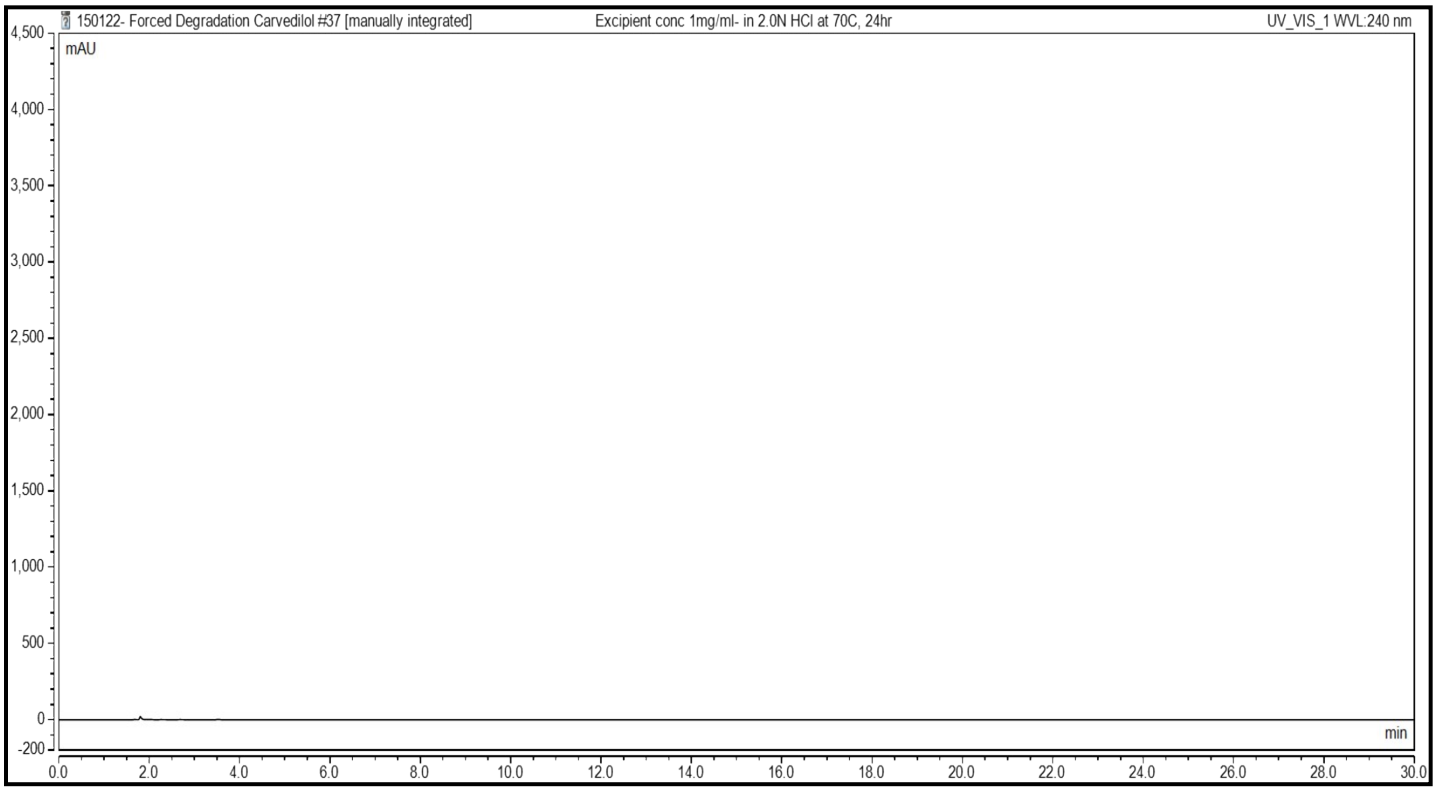


Figure 44S. HPLC Chromatogram of acid hydrolysis of excipients, 2.0 M HCl for 24 h at 70 ℃.

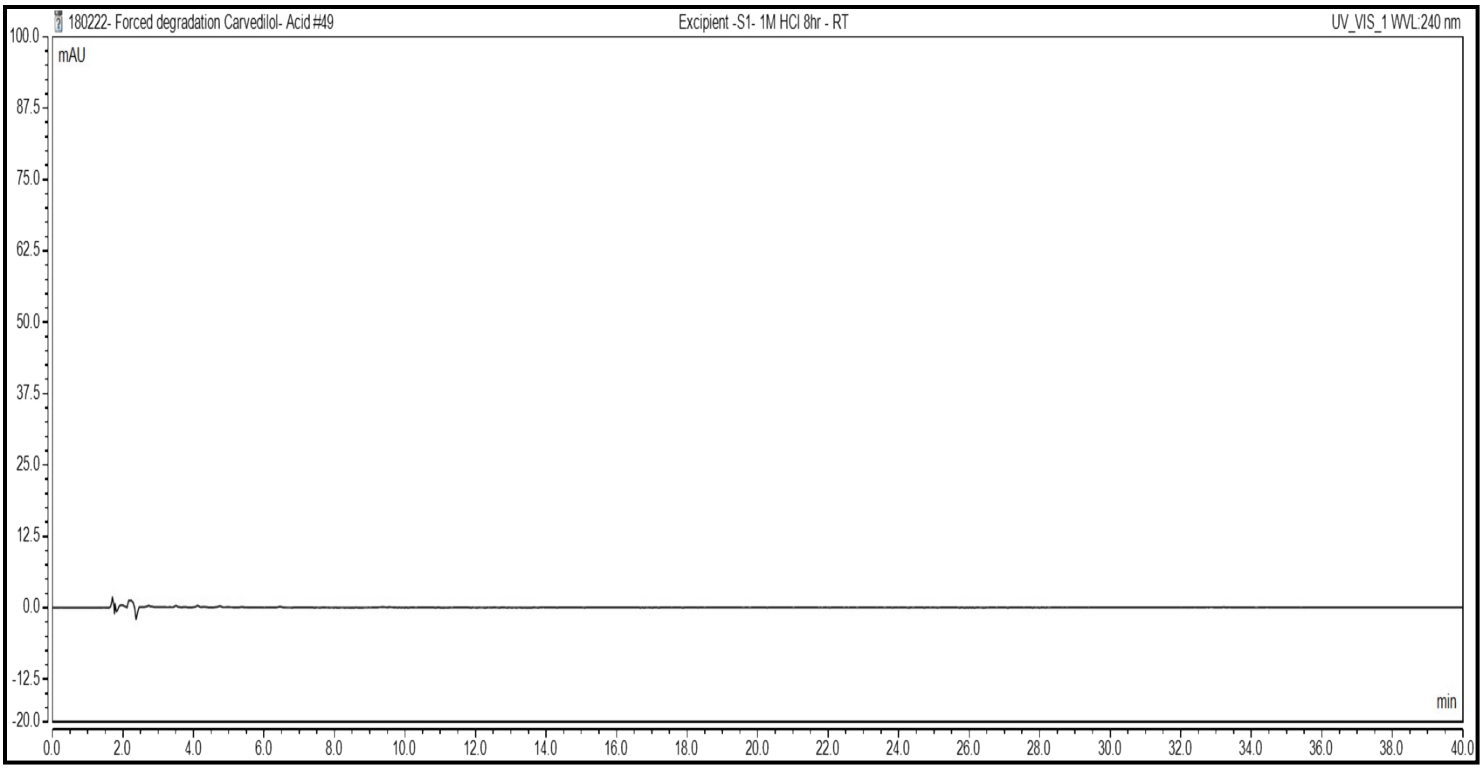


Figure 45S. HPLC chromatogram of acid hydrolysis of excipients, 1.0 M HCl for 8 h at RT.

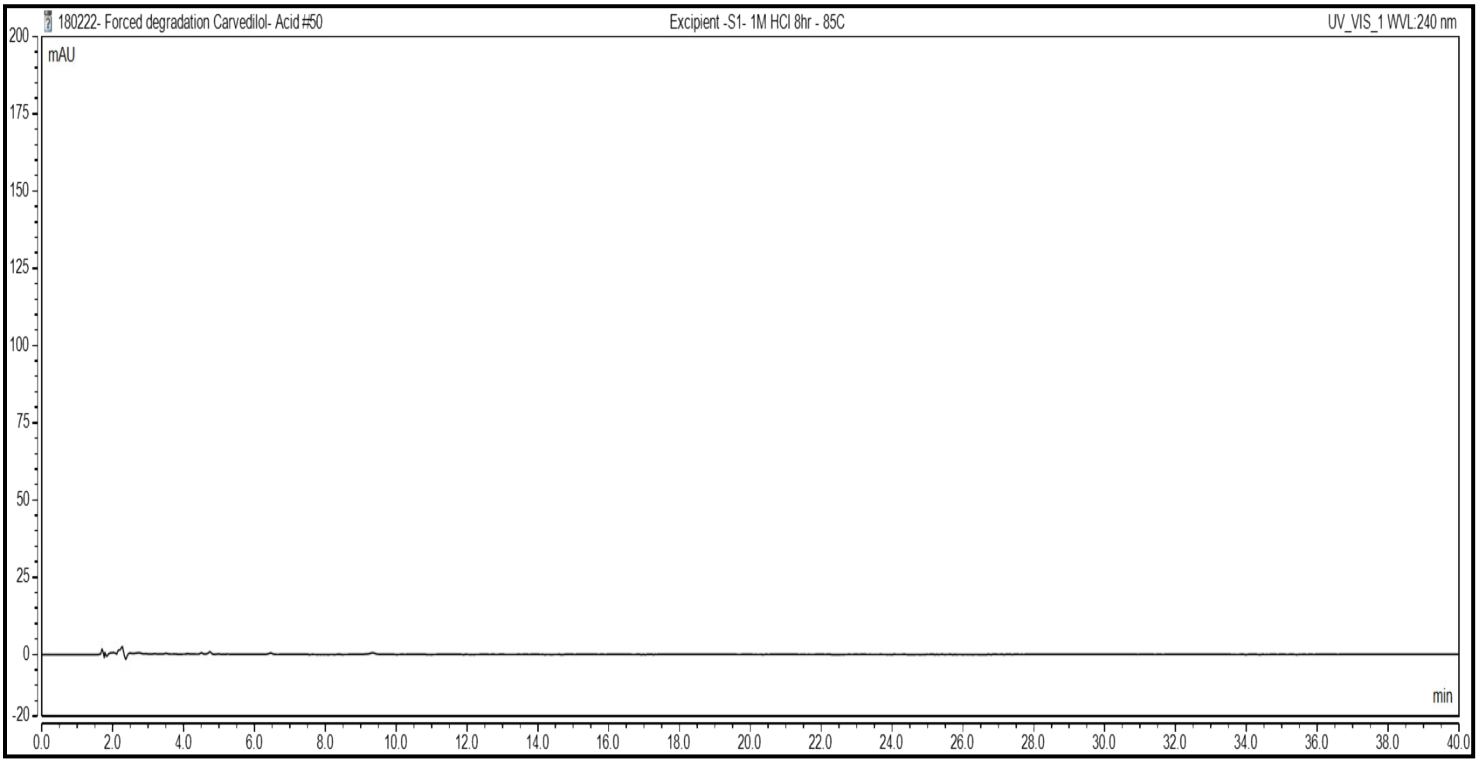


Figure 46S. HPLC chromatogram of acid hydrolysis of excipients, 1.0 M HCl for 8 h at 85 °C.

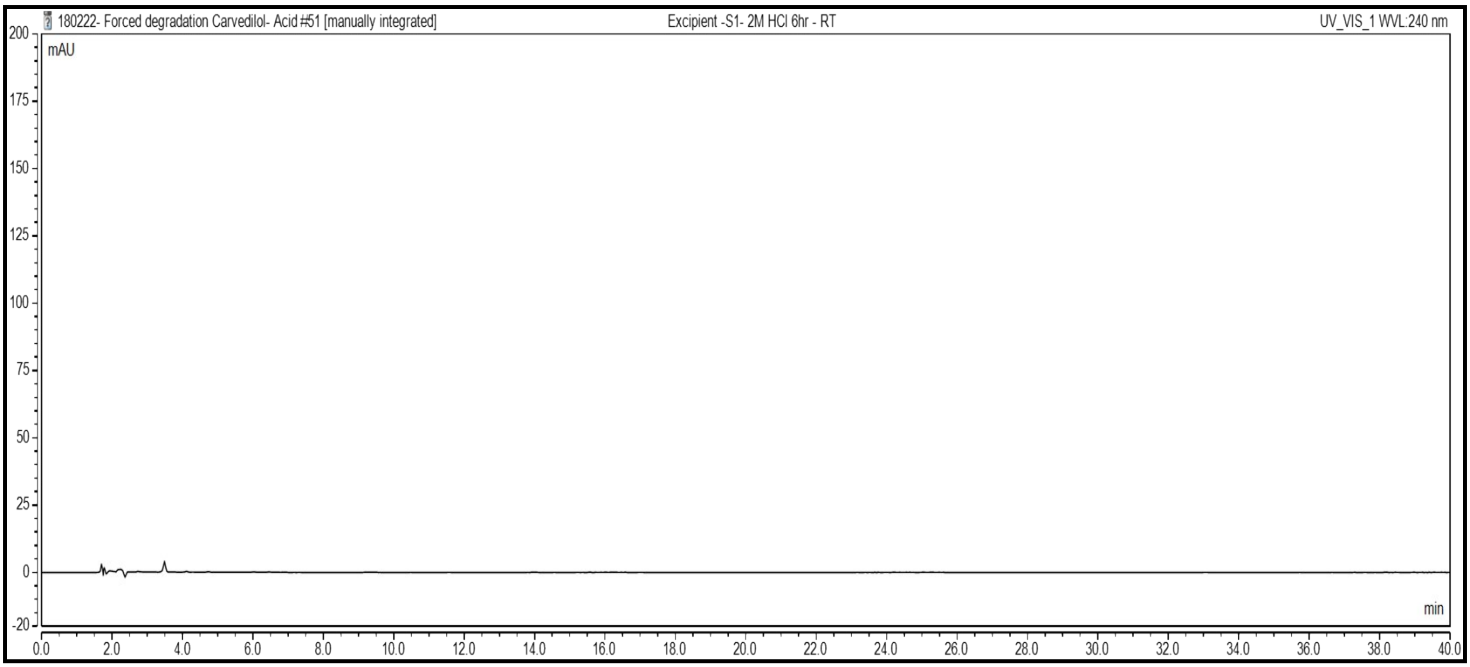


Figure 47S. HPLC chromatogram of acid hydrolysis of excipients, 2.0 M HCl for 6 h at RT.

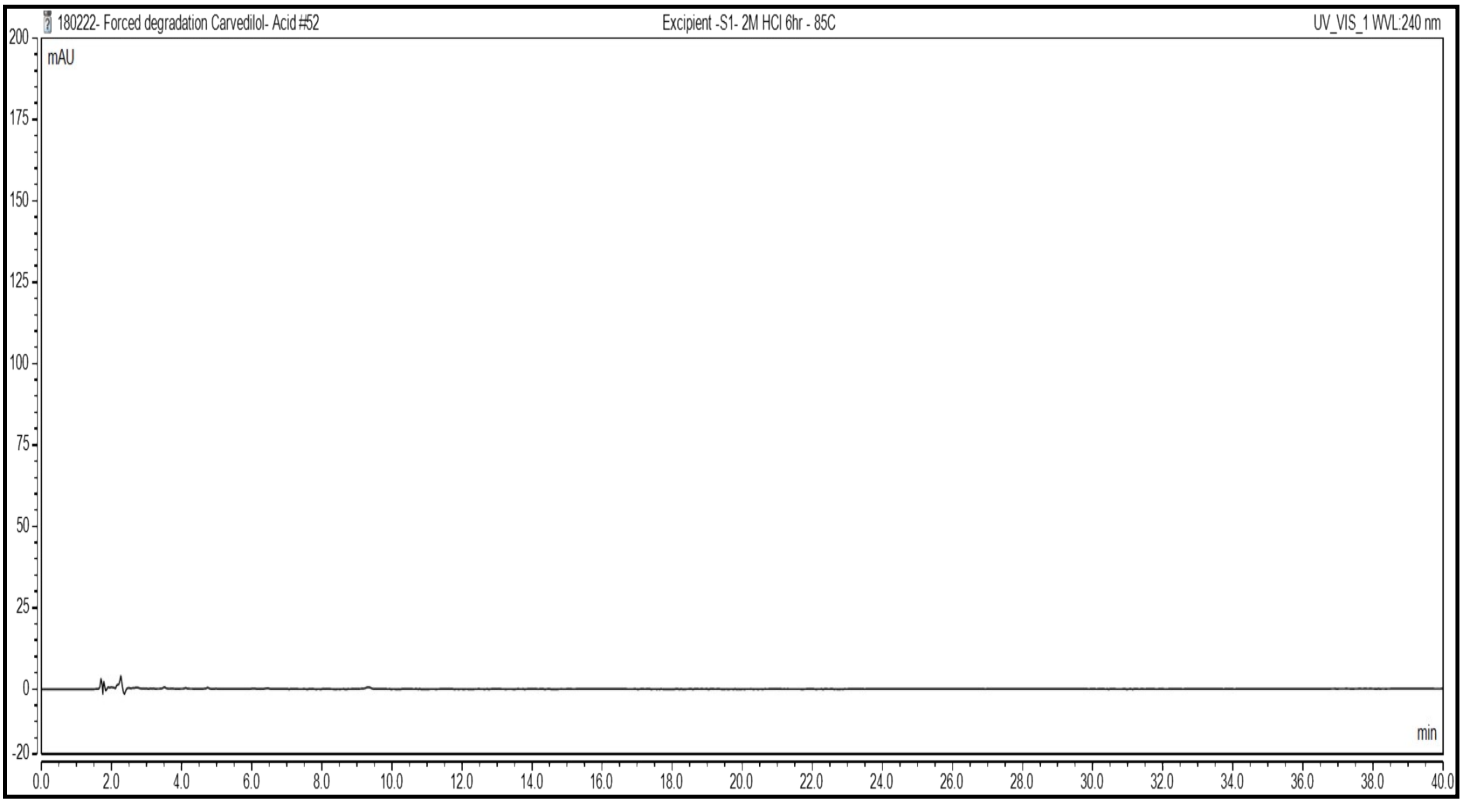


Figure 48S. HPLC chromatogram of acid hydrolysis of excipients, 2.0 M HCl for 6 h at 85 °C.

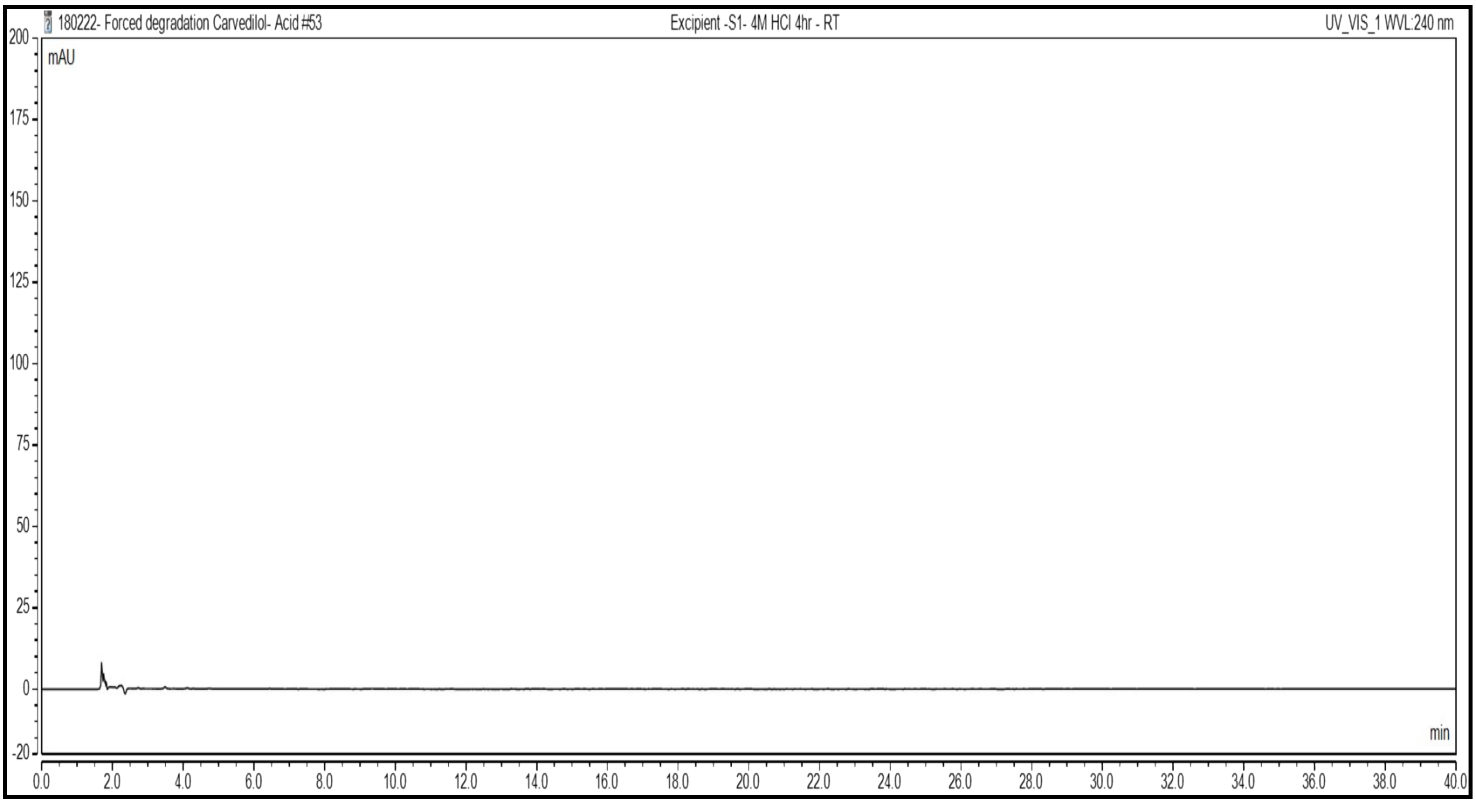


Figure 49S. HPLC chromatogram of acid hydrolysis of excipients, 4.0 M HCl for 4 h at RT.

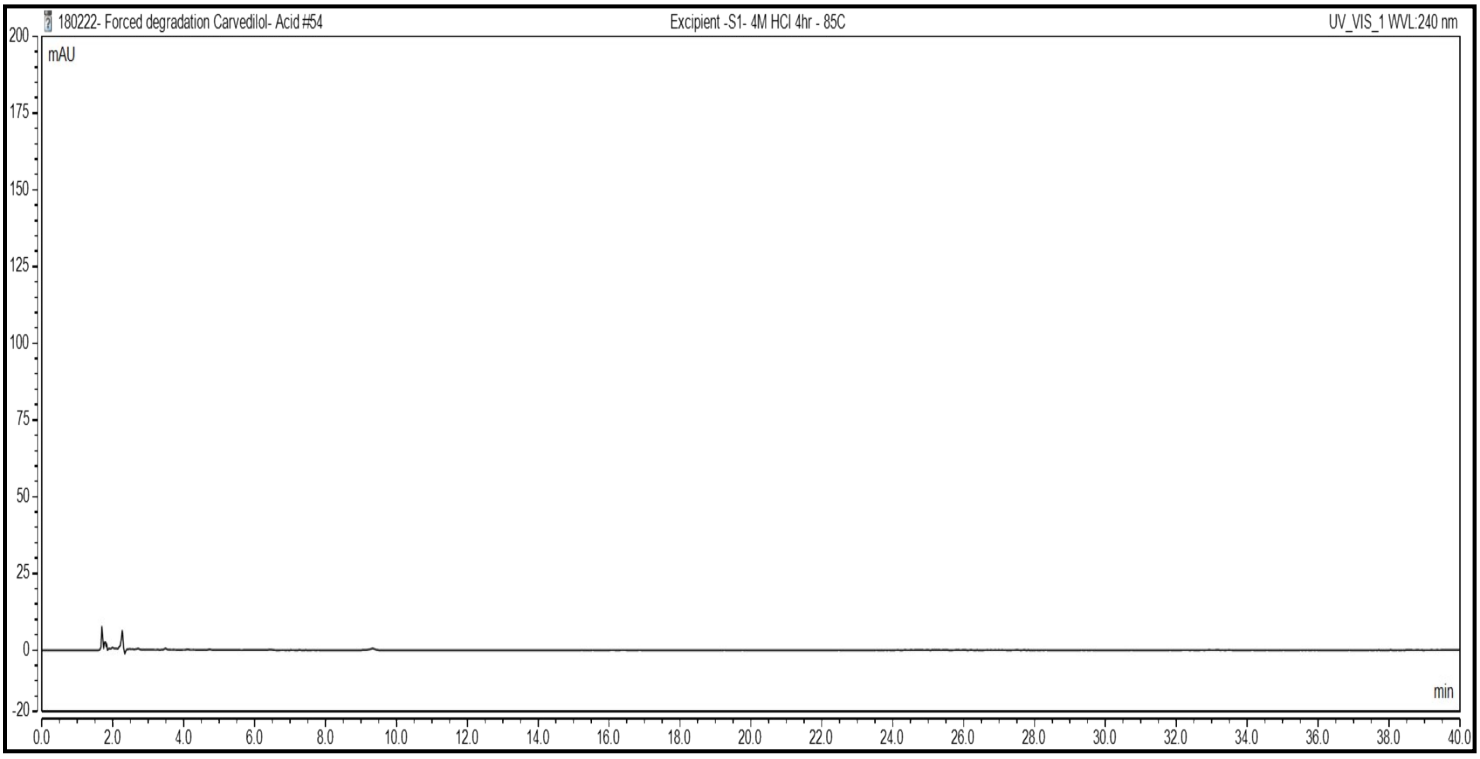


Figure 50S. HPLC chromatogram of acid hydrolysis of excipients, 4.0 M HCl for 4 h at 85 ℃.

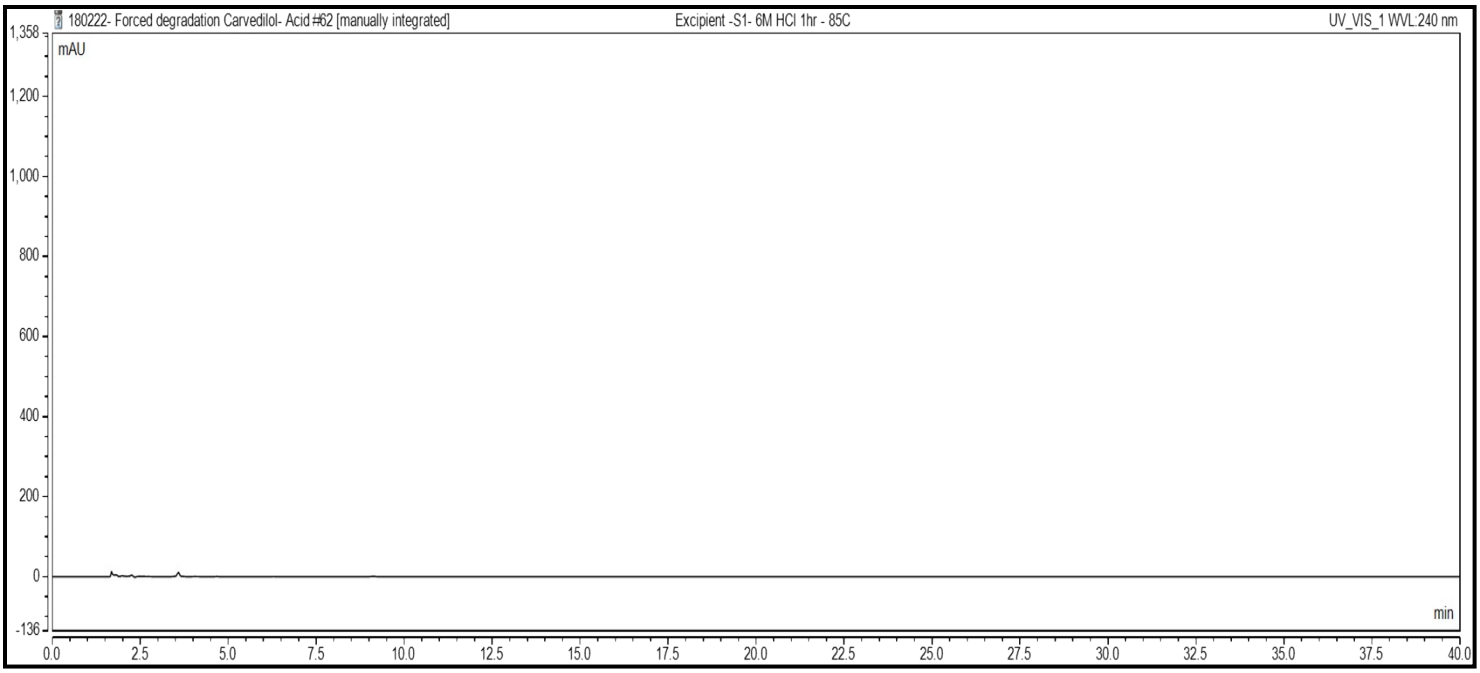


Figure 51S. HPLC chromatogram of acid hydrolysis of excipients, 6.0 M HCl for 1 h at 85 °C.

Base Degradation: CARV

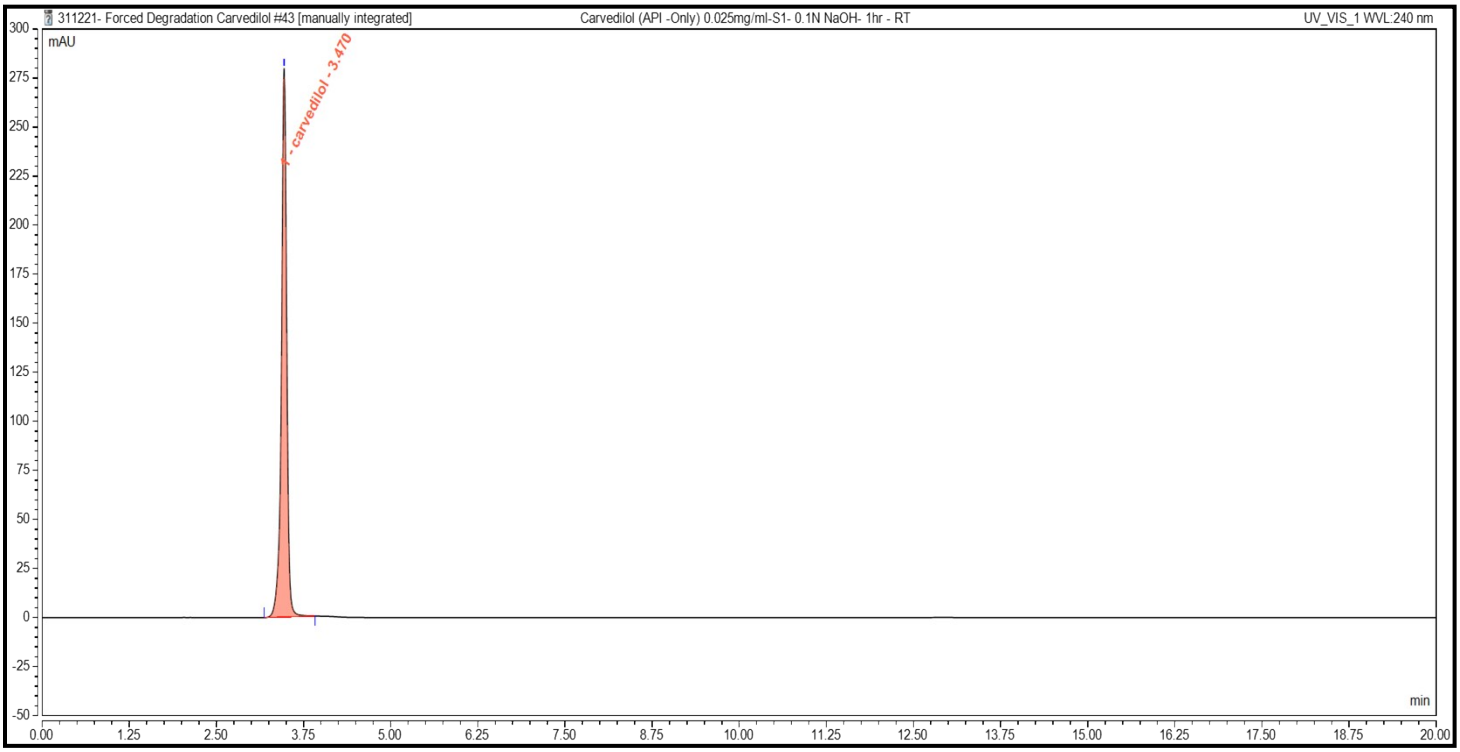


Figure 52S. HPLC chromatogram of base hydrolysis of CARV, 0.1 M NaOH for 1 h at RT.

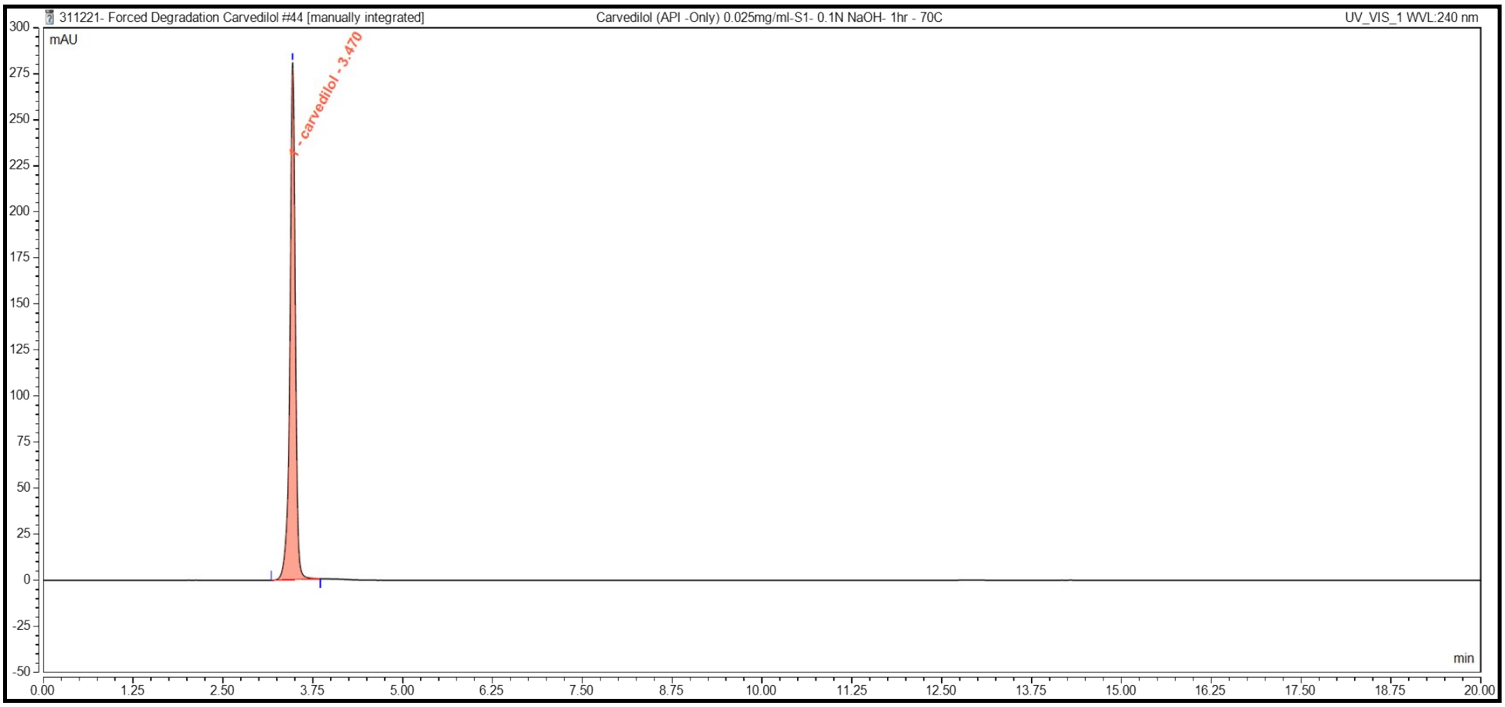


Figure 53S. HPLC chromatogram of base hydrolysis of CARV, 0.1 M NaOH for 1 h at 70 °C.

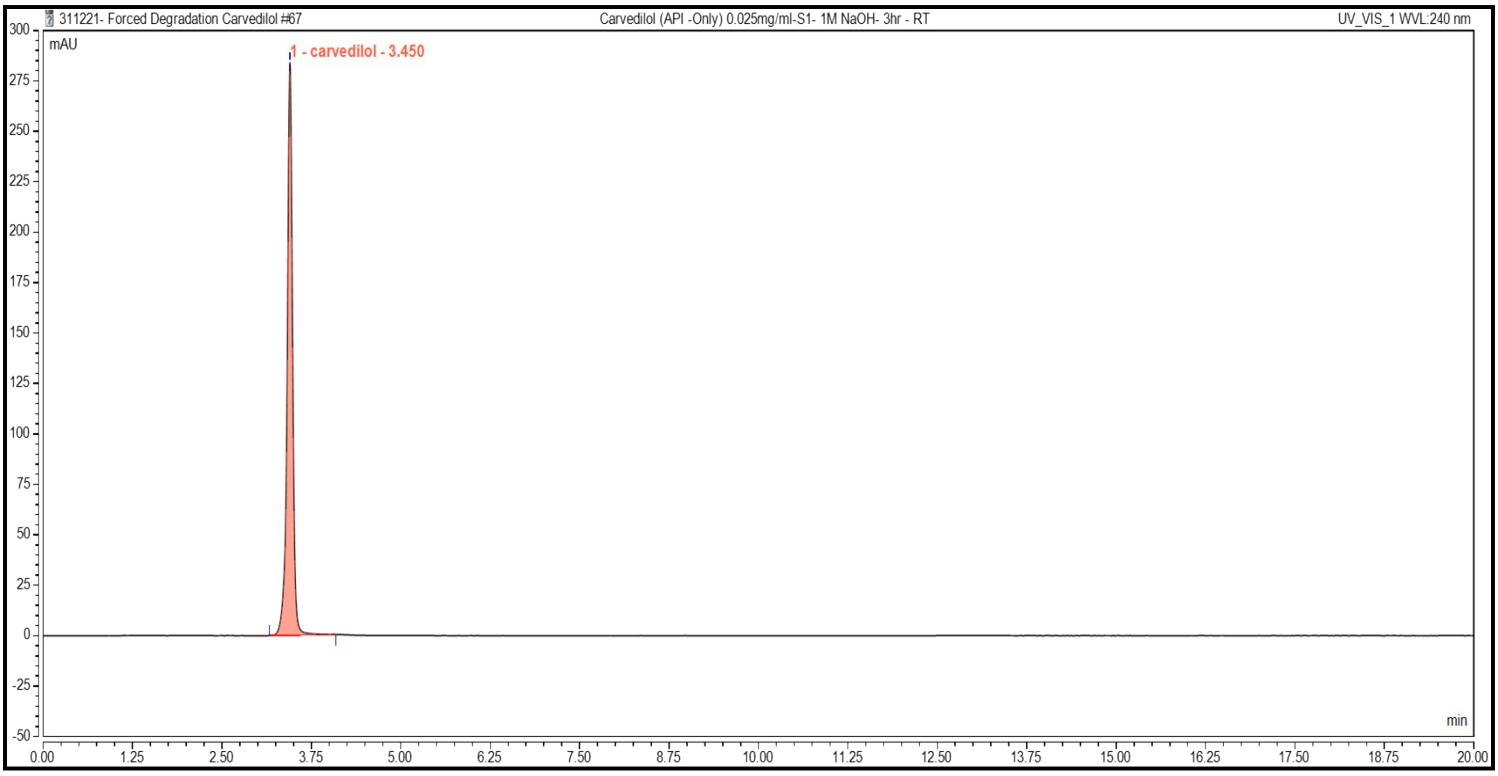


Figure 54S. HPLC chromatogram of base hydrolysis of CARV, 1.0 M NaOH for 3 h at RT.

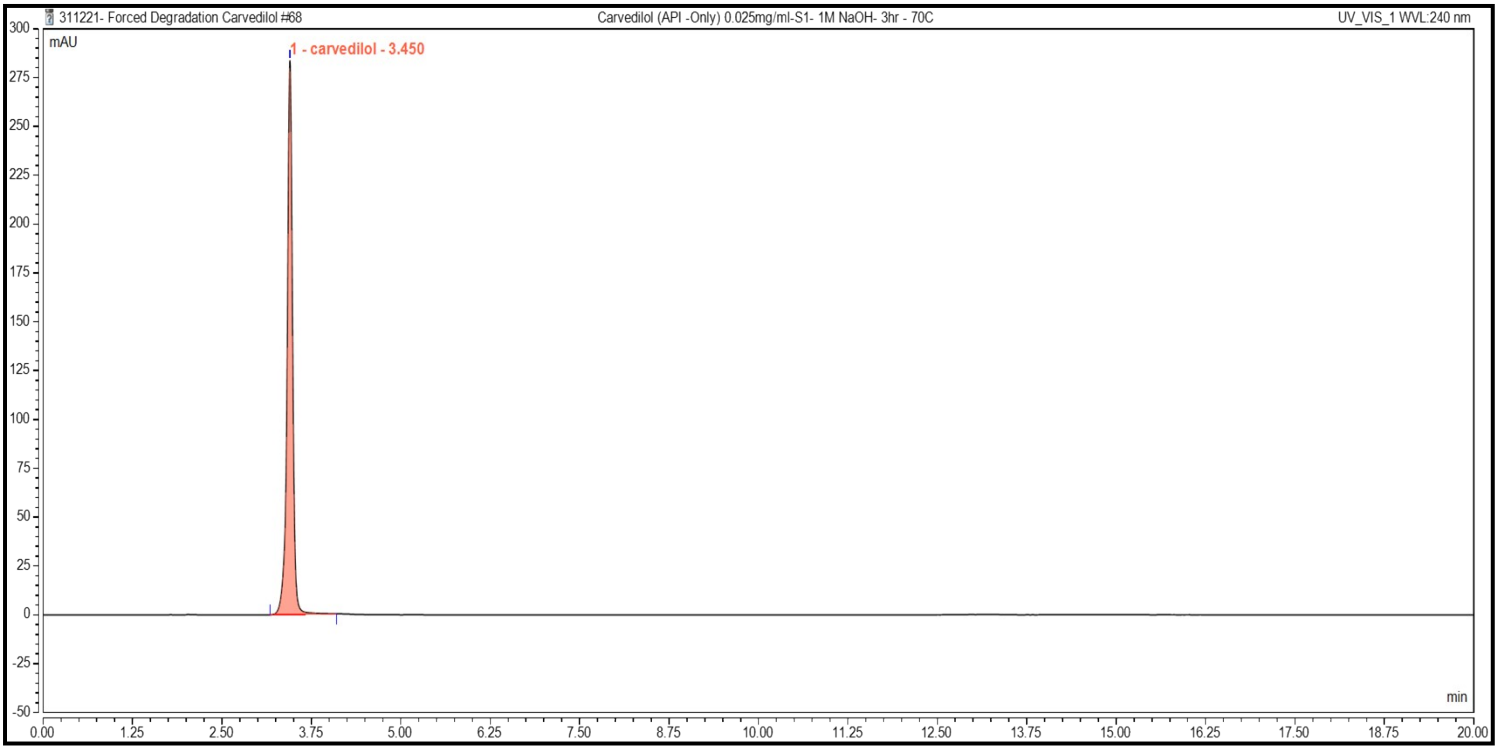


Figure 55S. HPLC chromatogram of base hydrolysis of CARV, 1.0 M NaOH for 3 h at 70 °C.

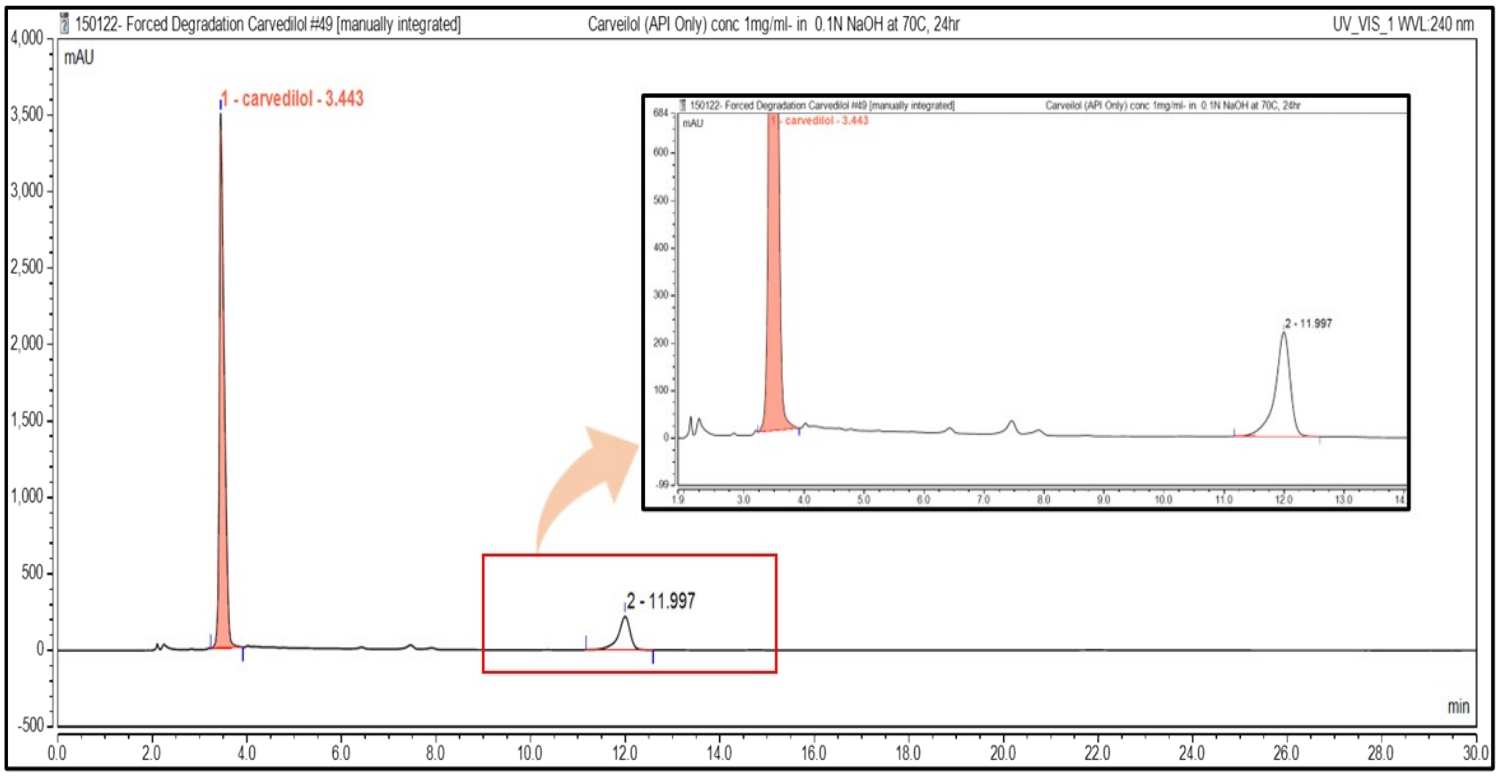


Figure 56S. HPLC chromatogram of base hydrolysis of CARV, 0.1 M NaOH for 24 h at 70 °C.

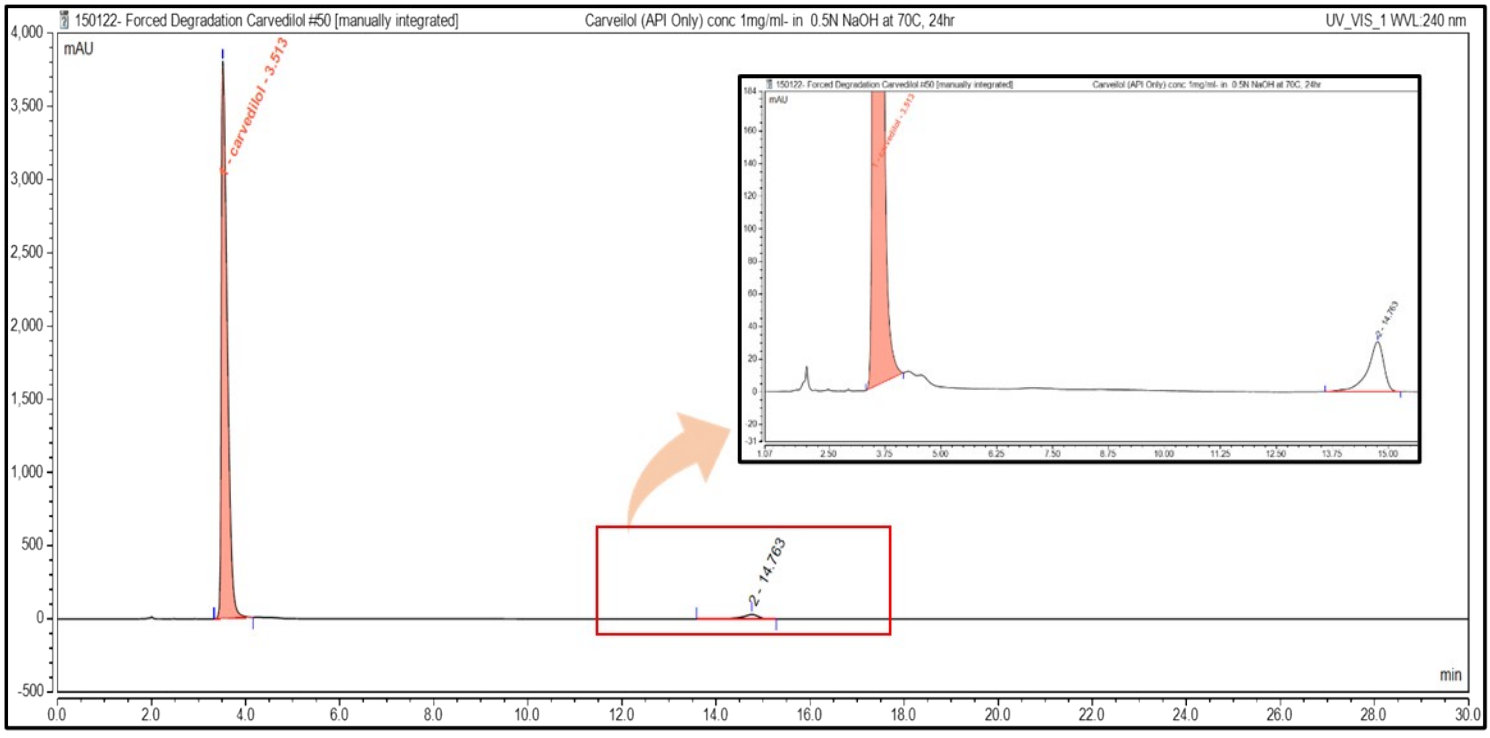


Figure 57S. HPLC chromatogram of base hydrolysis of CARV, 0.5 M NaOH for 24 h at 70 °C.

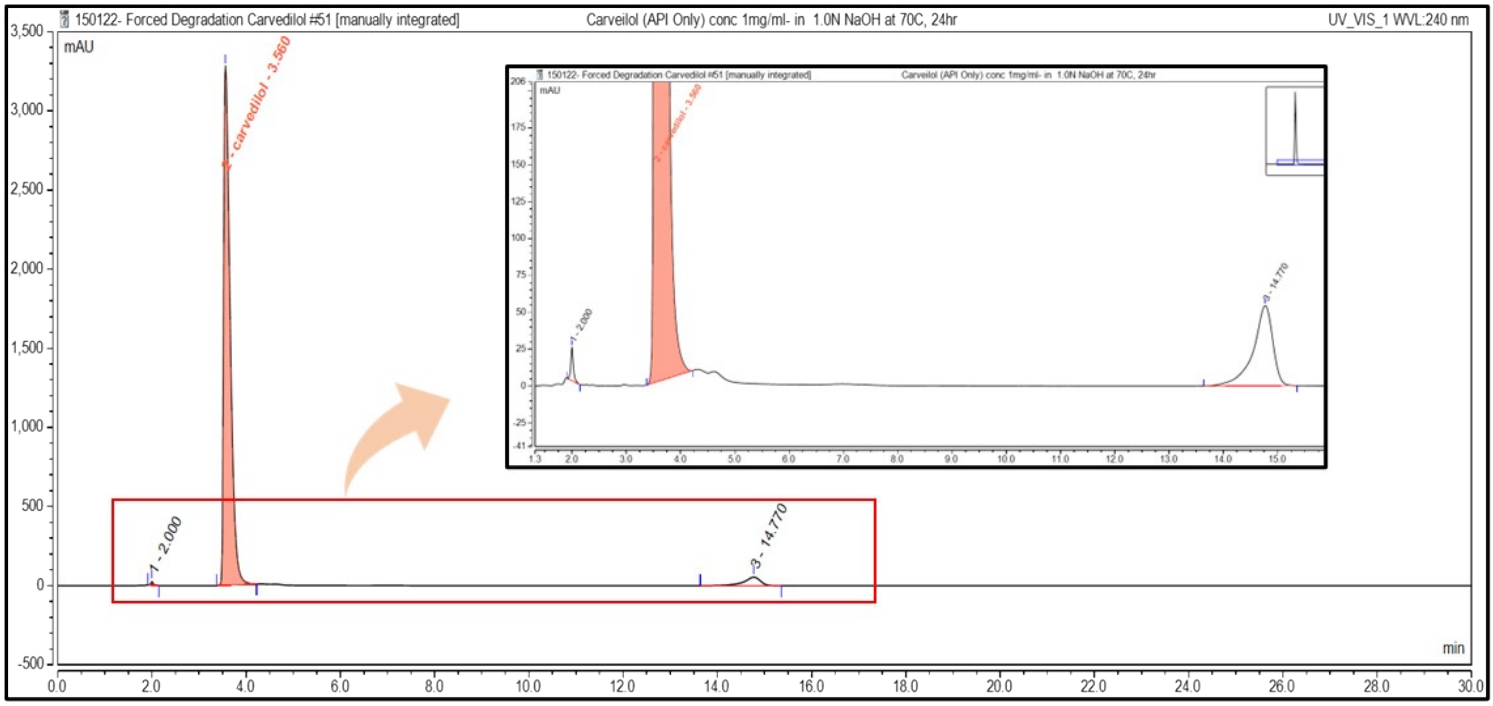


Figure 58S. HPLC chromatogram of base hydrolysis of CARV, 1.0 M NaOH for 24 h at 70 ℃.

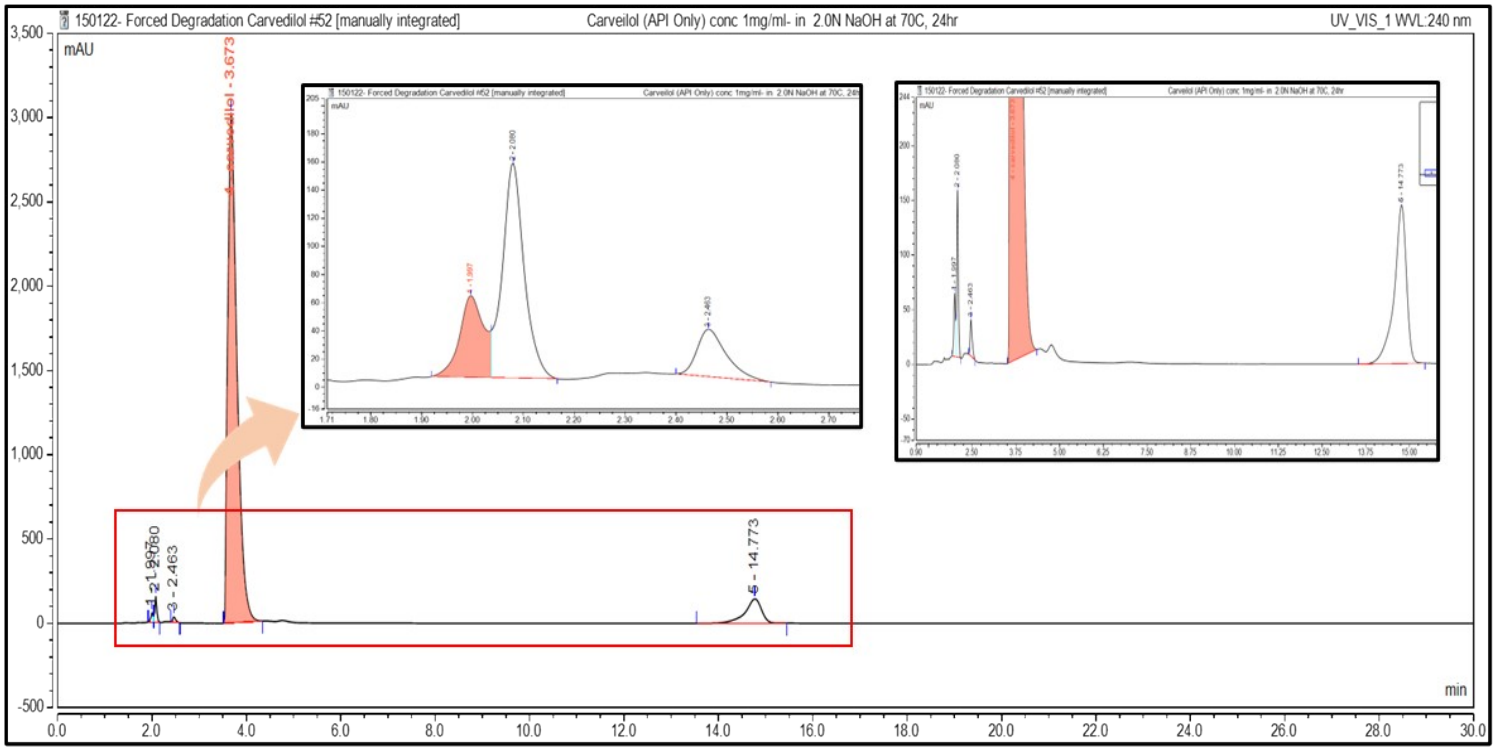


Figure 59S. HPLC chromatogram of base hydrolysis of CARV, 2.0 M NaOH for 24 h at 70 ℃.

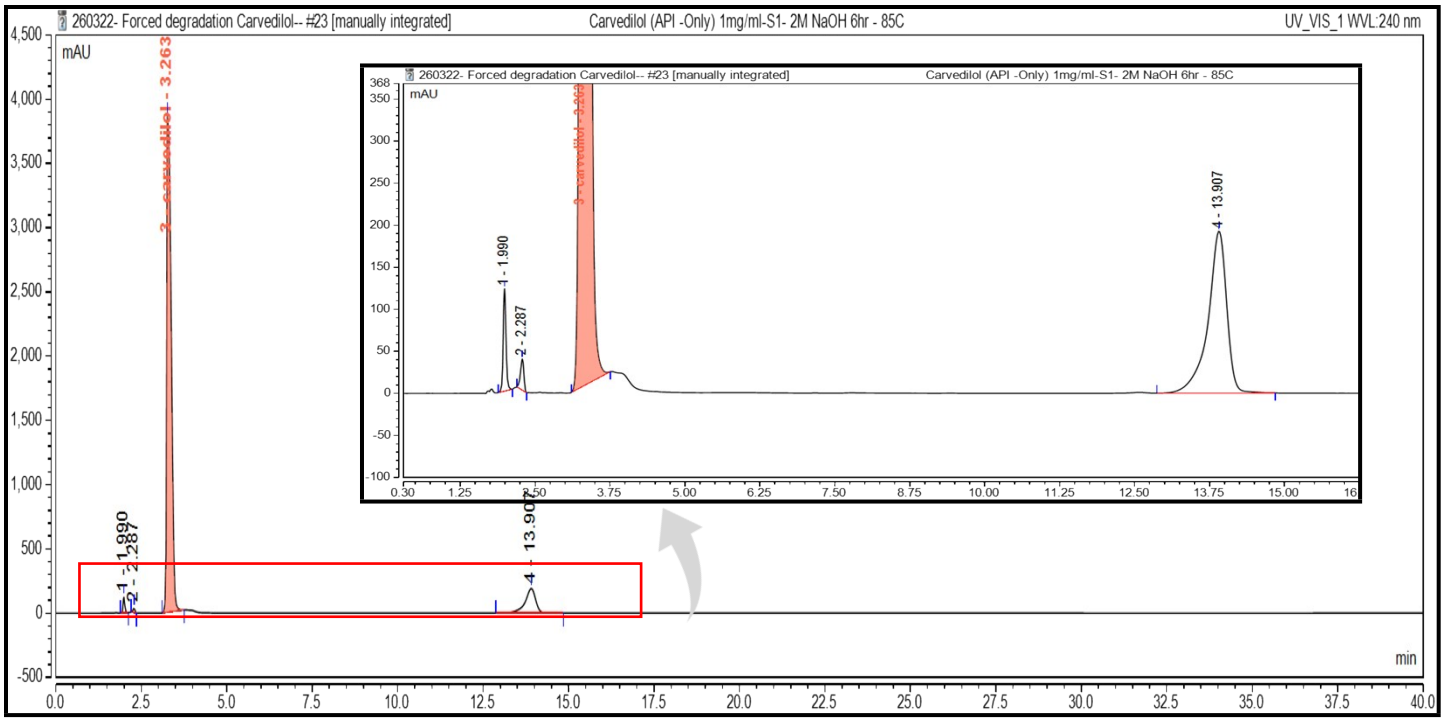


Figure 60S. HPLC chromatogram of base hydrolysis of CARV, 2.0 M NaOH for 6 h at 85 °C.

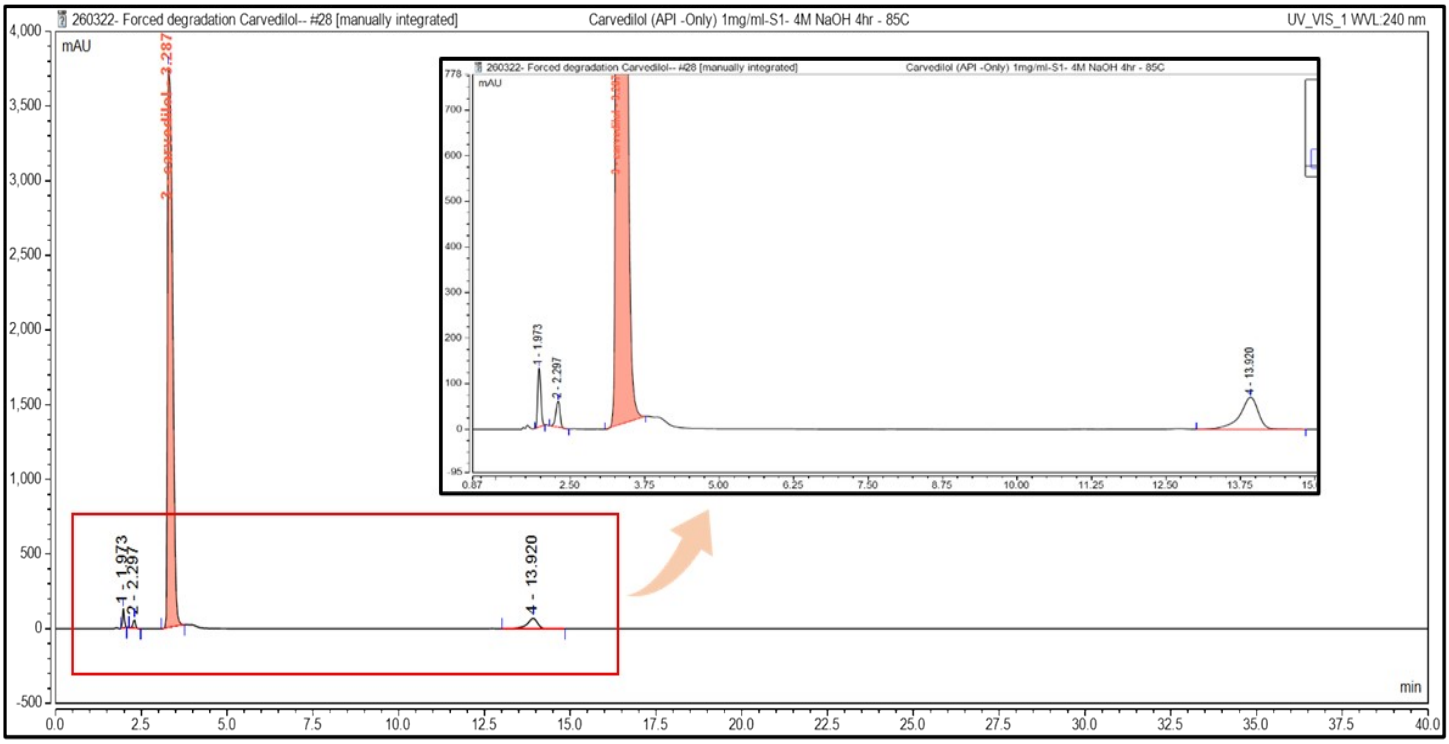


Figure 61S. HPLC chromatogram of base hydrolysis of CARV, 4.0 M NaOH for 4 h at 85 °C.

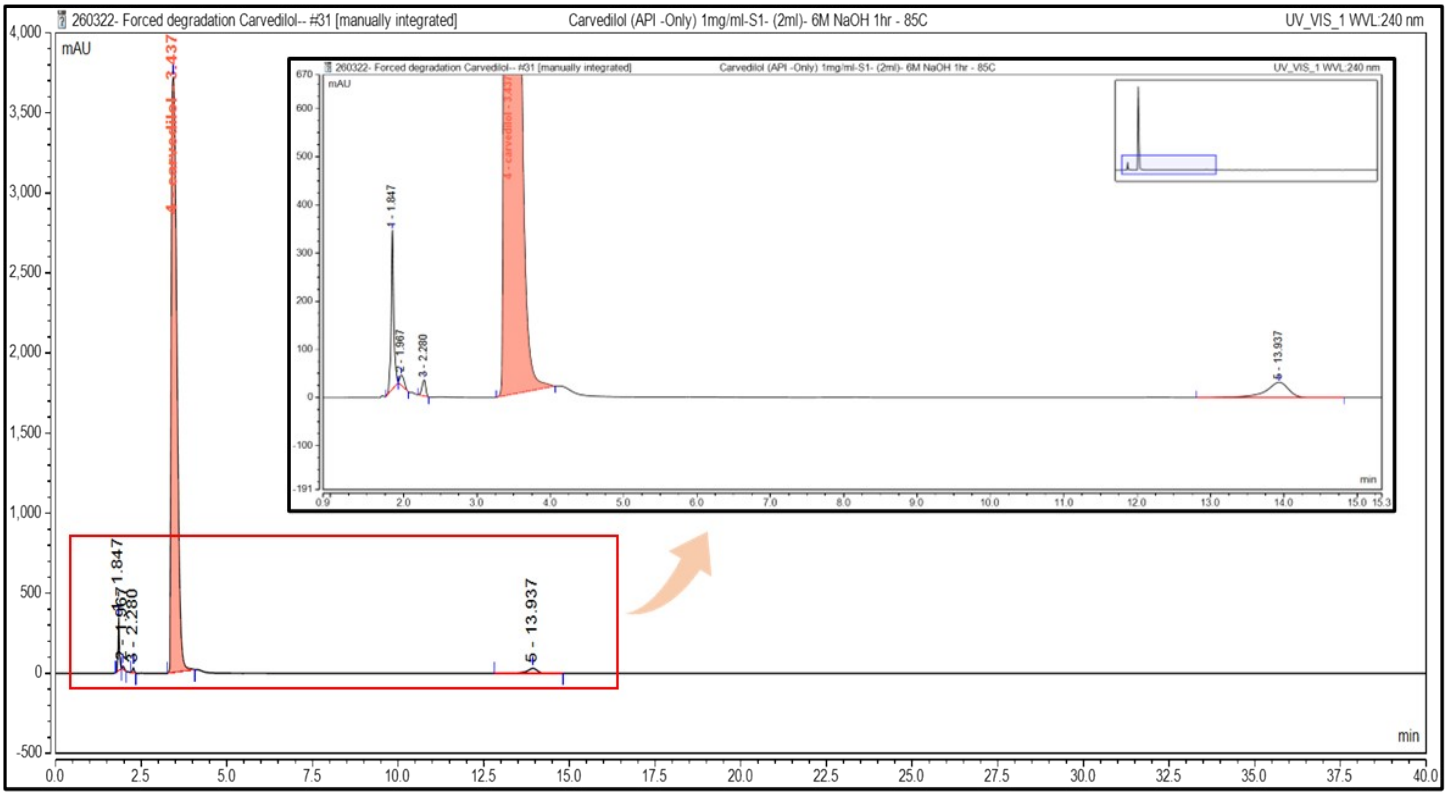


Figure 62S. HPLC chromatogram of base hydrolysis of CARV, 6.0 M NaOH (2 ml) for 1 h at 85 ℃.

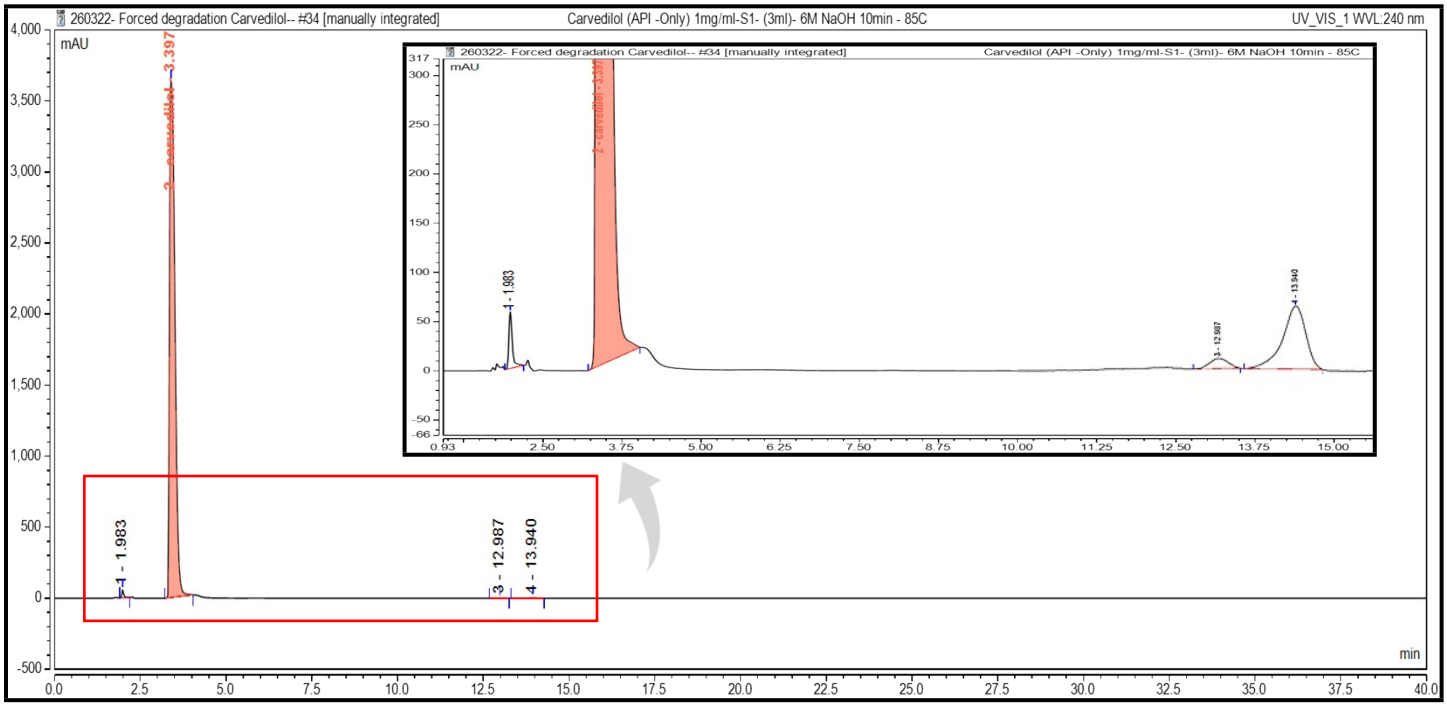


Figure 63S. HPLC chromatogram of base hydrolysis of CARV, 6.0 M NaOH (3 ml) for 10 min at 85 ℃.

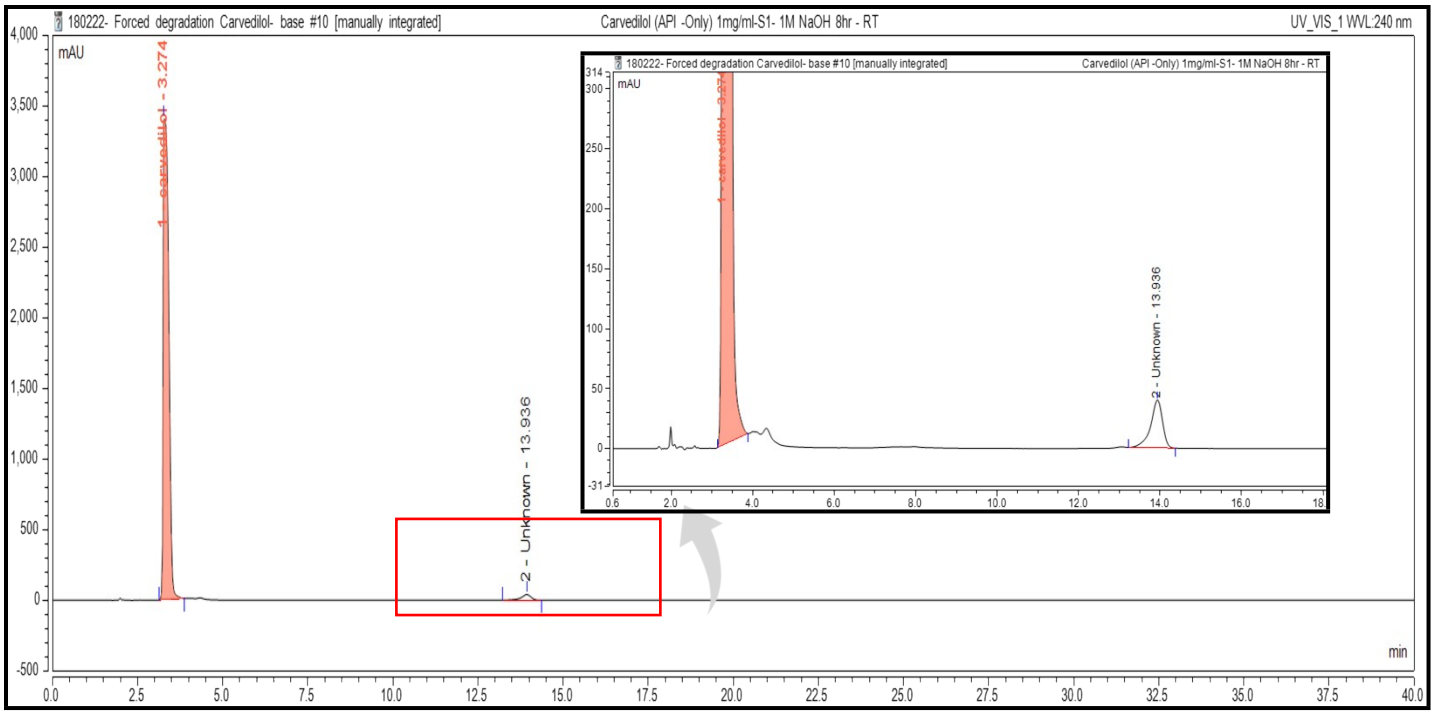


Figure 64S. HPLC chromatogram of base hydrolysis of CARV, 1.0 M NaOH for 8 h at RT.

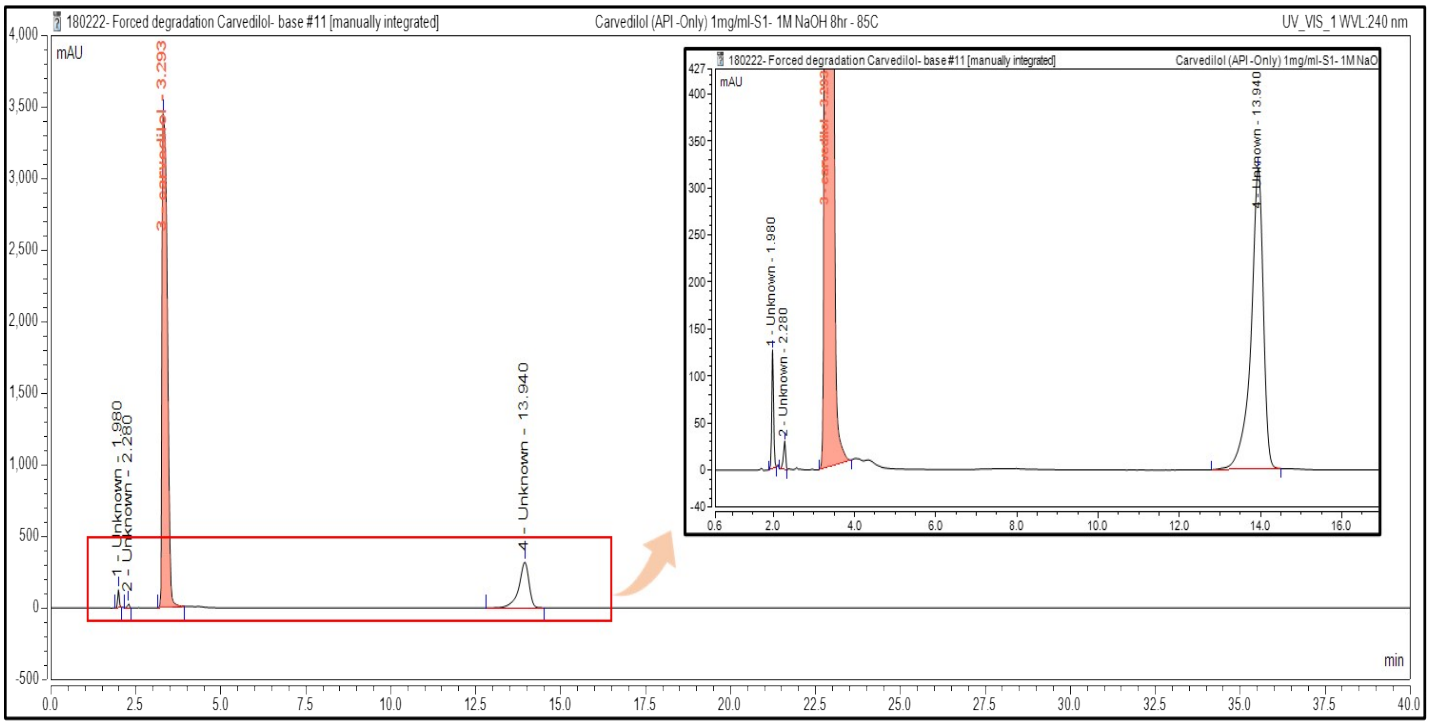


Figure 65S. HPLC chromatogram of base hydrolysis of CARV, 1.0 M NaOH for 8 h at 85 ℃.

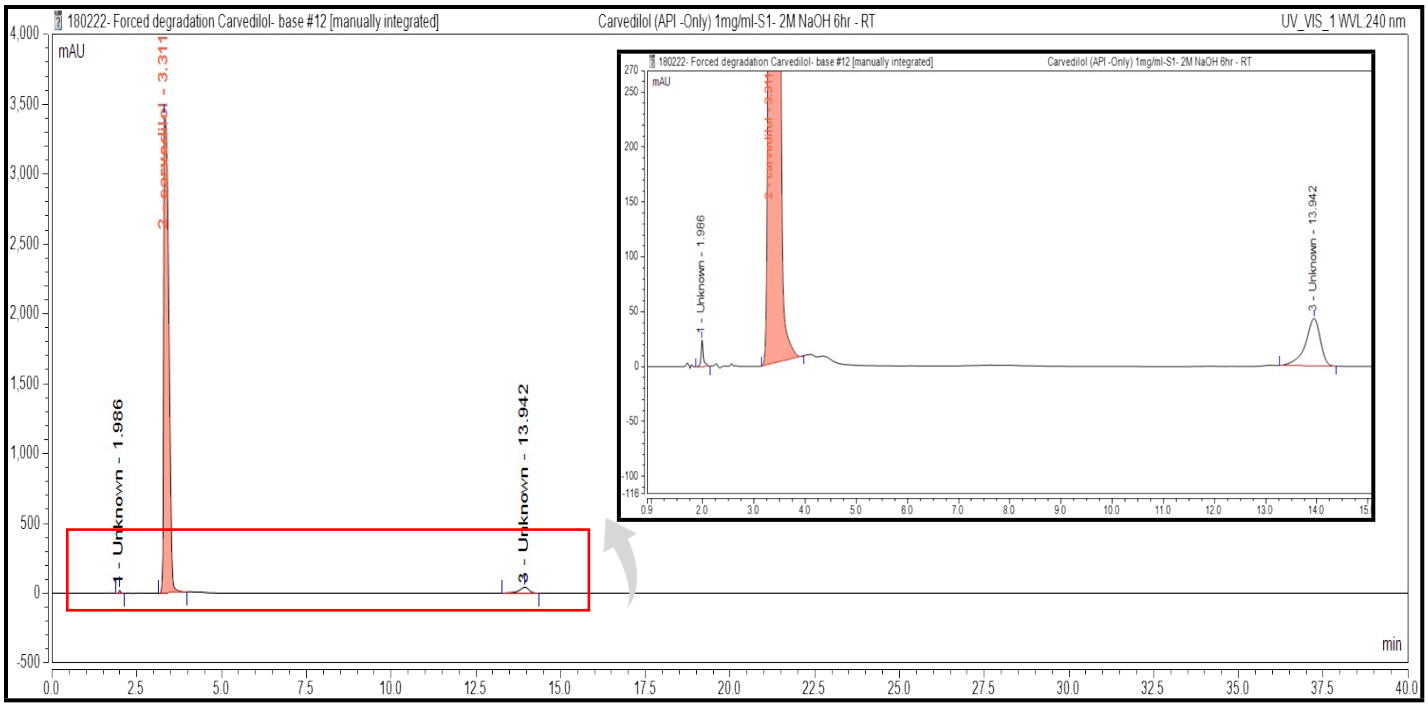


Figure 66S. HPLC Chromatogram of base hydrolysis of CARV, 2.0 M NaOH for 6 h at RT.

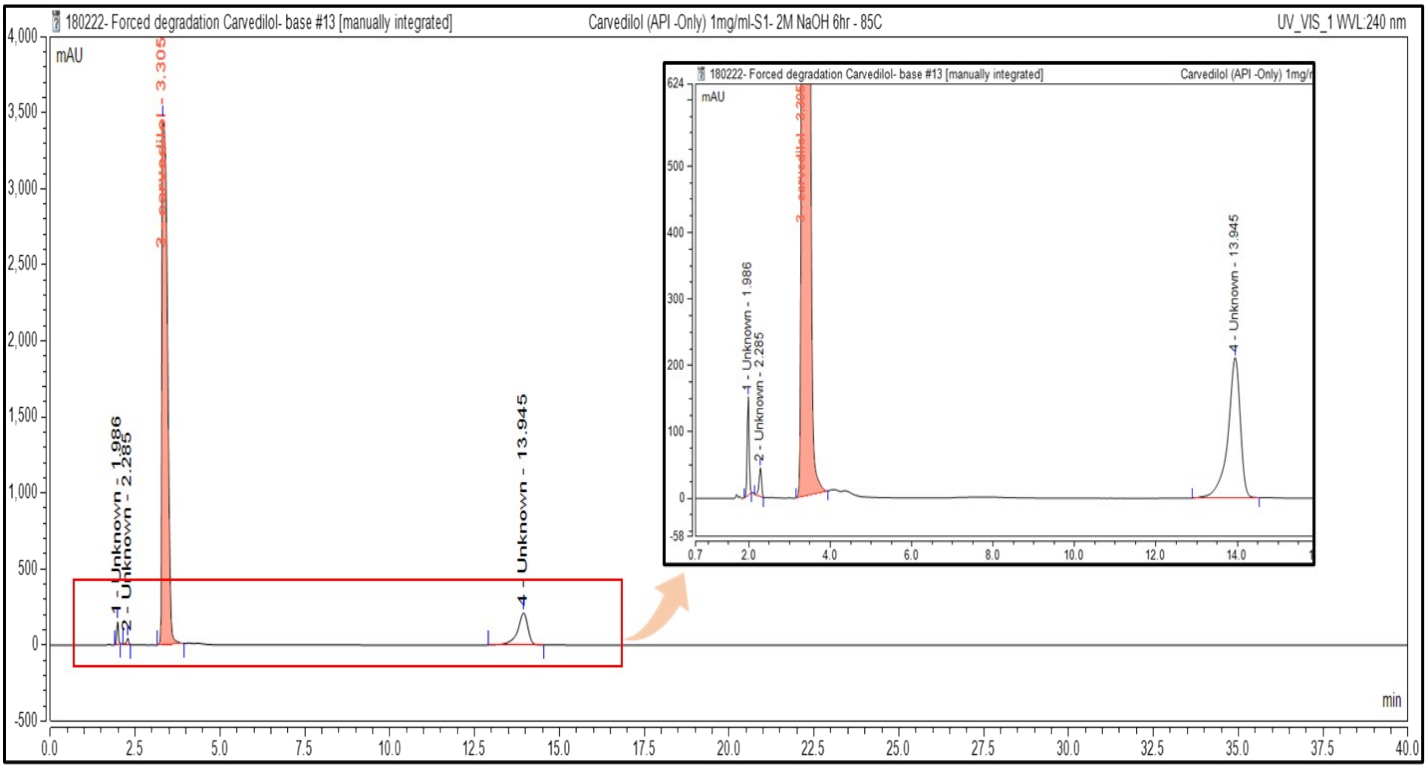


Figure 67S. HPLC Chromatogram of base hydrolysis of CARV, 2.0 M NaOH for 6 h at 85 °C.

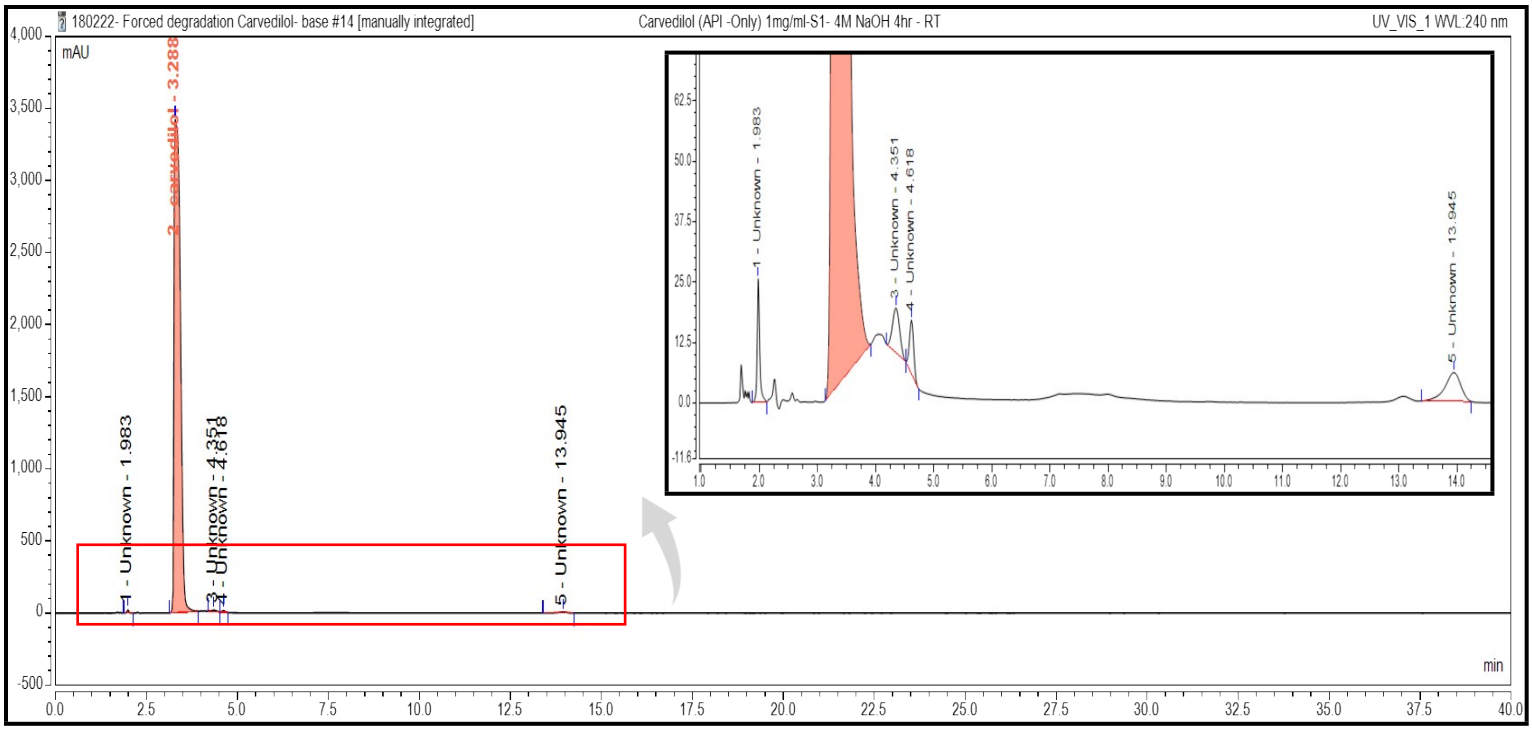


Figure 68S. HPLC chromatogram of base hydrolysis of CARV, 4.0 M NaOH for 4 h at RT.

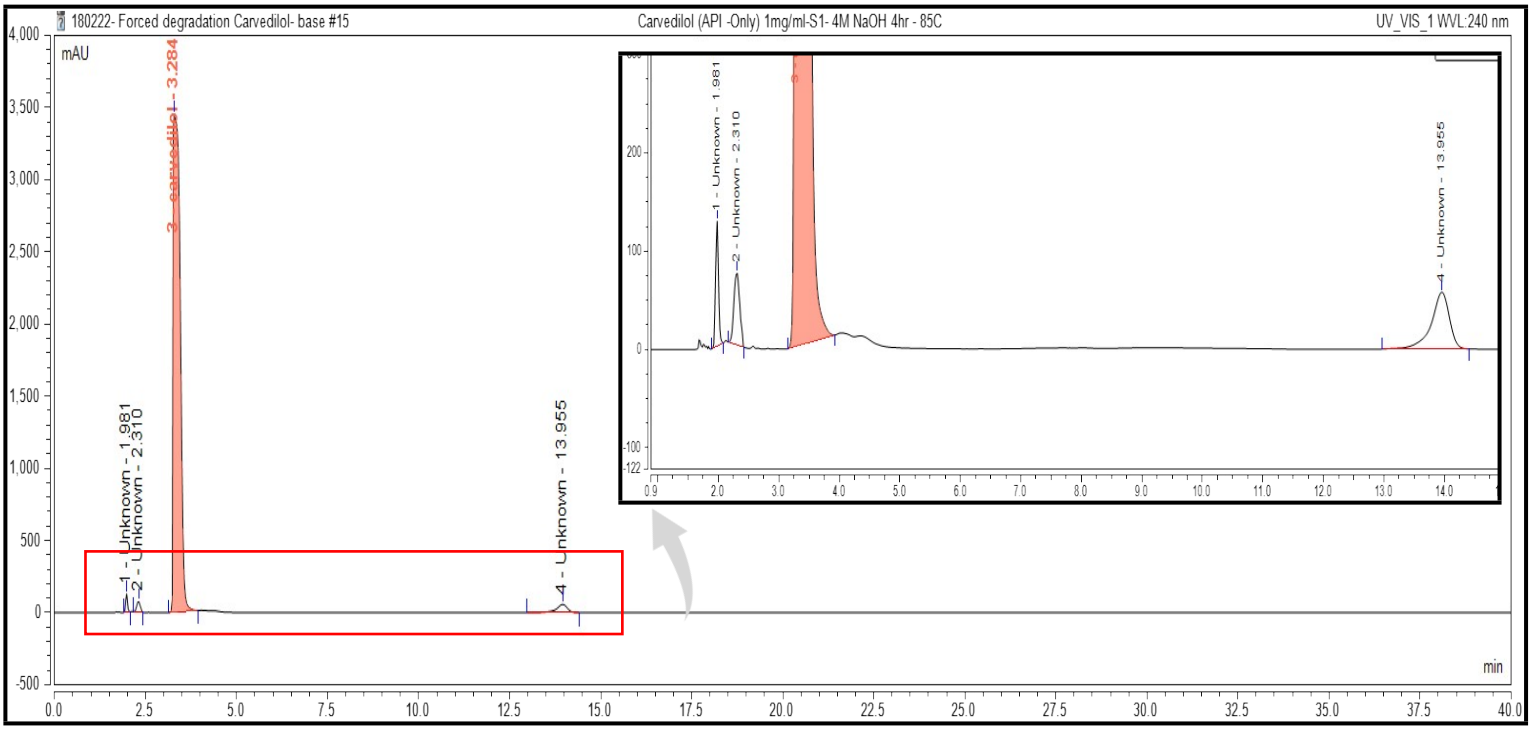


Figure 69S. HPLC chromatogram of base hydrolysis of CARV, 4.0 M NaOH for 4 h at 85 °C.

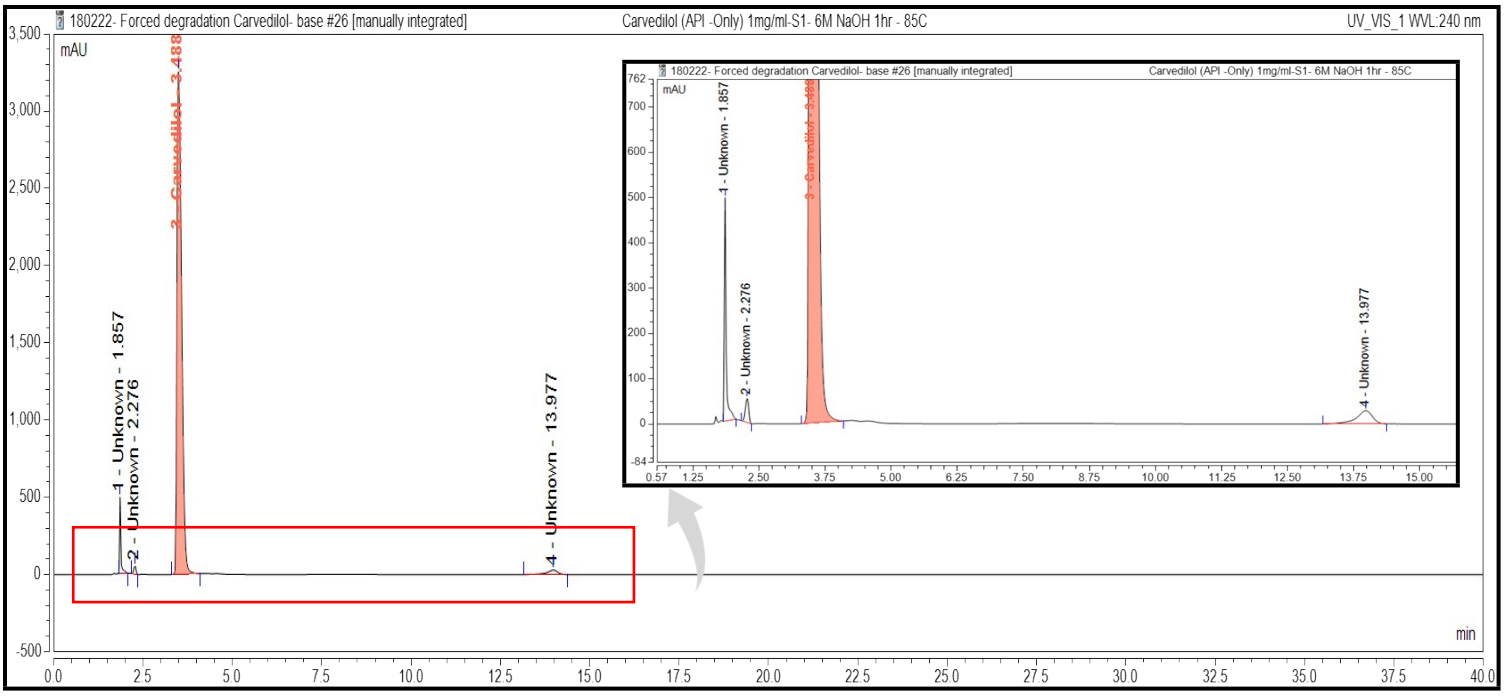


Figure 70S. HPLC chromatogram of base hydrolysis of CARV, 6.0 M NaOH for 1 h at 85 ℃.

CARV-MEOG - Base Degradation:

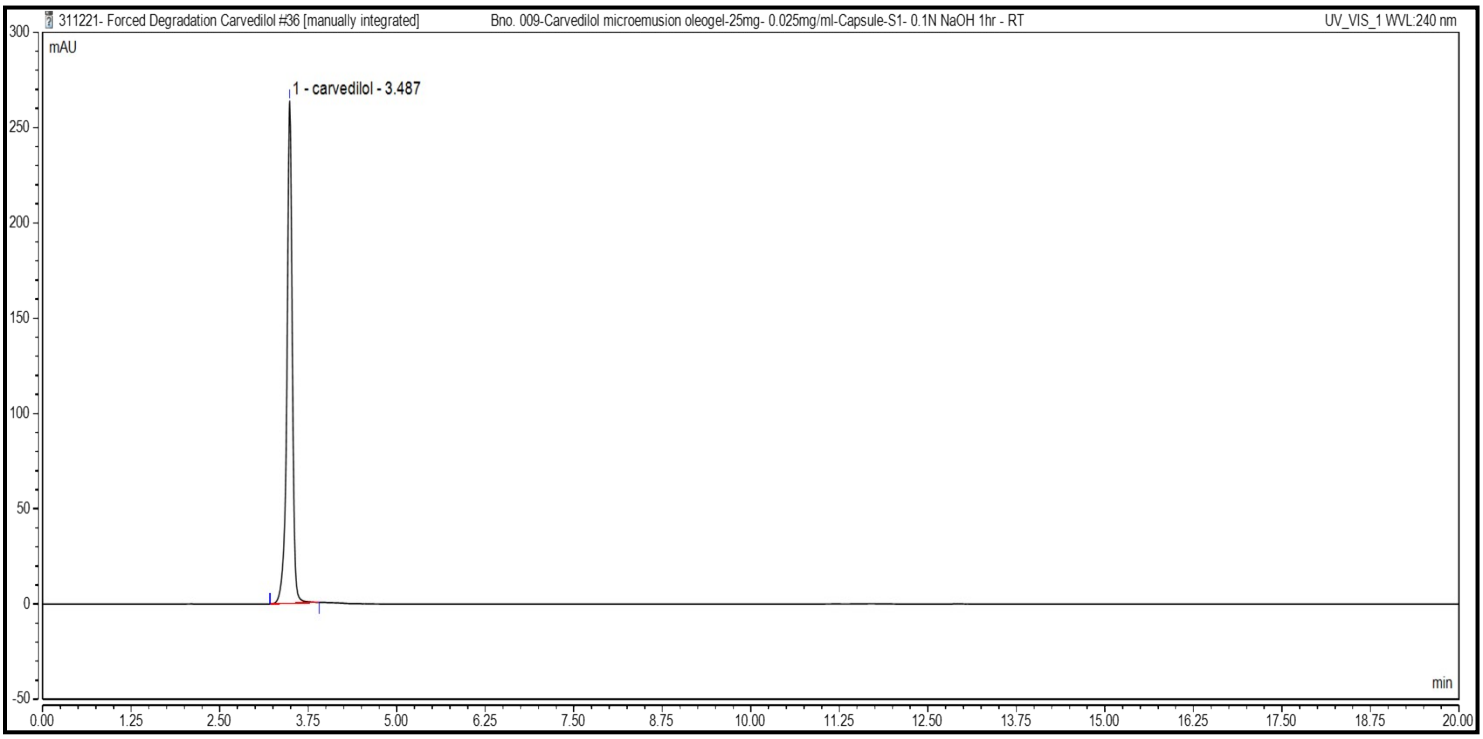


Figure 71S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 0.1 M NaOH for 1 h at RT.

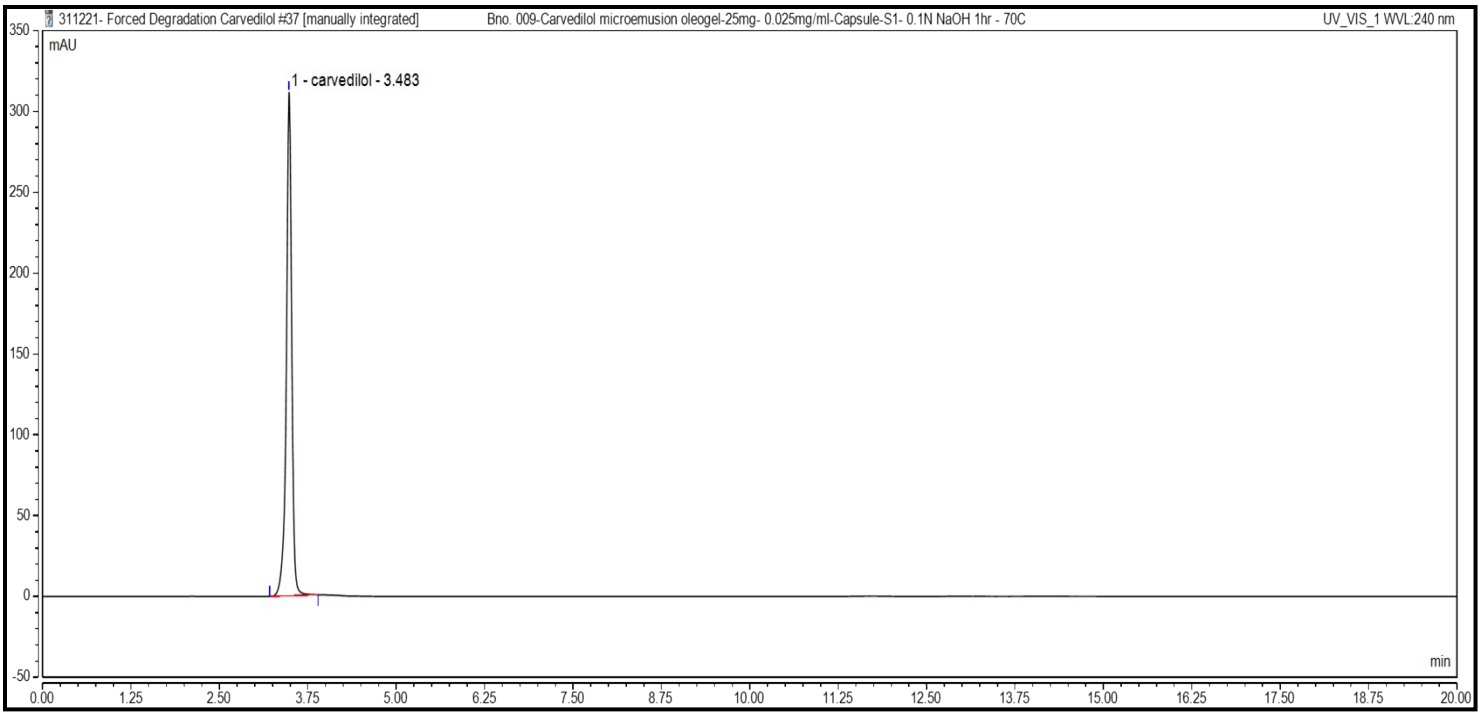


Figure 72S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 0.1 M NaOH for 1 h at 70 ℃.

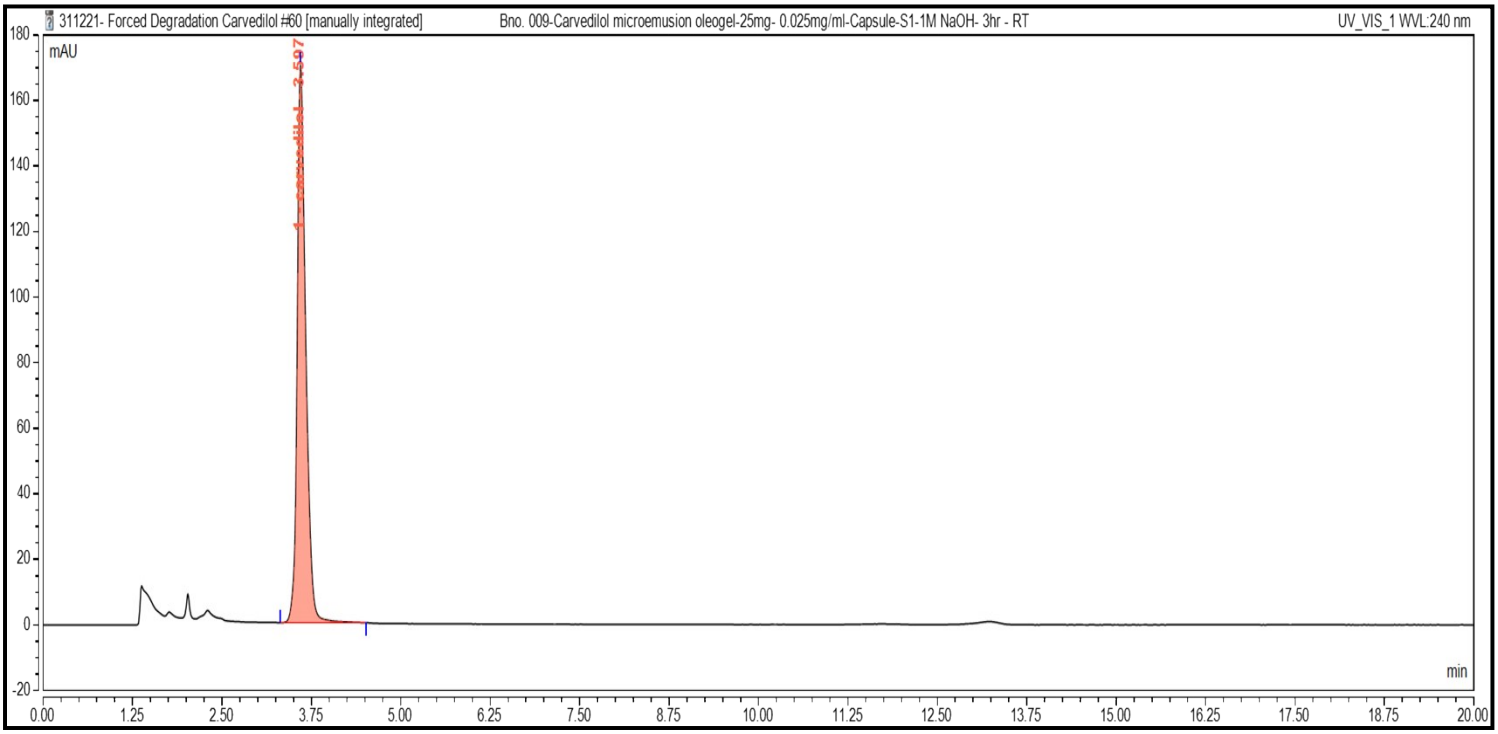


Figure 73S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 1.0 M NaOH for 3 h at RT.
(Note: peak at retention time 2.023 min is related for the excipient degradation)

Figure 74S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 1.0 M NaOH for 3 h at 70 °C.

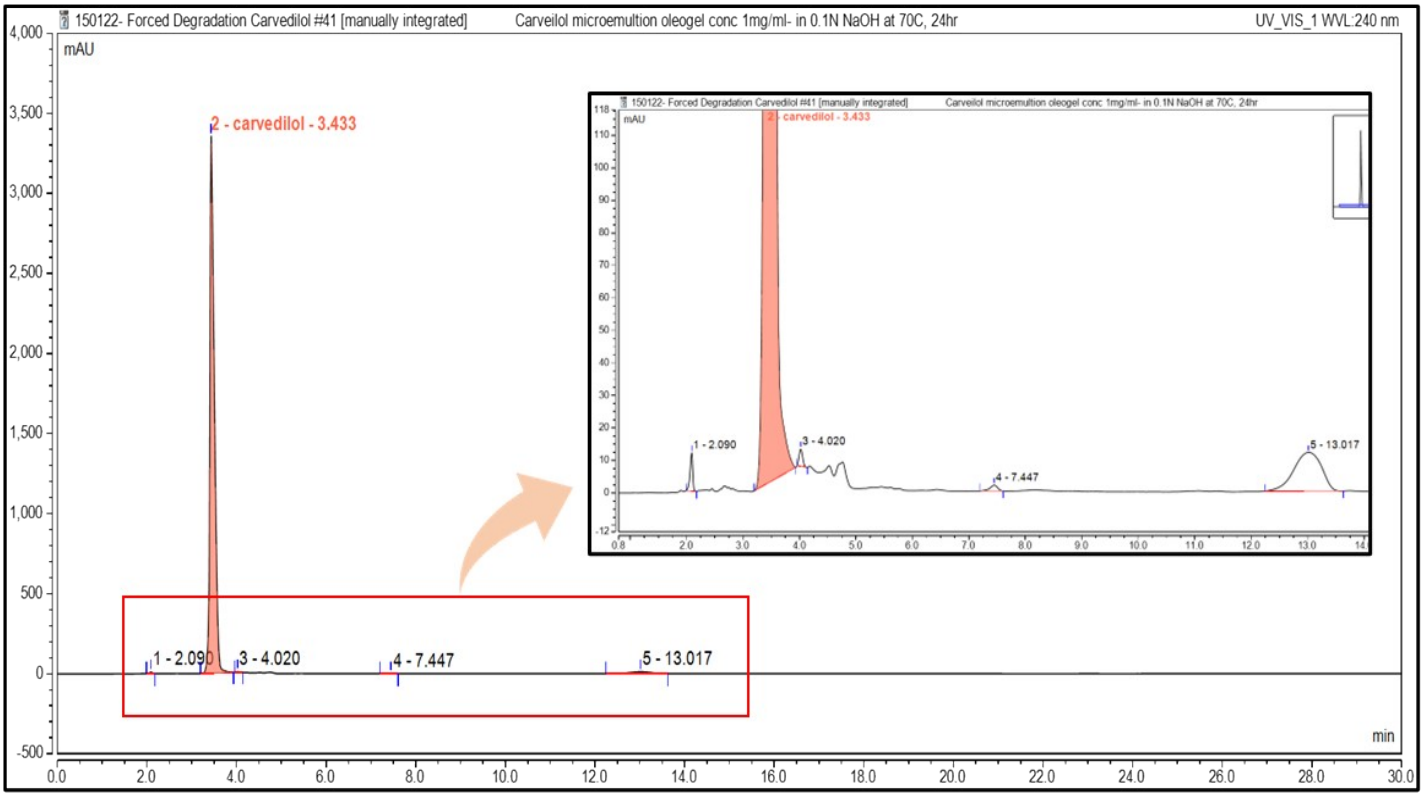


Figure 75S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 0.1 M NaOH for 24 h at 70 °C.

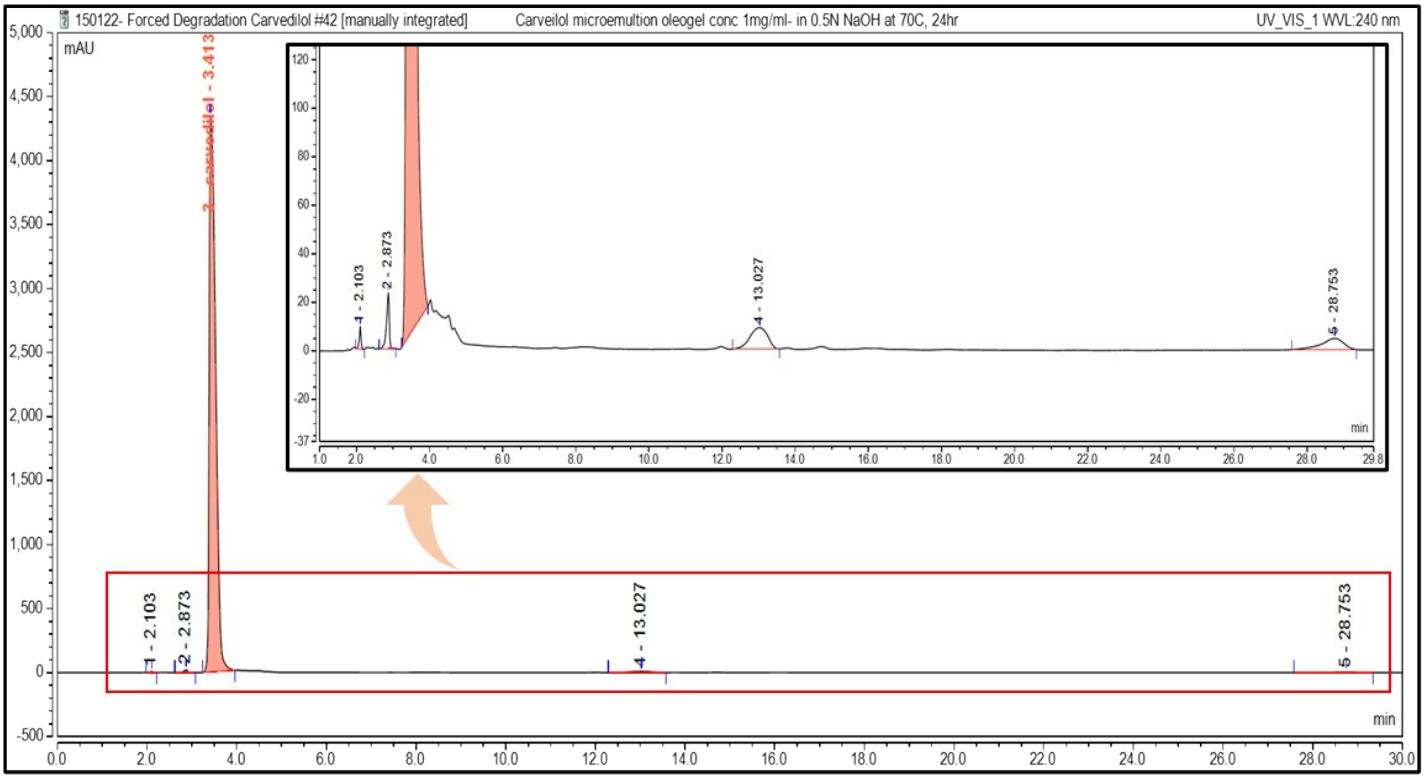


Figure 76S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 0.5 M NaOH for 24 h at 70 ℃.

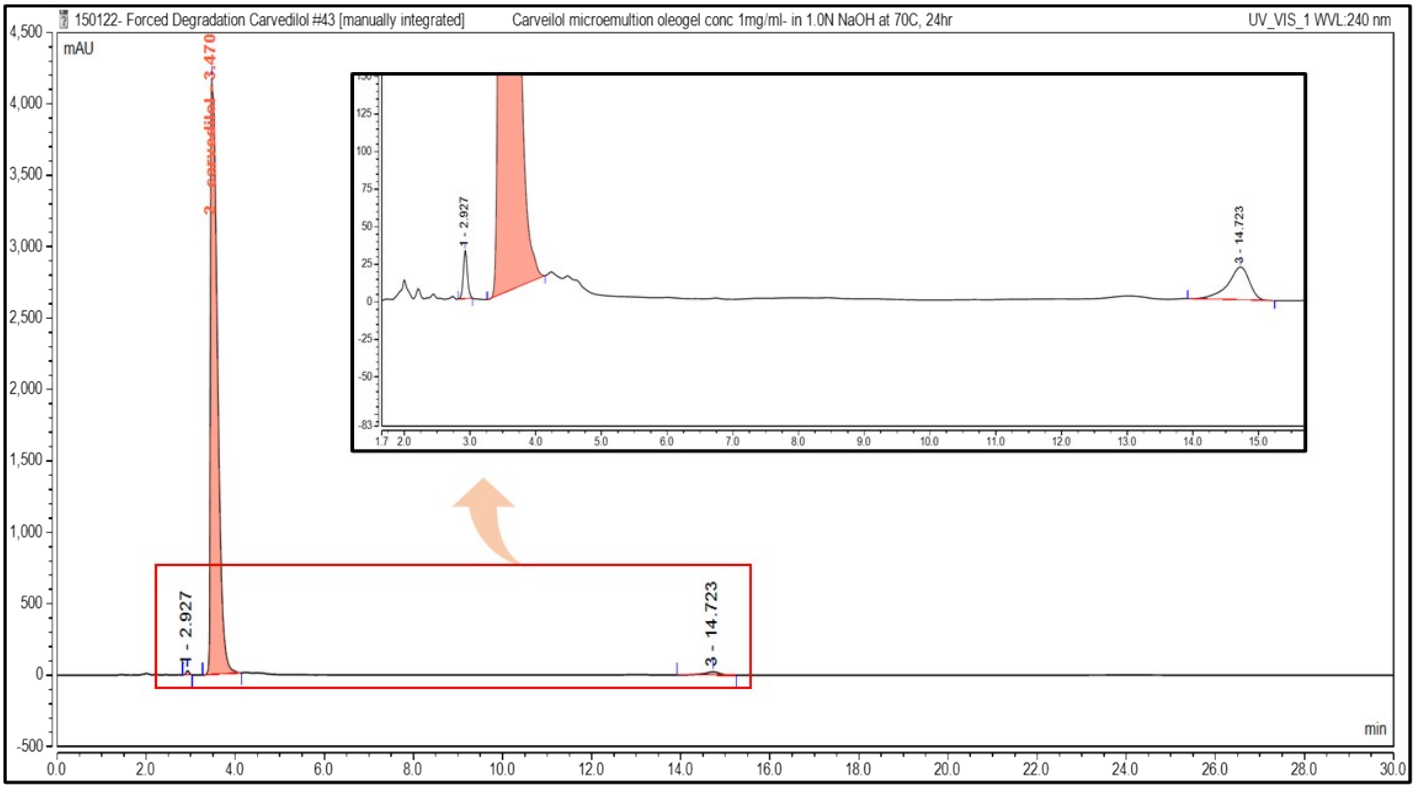


Figure 77S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 1.0 M NaOH for 24 h at 70 ℃.

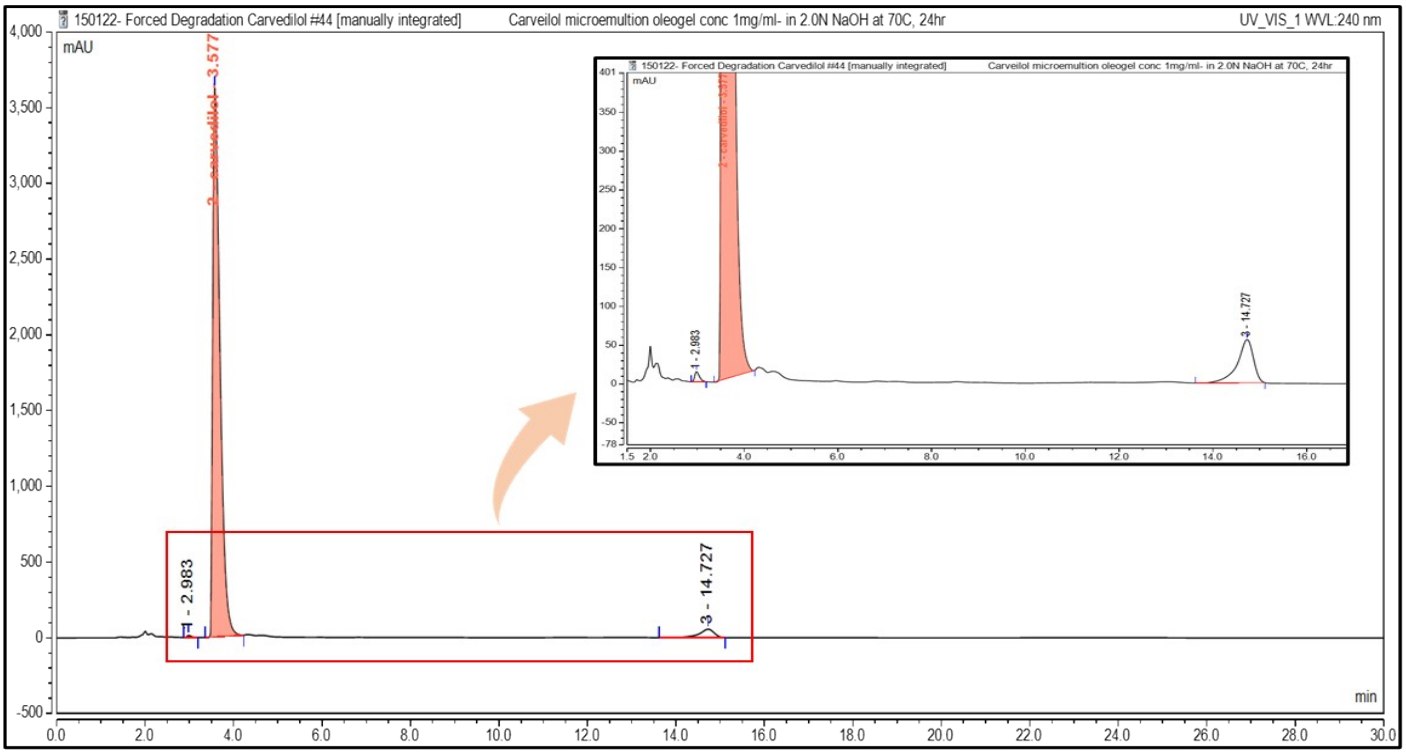


Figure 78S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 2.0 M NaOH for 24 h at 70 °C.

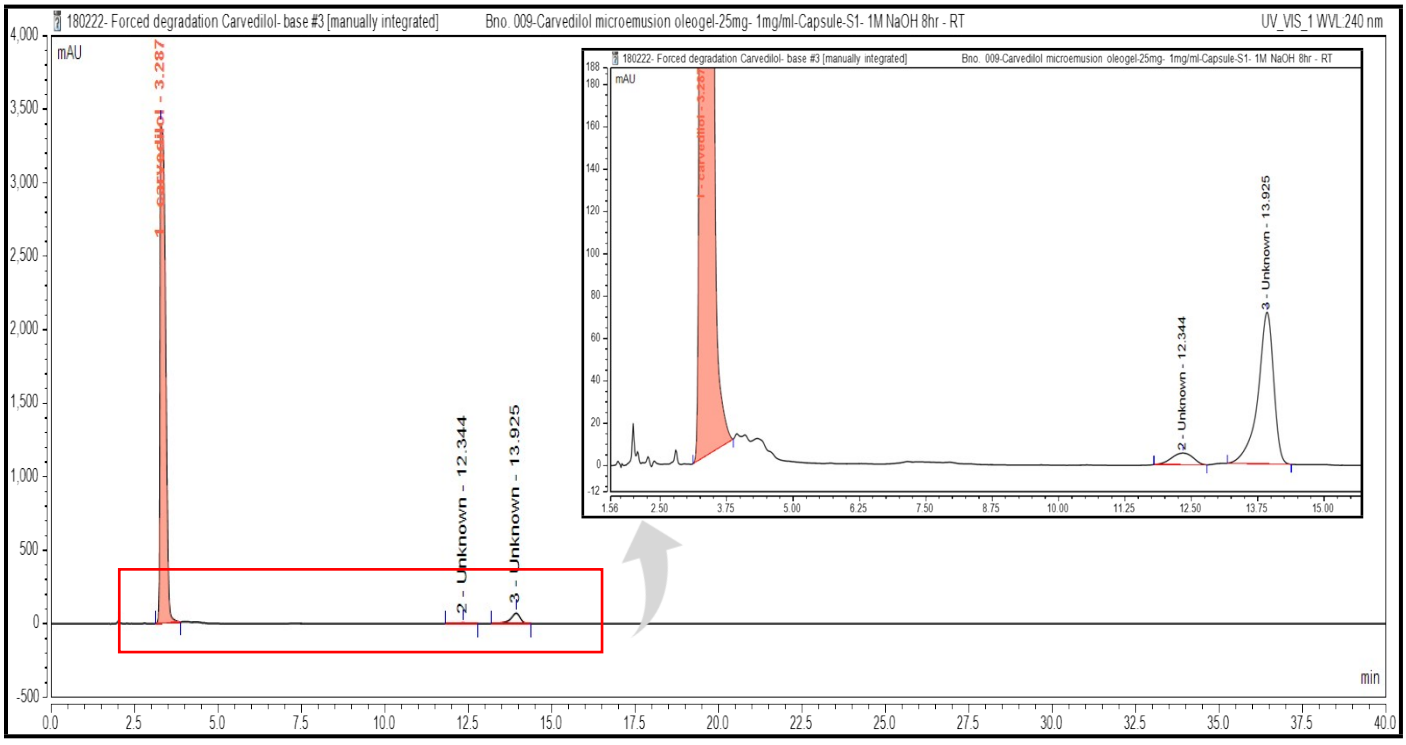


Figure 79S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 1.0 M NaOH for 8 h at RT.

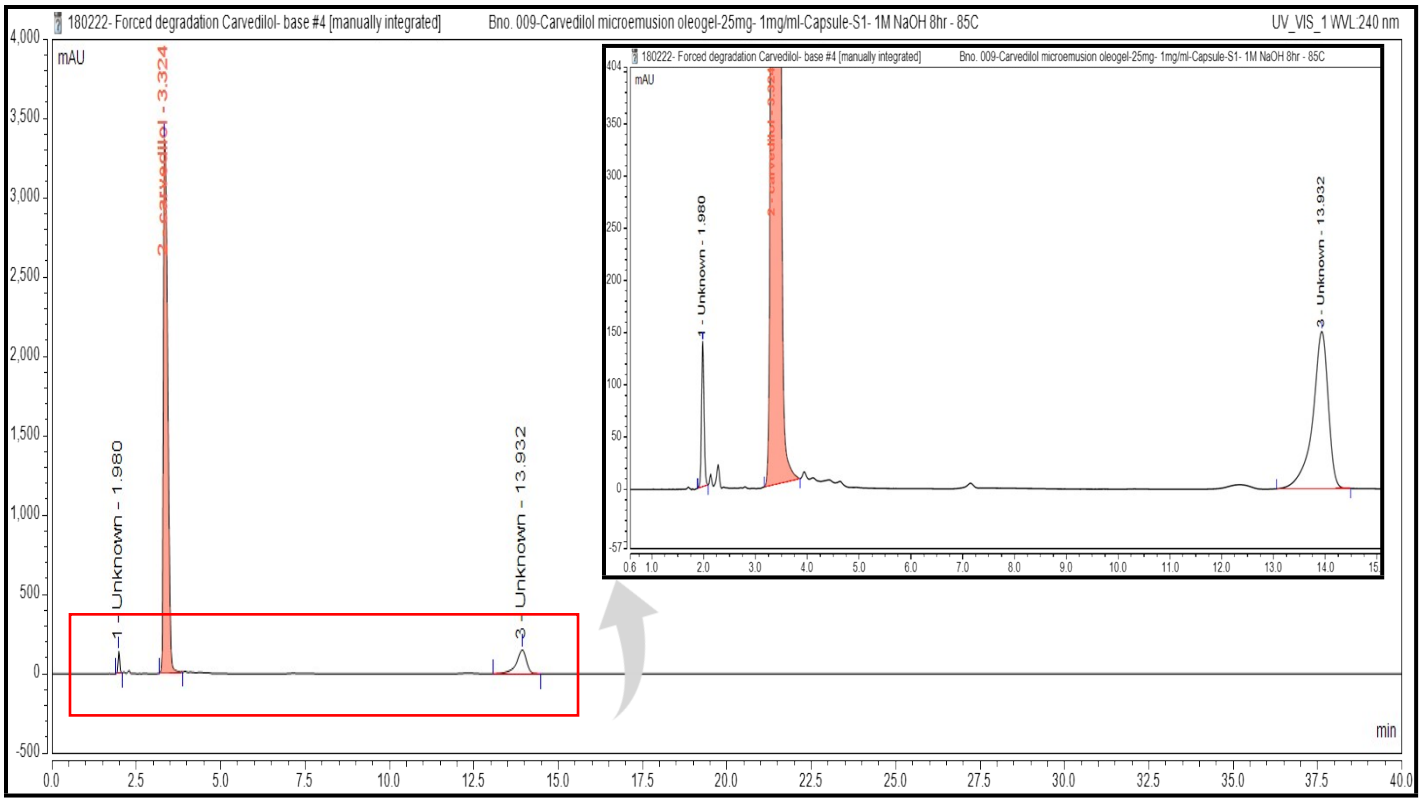


Figure 80S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 1.0 M NaOH for 8 h at 85 ℃.

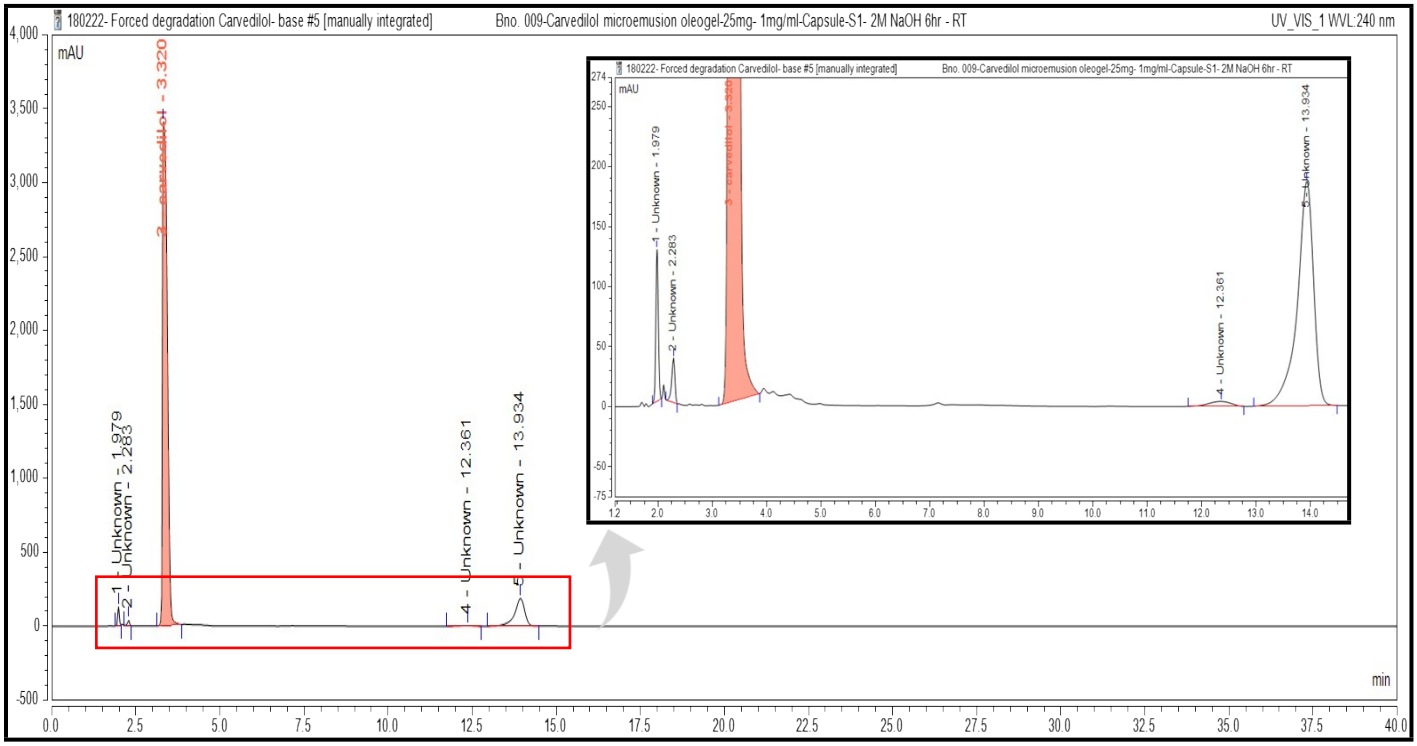


Figure 81S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 2.0 M NaOH for 6 h at RT.

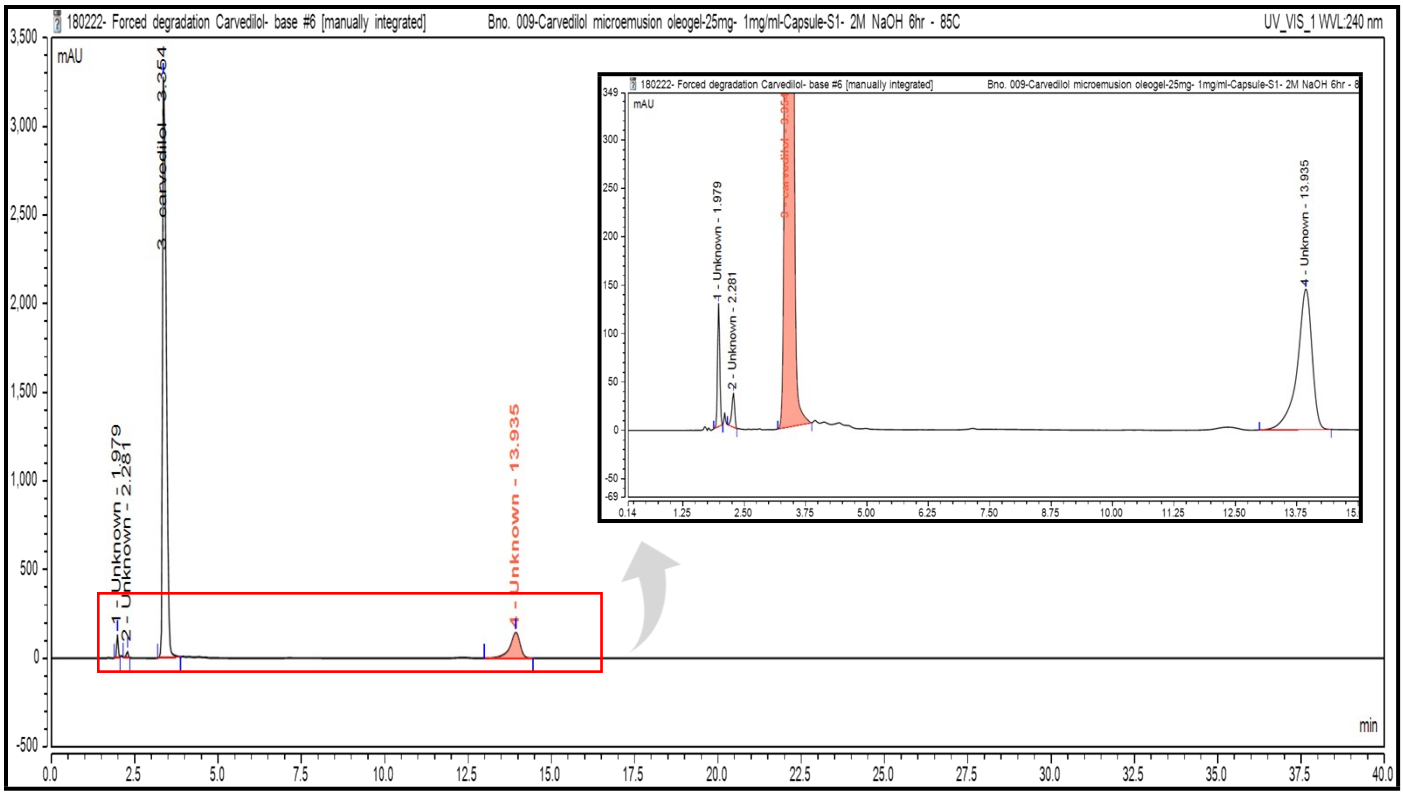


Figure 82S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 2.0 M NaOH for 6 h at 85 °C.

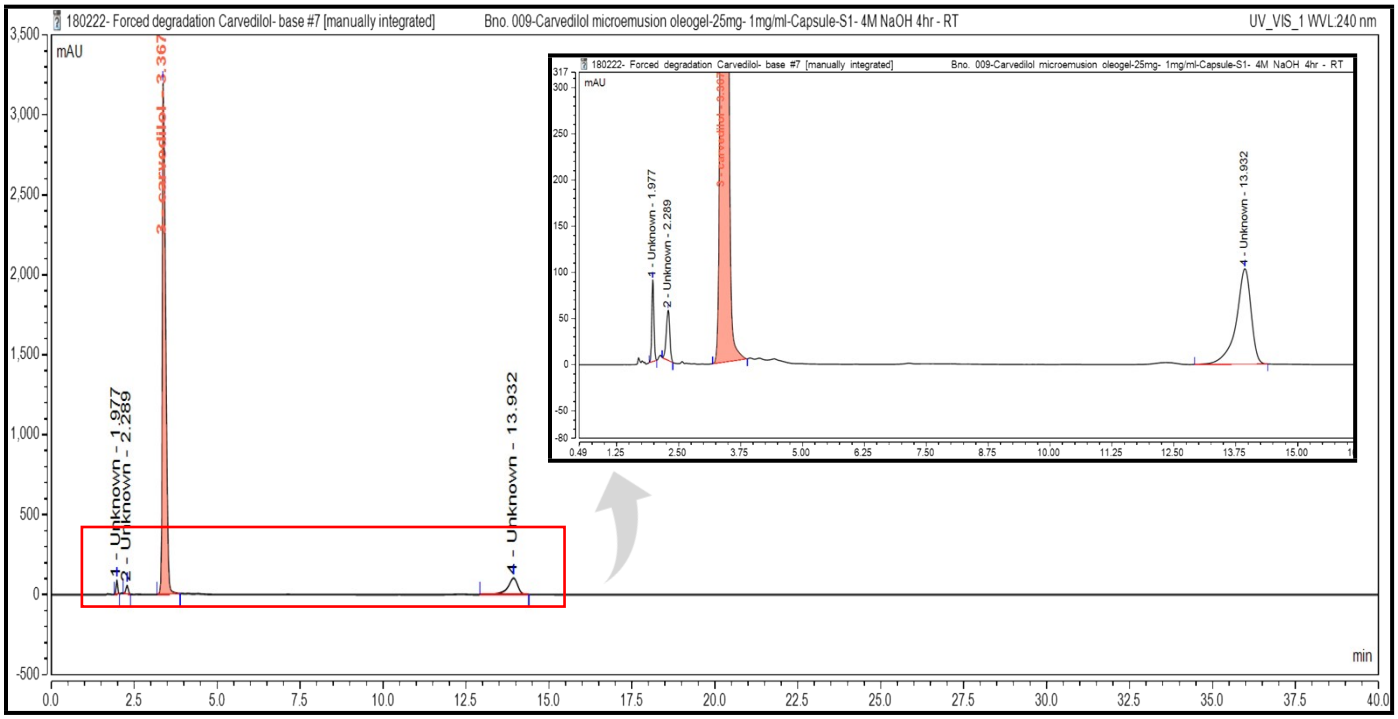


Figure 83S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 4.0 M NaOH for 4 h at RT.

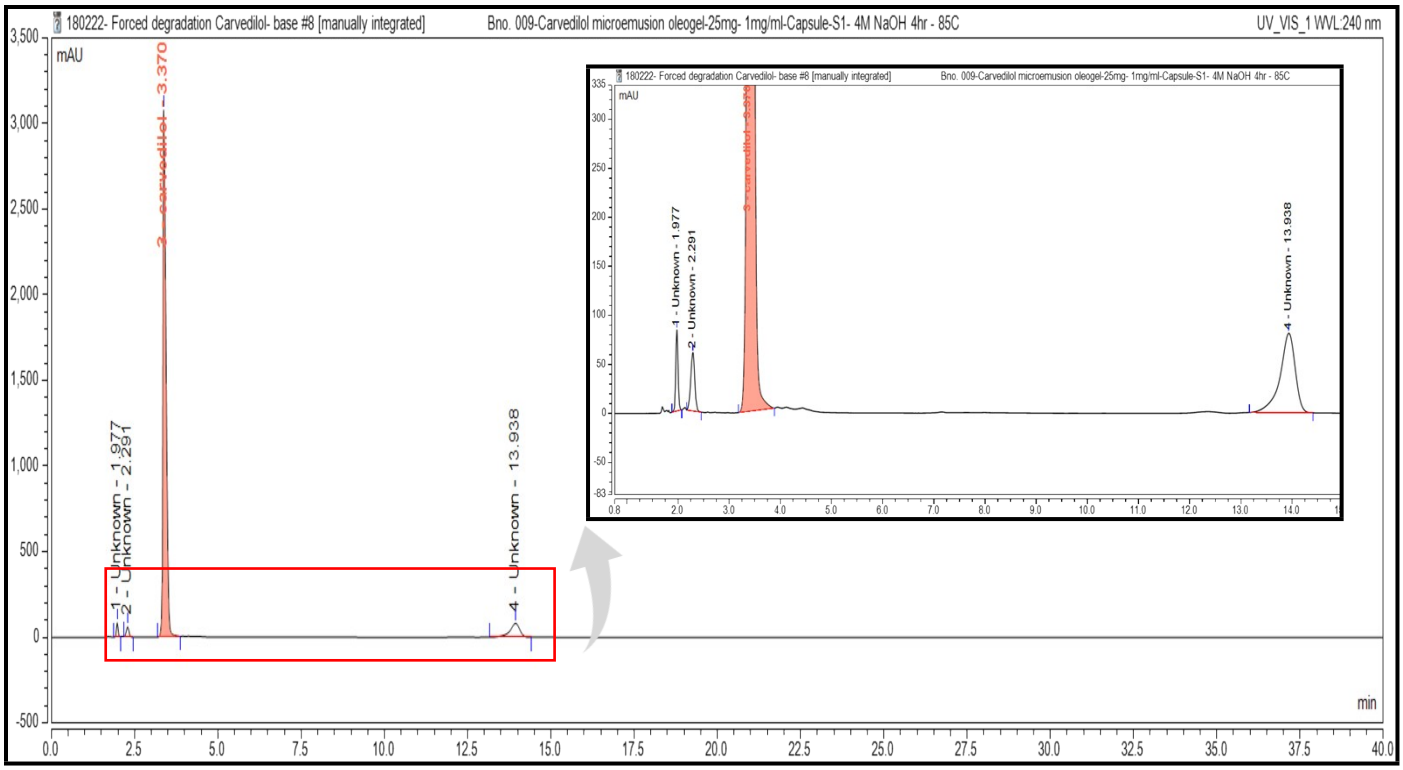


Figure 84S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 4.0 M NaOH for 4 h at 85 ℃.

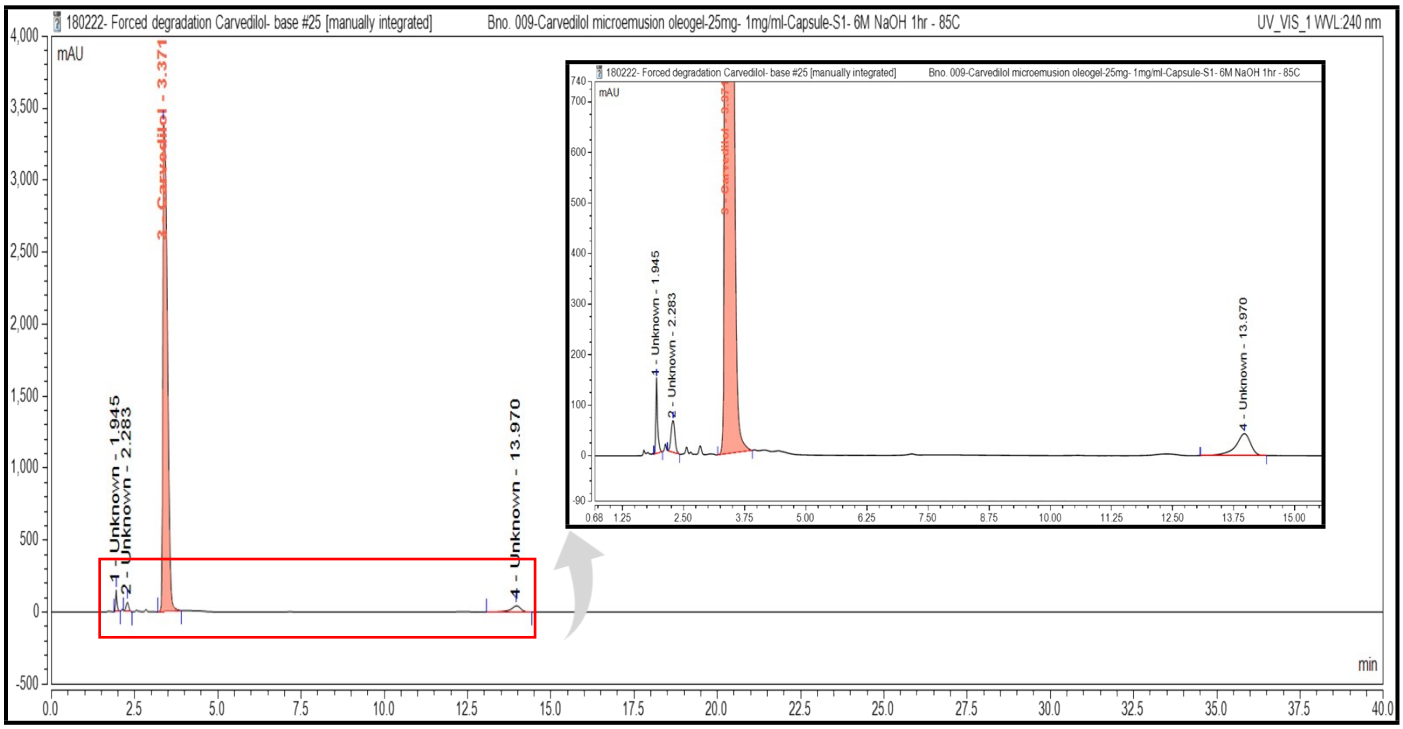


Figure 85S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 6.0 M NaOH for 1 h at 85 ℃.

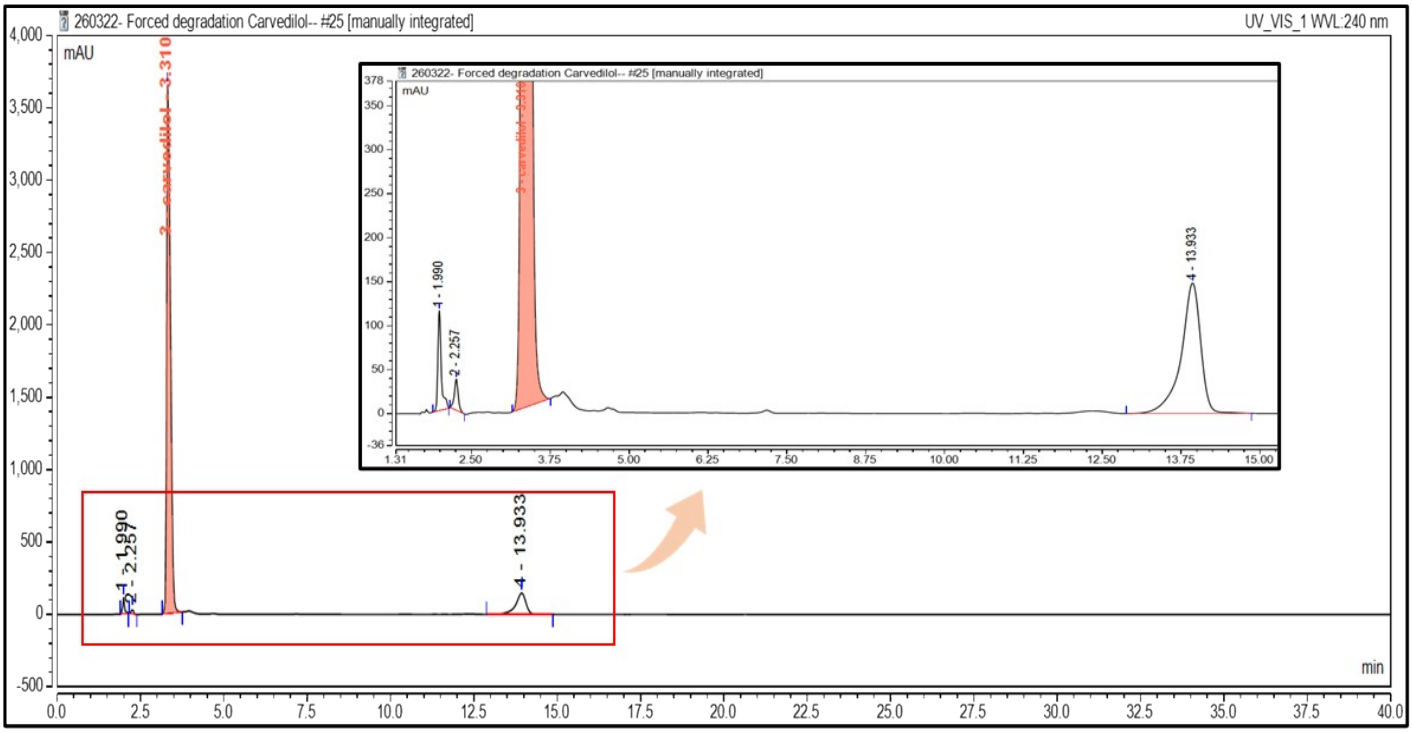


Figure 86S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 2.0 M NaOH for 6 h at 85 ℃.

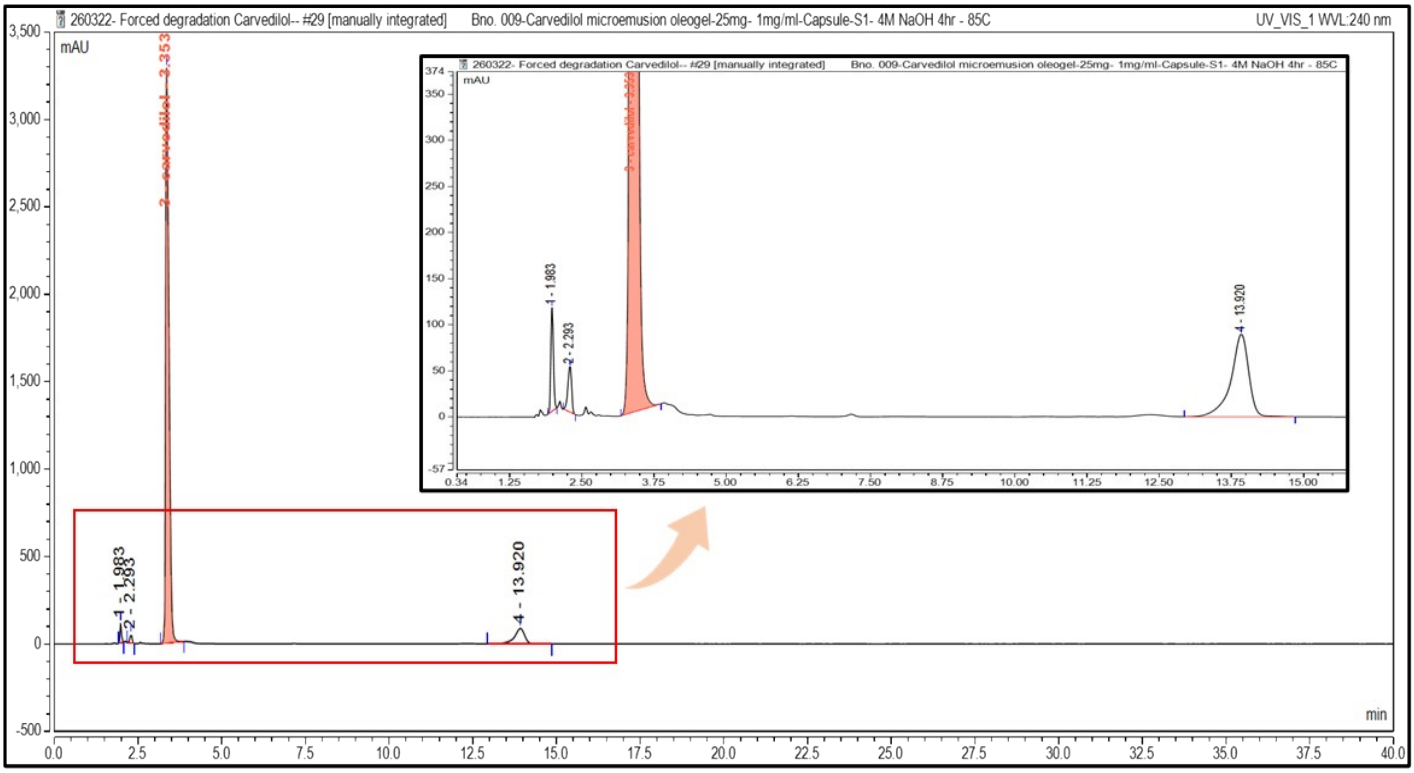


Figure 87S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 4.0 M NaOH for 4 h at 85 ℃.

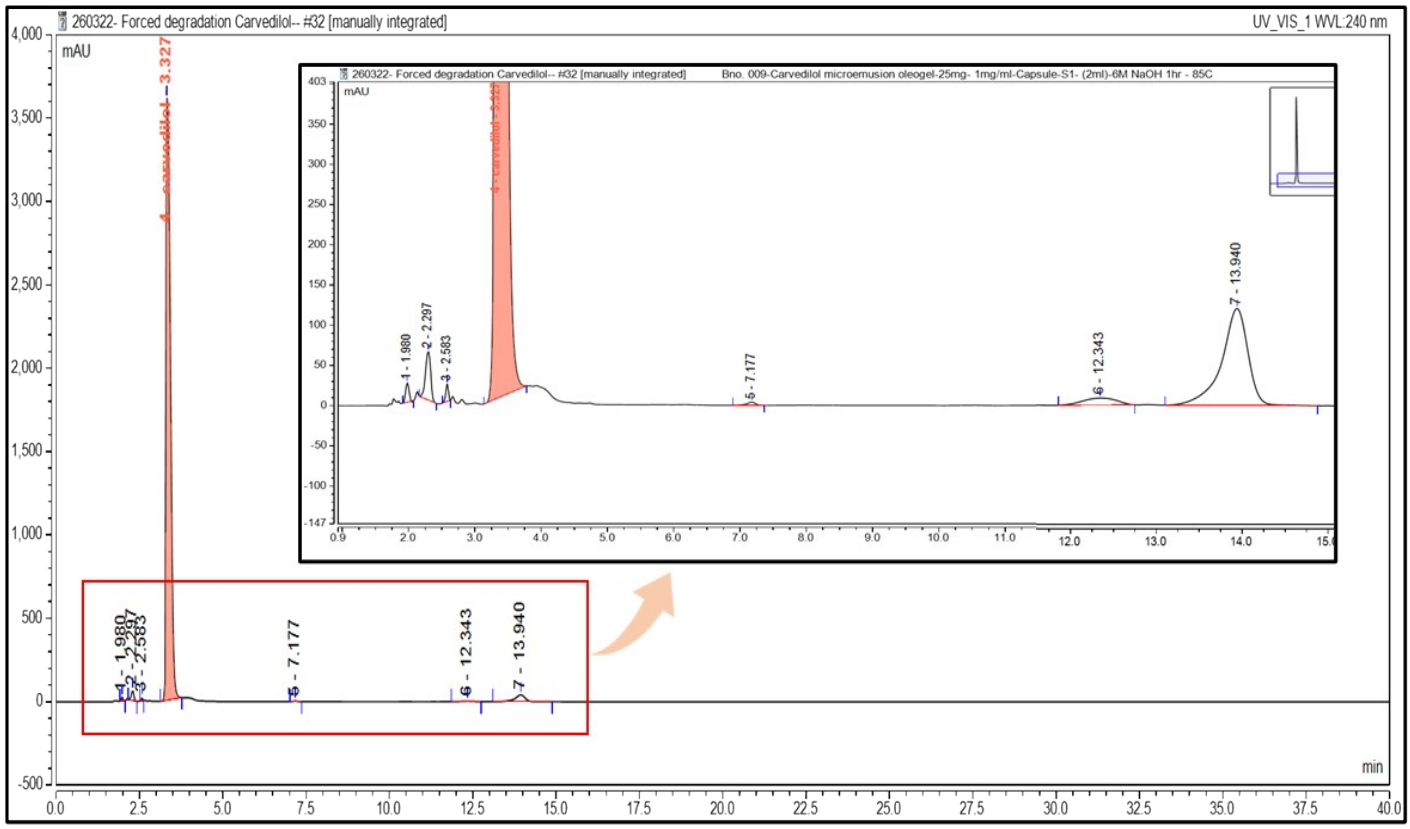


Figure 88S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 6.0 M NaOH (2ml) for 1 h at 85 ℃.

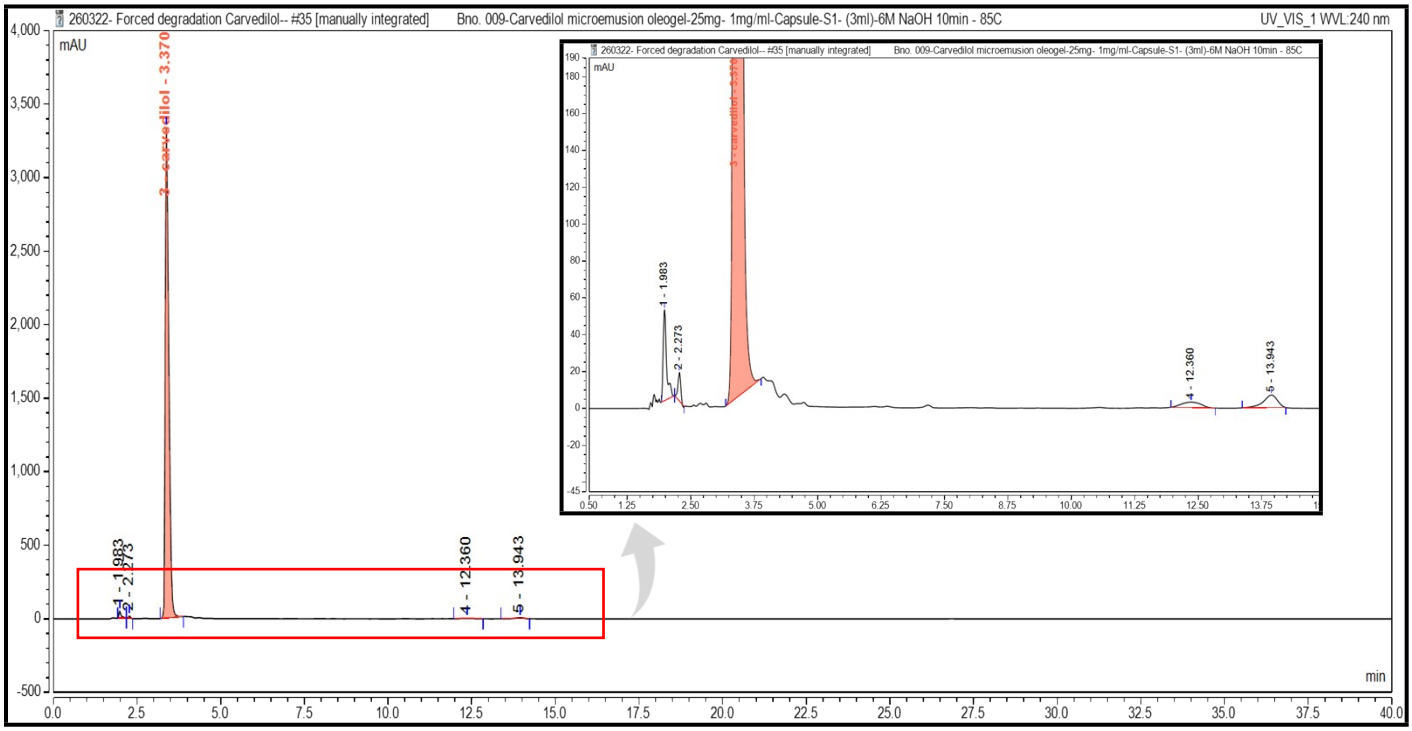


Figure 89S. HPLC chromatogram of base hydrolysis of CARV-MEOG, 6.0 M NaOH for 10 min at 85 ℃.

Excipient- Base Degradation:

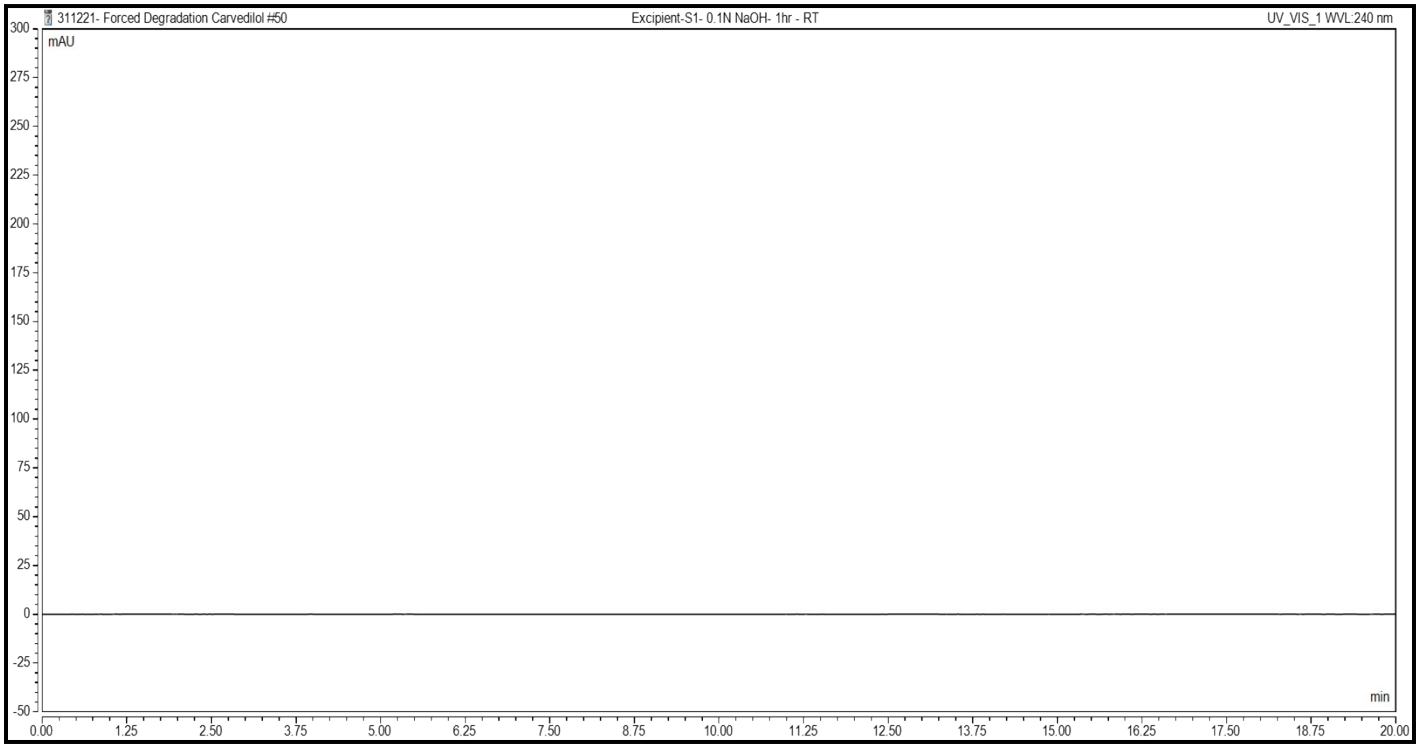


Figure 90S. HPLC chromatogram of base hydrolysis of excipients, 0.1 M NaOH for 1 h at RT.

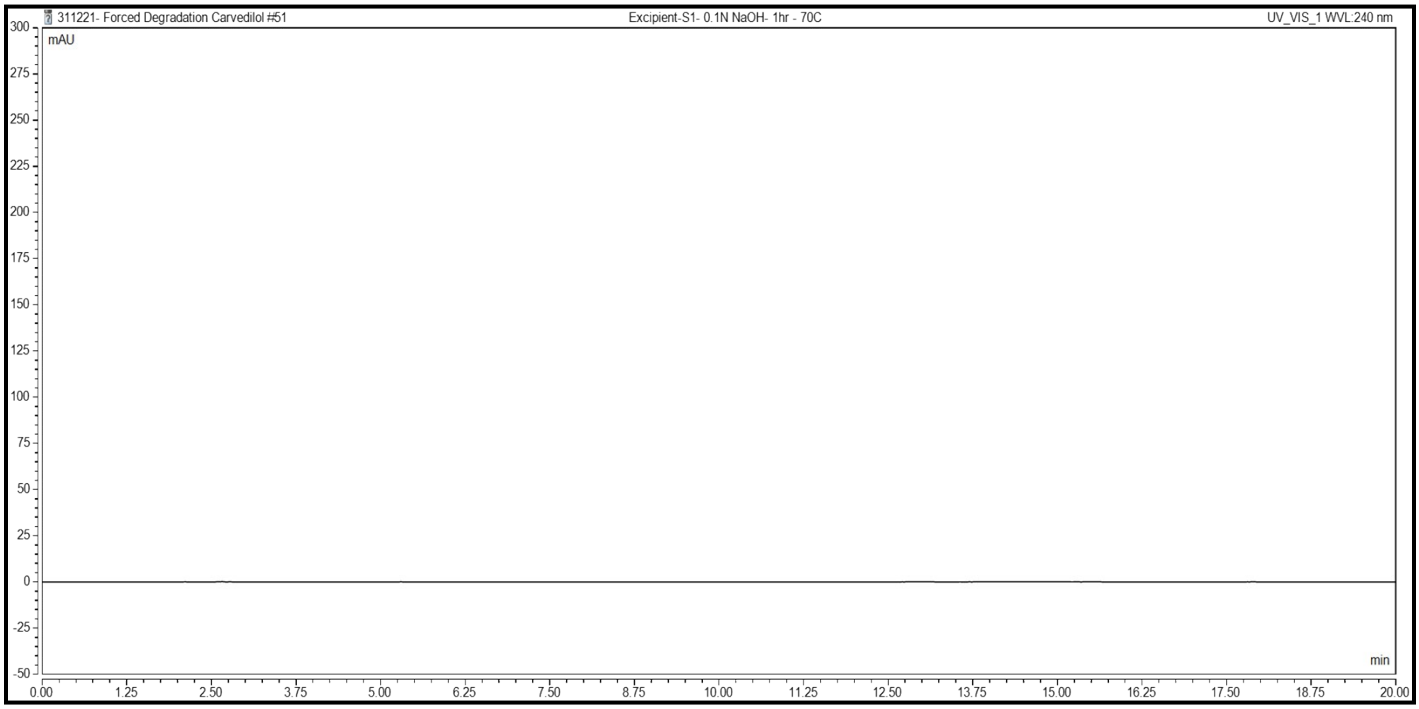


Figure 91S. HPLC chromatogram of base hydrolysis of excipients, 0.1 M NaOH for 1 h at 70 °C.

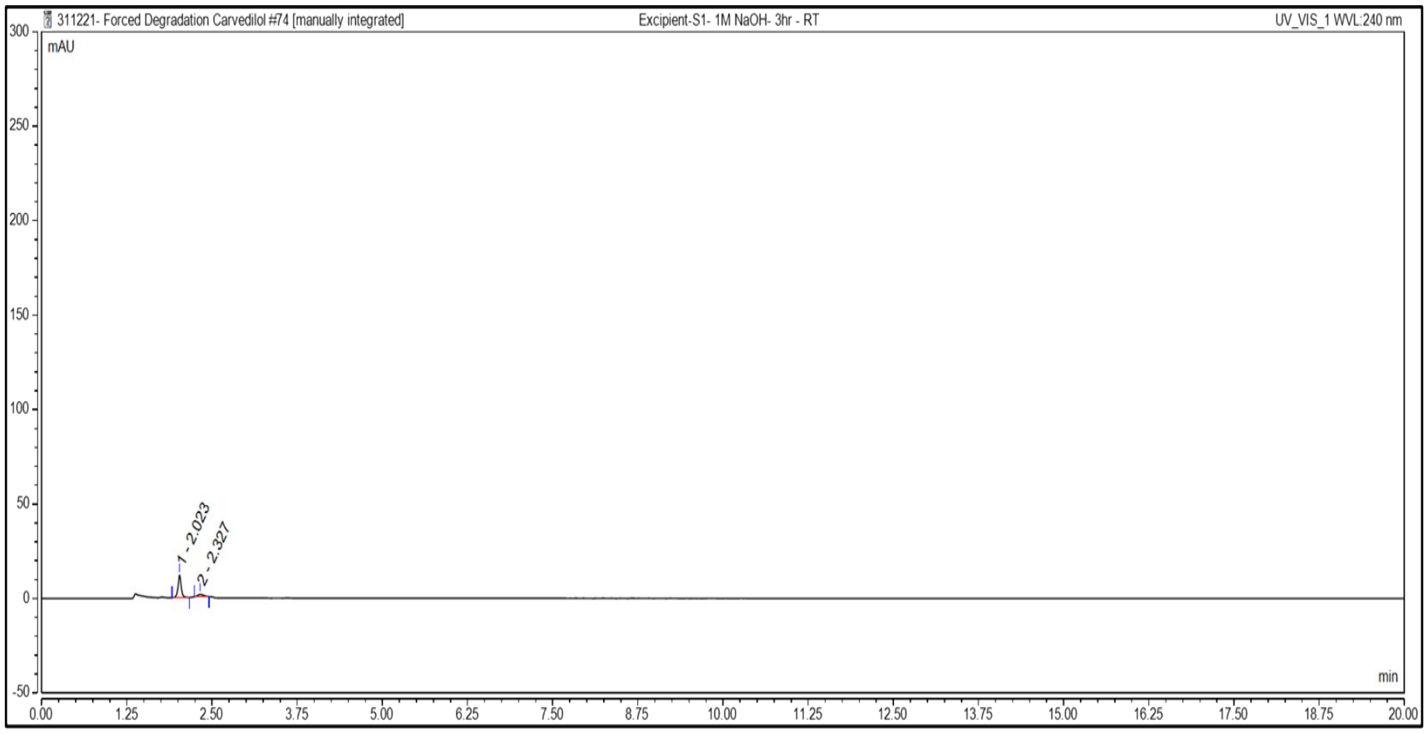


Figure 92S. HPLC chromatogram of base hydrolysis of excipient, 1.0 M NaOH for 3 h at RT.

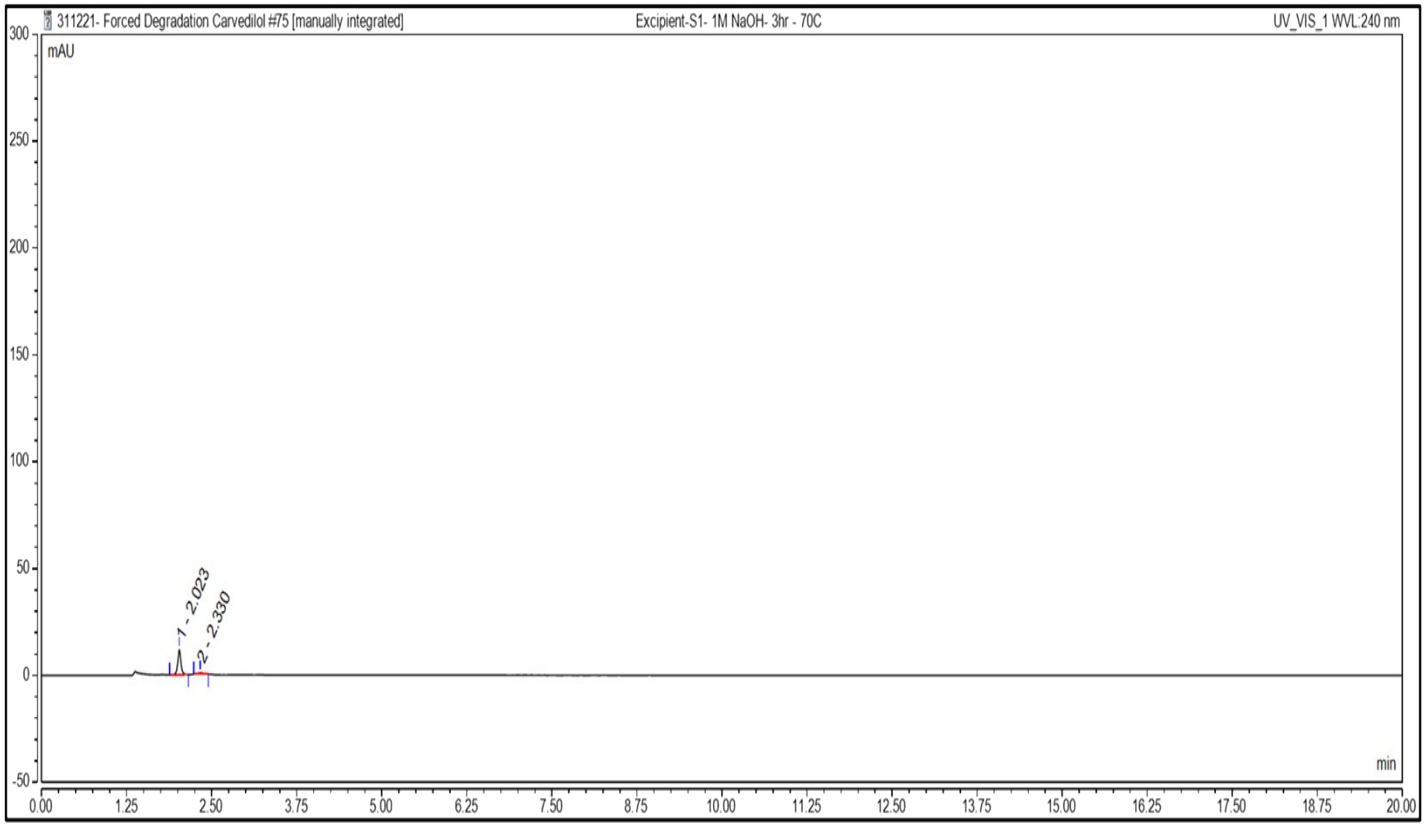


Figure 93S. HPLC chromatogram of base hydrolysis of excipient, 1.0 M NaOH for 3 h at 70 ℃.

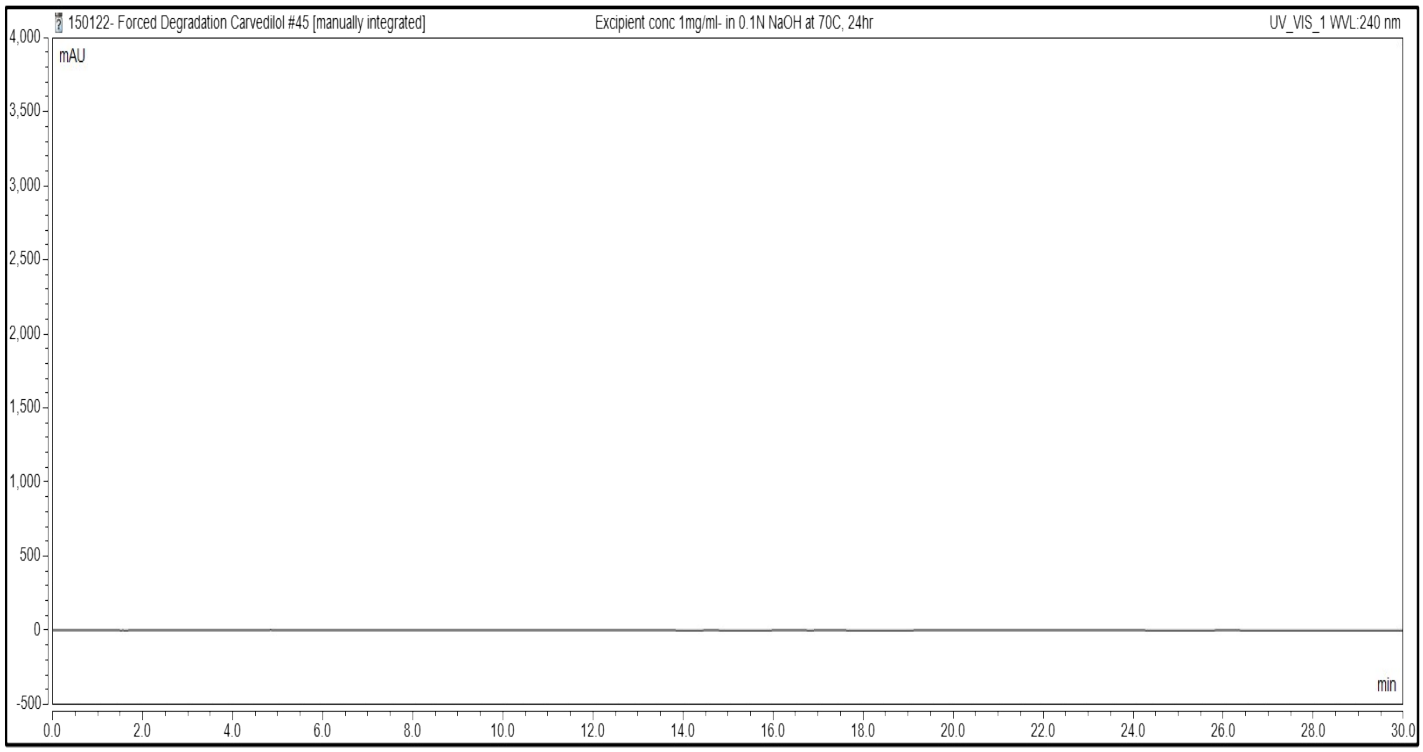


Figure 94S. HPLC chromatogram of base hydrolysis of excipient, 0.1 M NaOH for 24 h at 70 °C.

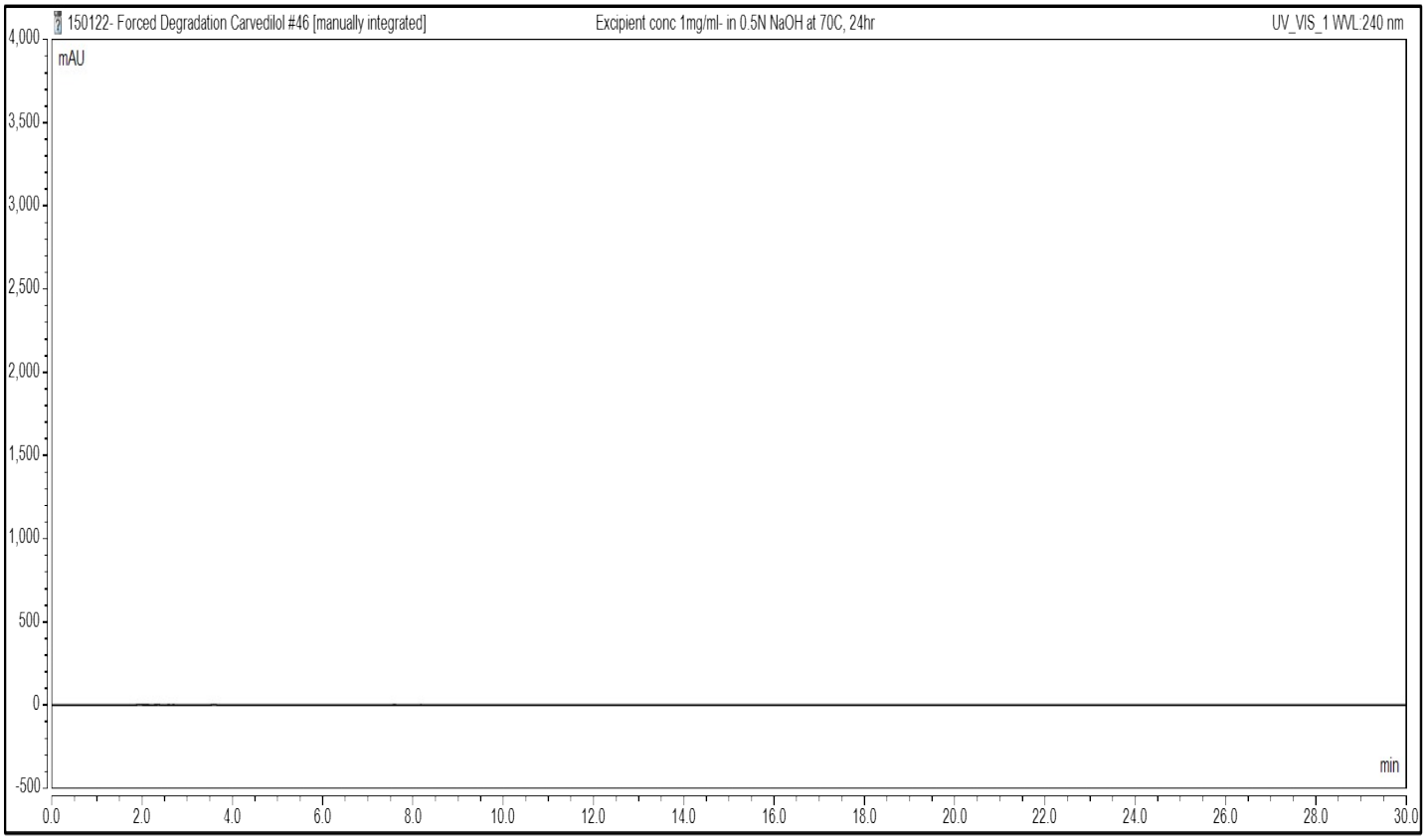


Figure 95S. HPLC chromatogram of base hydrolysis of excipient, 0.5 M NaOH for 24 h at 70 °C.

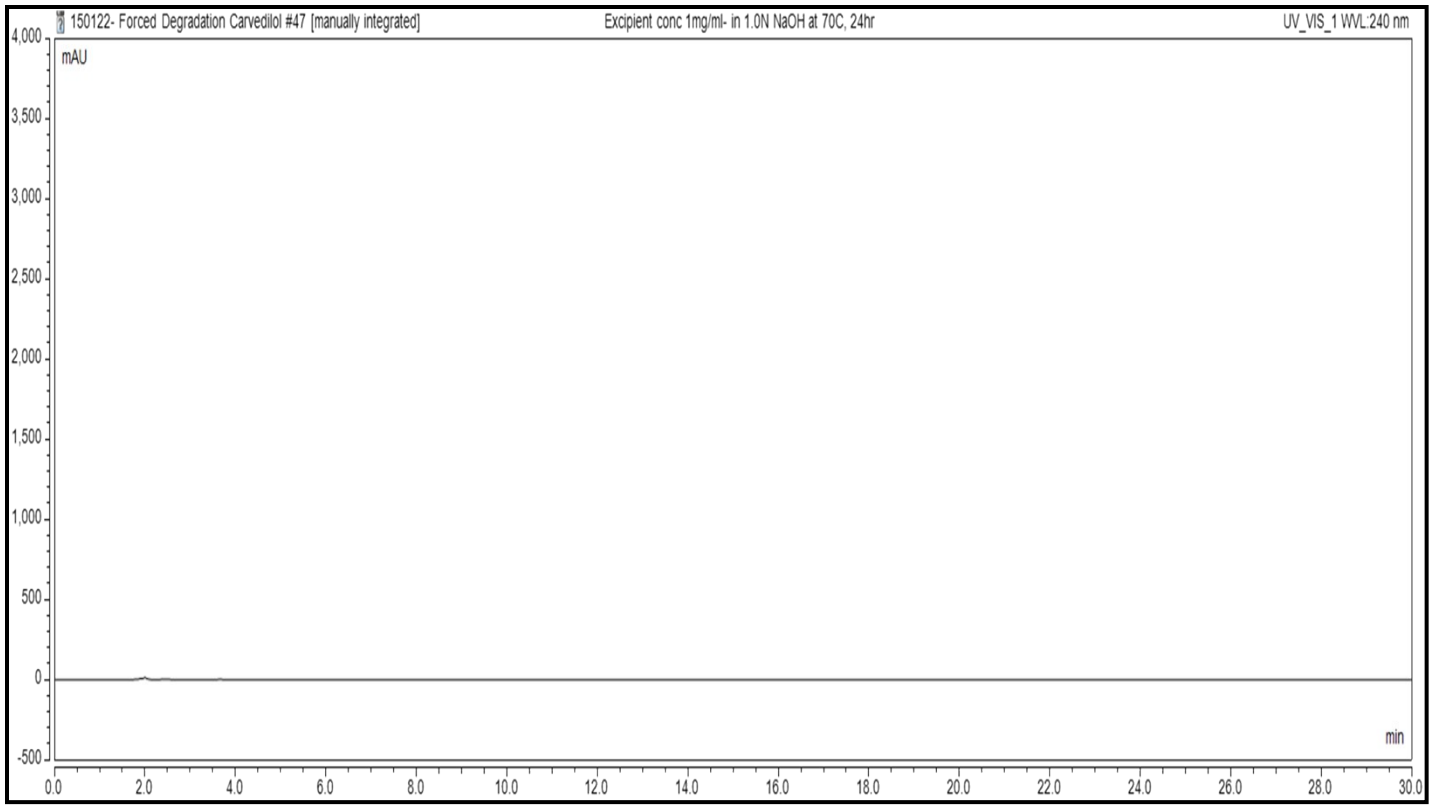


Figure 96S. HPLC chromatogram of base hydrolysis of excipient, 1.0 M NaOH for 24 h at 70 ℃.

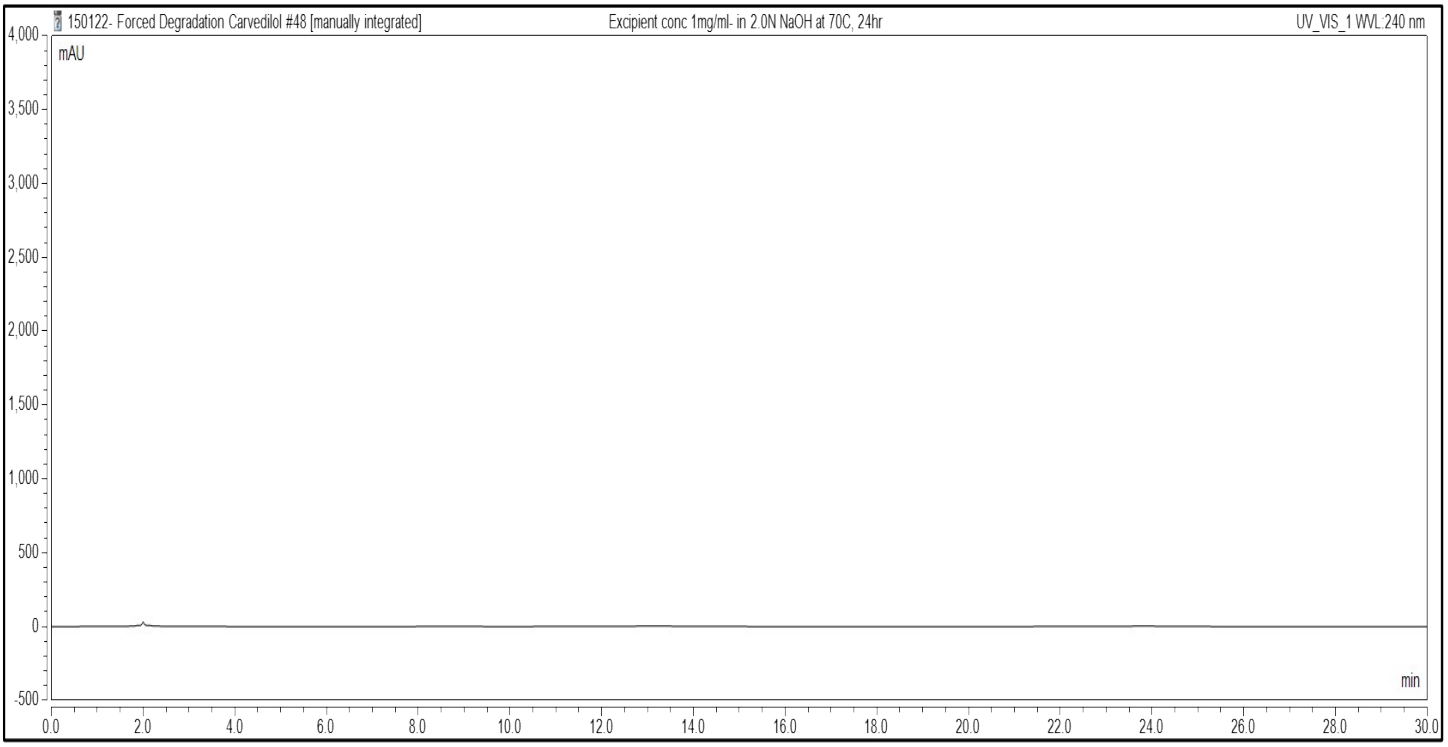


Figure 97S. HPLC chromatogram of base hydrolysis of excipient, 2.0 M NaOH for 24 h at 70 ℃.

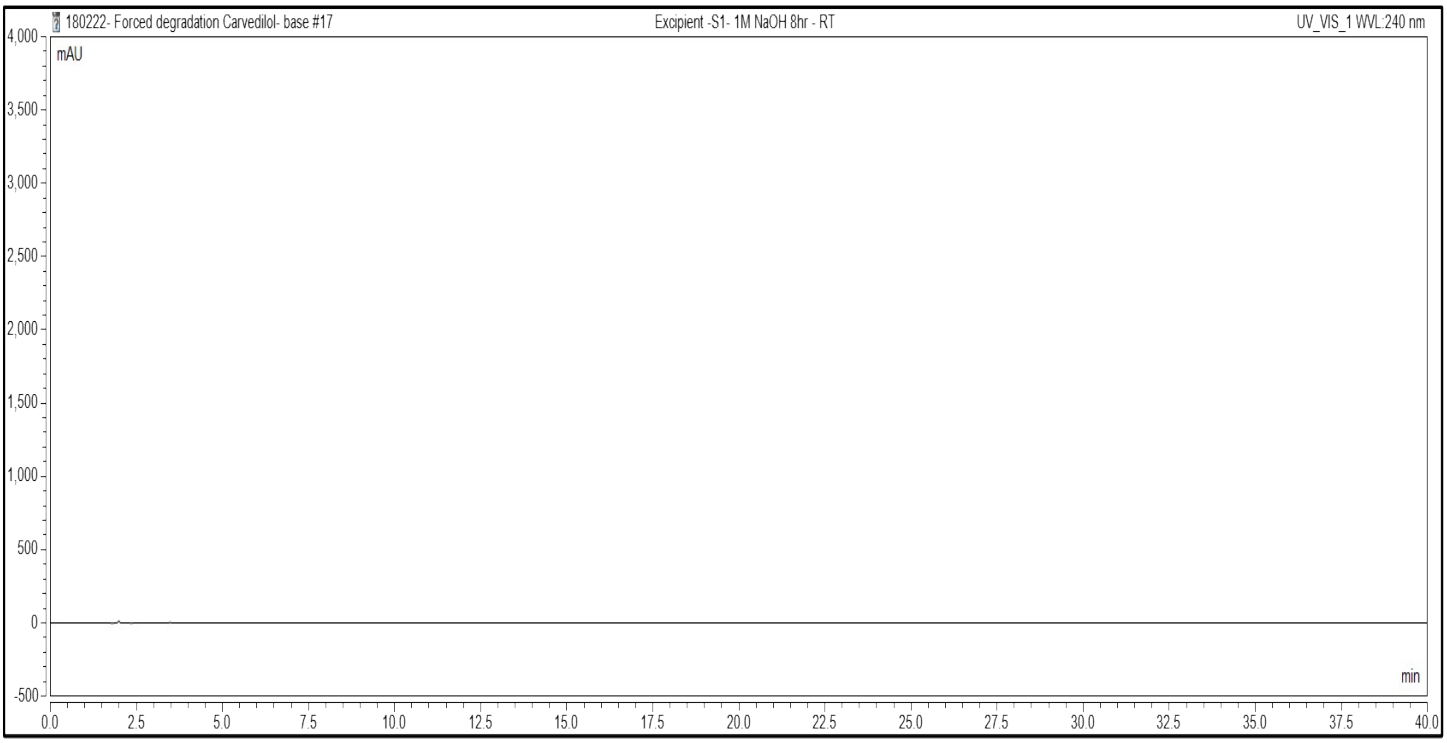


Figure 98S. HPLC chromatogram of base hydrolysis of excipient, 1.0 M NaOH for 8 h at RT.

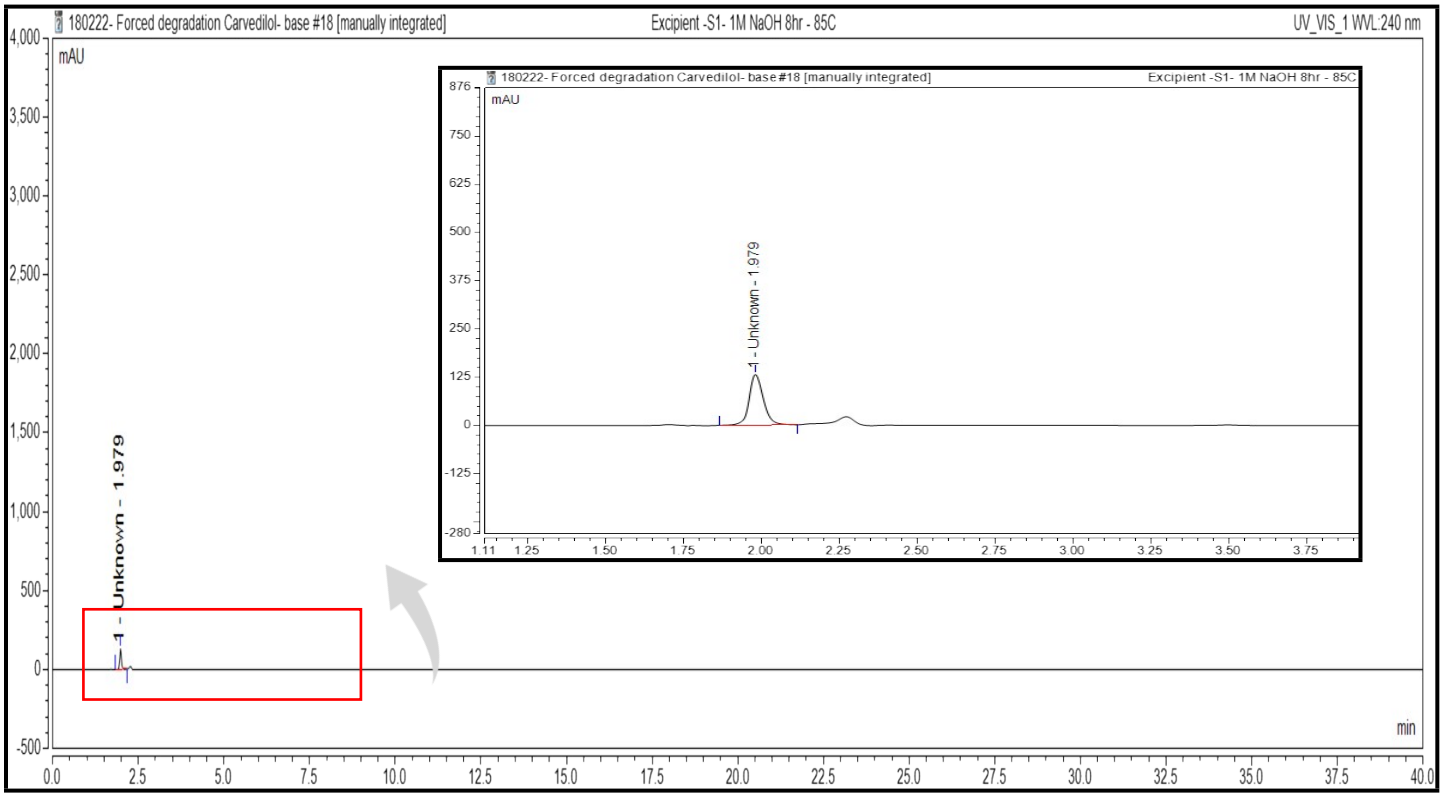


Figure 99S. HPLC chromatogram of base hydrolysis of excipient, 1.0 M NaOH for 8 h at 85 ℃.

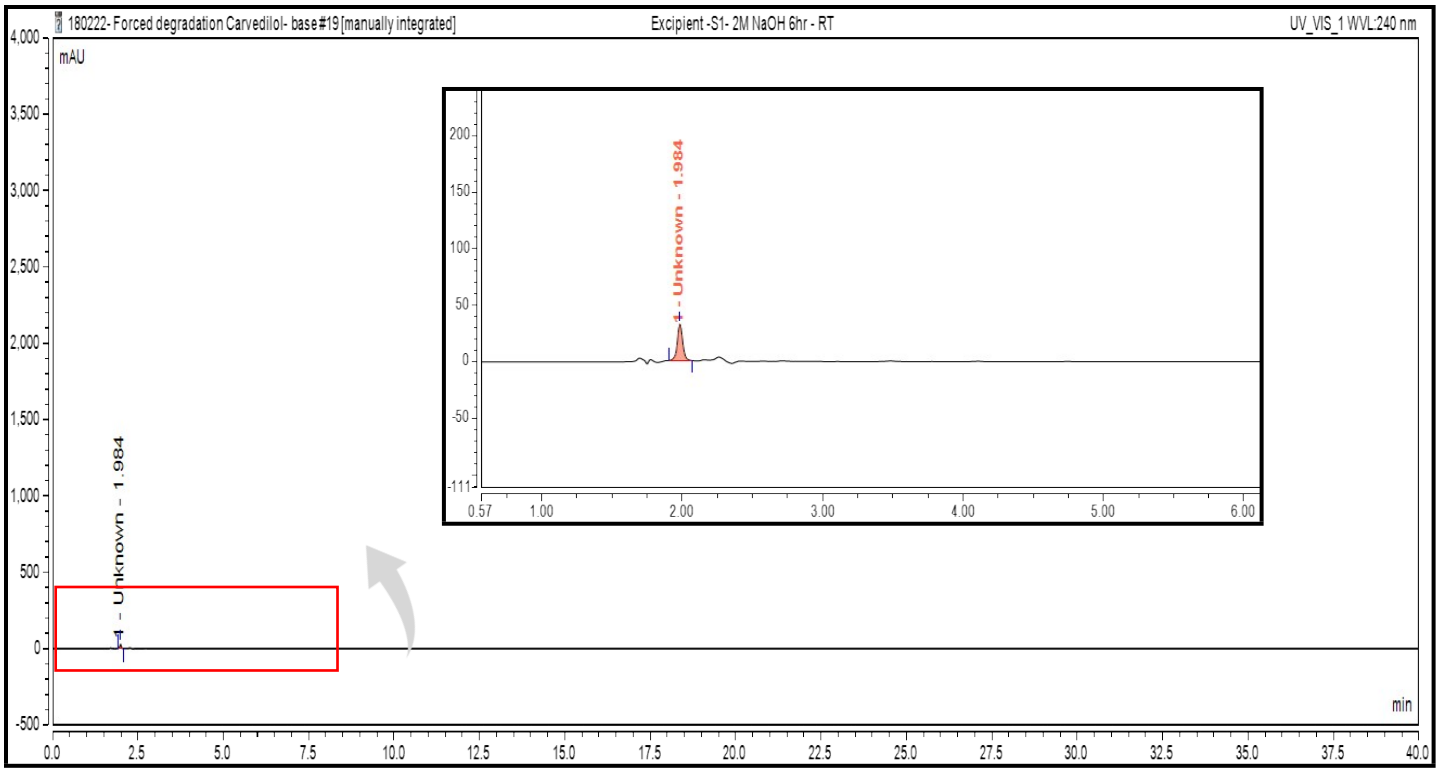


Figure 100S. HPLC chromatogram of base hydrolysis of excipient, 2.0 M NaOH for 6 h at RT.

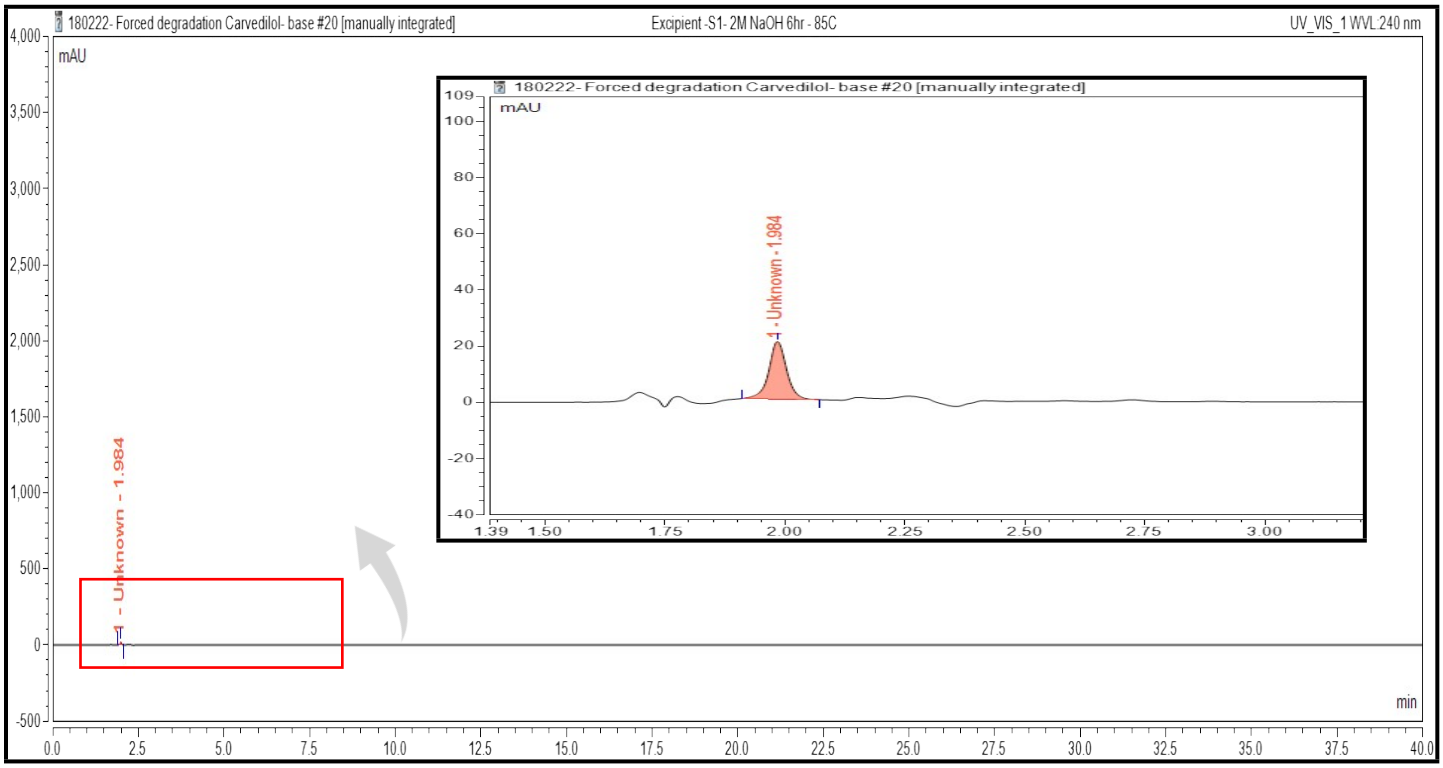


Figure 101S. HPLC chromatogram of base hydrolysis of excipient, 2.0 M NaOH for 6 h at 85 ℃.

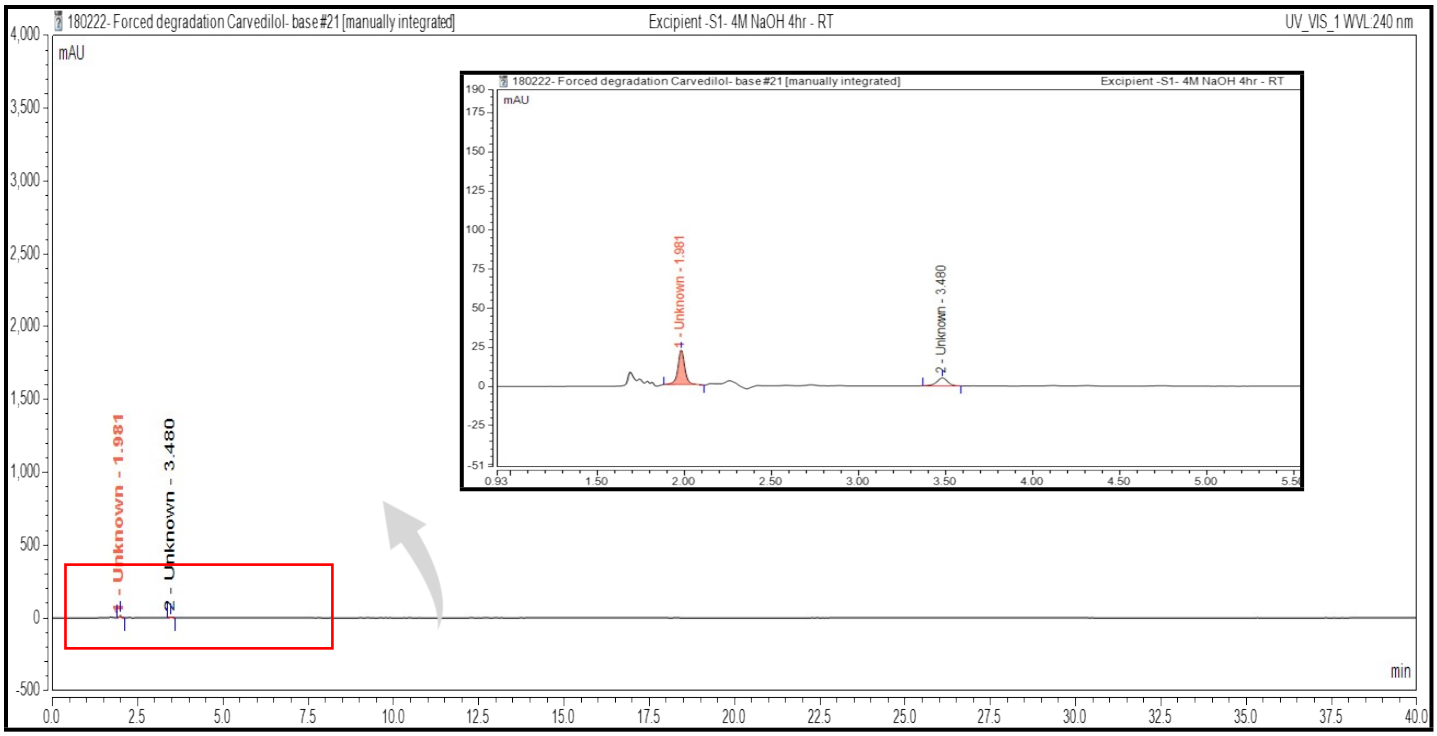


Figure 102S. HPLC chromatogram of base hydrolysis of excipient, 4.0 M NaOH for 4 h at RT.

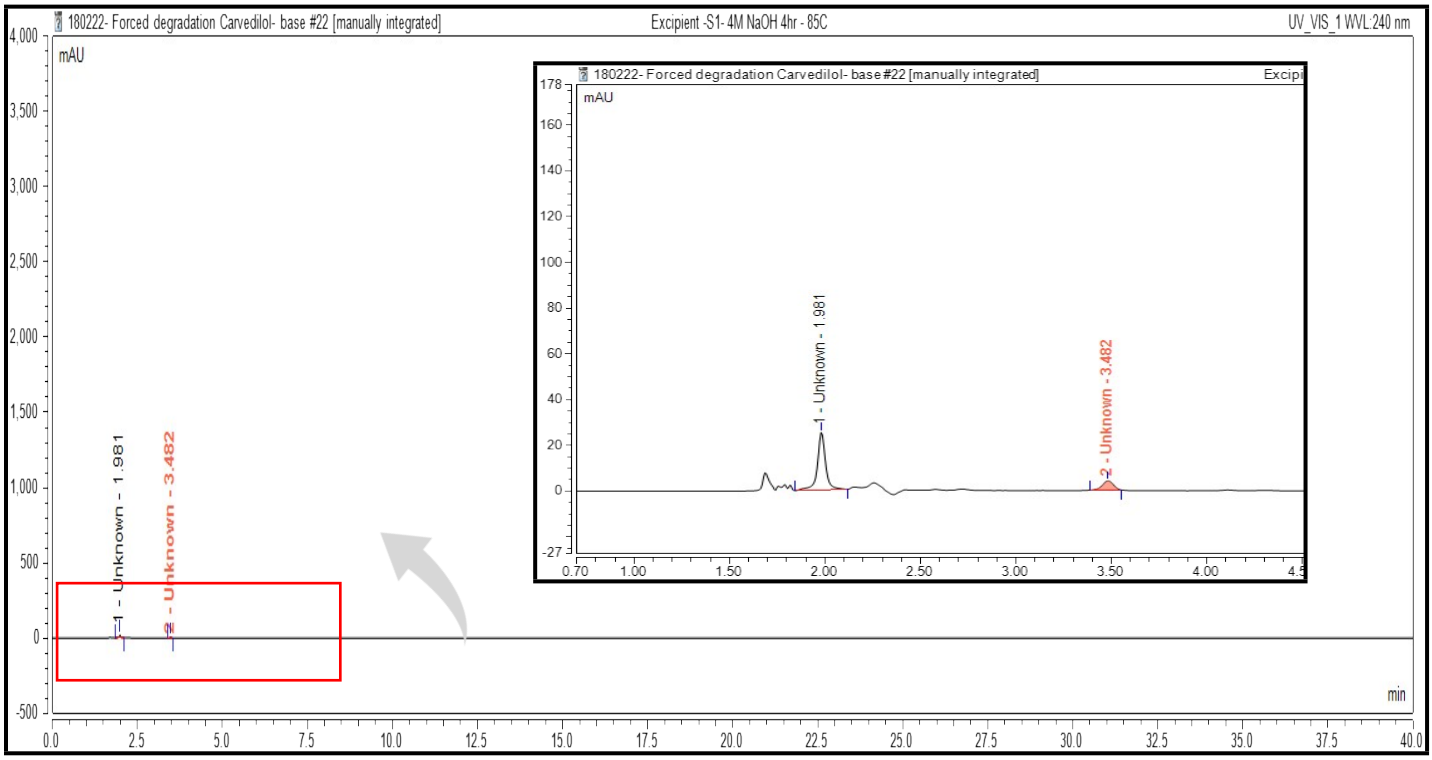


Figure 103S. HPLC chromatogram of base hydrolysis of excipient, 4.0 M NaOH for 4 h at 85 °C.

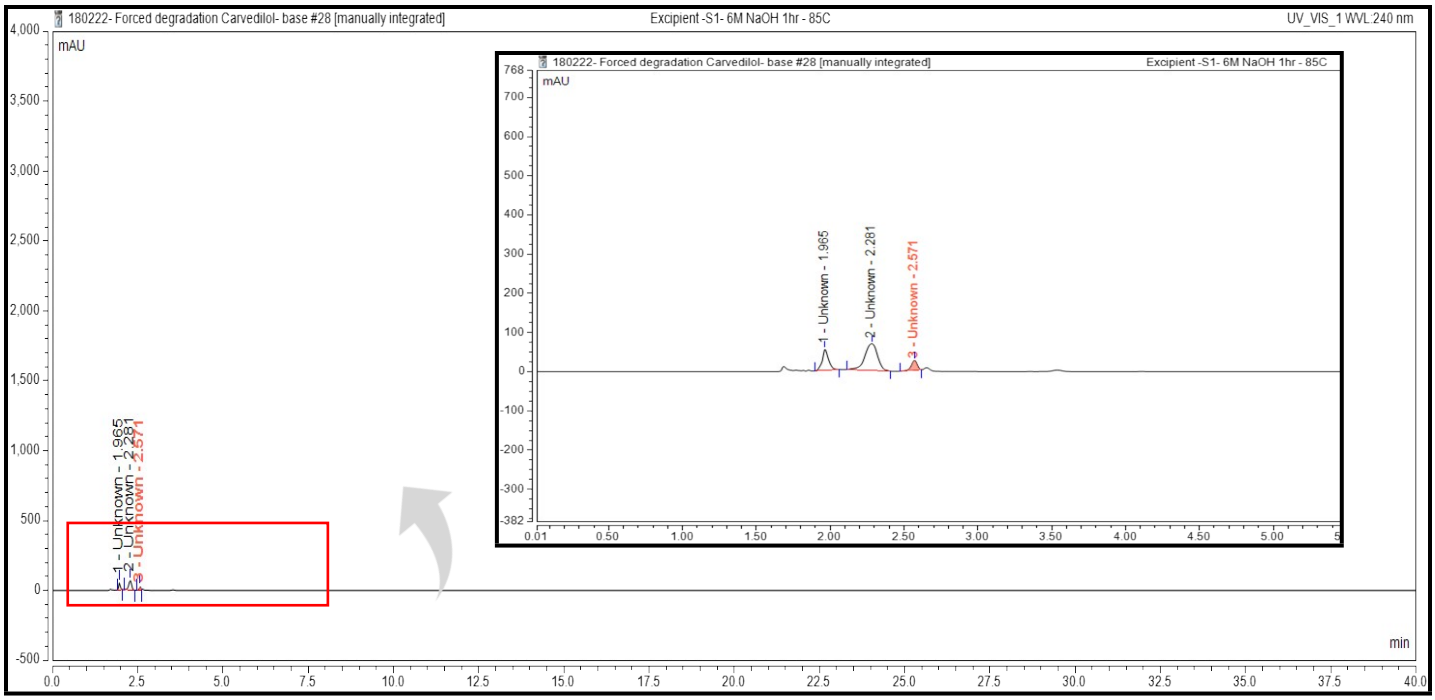


Figure 104S. HPLC chromatogram of base hydrolysis of excipient, 6.0 M NaOH for 1 h at 85 ℃.

Neutral aqueous hydrolysis CARV:

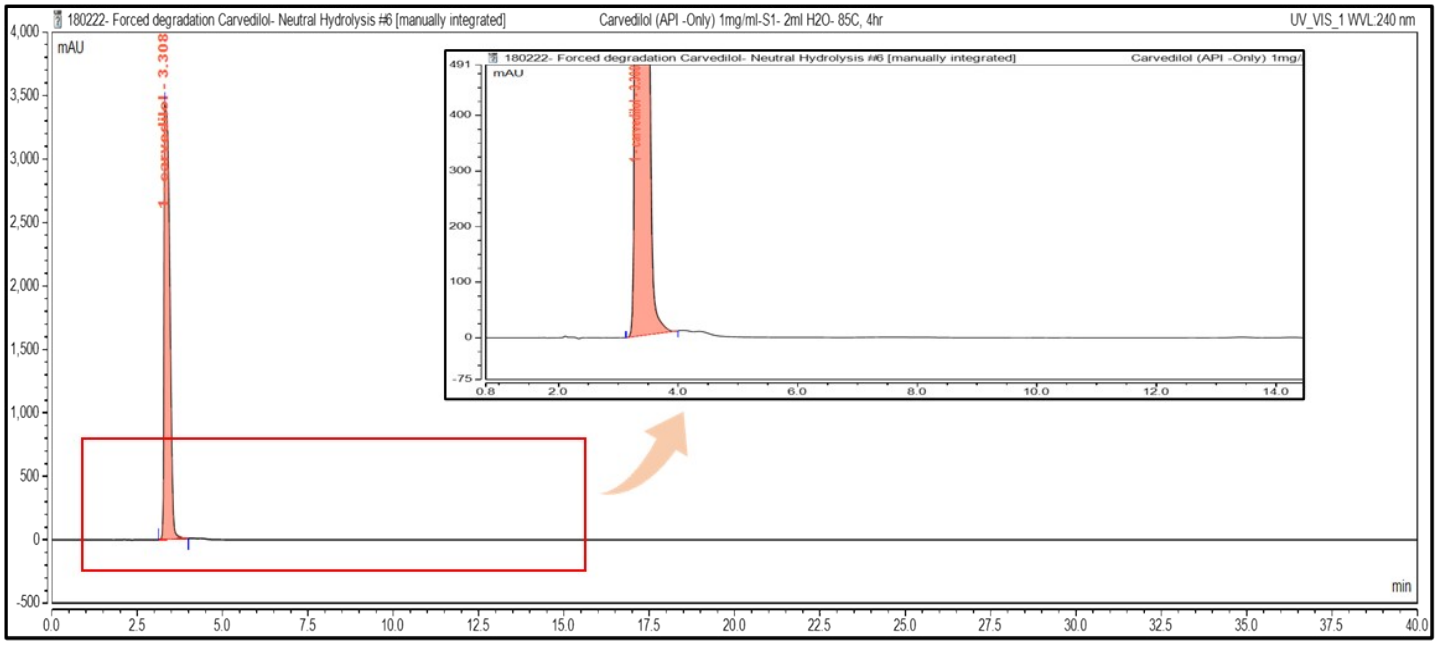


Figure 105S. HPLC chromatogram of neutral hydrolysis of CARV for 4 h at 85 ℃.

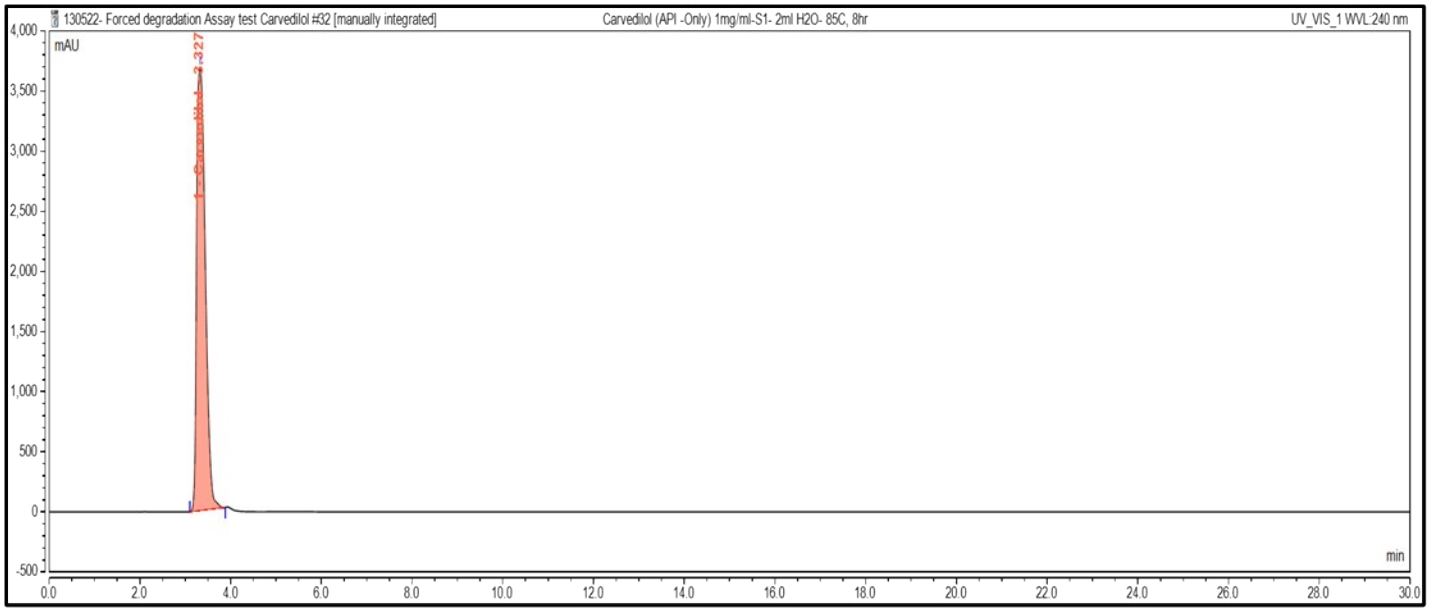


Figure 106S. HPLC chromatogram of neutral hydrolysis of CARV for 8 h at 85 ℃.

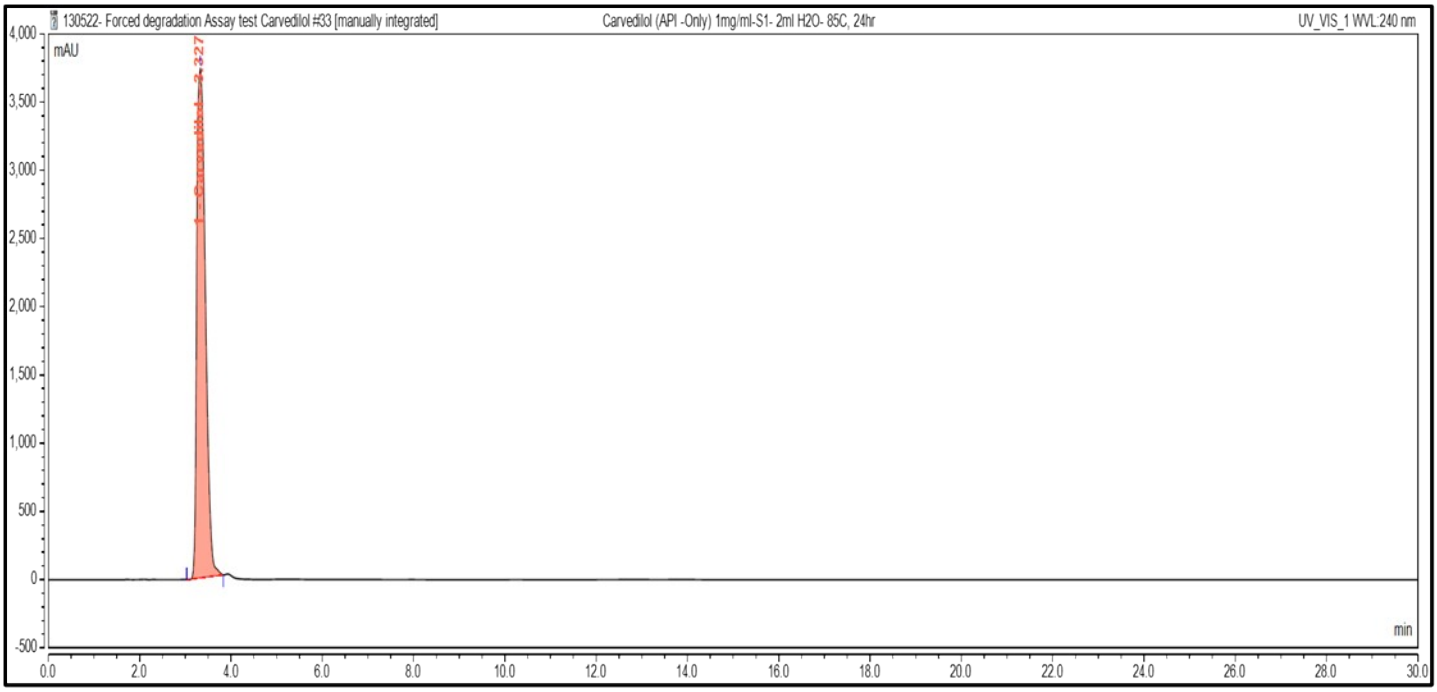


Figure 107S. HPLC chromatogram of neutral hydrolysis of CARV for 24 h at 85 °C.

Neutral aqueous hydrolysis CARV-MEOG:

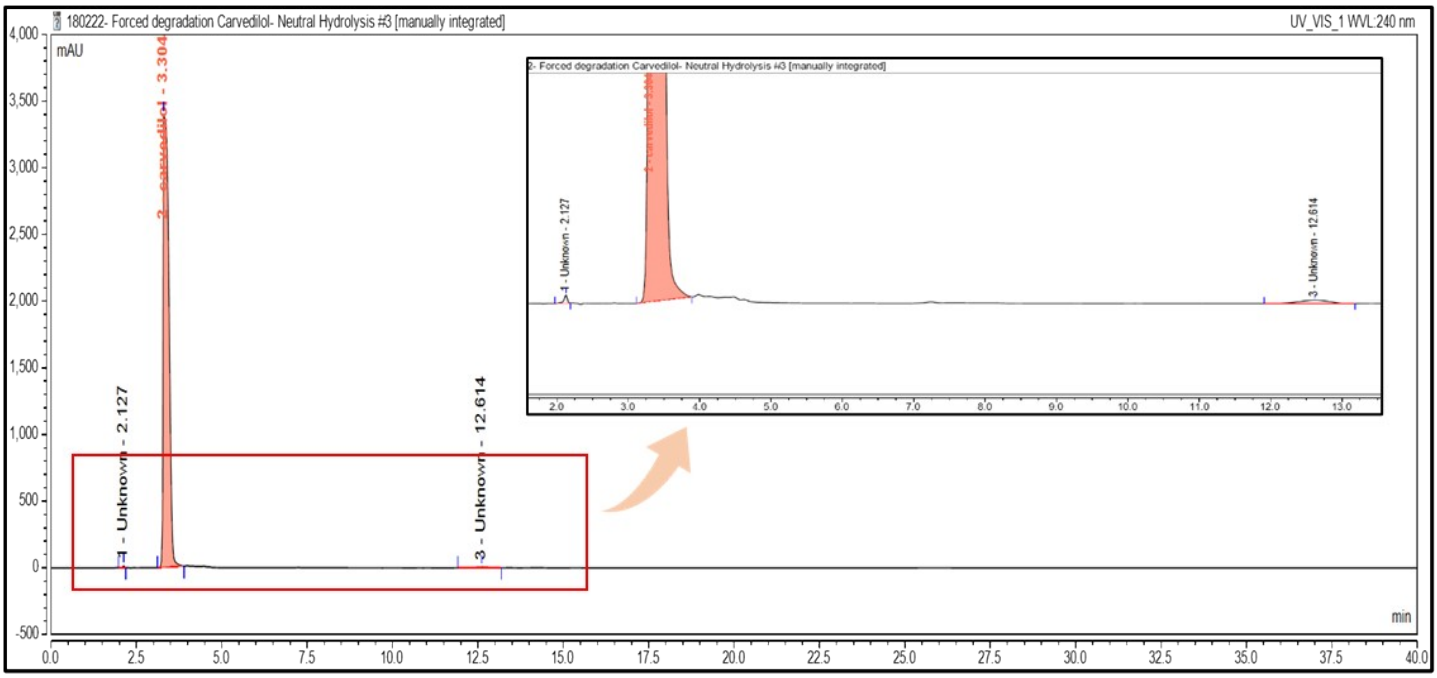


Figure 108S. HPLC chromatogram of neutral hydrolysis of CARV-MEOG for 4 h at 85 °C.

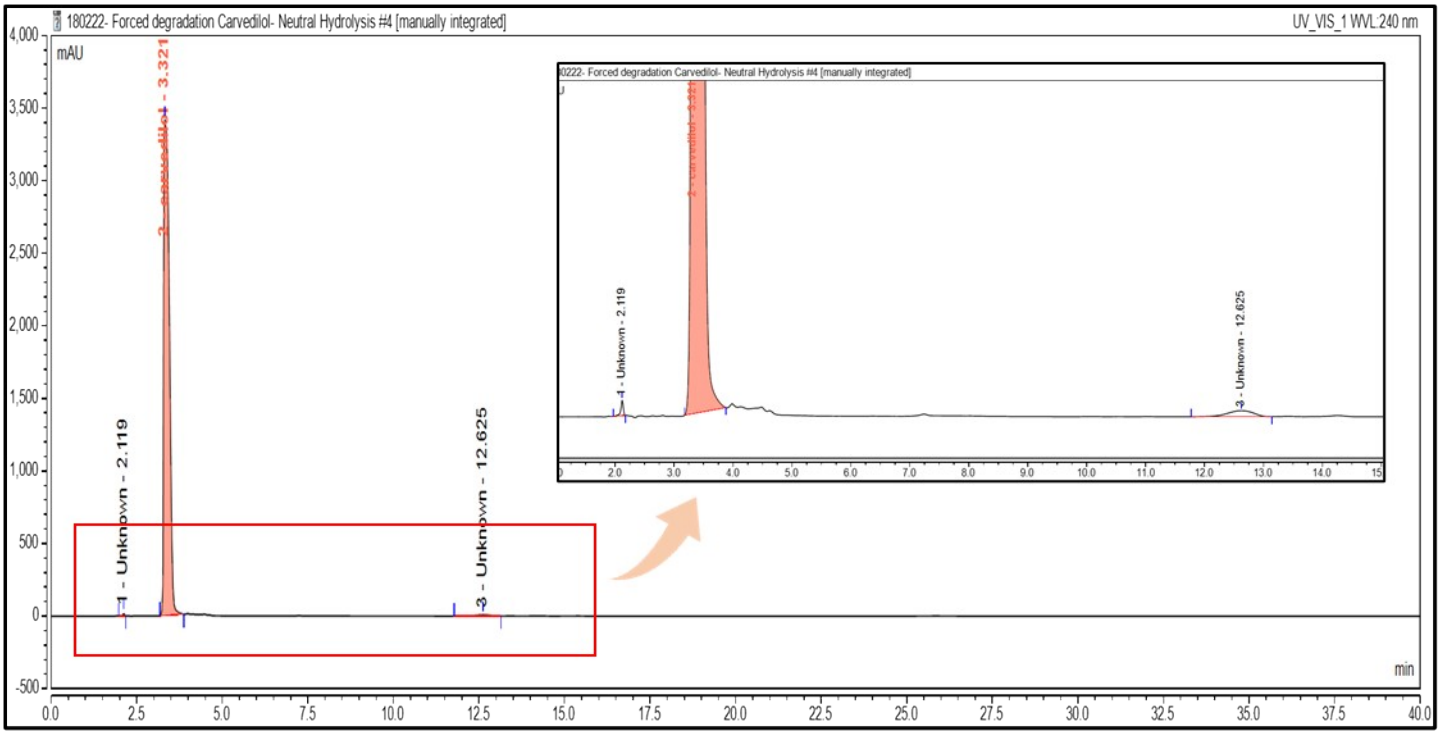


Figure 109S. HPLC chromatogram of neutral hydrolysis of CARV-MEOG for 8 h at 85 °C.

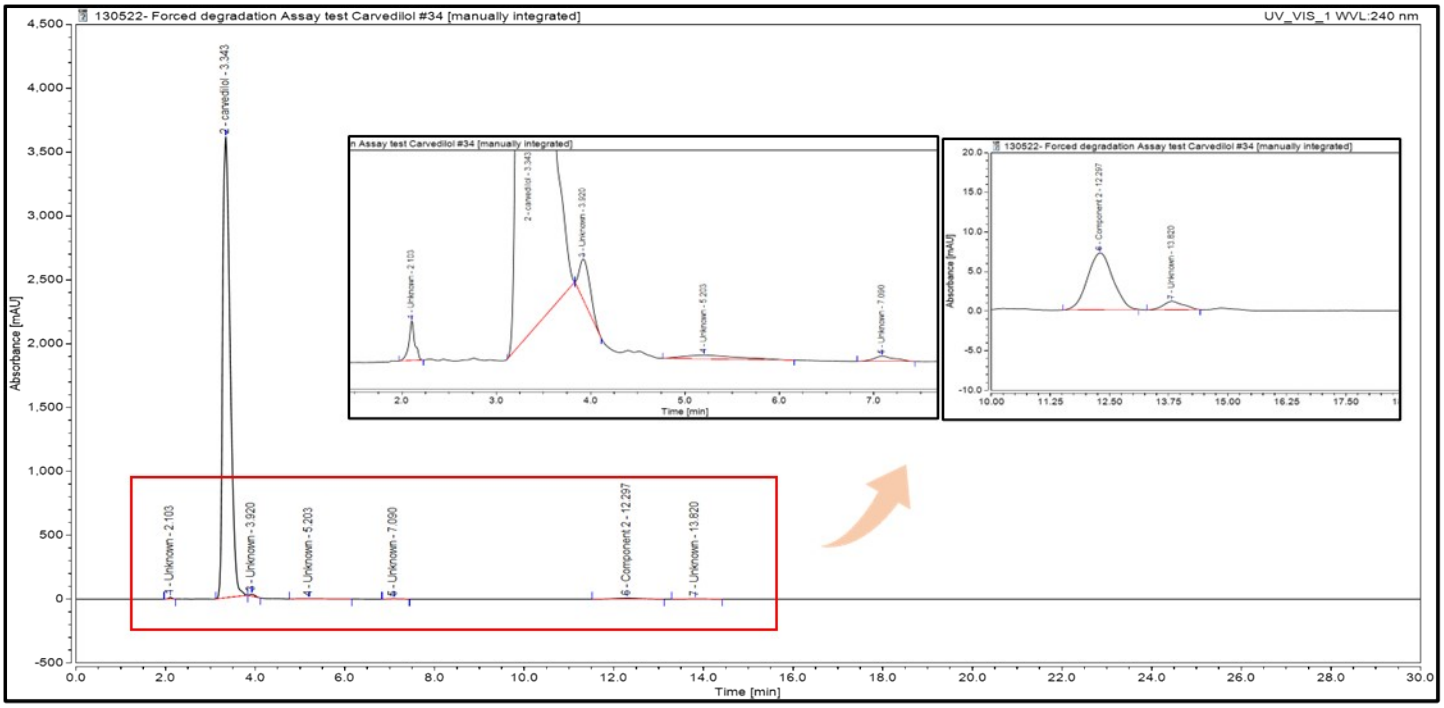


Figure 110S. HPLC chromatogram of neutral hydrolysis of CARV-MEOG for 24 h at 85 °C.

Neutral aqueous hydrolysis CARV-MEOG:

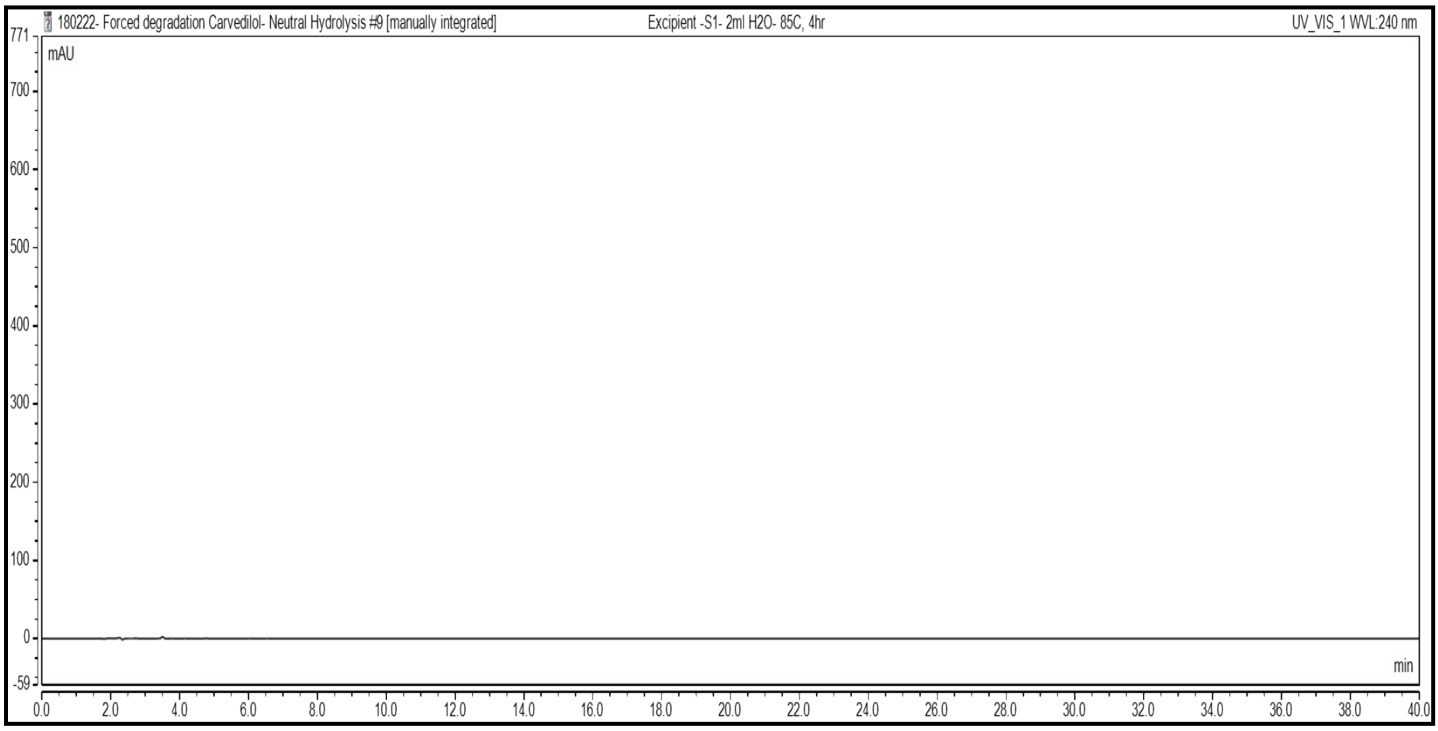


Figure 111S. HPLC chromatogram of neutral hydrolysis of excipient for 4 h at 85 ℃.

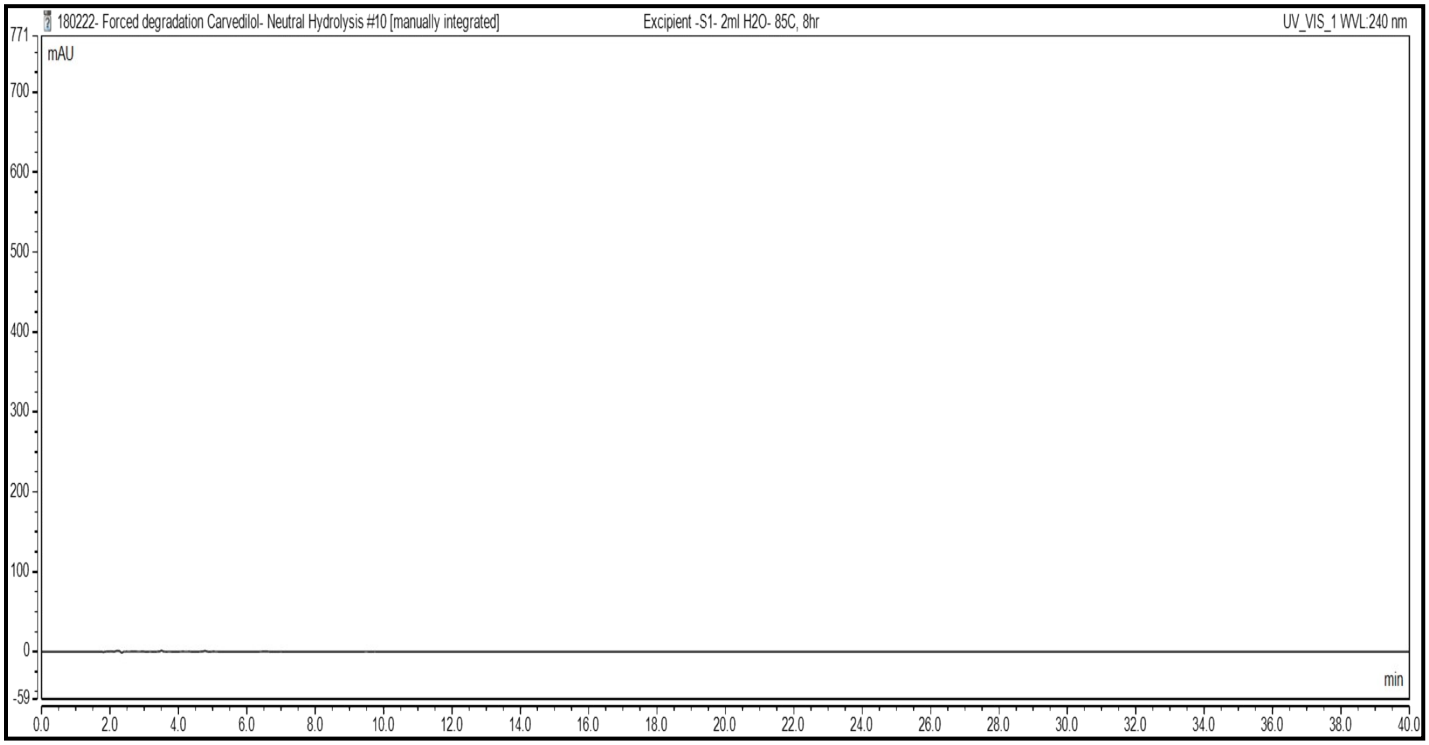


Figure 112S. HPLC chromatogram of neutral hydrolysis of excipient for 8 h at 85 ℃.

Oxidation Degradation-CARV

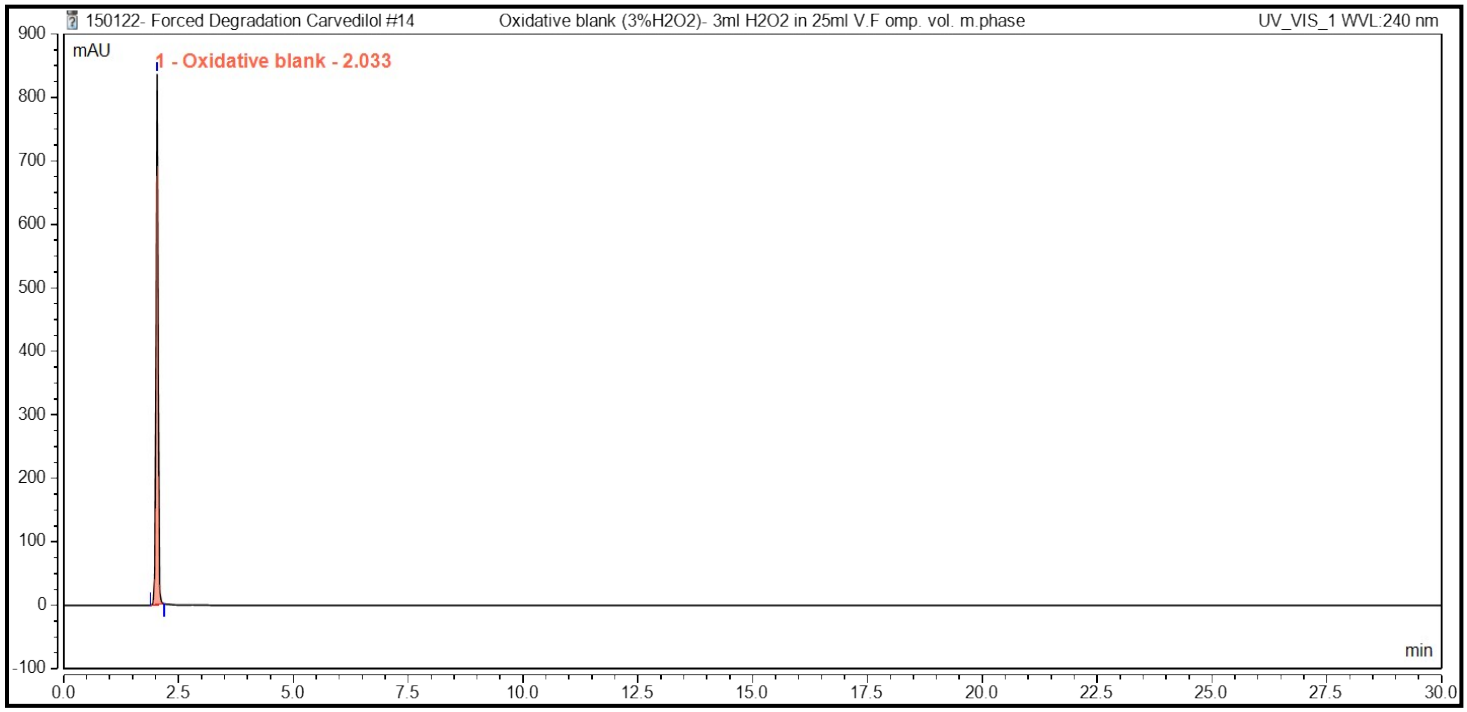


Figure 113S. HPLC chromatogram of oxidation blank solution (3% H_2O_2 in mobile phase).

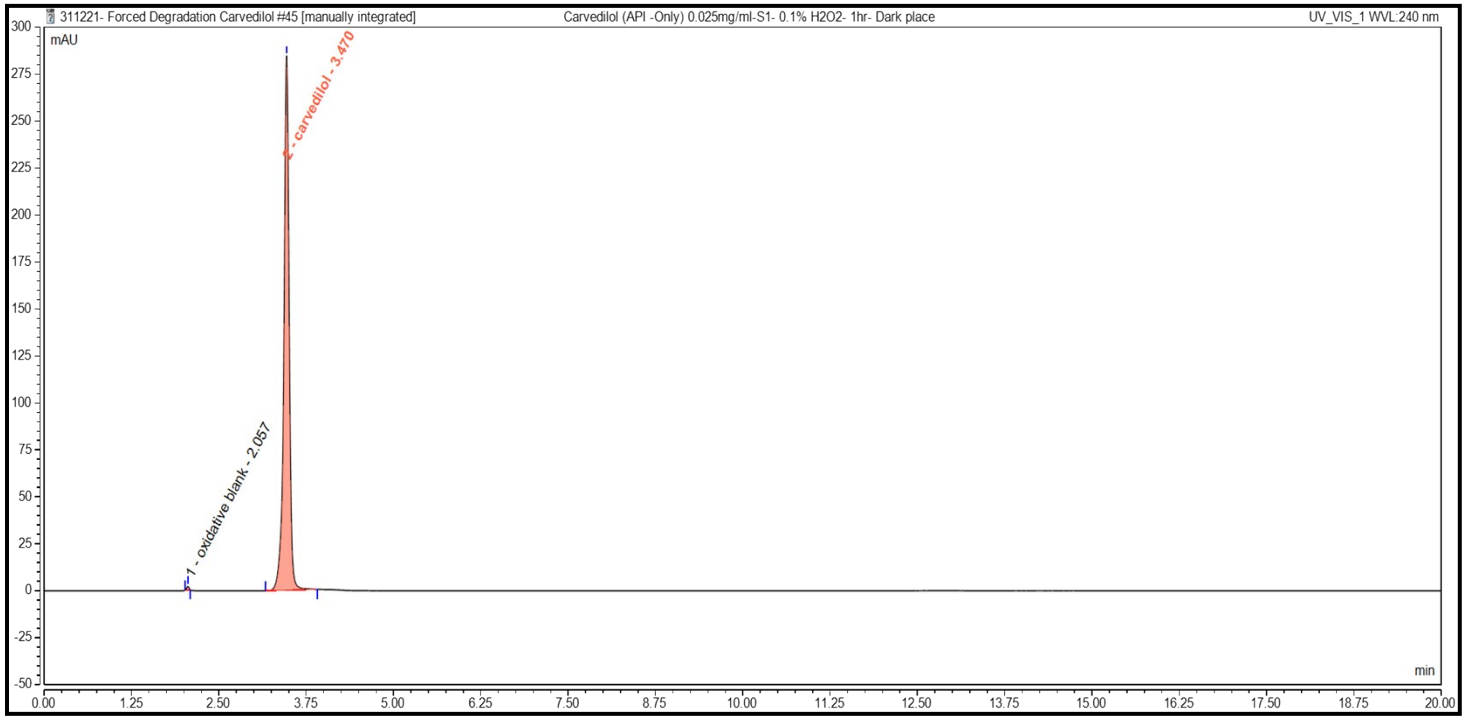


Figure 114S. HPLC chromatogram of oxidation degradation of CARV at 0.1% H_2O_2 for 1 h.

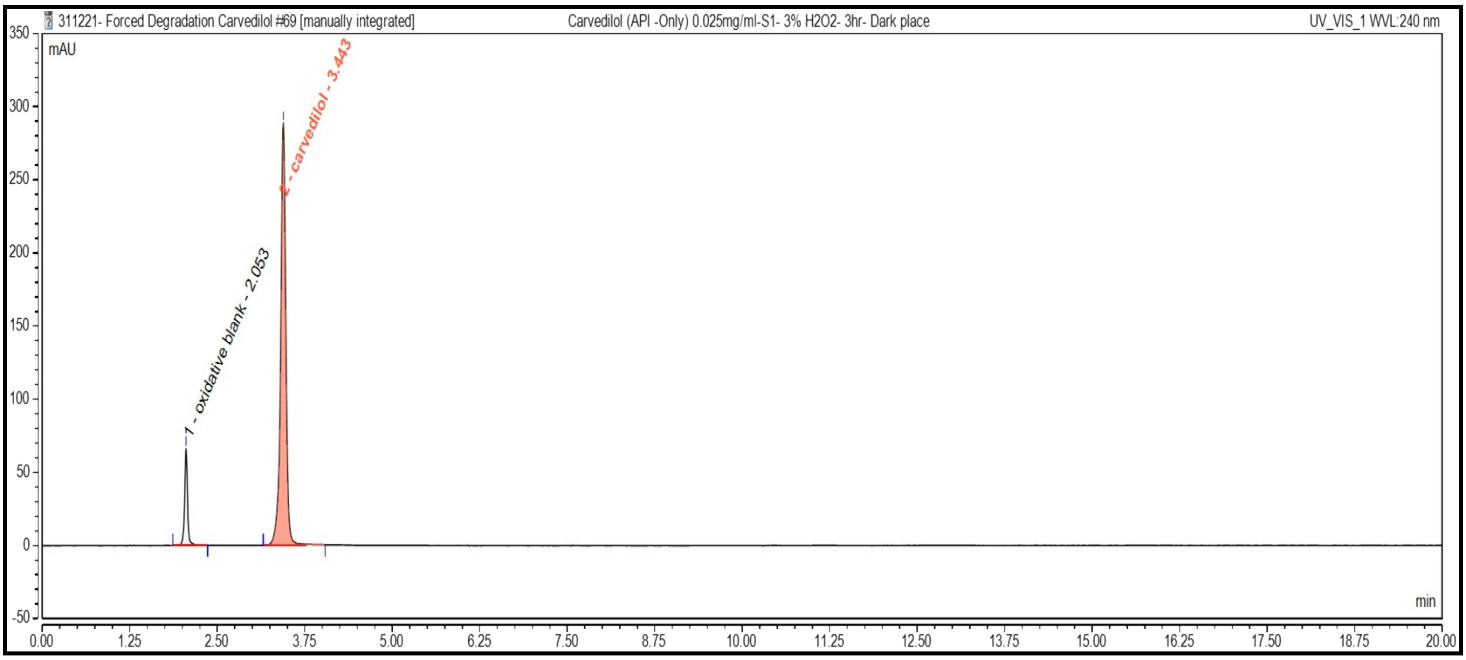


Figure 115S. HPLC chromatogram of oxidation degradation of CARV at 3.0% H_2O_2 for 3 h.

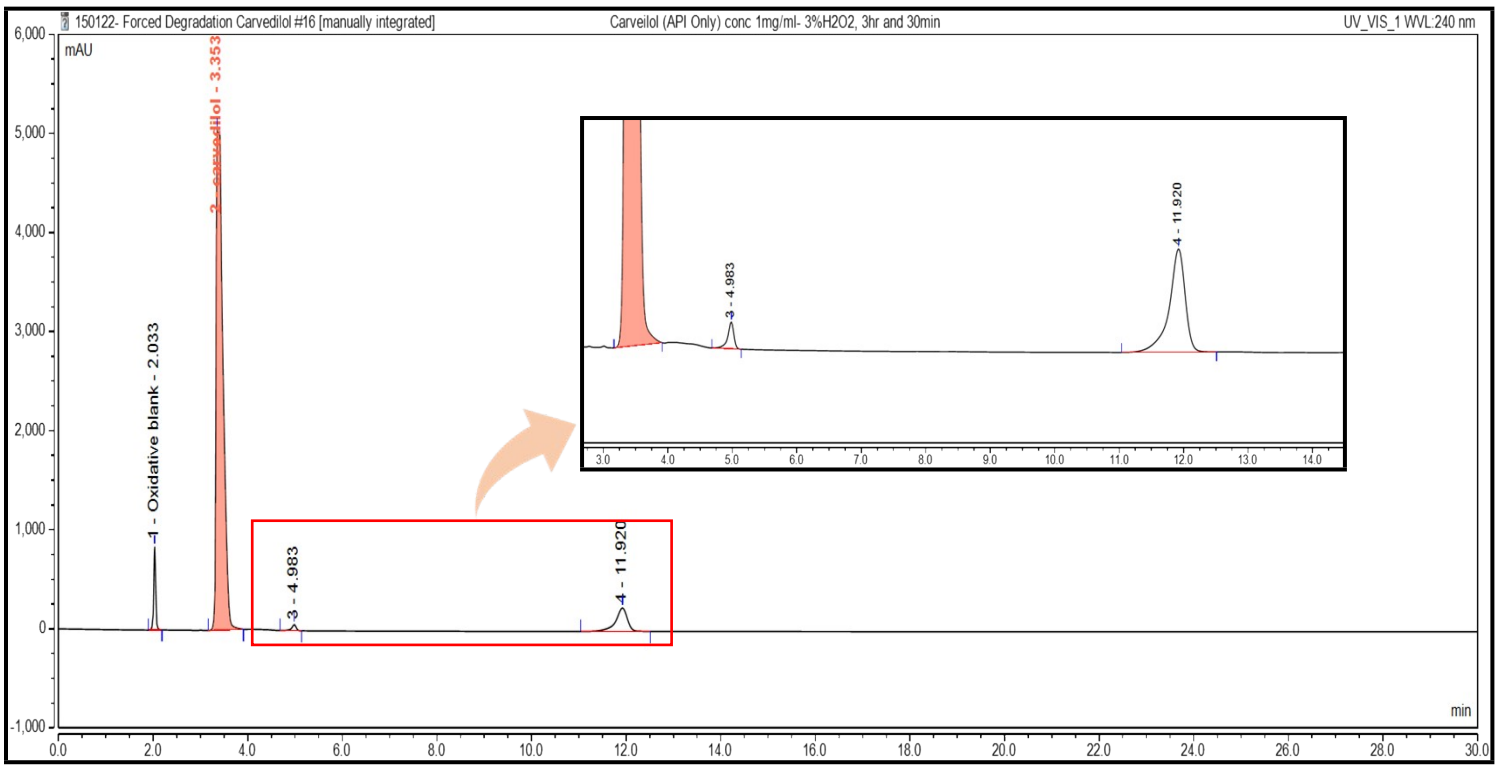


Figure 116S. HPLC chromatogram of oxidation degradation of CARV at 3.0% H_2O_2 for 3 hr and 30min (210min).

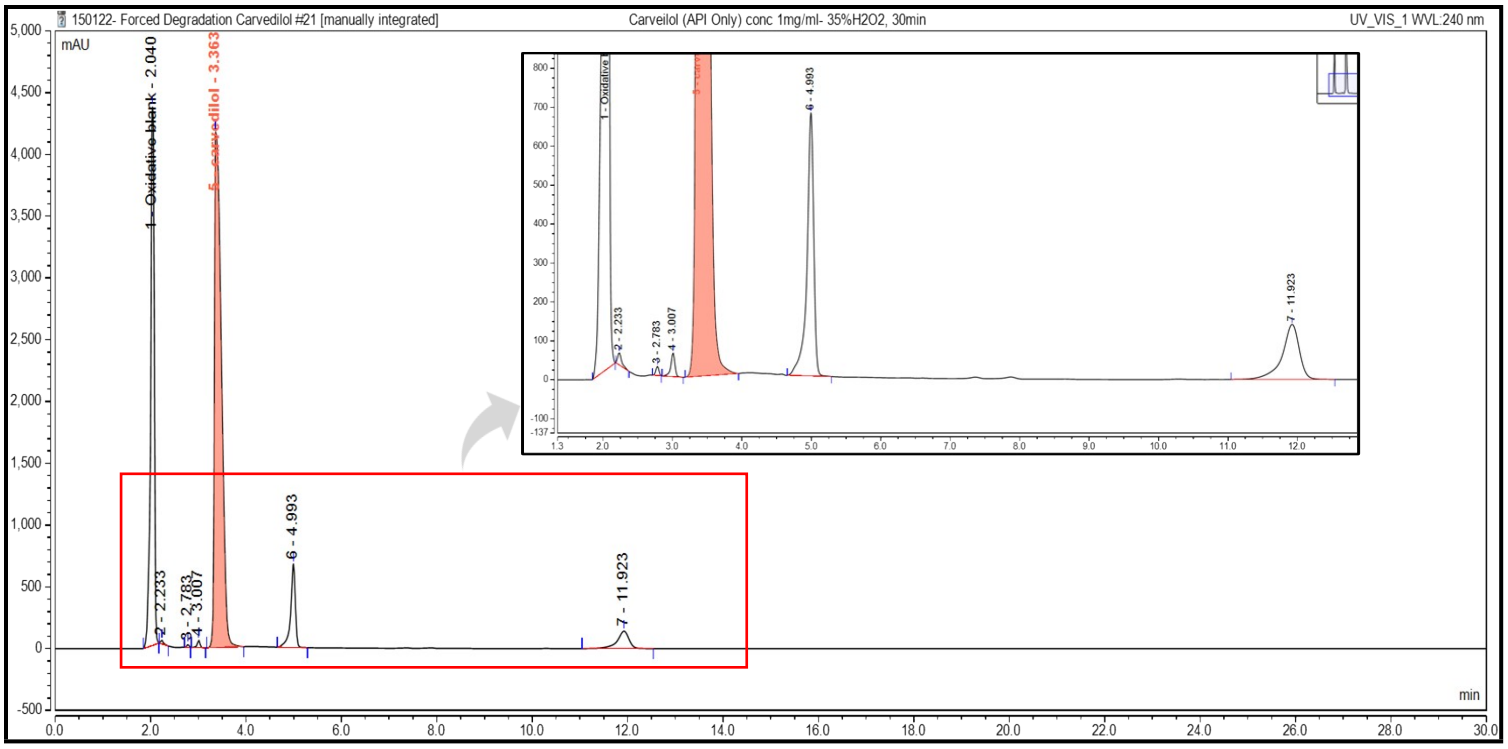


Figure 117S. HPLC chromatogram of oxidation degradation of CARV at 35.0% H_2O_2 for 30 min.

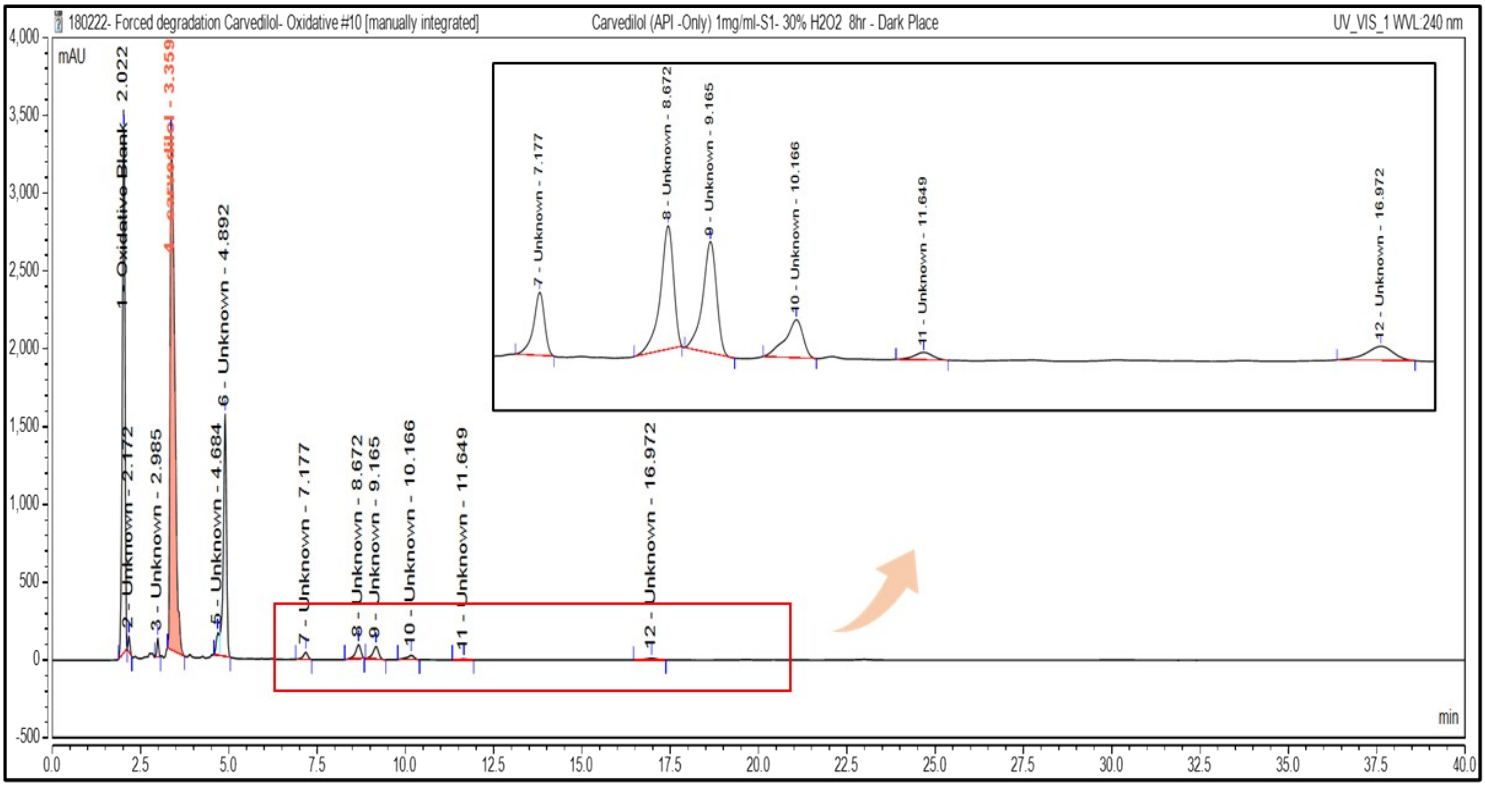


Figure 118S. HPLC chromatogram of oxidation degradation of CARV at 30.0% H_2O_2 for 8 h.

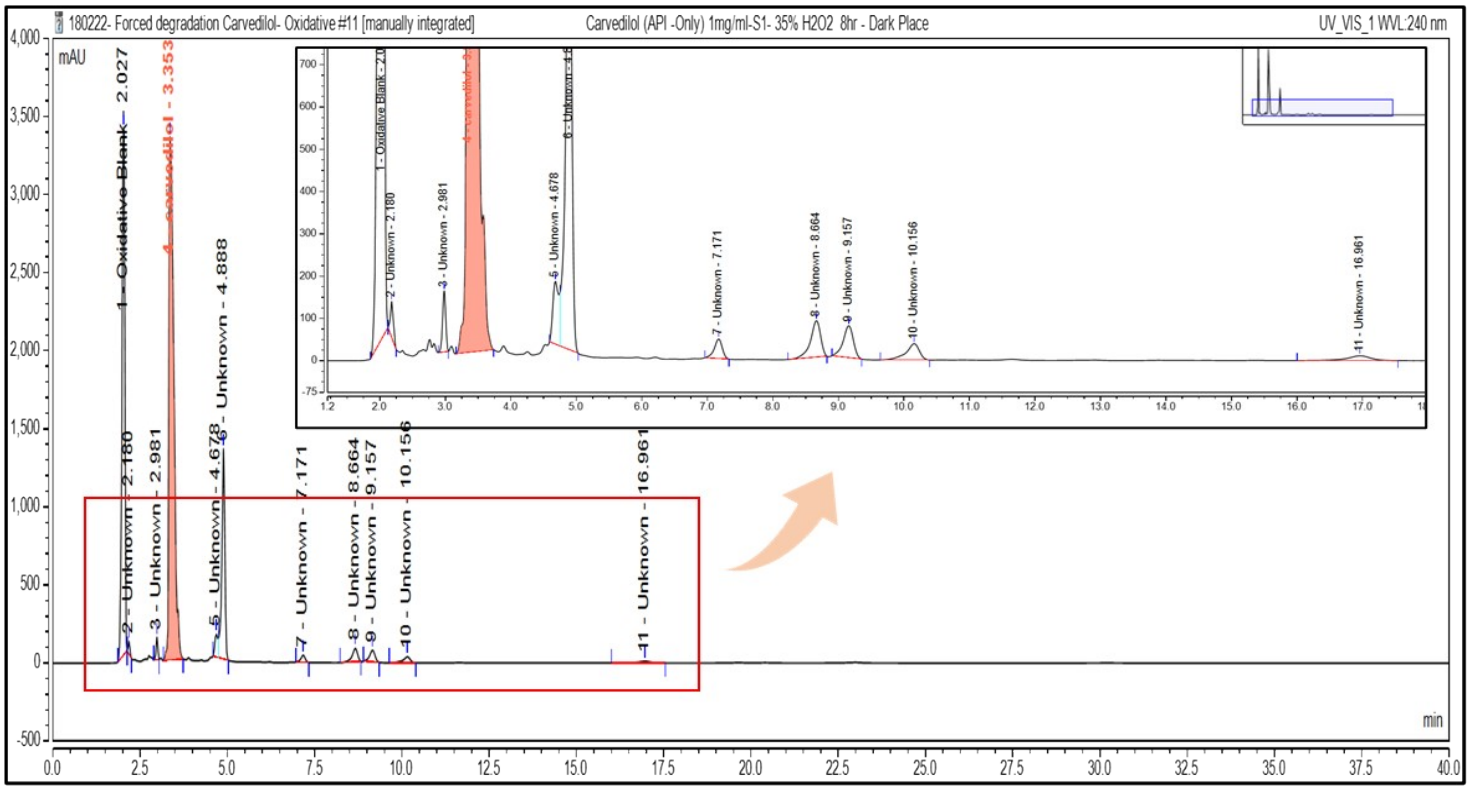


Figure 119S. HPLC chromatogram of oxidation degradation of CARV at 35.0% H_2O_2 for 8 h.

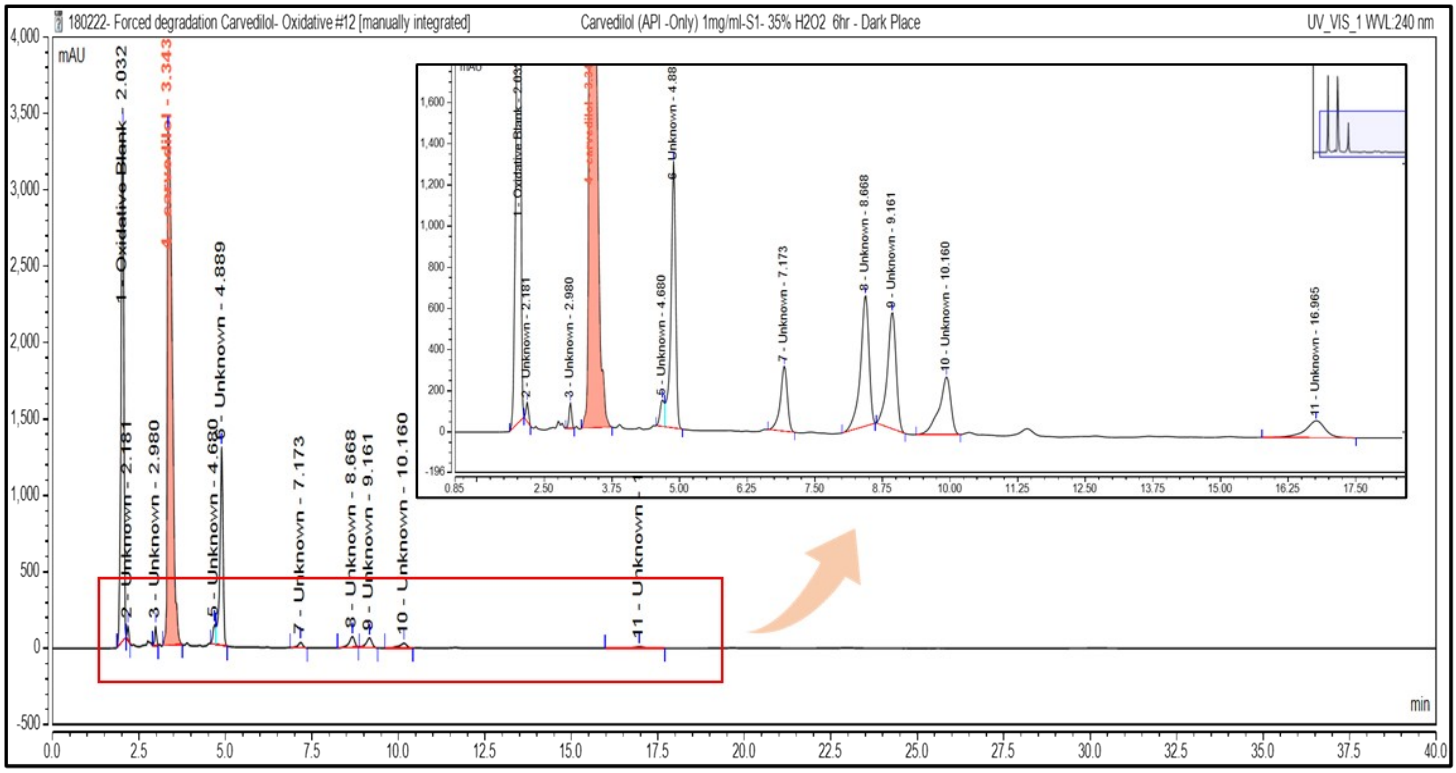


Figure 120S. HPLC chromatogram of oxidation degradation of CARV at 35.0% H_2O_2 for 6 h.

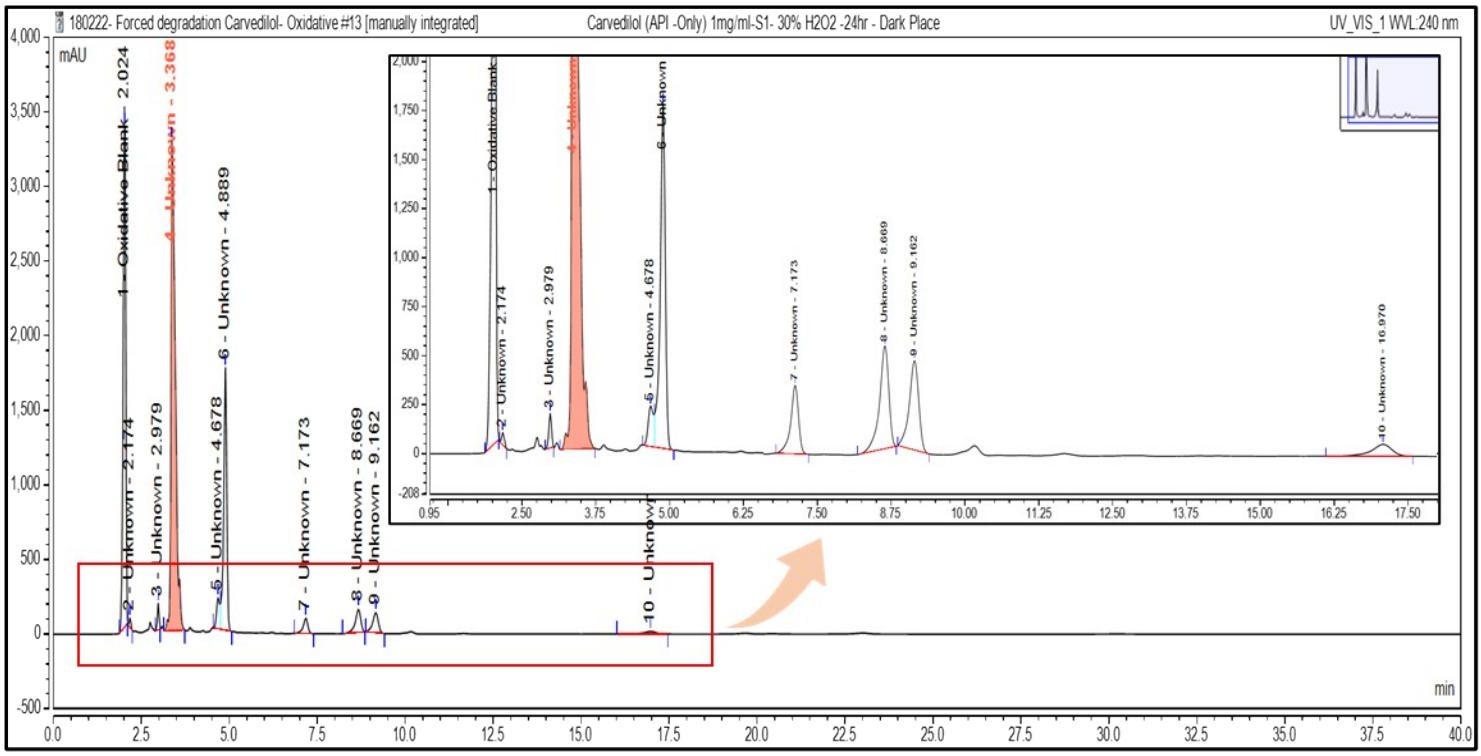


Figure 121S. HPLC chromatogram of oxidation degradation of CARV at 30.0% H_2O_2 for 24 h.

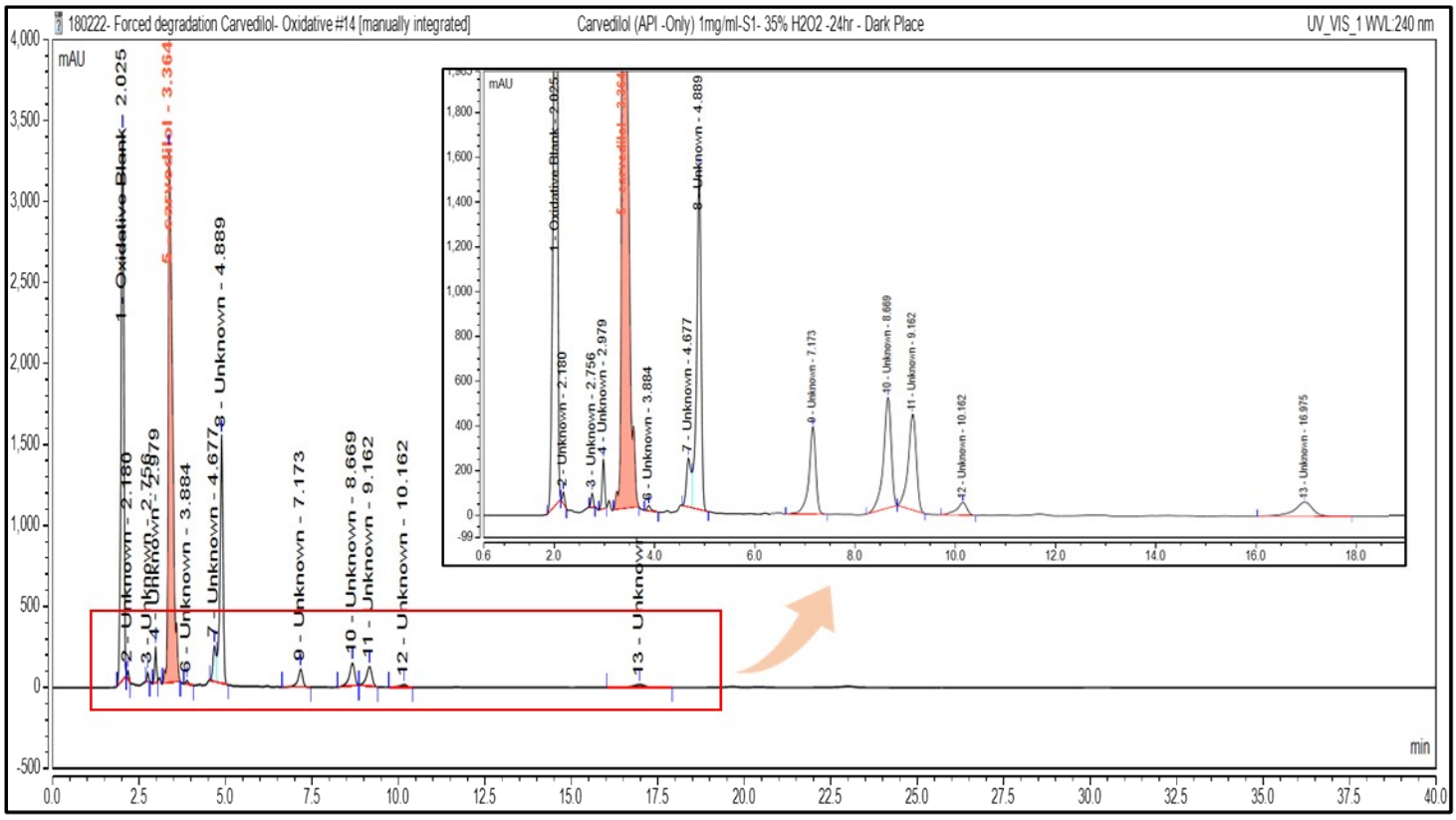


Figure 122S. HPLC chromatogram of oxidation degradation of CARV at 35.0% H_2O_2 for 24 h.

CARV-MEOG-Oxidation Degradation

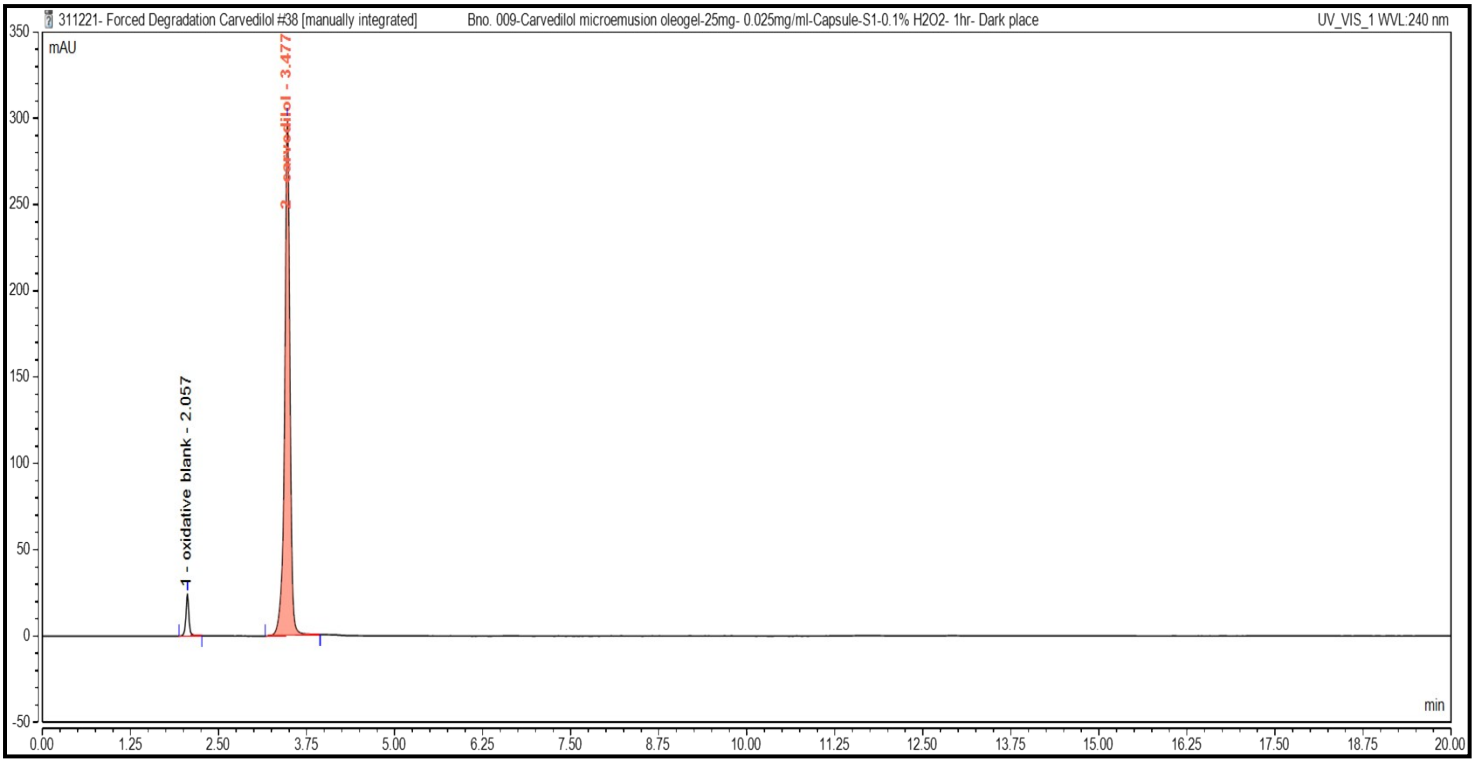


Figure 123S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 0.1% H_2O_2 for 1 h.

Figure 124S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 3.0% H_2O_2 for 3 h.

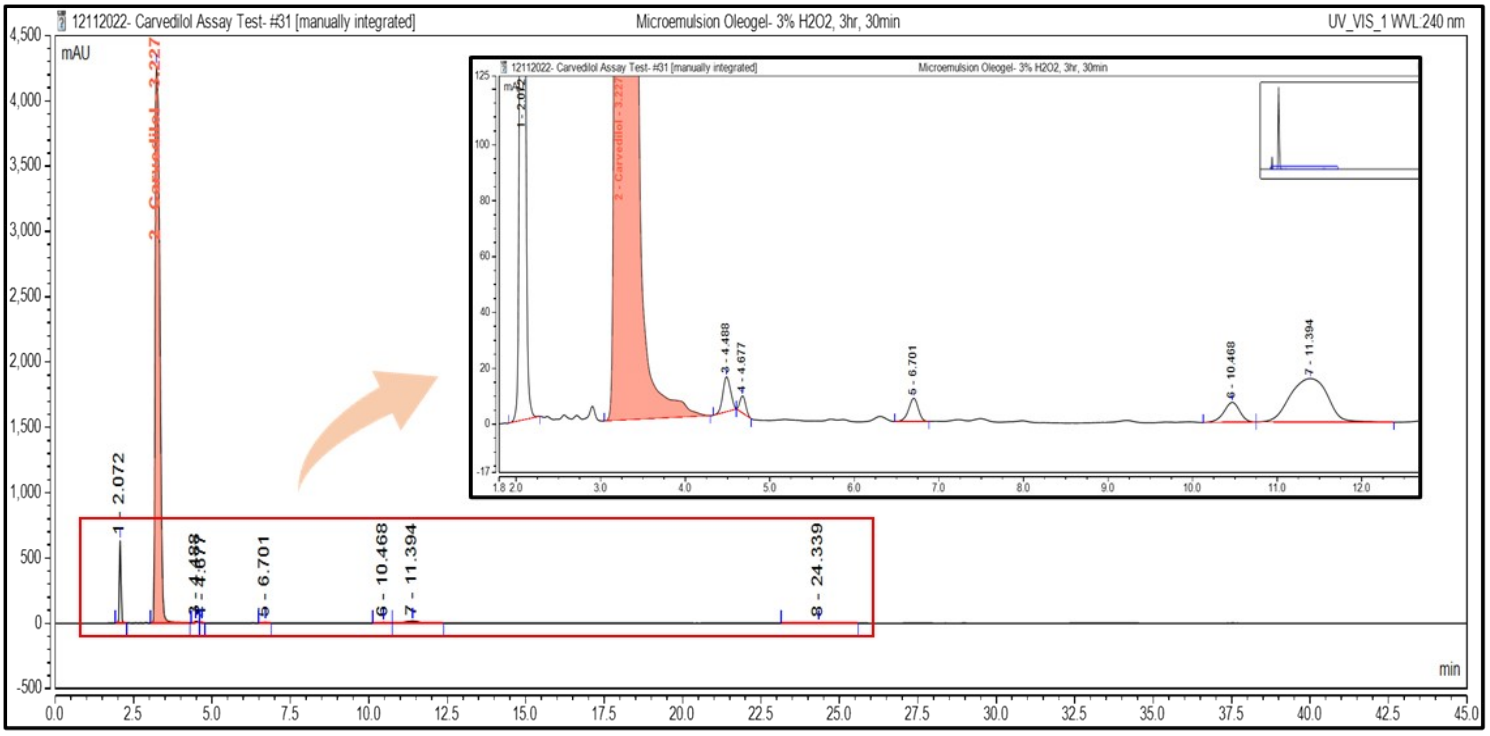


Figure 125S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 3.0% H_2O_2 for 3 h and 30min (210min).

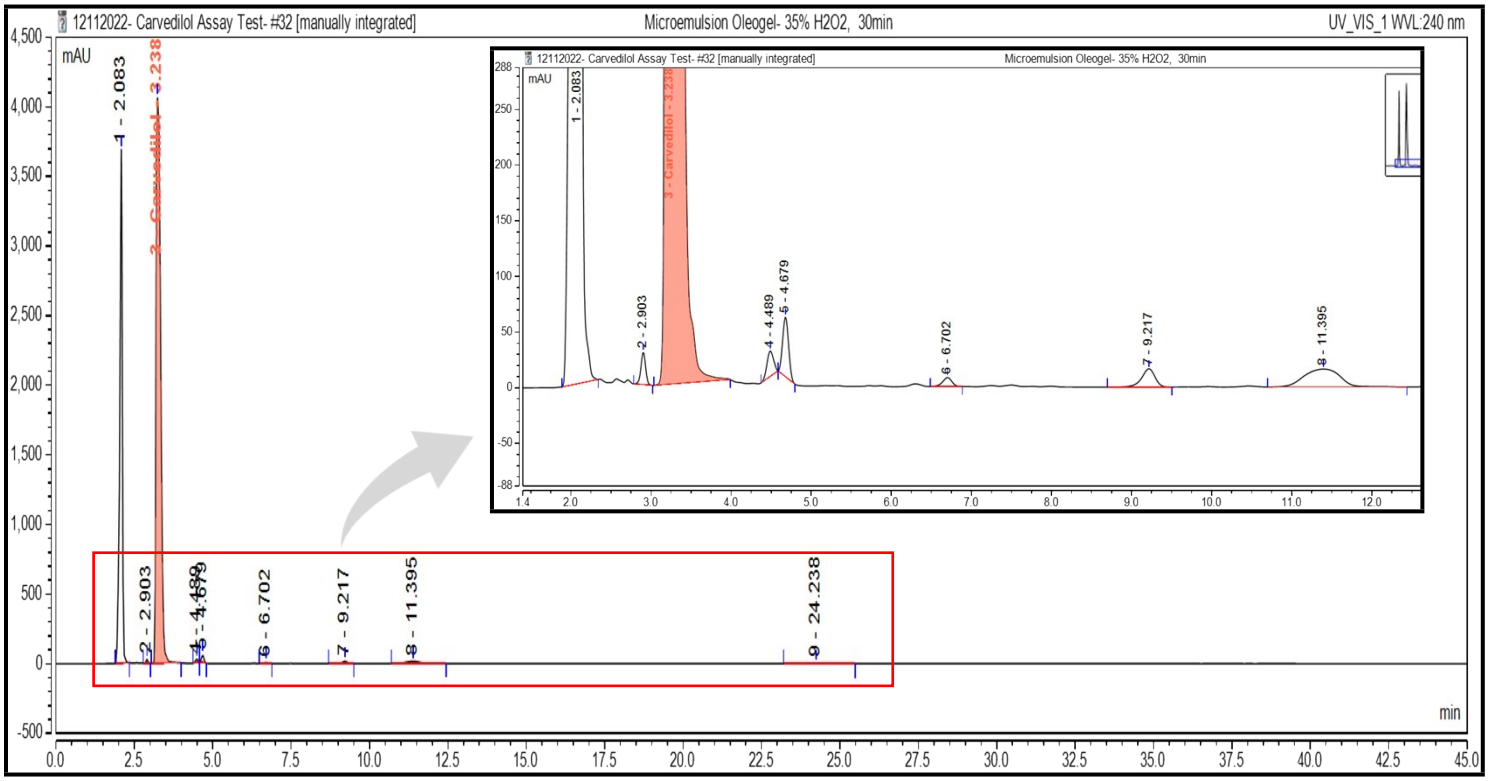


Figure 126S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 35.0% H_2O_2 for 30 min.

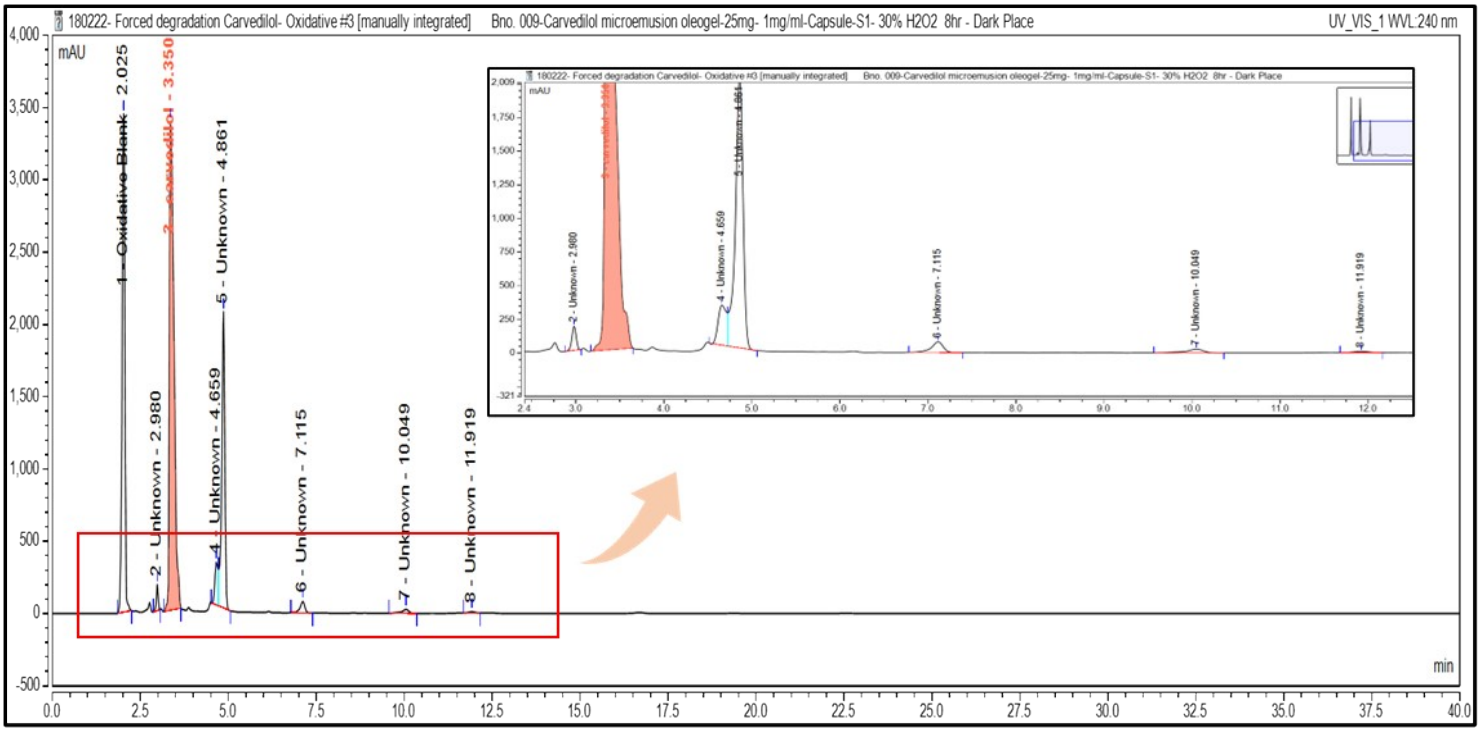


Figure 127S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 30.0% H_2O_2 for 8 h.

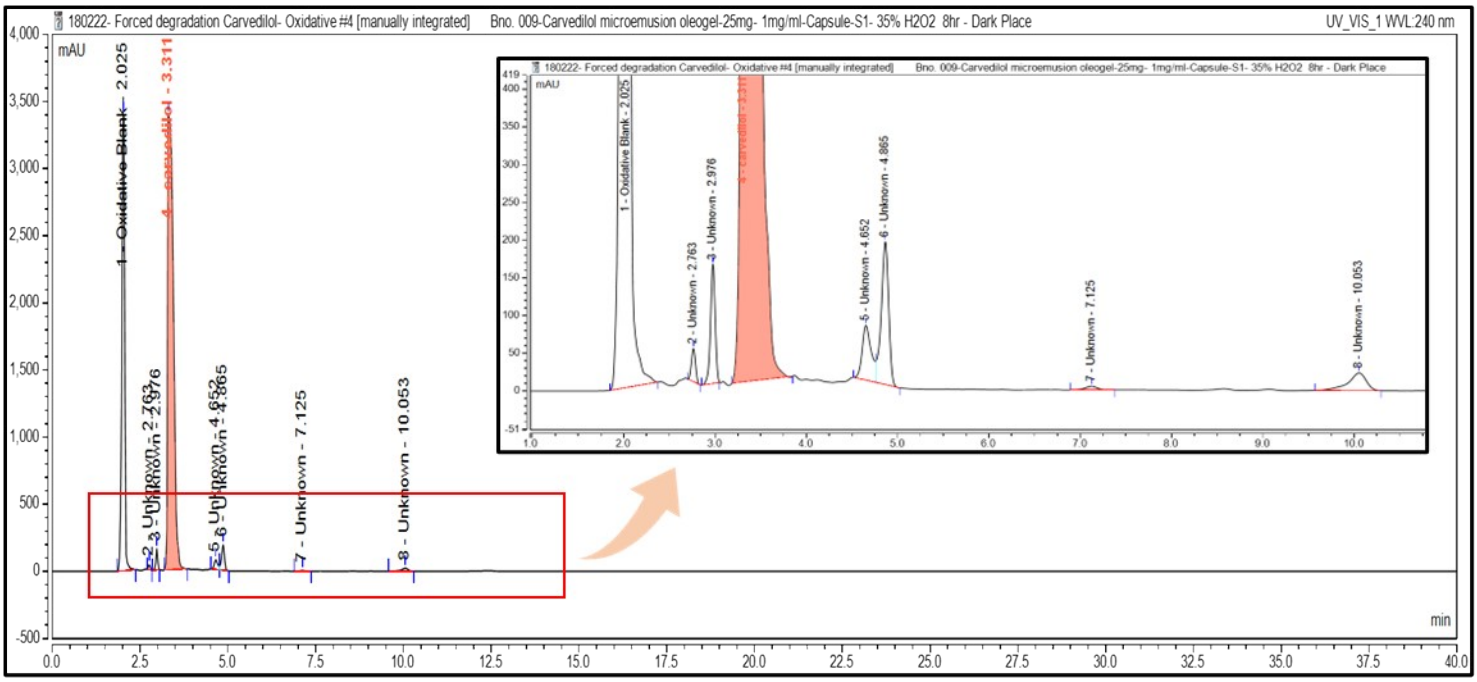


Figure 128S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 35.0% H_2O_2 for 8 h.

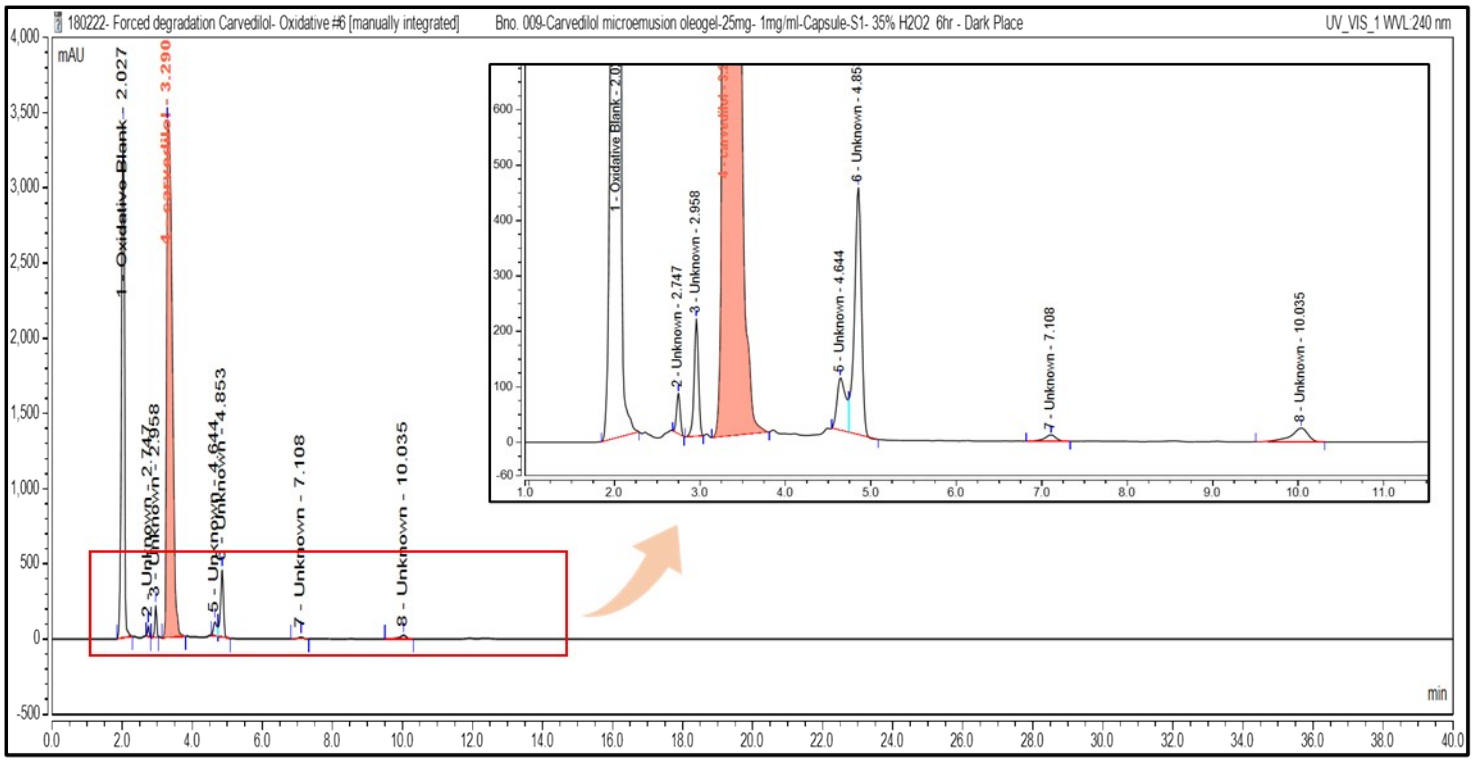


Figure 129S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 35.0% H_2O_2 for 6 h.

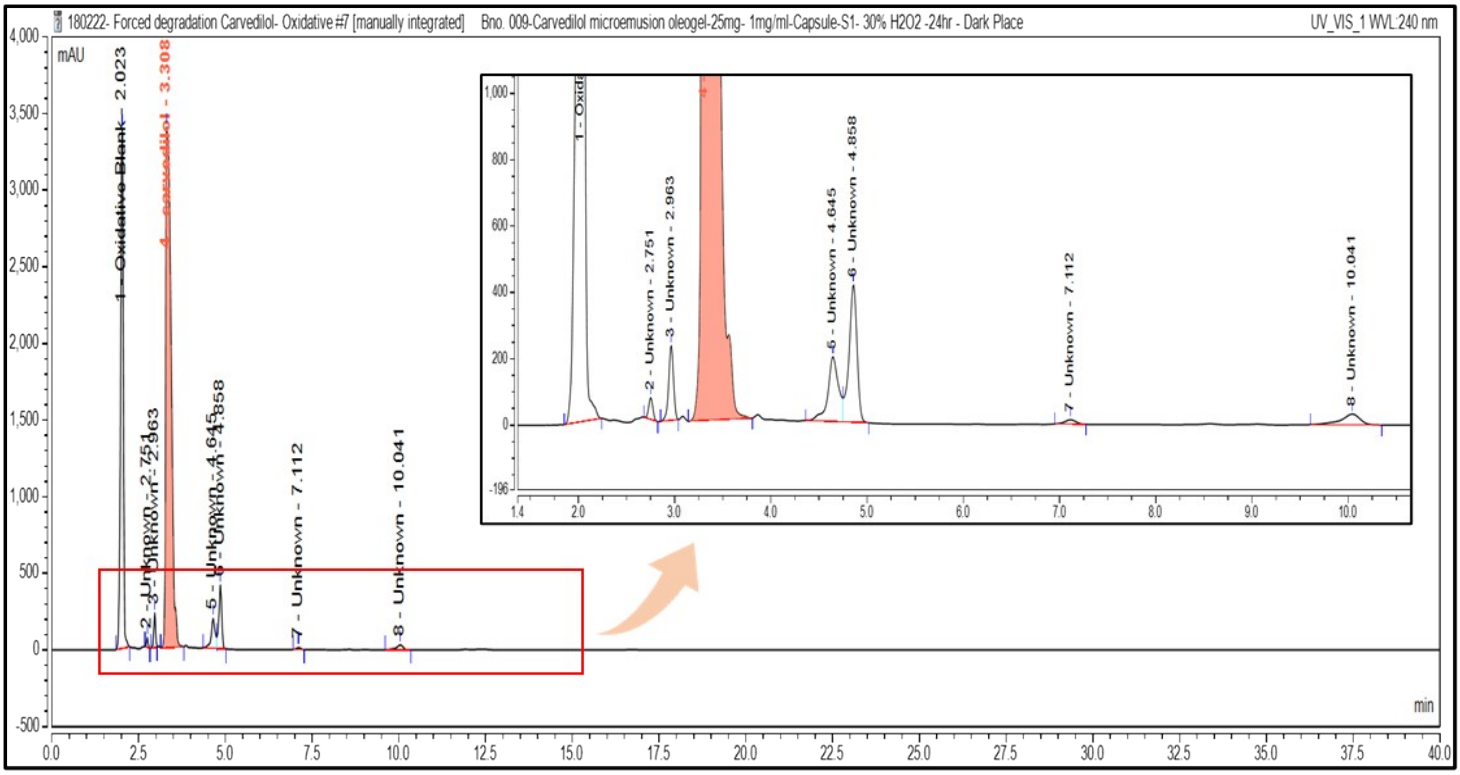


Figure 130S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 30.0% H_2O_2 for 24 h.

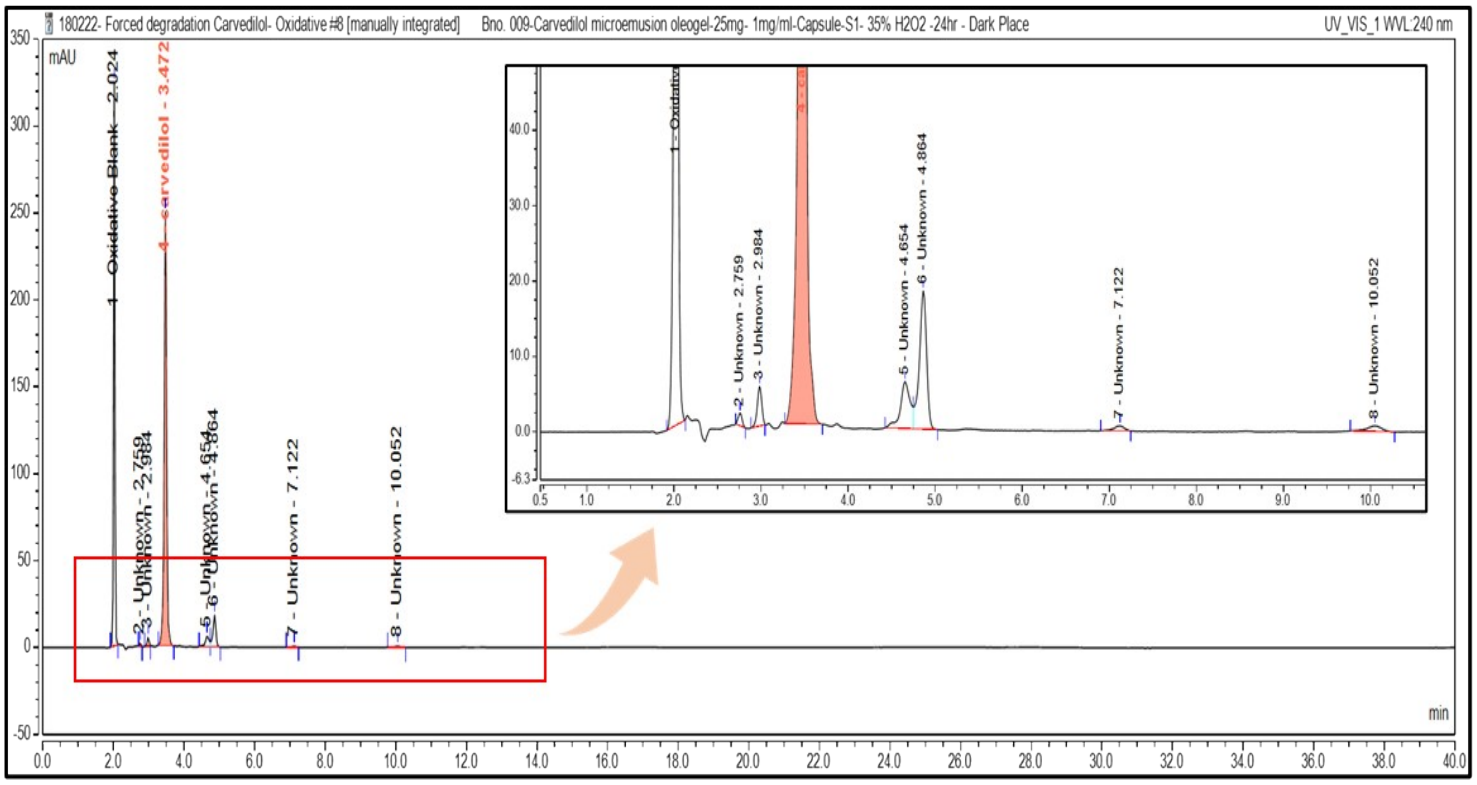


Figure 131S. HPLC chromatogram of oxidation degradation of CARV-MEOG at 35.0% H_2O_2 for 24 h.

Excipient- Microemulsion Loaded Oleogel-Oxidation Degradation

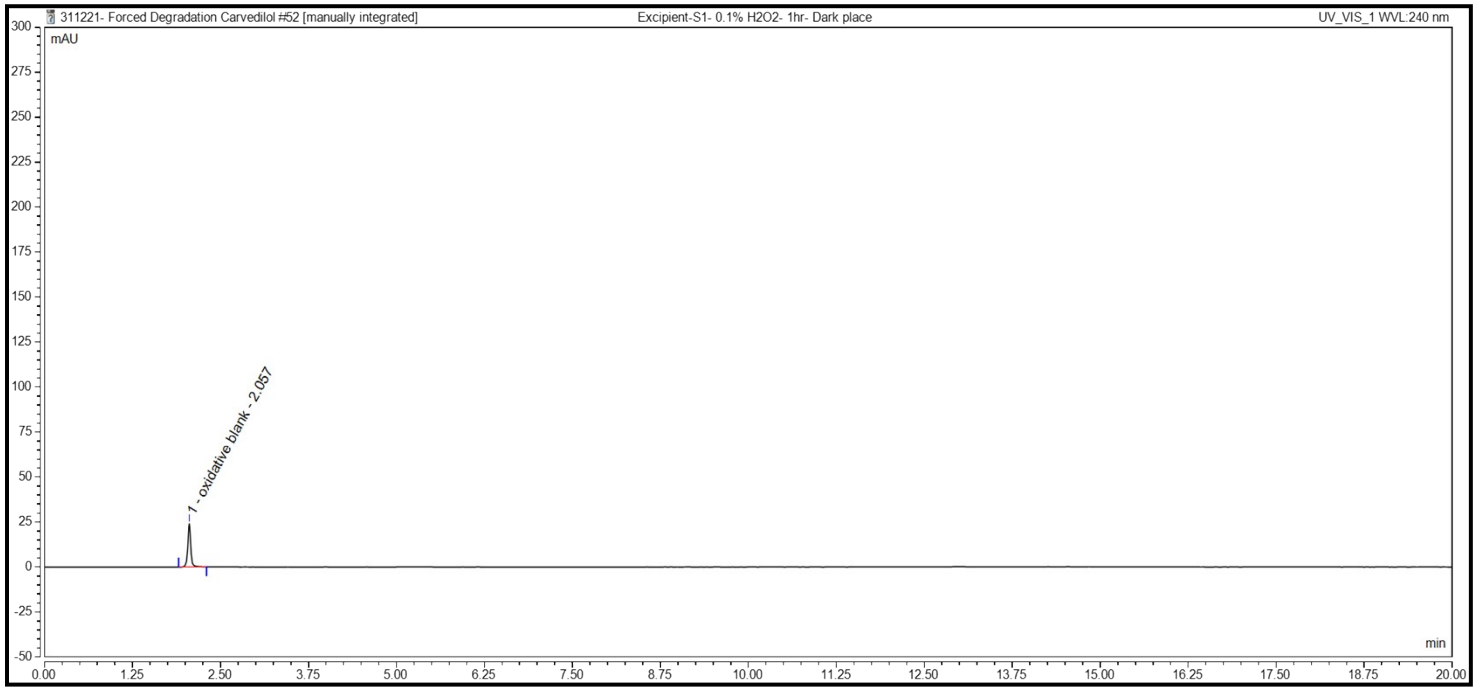


Figure 132S. HPLC chromatogram of oxidation degradation of excipients at 0.1% H_2O_2 for 1 h.

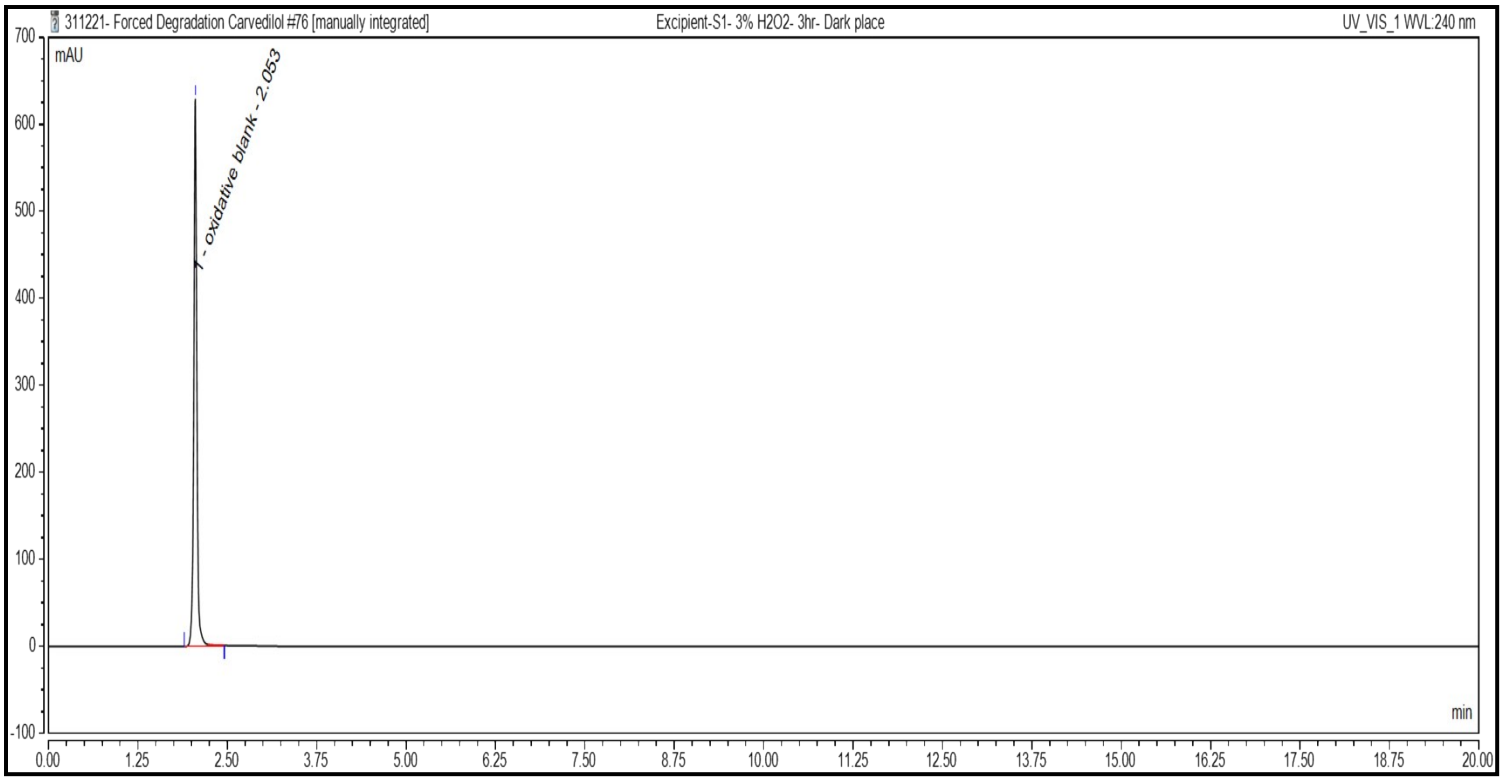


Figure 133S. HPLC chromatogram of oxidation degradation of excipients at 3.0% H_2O_2 for 3 h.

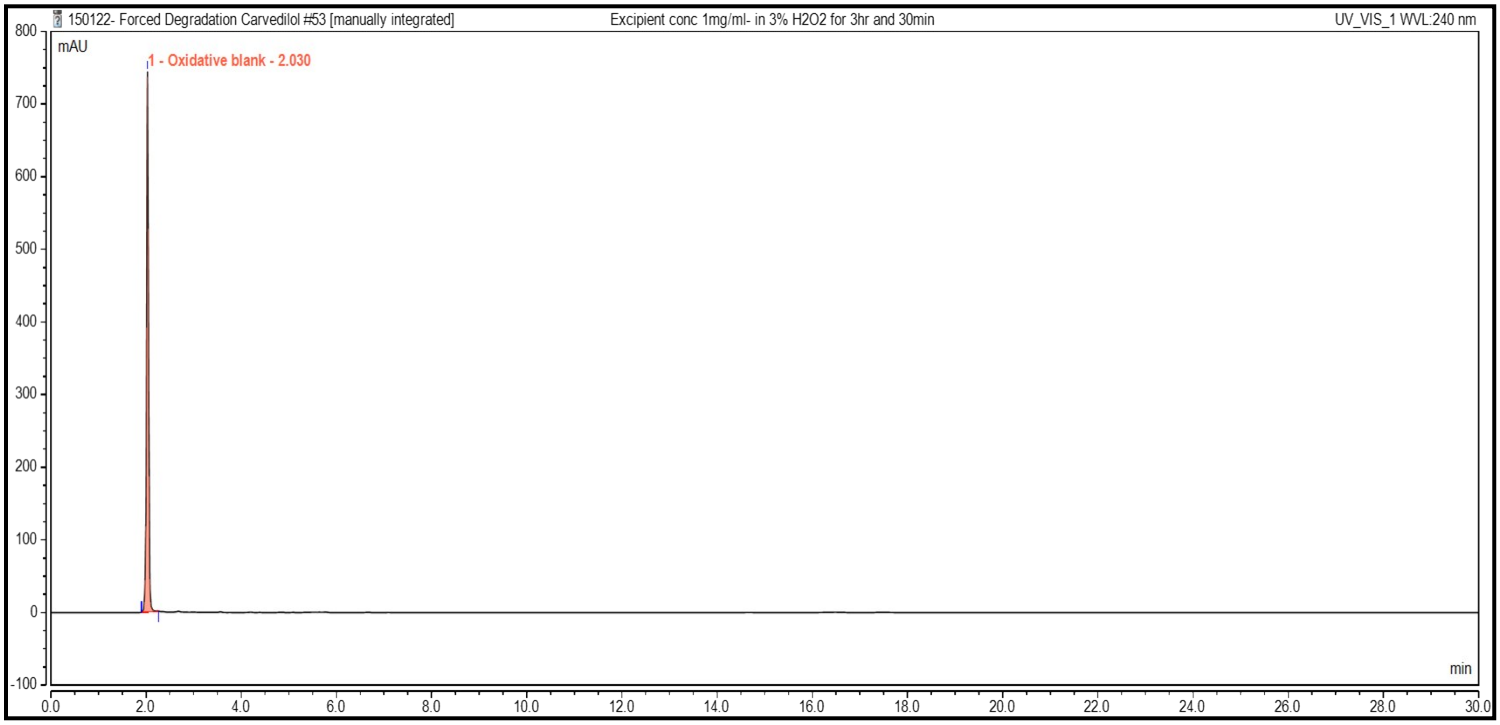


Figure 134S. HPLC chromatogram of oxidation degradation of excipients at 3.0% H_2O_2 for 3 h and 30 min (210min).

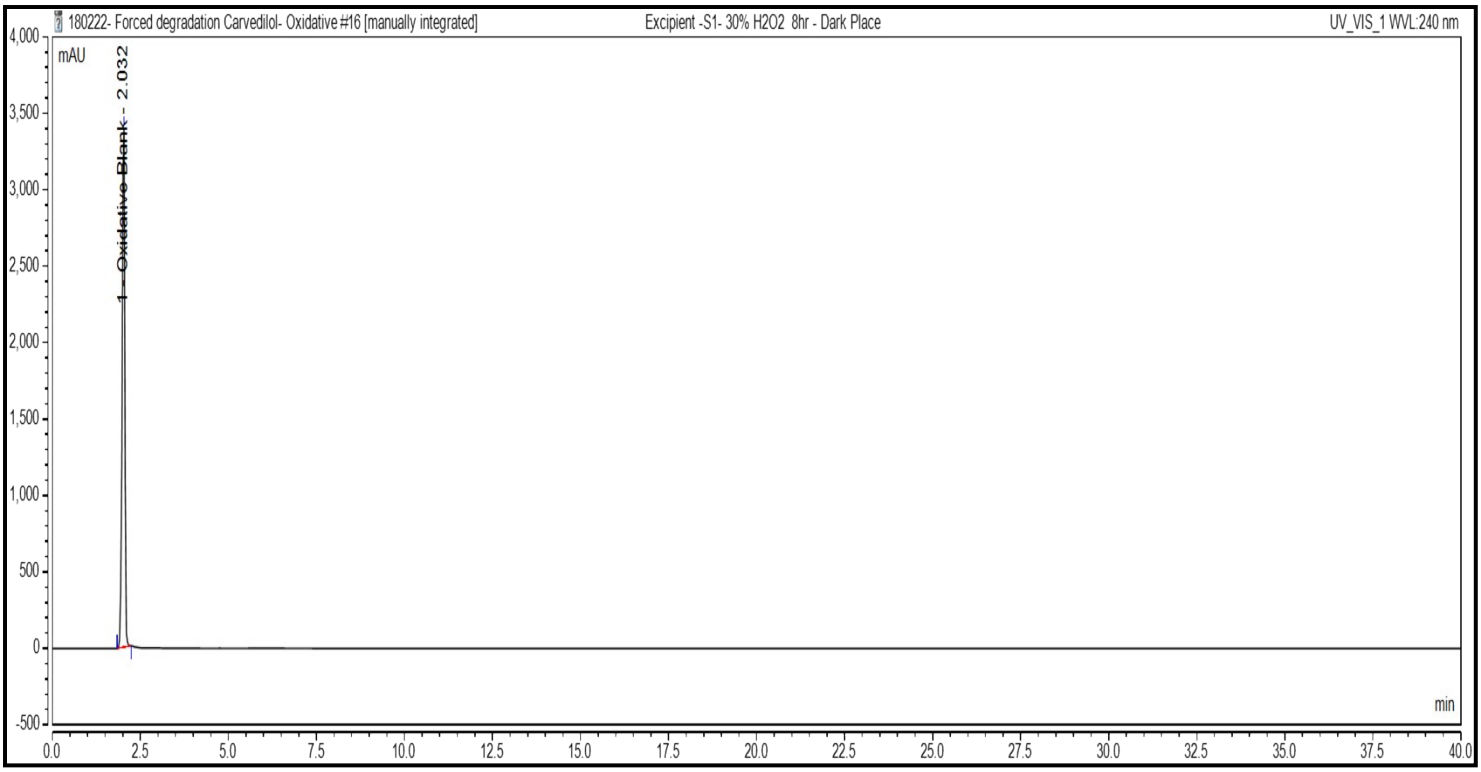


Figure 135S. HPLC chromatogram of oxidation degradation of excipients at 30.0% H_2O_2 for 8 h.

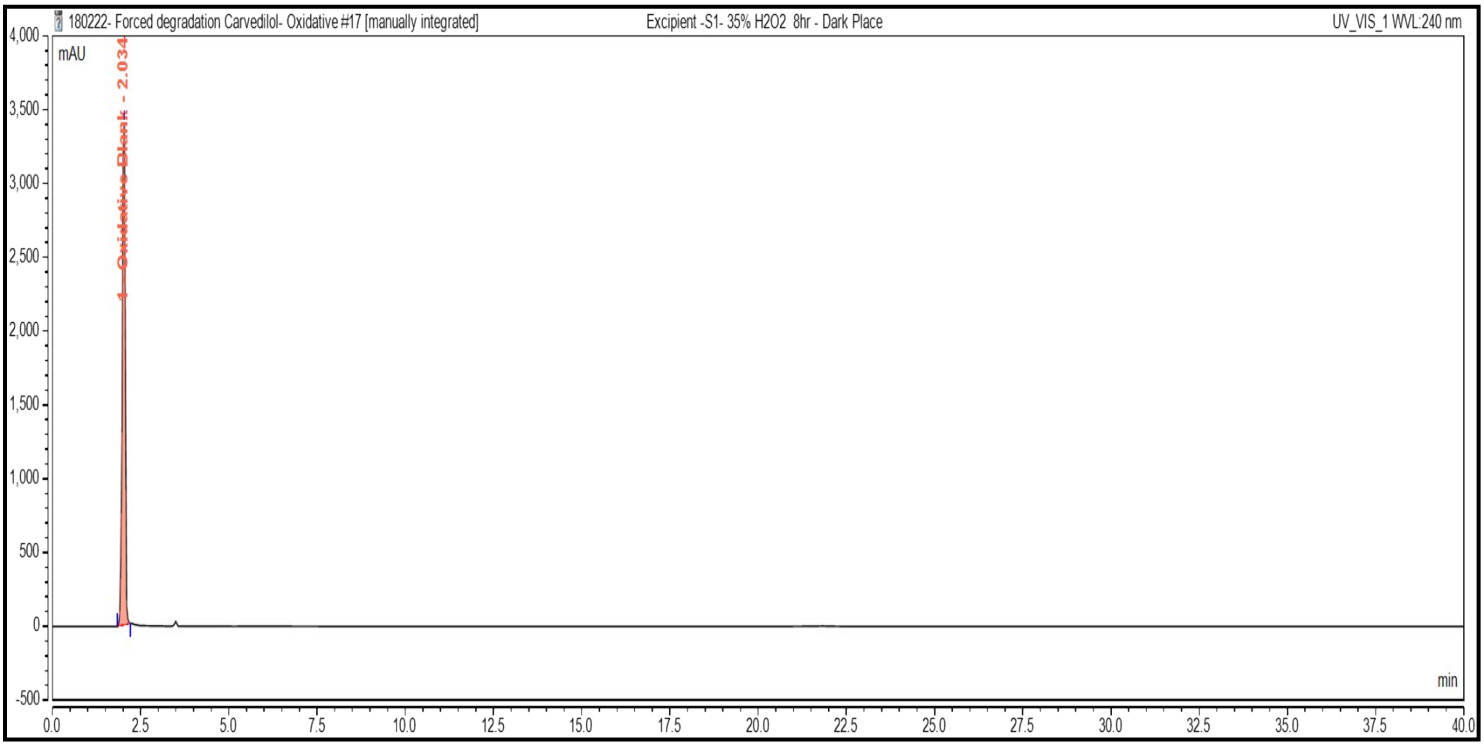


Figure 136S. HPLC chromatogram of oxidation degradation of excipients at 35.0% H_2O_2 for 8 h.

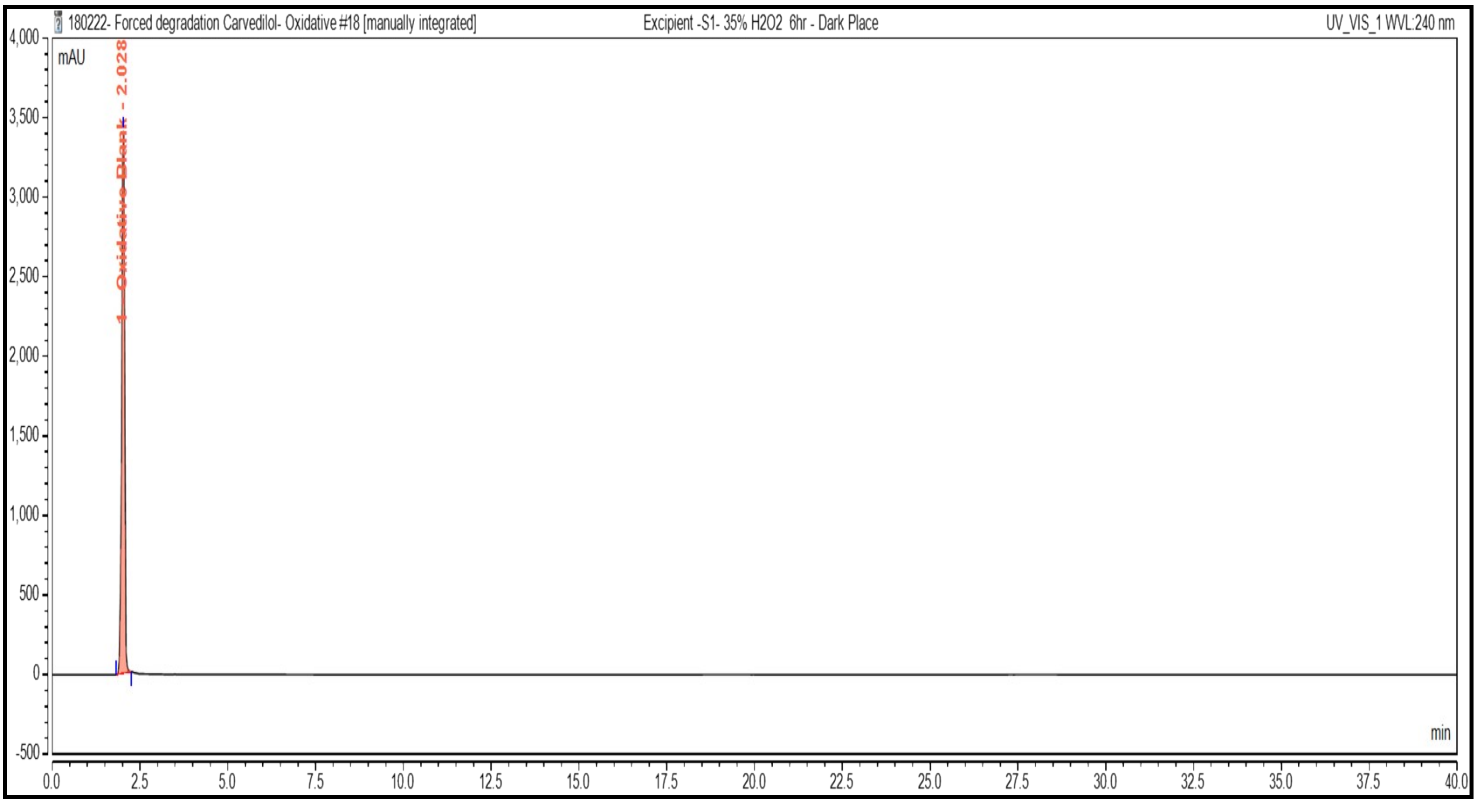


Figure 137S. HPLC chromatogram of oxidation degradation of excipients at 35.0% H_2O_2 for 6 h.

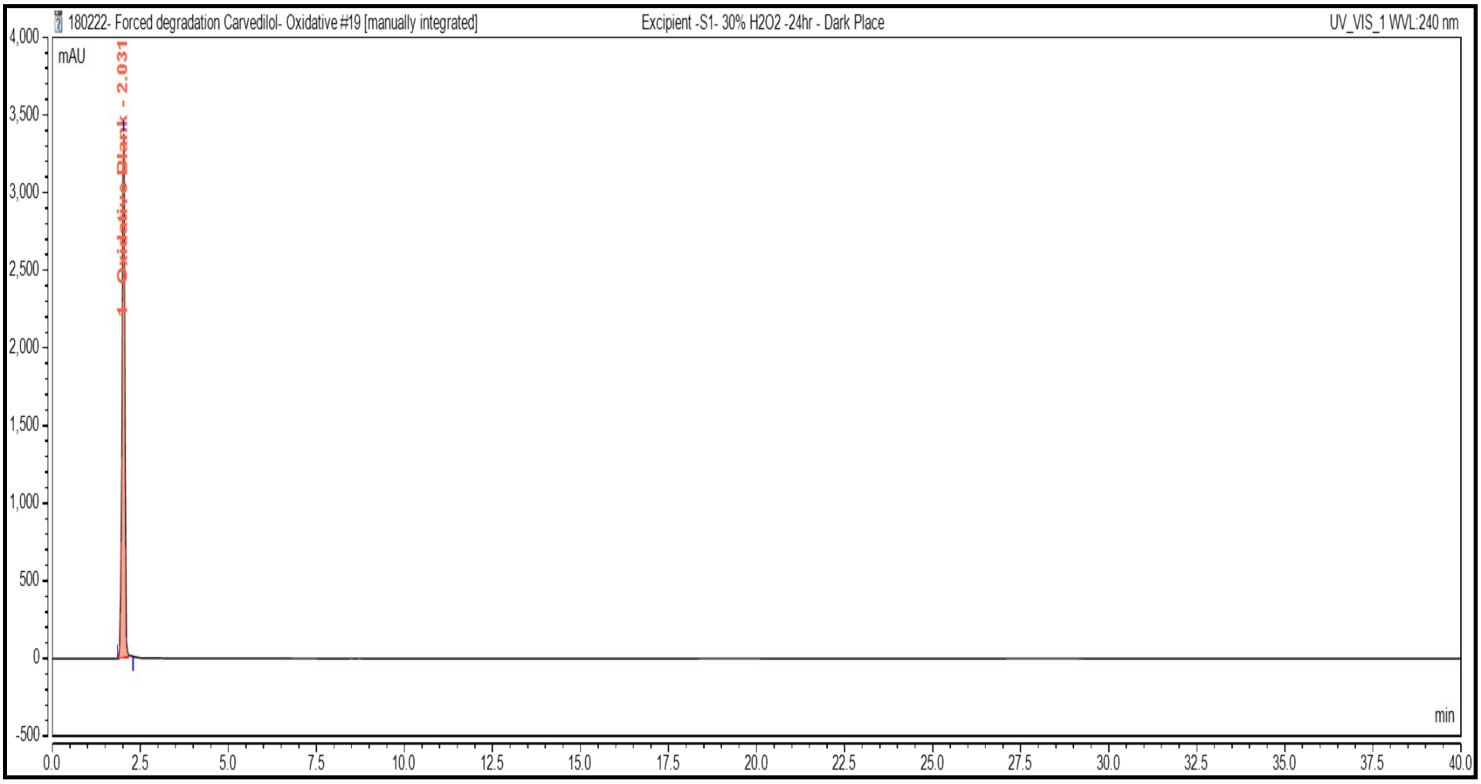


Figure 138S. HPLC chromatogram of oxidation degradation of excipients at 30.0% H_2O_2 for 24 h.

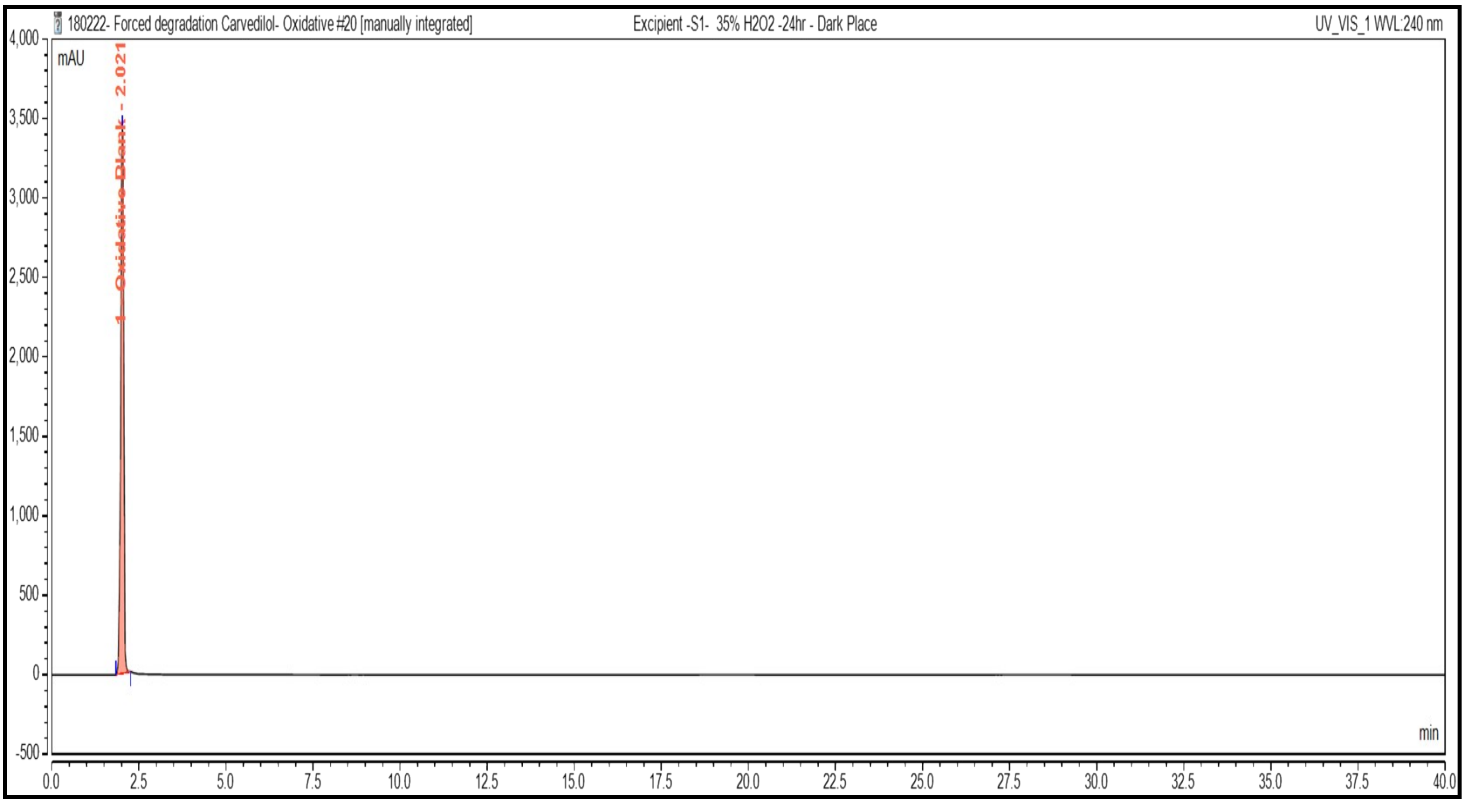


Figure 139S. HPLC chromatogram of oxidation degradation of excipients at 35.0% H_2O_2 for 24 h.

Thermal Degradation CARV:

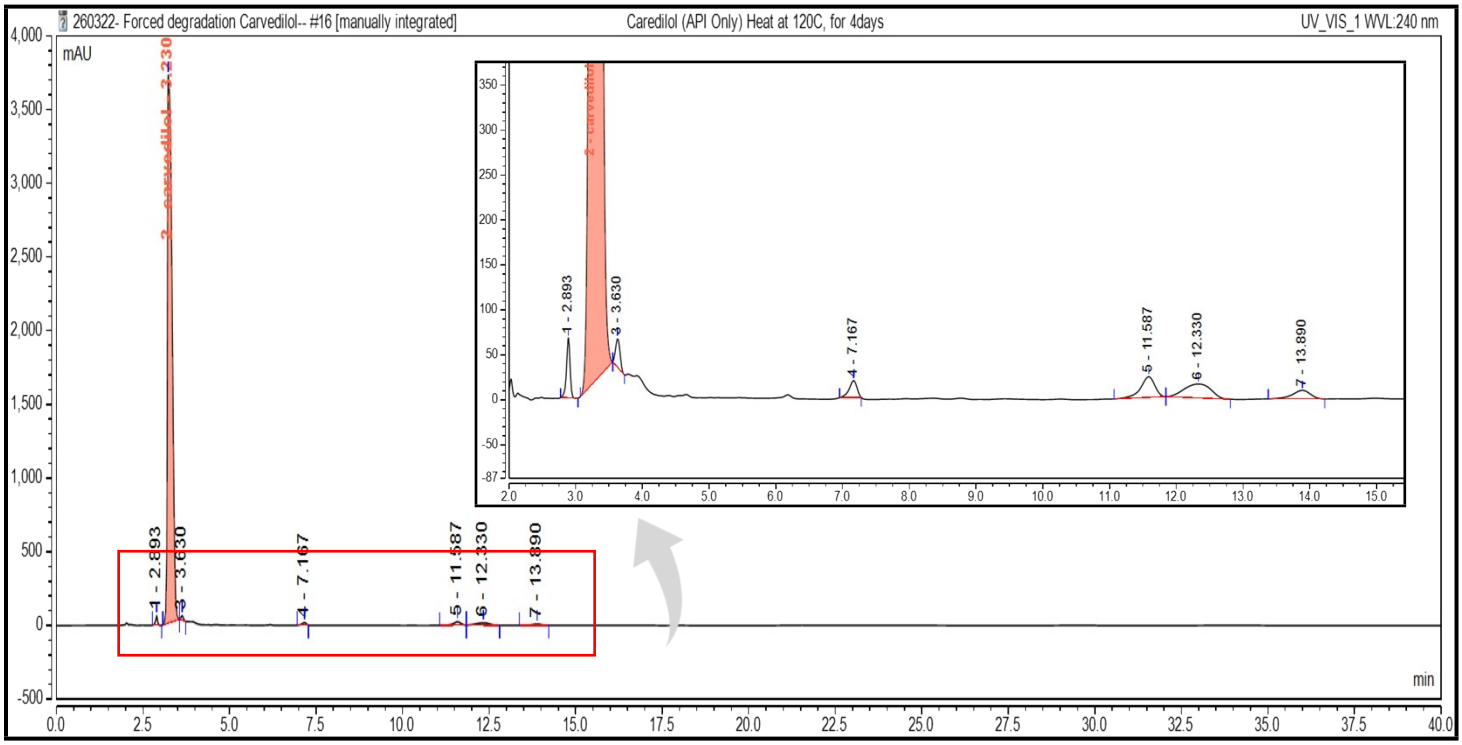


Figure 140S. HPLC chromatogram of thermal degradation of CARV at 120 ℃ for 4 days.

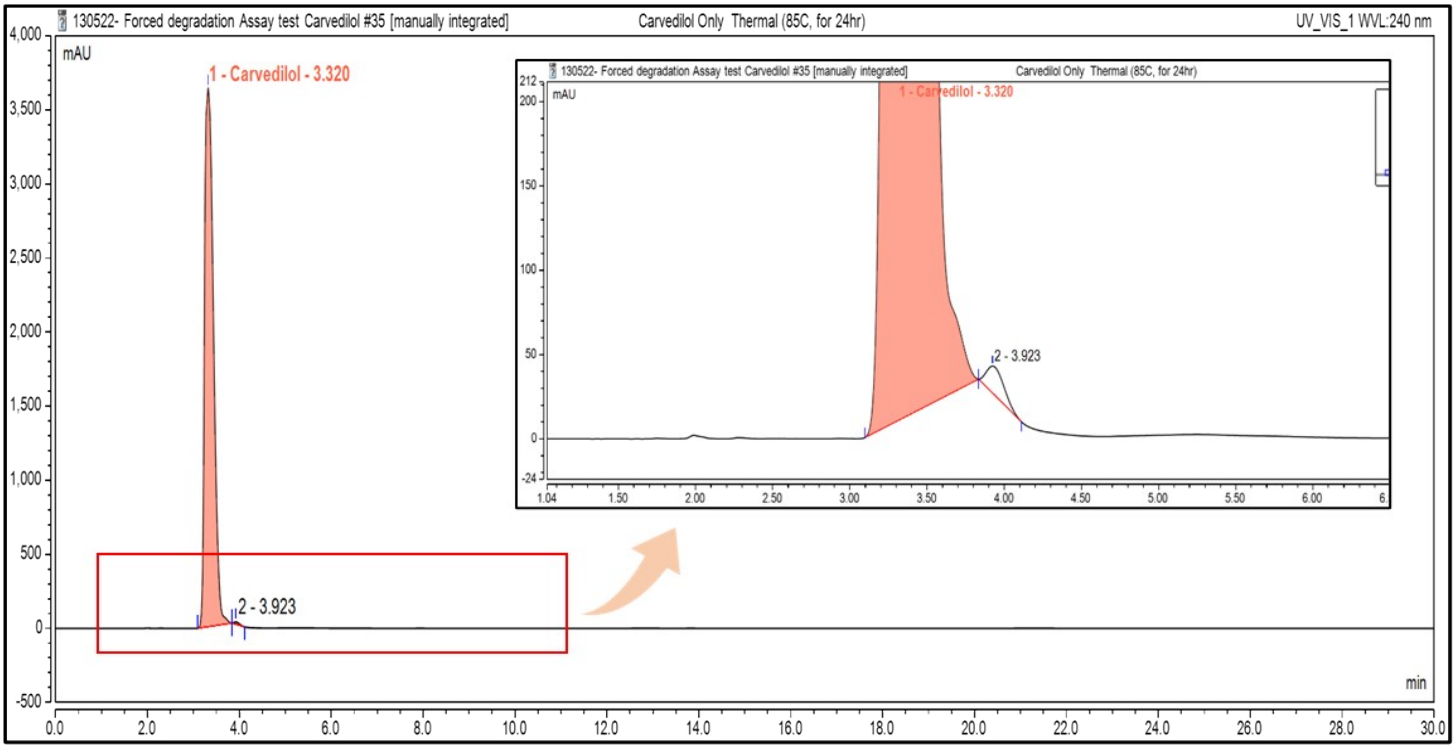


Figure 141S. HPLC chromatogram of thermal degradation of CARV at 85 ℃ for 24 h.

CARV-MEOG- Thermal Degradation:

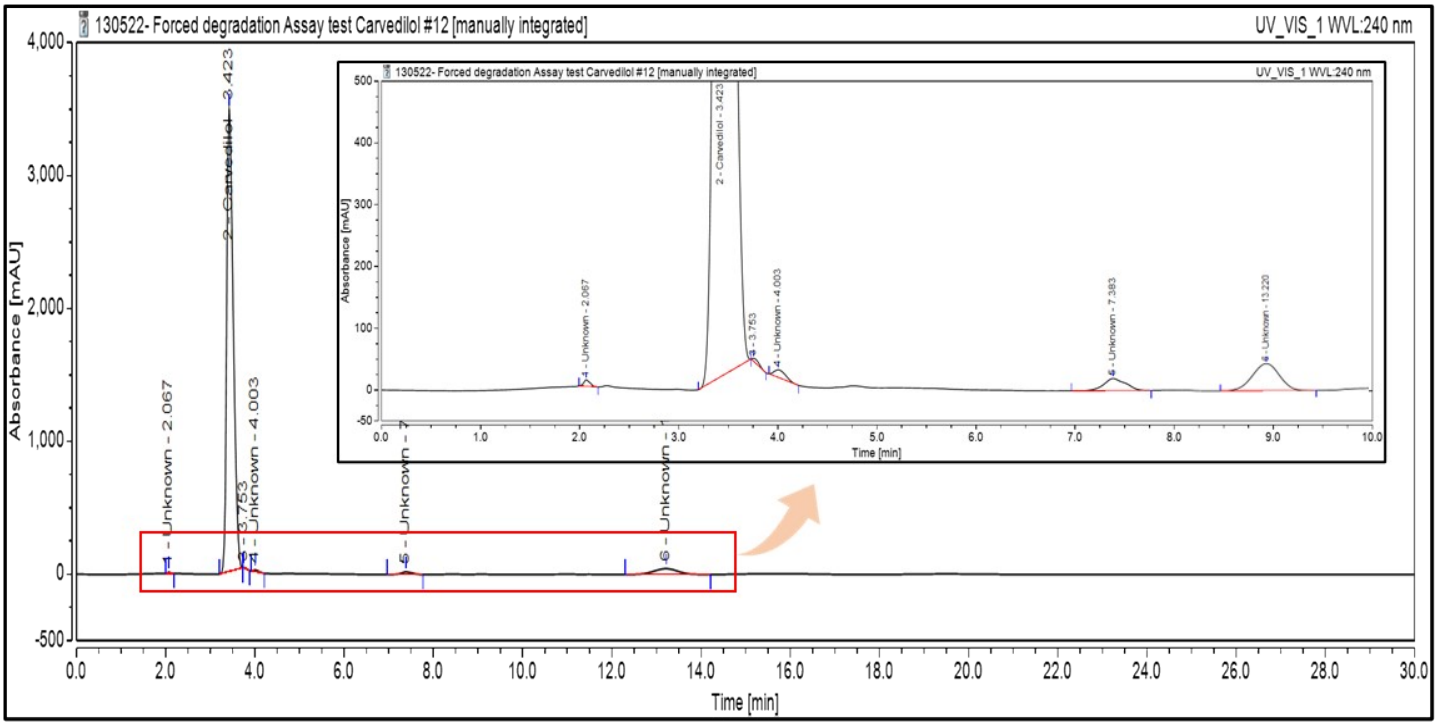


Figure 142S. HPLC chromatogram of thermal degradation of CARV-MEOG at 150 ℃ for 1 h.

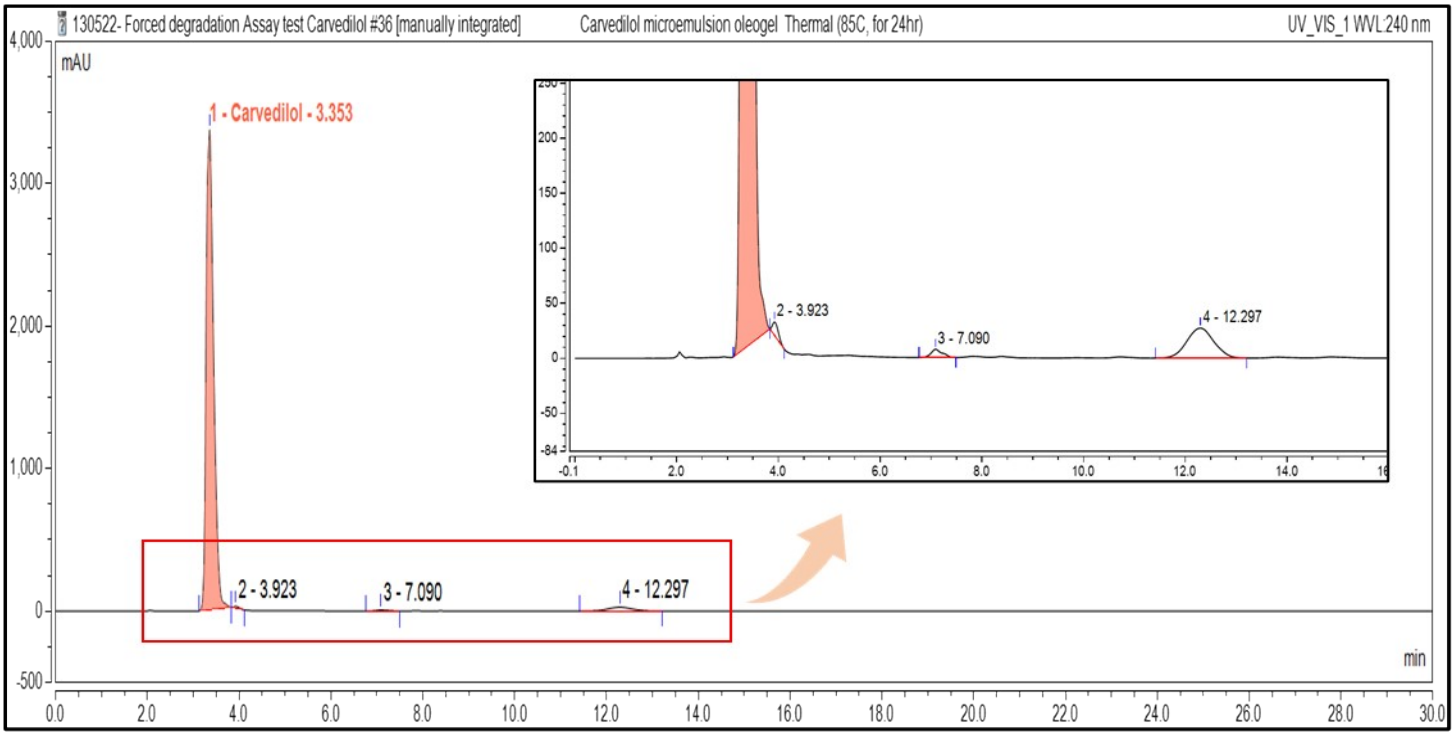


Figure 143S. HPLC chromatogram of thermal degradation of CARV-MEOG at 85 ℃ for 24 h.

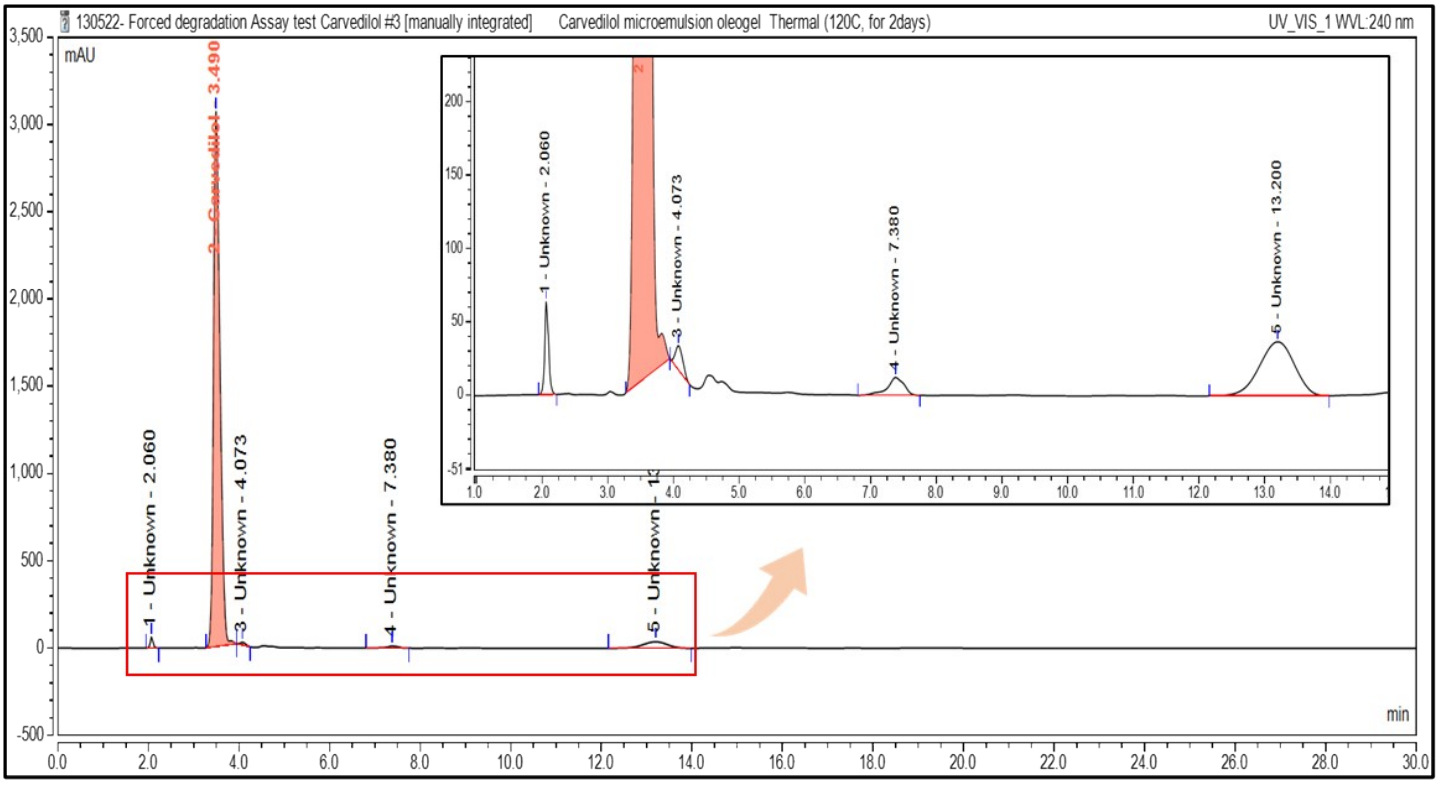


Figure 144S. HPLC chromatogram of thermal degradation of CARV-MEOG at 120 ℃ for 2 days.

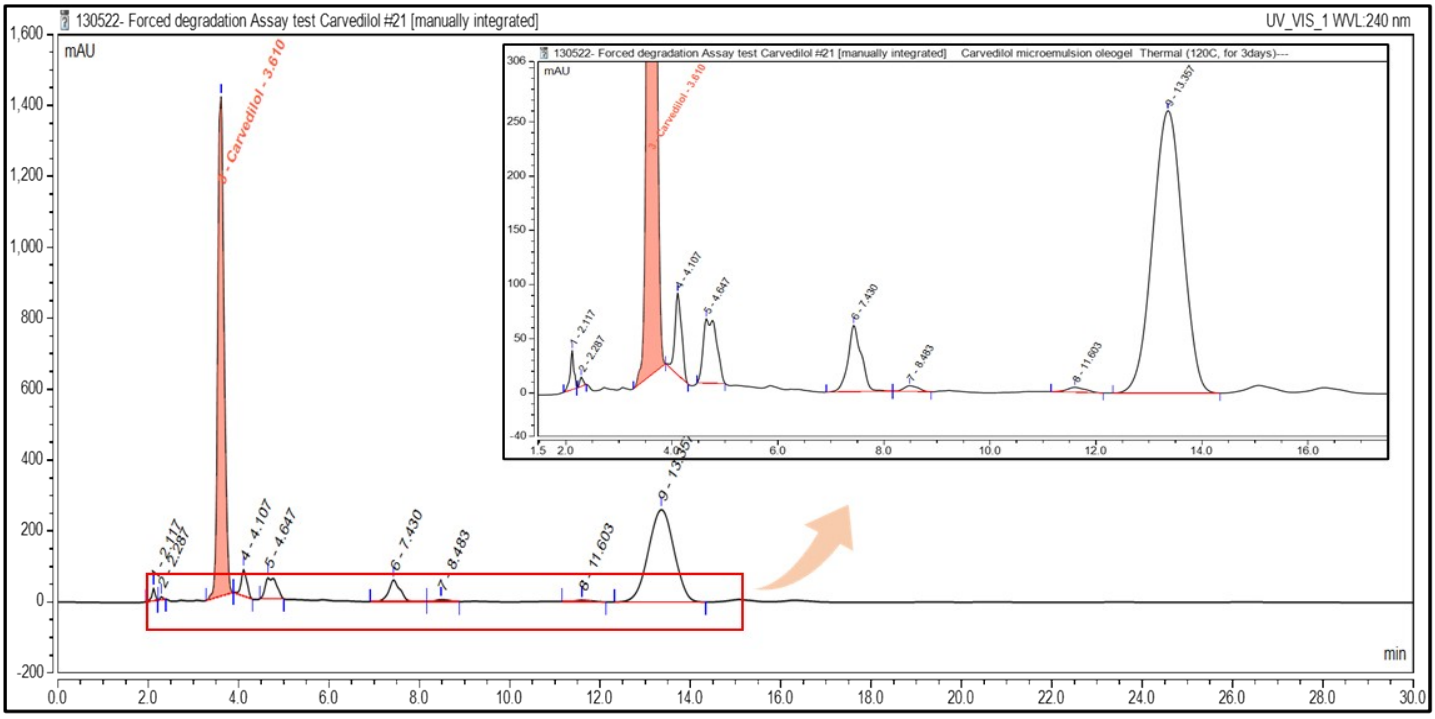


Figure 145S. HPLC chromatogram of thermal degradation of CARV-MEOG at 120 ℃ for 3 days.

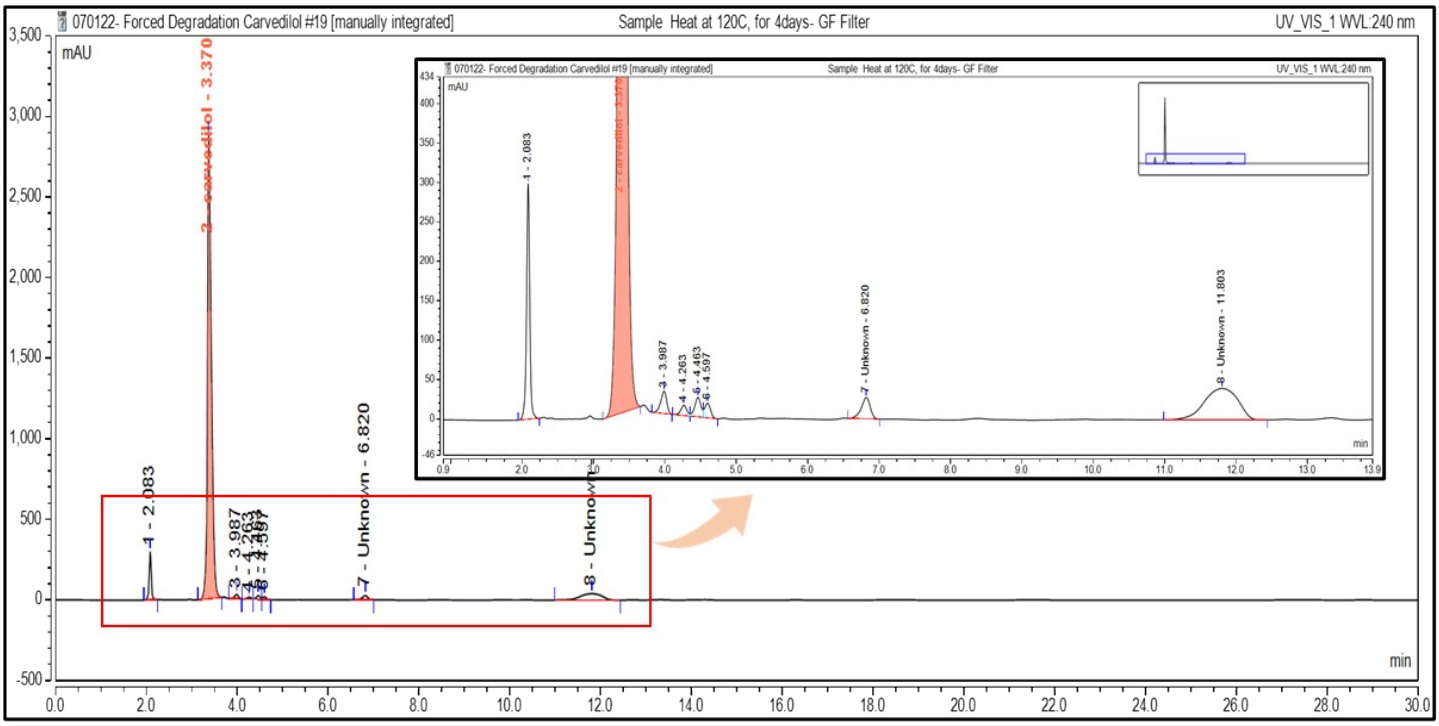


Figure 146S. HPLC chromatogram of thermal degradation of CARV-MEOG at 120 ℃ for 4 days.

Excipient- Microemulsion Loaded Oleogel-Thermal Degradation:

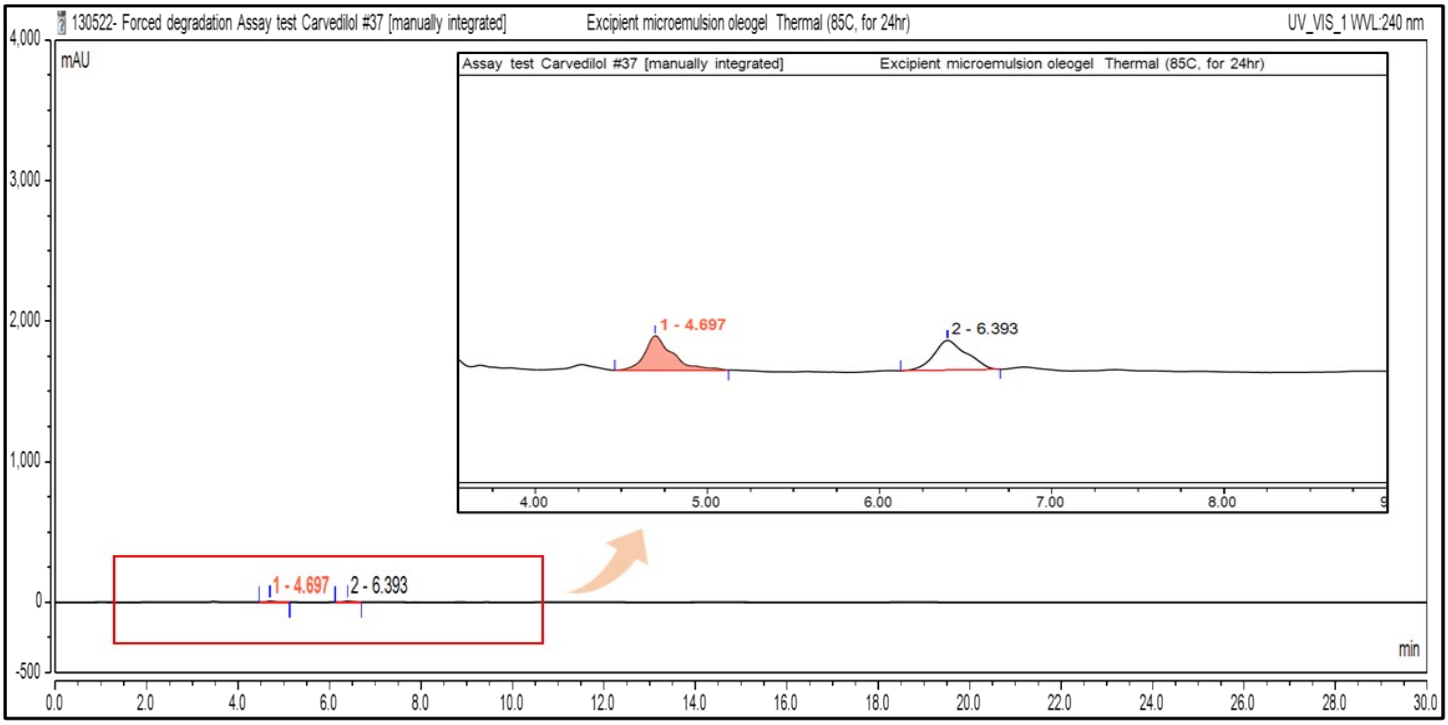


Figure 147S. HPLC chromatogram of thermal degradation of excipients at 85 ℃ 24 h.

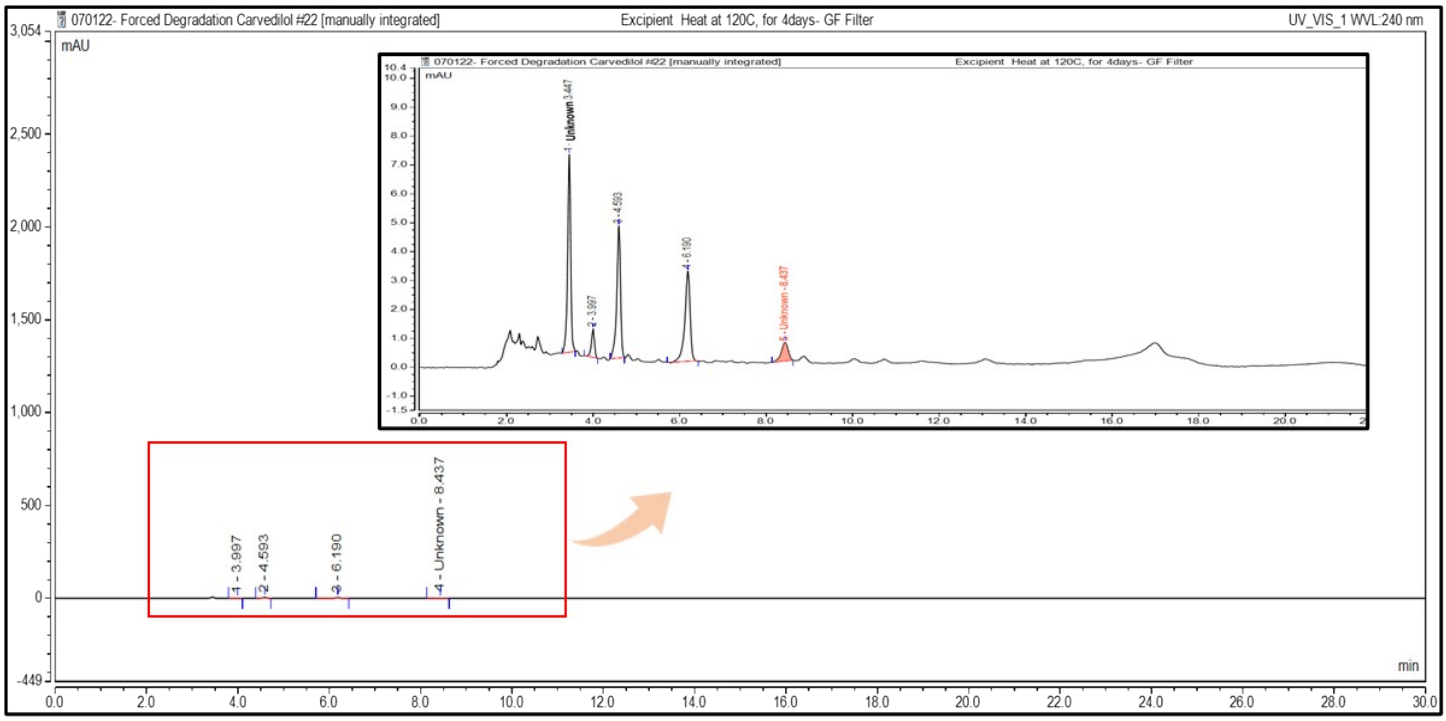


Figure 148S. HPLC chromatogram of thermal degradation of excipients at 120 ℃ for 4 days.

Photostability (Sunlight degradation)- CARV

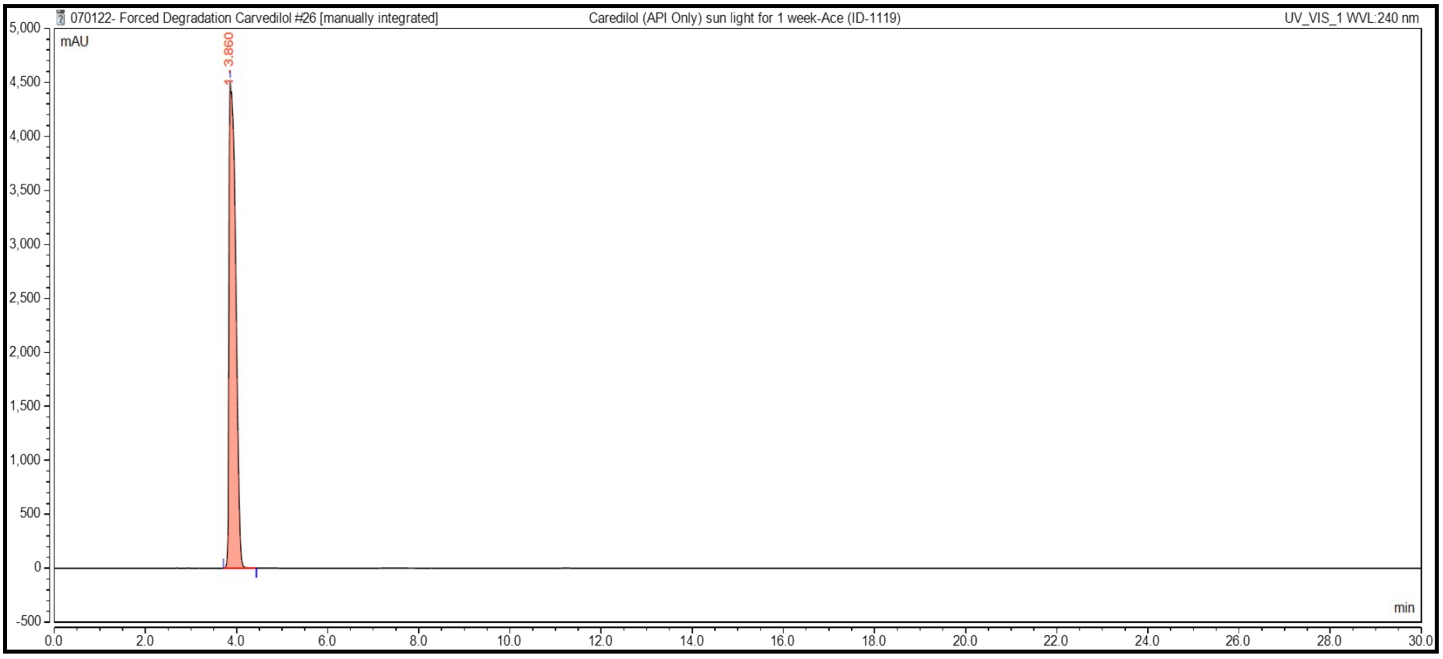


Figure 149S. HPLC Chromatogram of Photostability degradation of CARV for 1 week.

CARV-MEOG-Photostability (Sun light degradation)

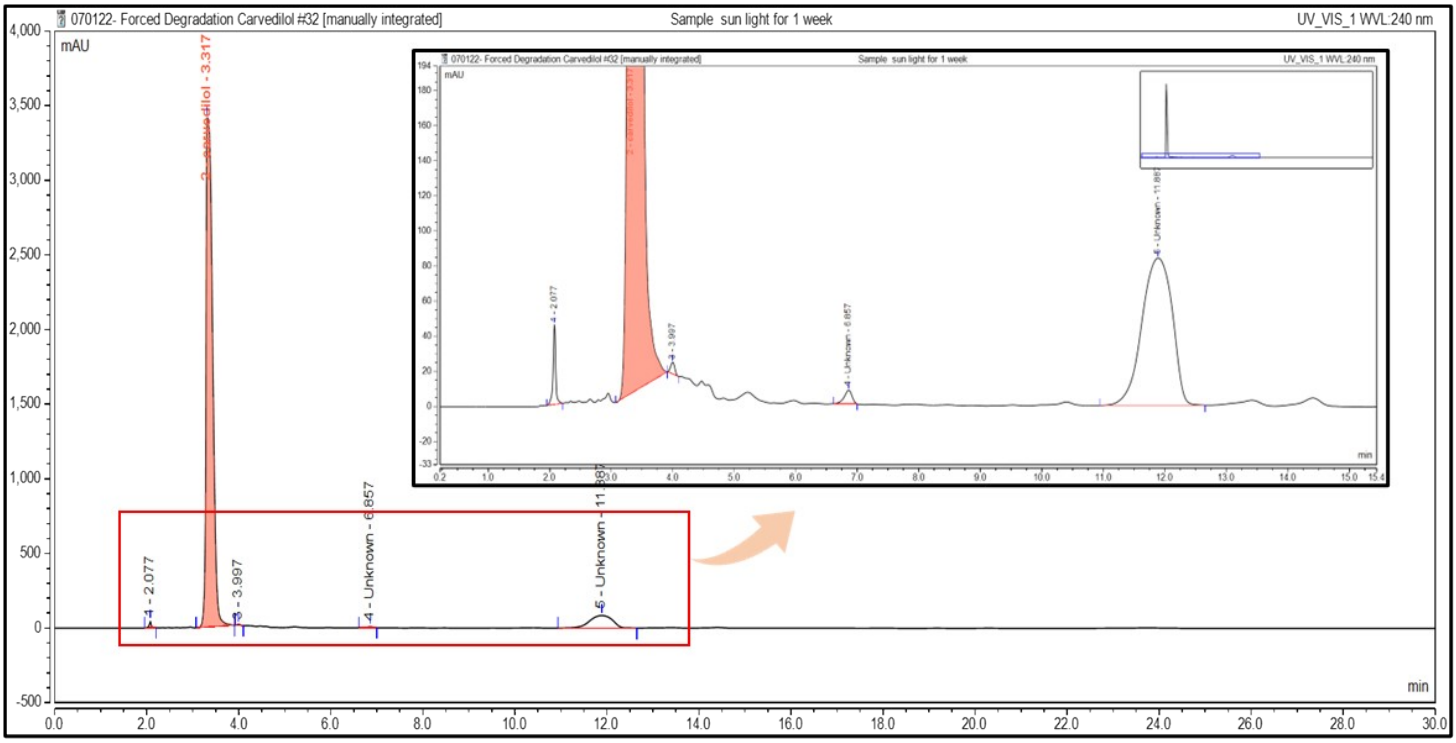


Figure 150S. HPLC chromatogram of photostability degradation of CARV-MEOG for 1 week.

Excipient- Microemulsion Loaded Oleogel-Thermal Degradation:

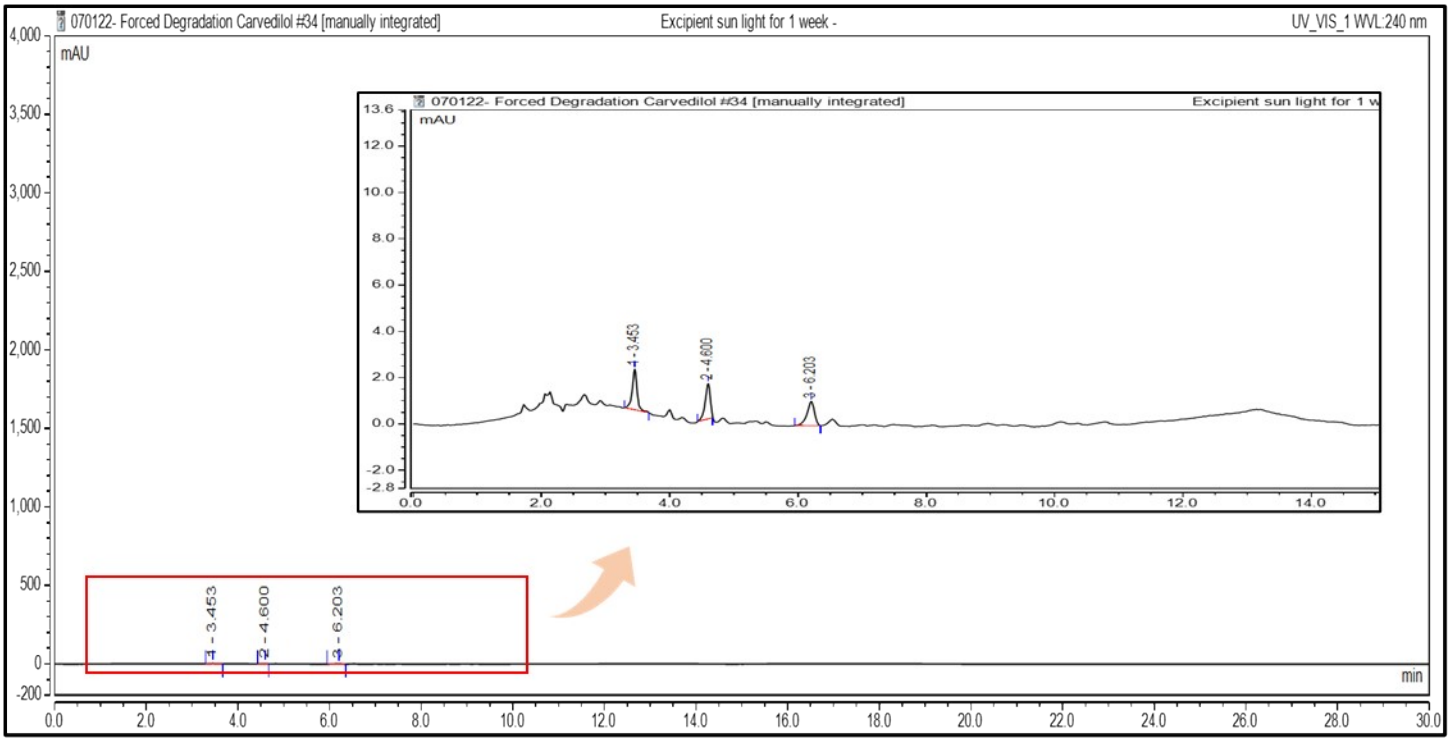


Figure 151S. HPLC chromatogram of photostability degradation of excipient for 1 week.

Air Degradation-CARV:

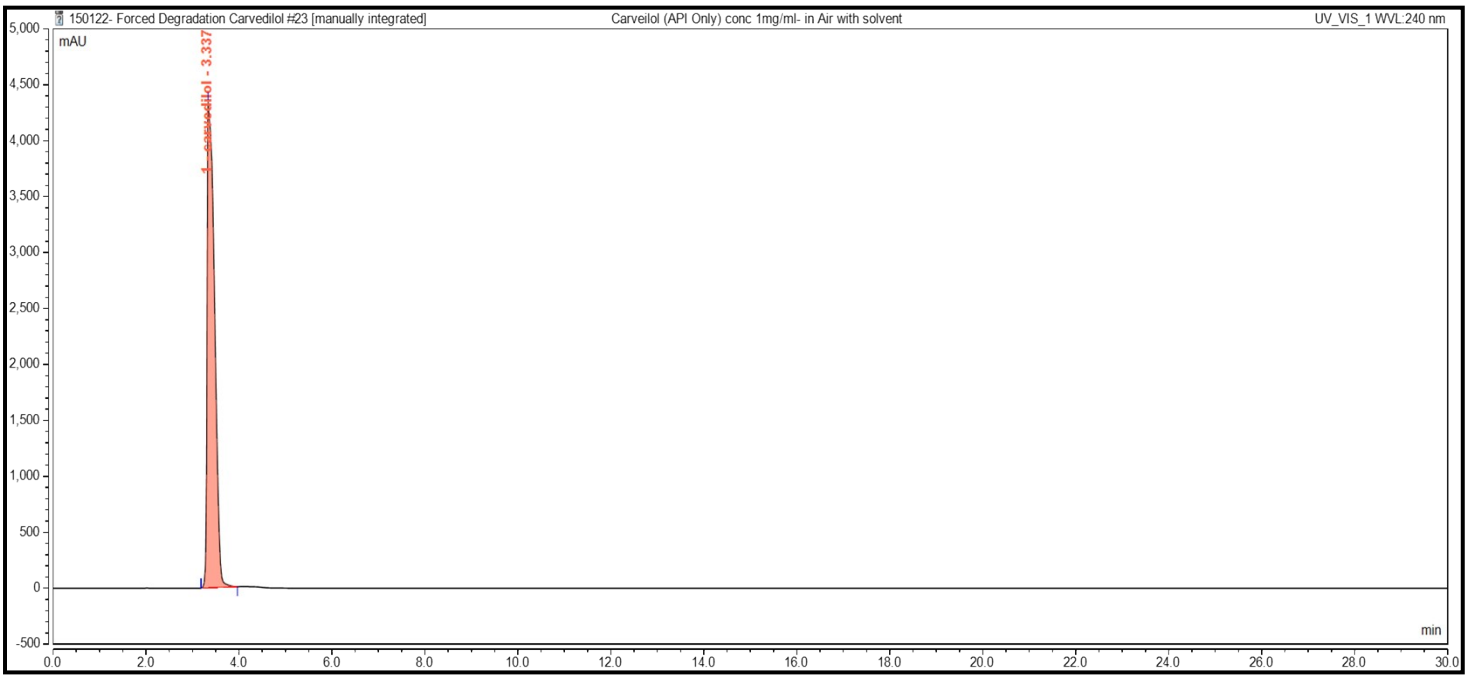


Figure 152S. HPLC chromatogram of air degradation of CARV with solvent for 24 h.

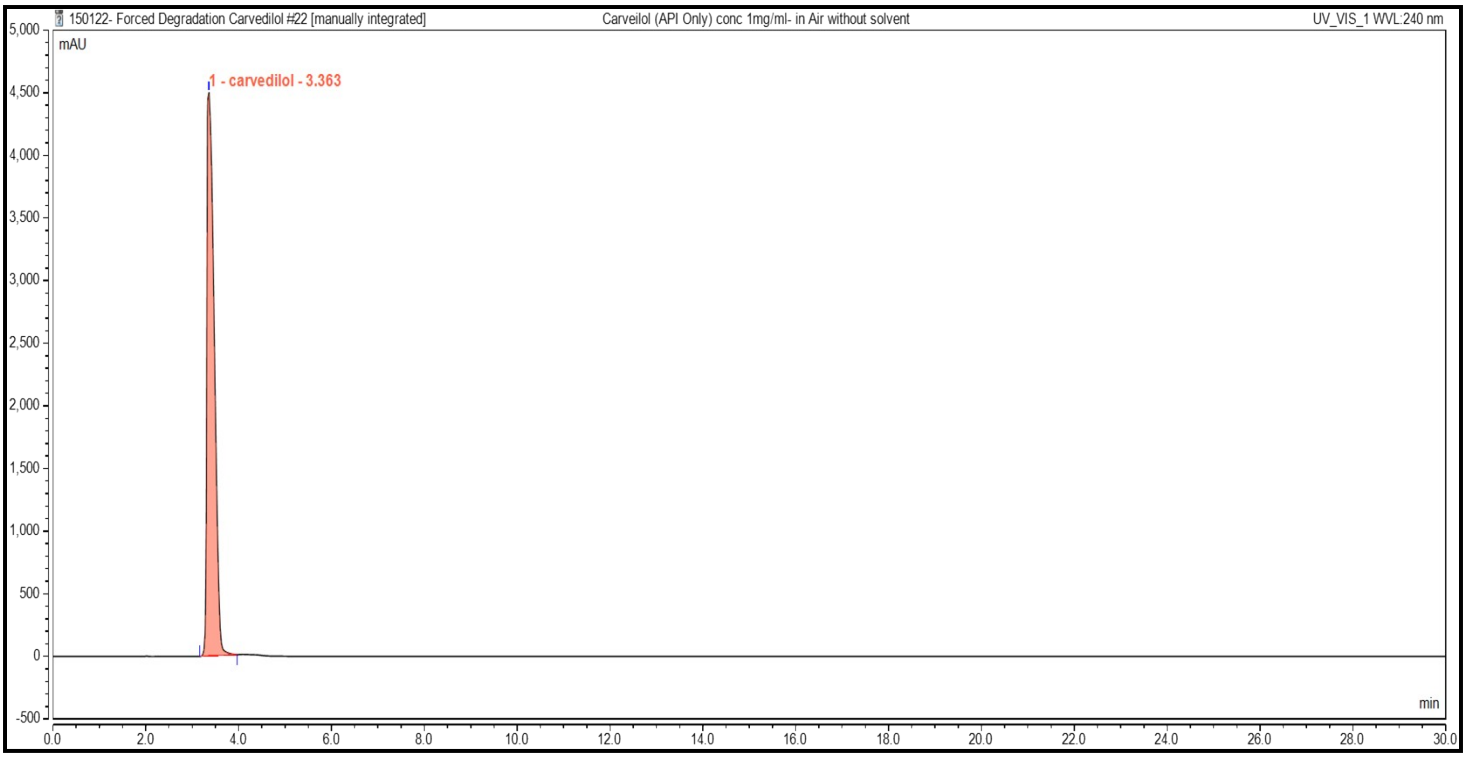


Figure 153S. HPLC chromatogram of air degradation of CARV without solvent for 24 h.

CARV-MEOG-Air Degradation:

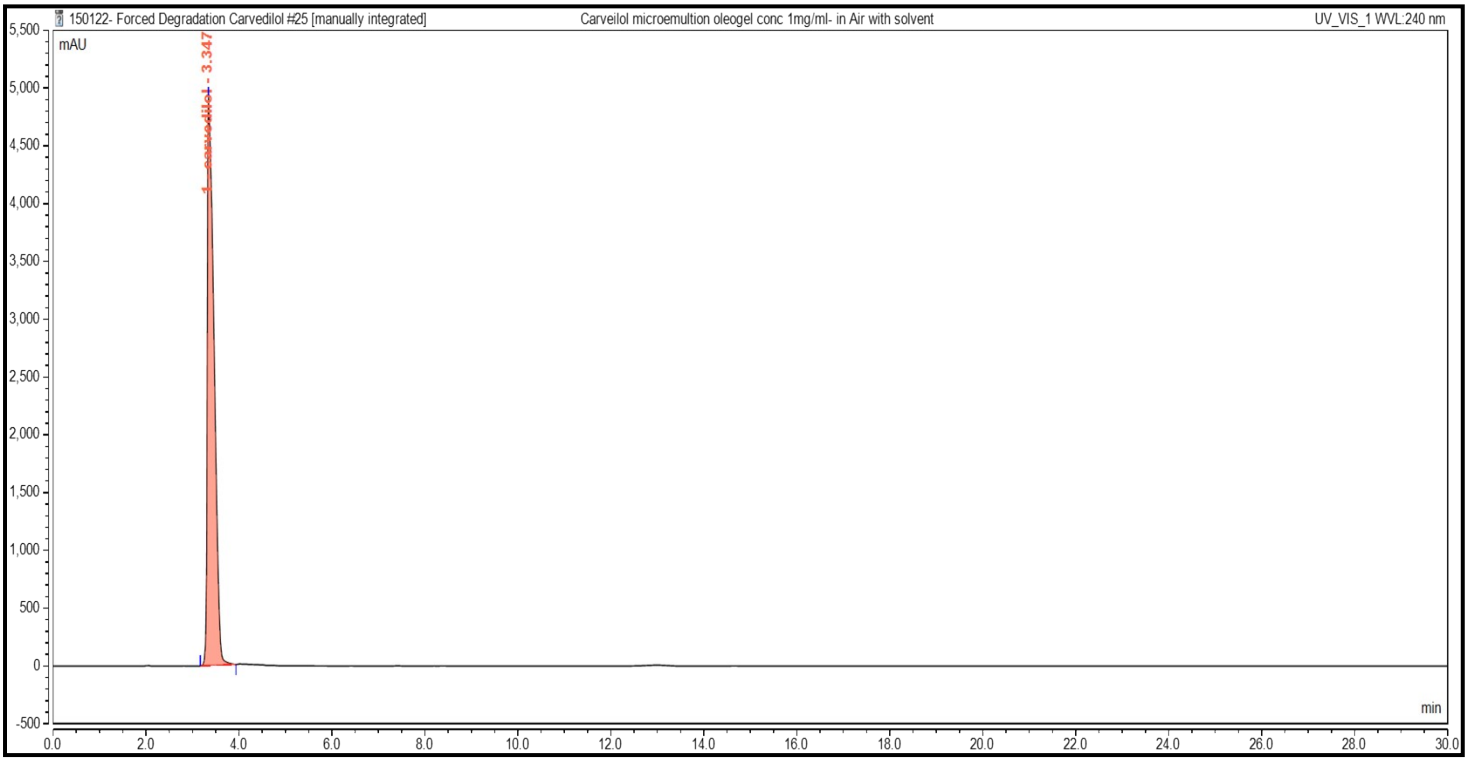


Figure 154S. HPLC chromatogram of air degradation of CARV-MEOG with solvent for 24 h.

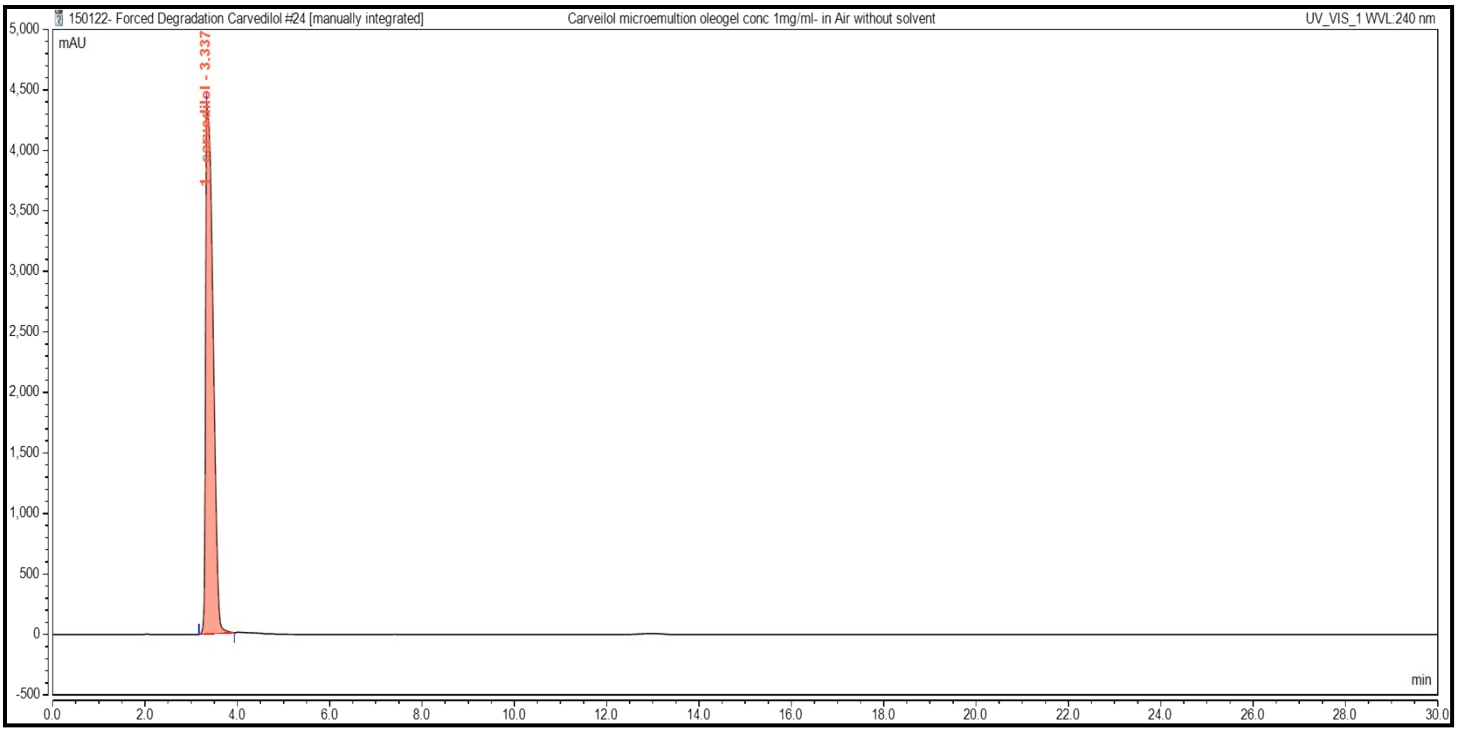


Figure 155S. HPLC chromatogram of air degradation of CARV-MEOG without solvent for 24 h.

Excipient microemulsion oleogel- Air Degradation:

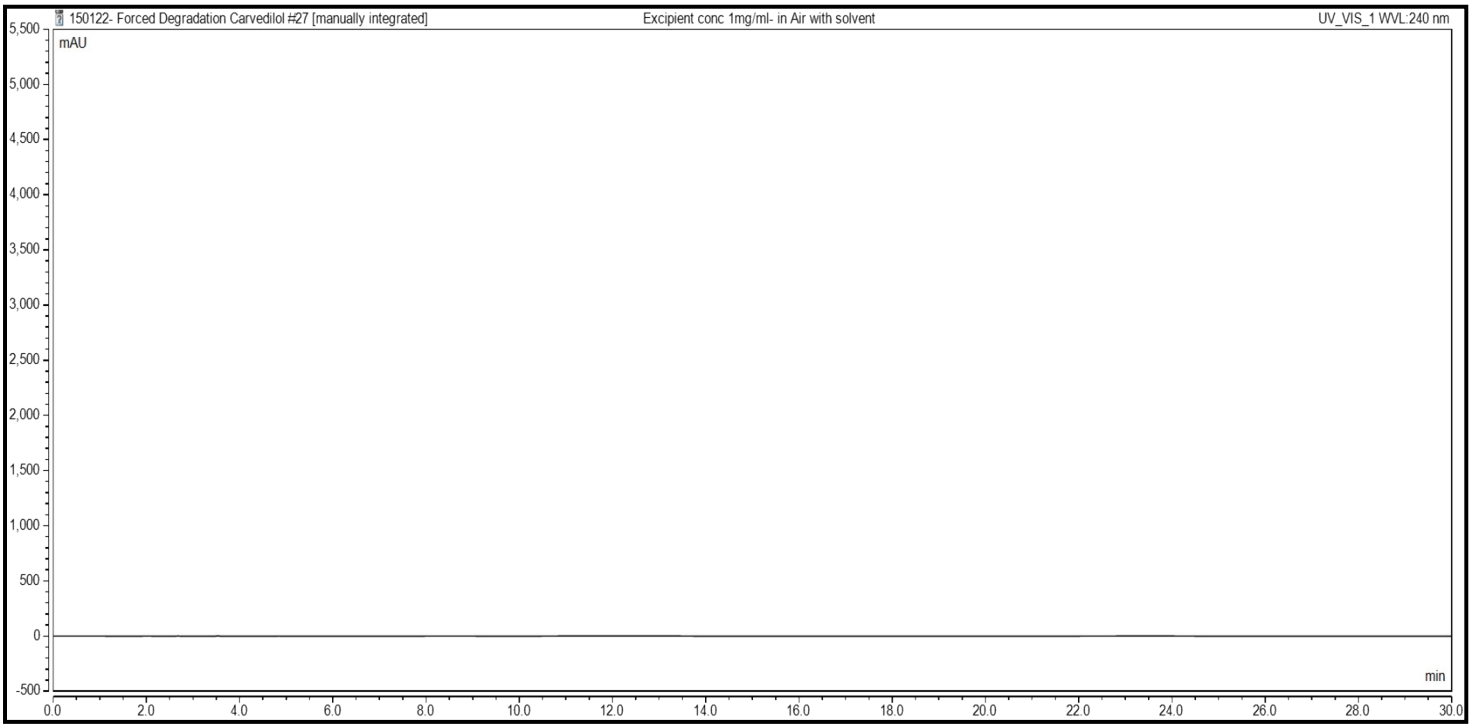


Figure 156S. HPLC chromatogram of air degradation of excipients with solvent for 24 h.

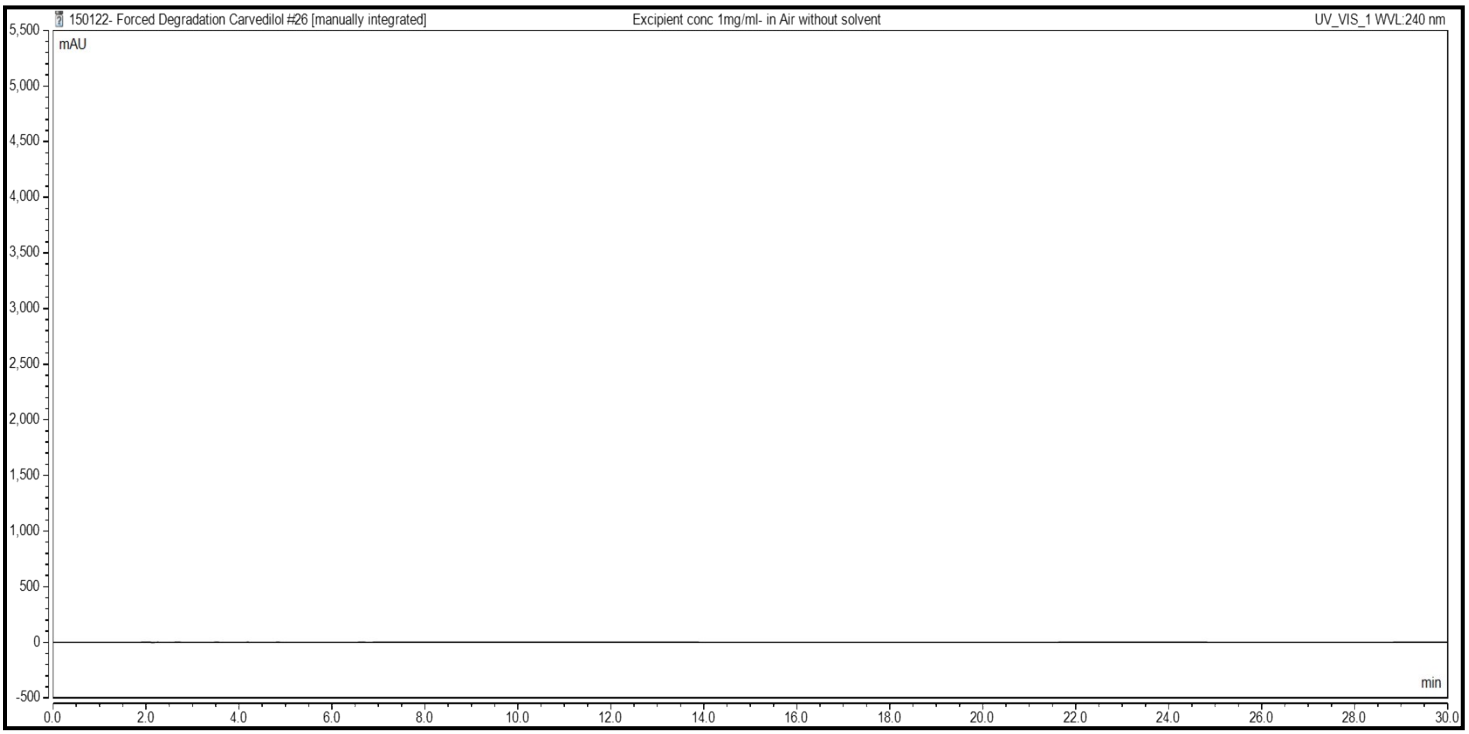


Figure 157S. HPLC chromatogram of air degradation of excipients without solvent for 24 h.

LC-MS Chromatograms:

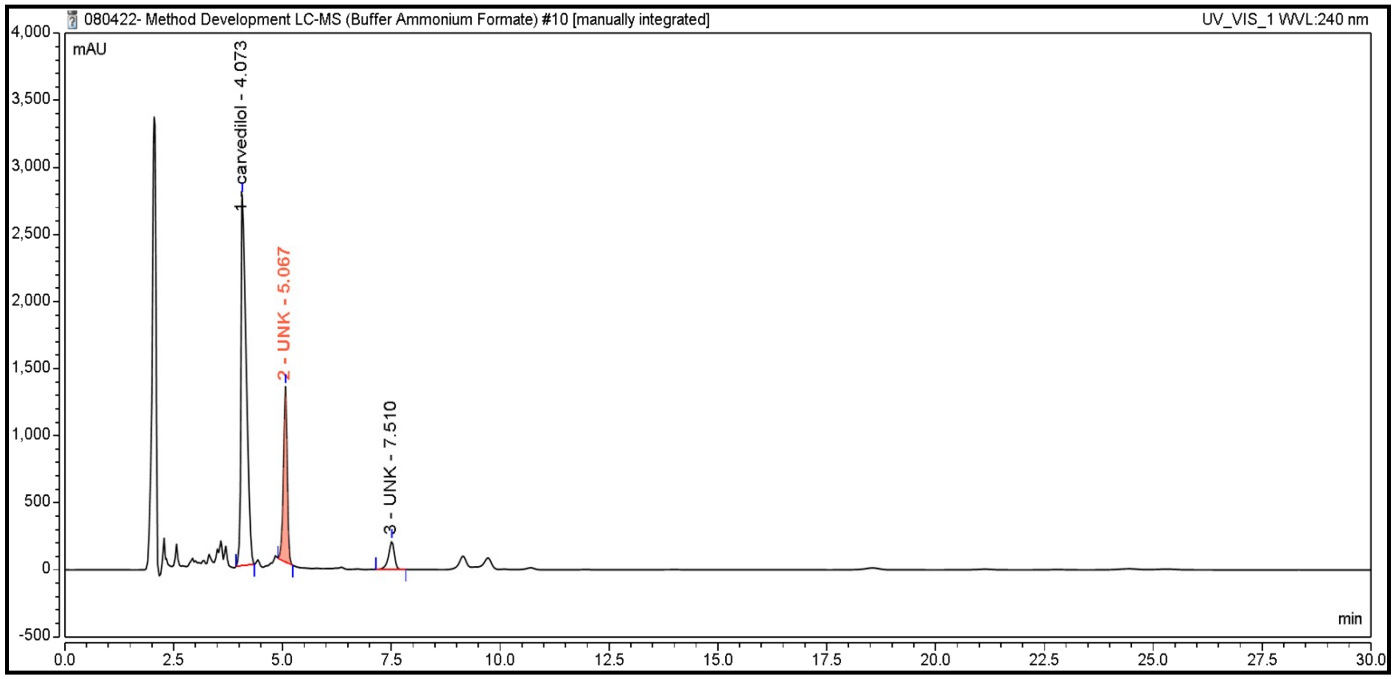


Figure 158S. HPLC chromatogram of oxidative degradation of CARV 35% H_2O_2 at RT for 24 h (ammonium formate buffer).

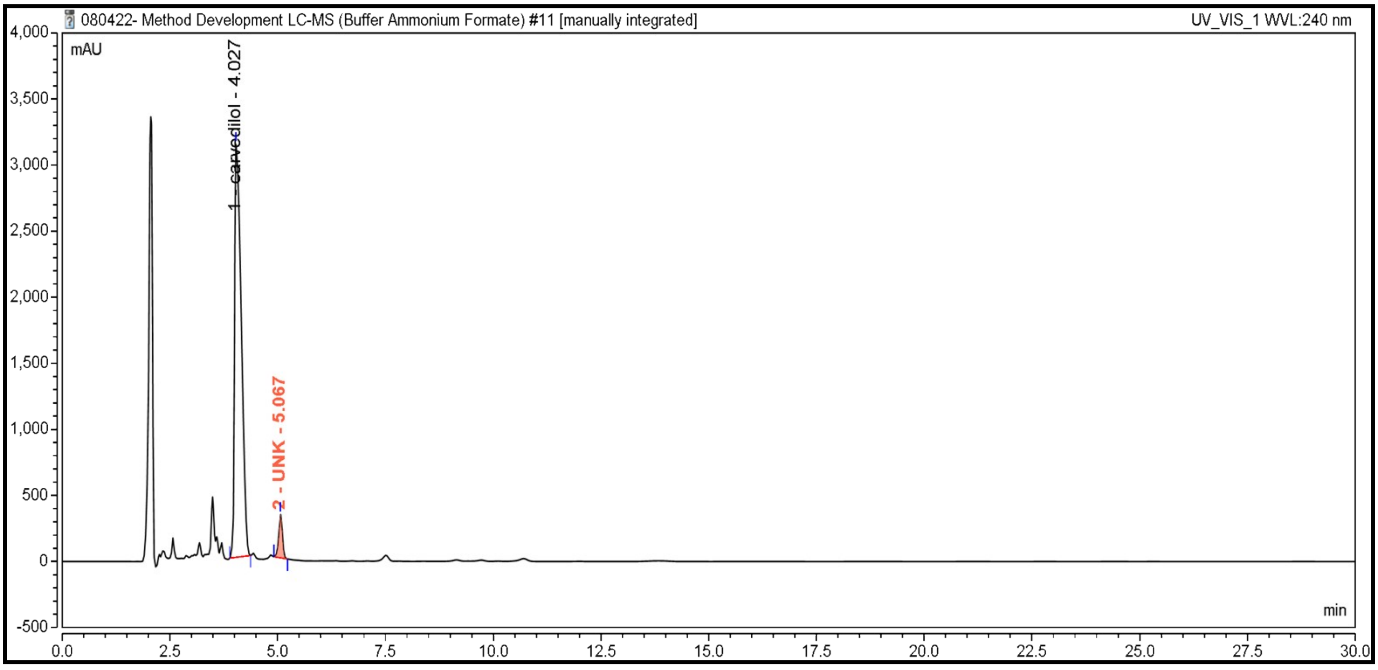


Figure 159S. HPLC chromatogram of oxidative degradation of CARV-MEOG 35% H_2O_2 at RT for 24 h (ammonium formate buffer).

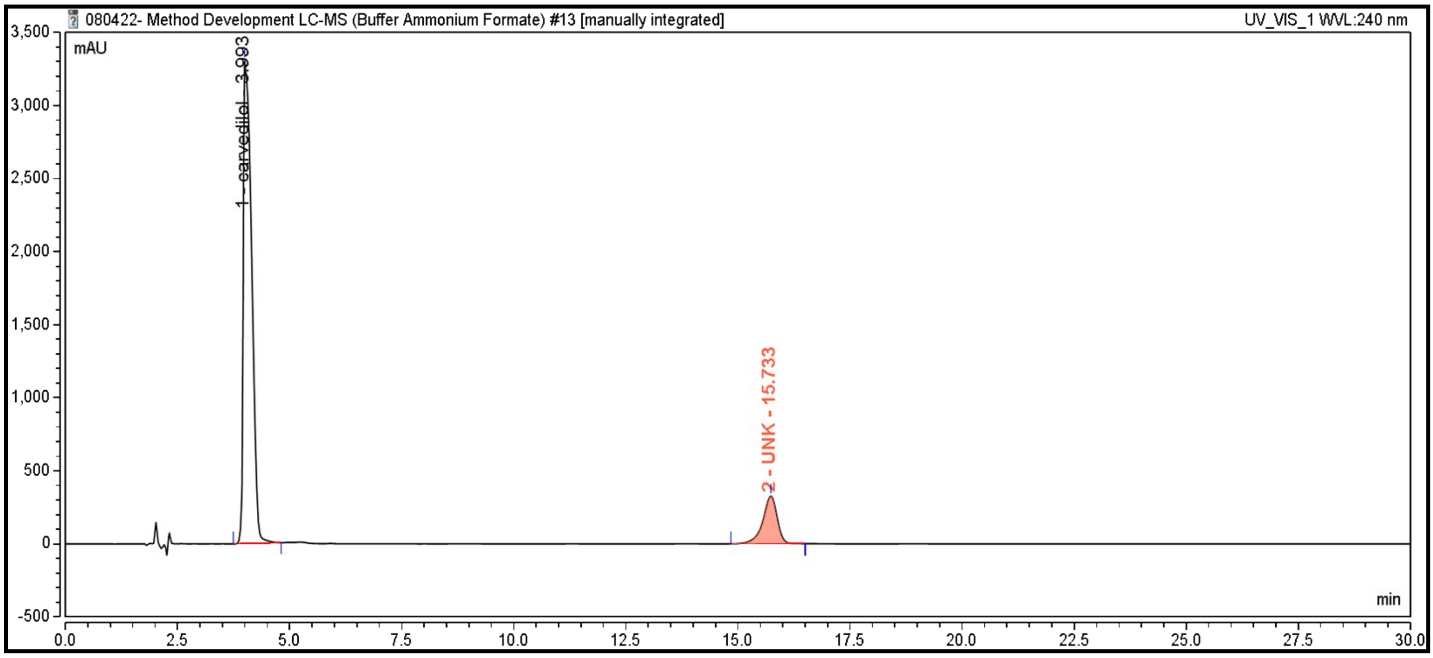


Figure 160S. HPLC chromatogram of basic degradation of carvedilol 1M NaOH at 85 °C for 14 h (ammonium formate buffer).

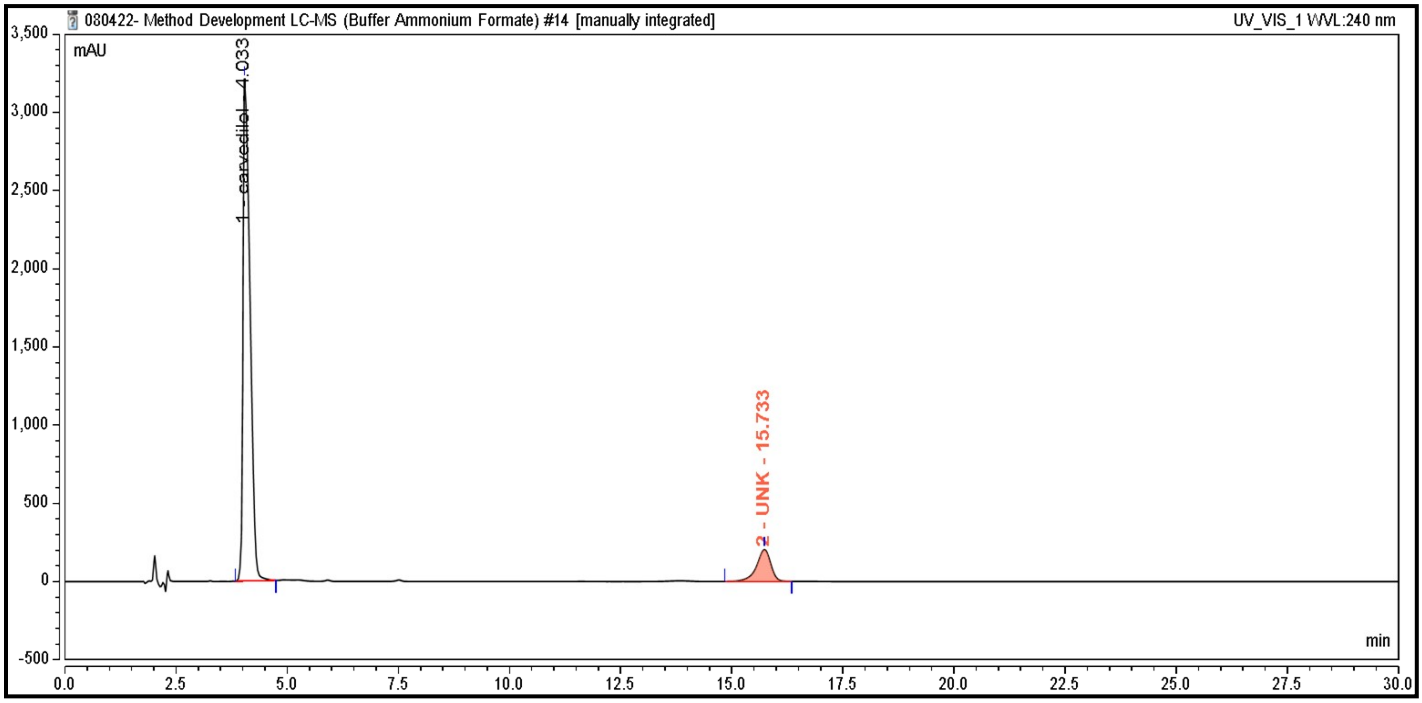


Figure 161S.. HPLC chromatogram of basic degradation of CARV-MEOG 1M NaOH at 85 °C for 14 h (ammonium formate buffer).

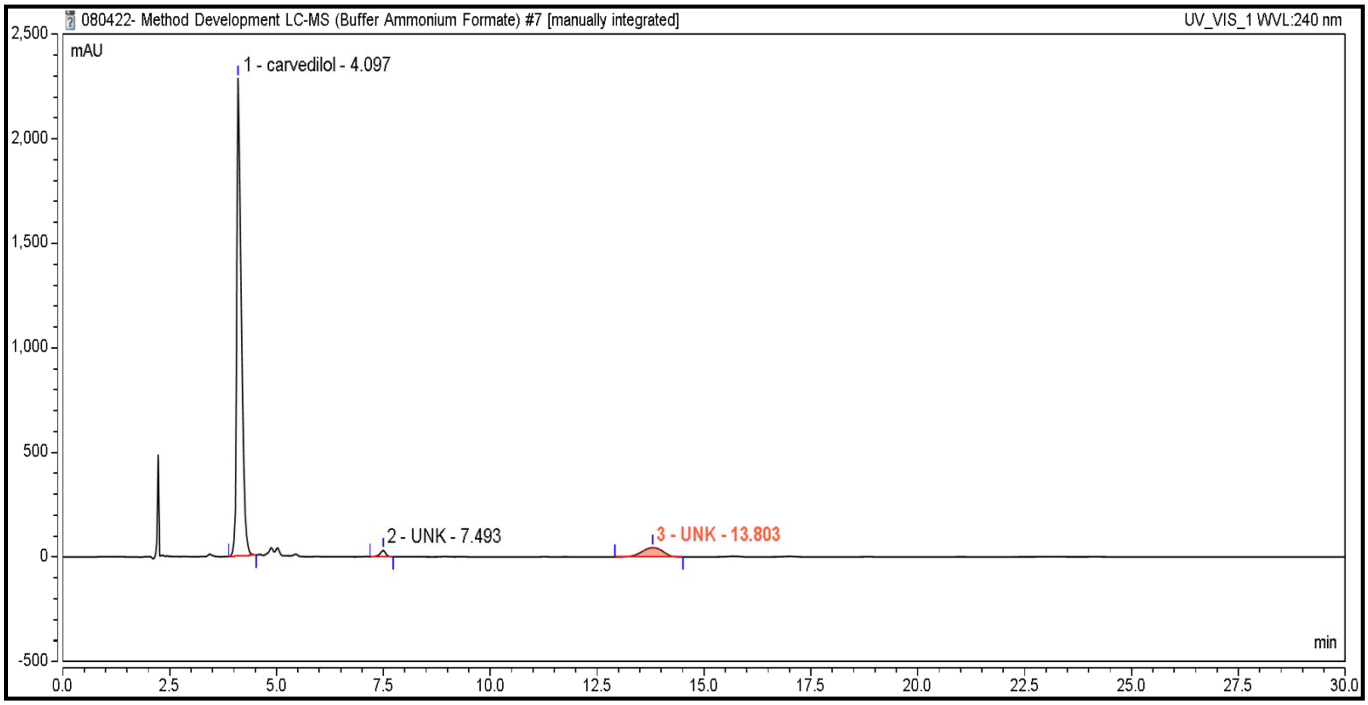


Figure 162S. HPLC chromatogram of thermal degradation of CARV-MEOG at 120 °C for 3 days (ammonium formate buffer)

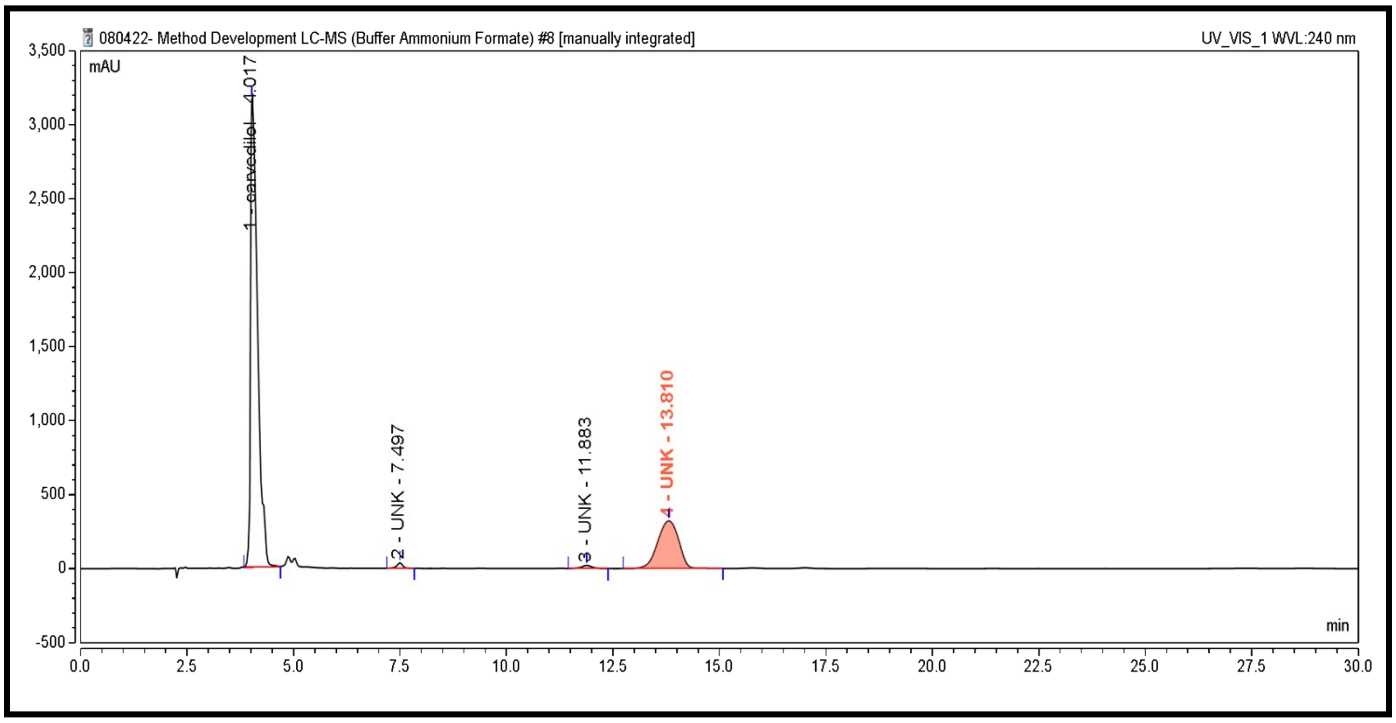


Figure 163S. HPLC chromatogram of CARV-MEOG-transcutol (old formula, 1 mg/ml)

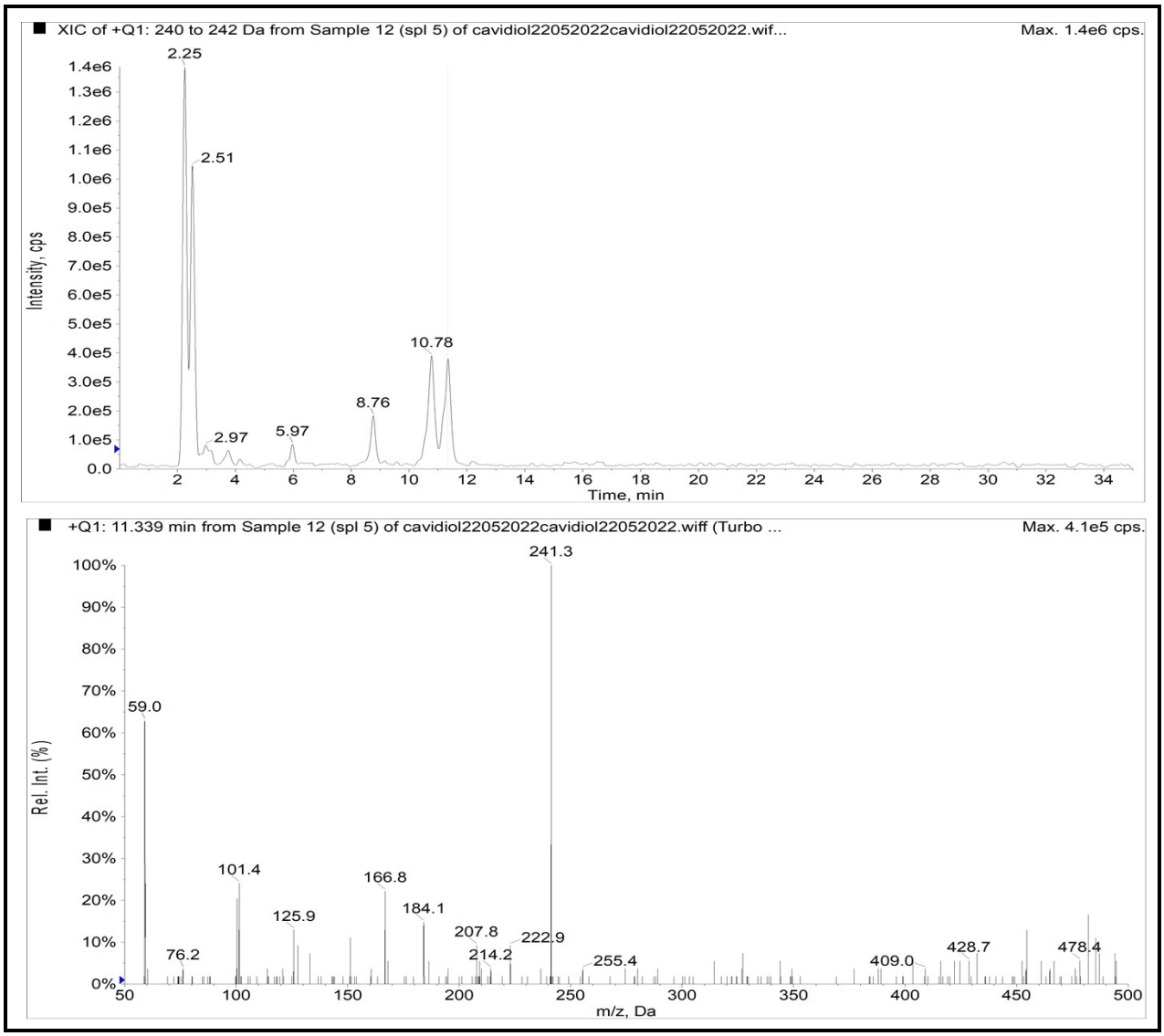


Figure 164S. LC/MS chromatogram of the degradant at RRT 1.4.

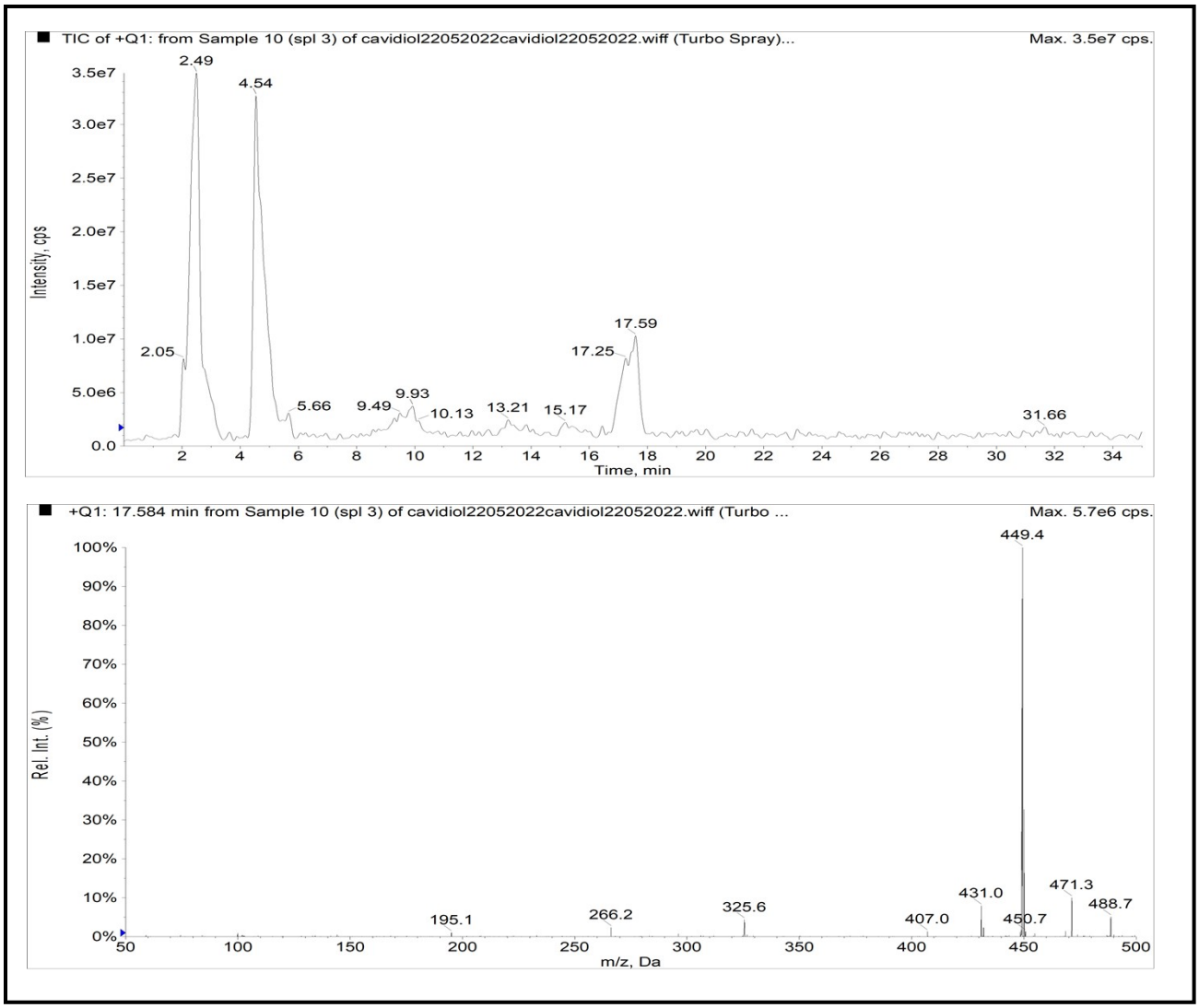


Figure 165S. LC/MS chromatogram of the degradant at RRT 4.2.

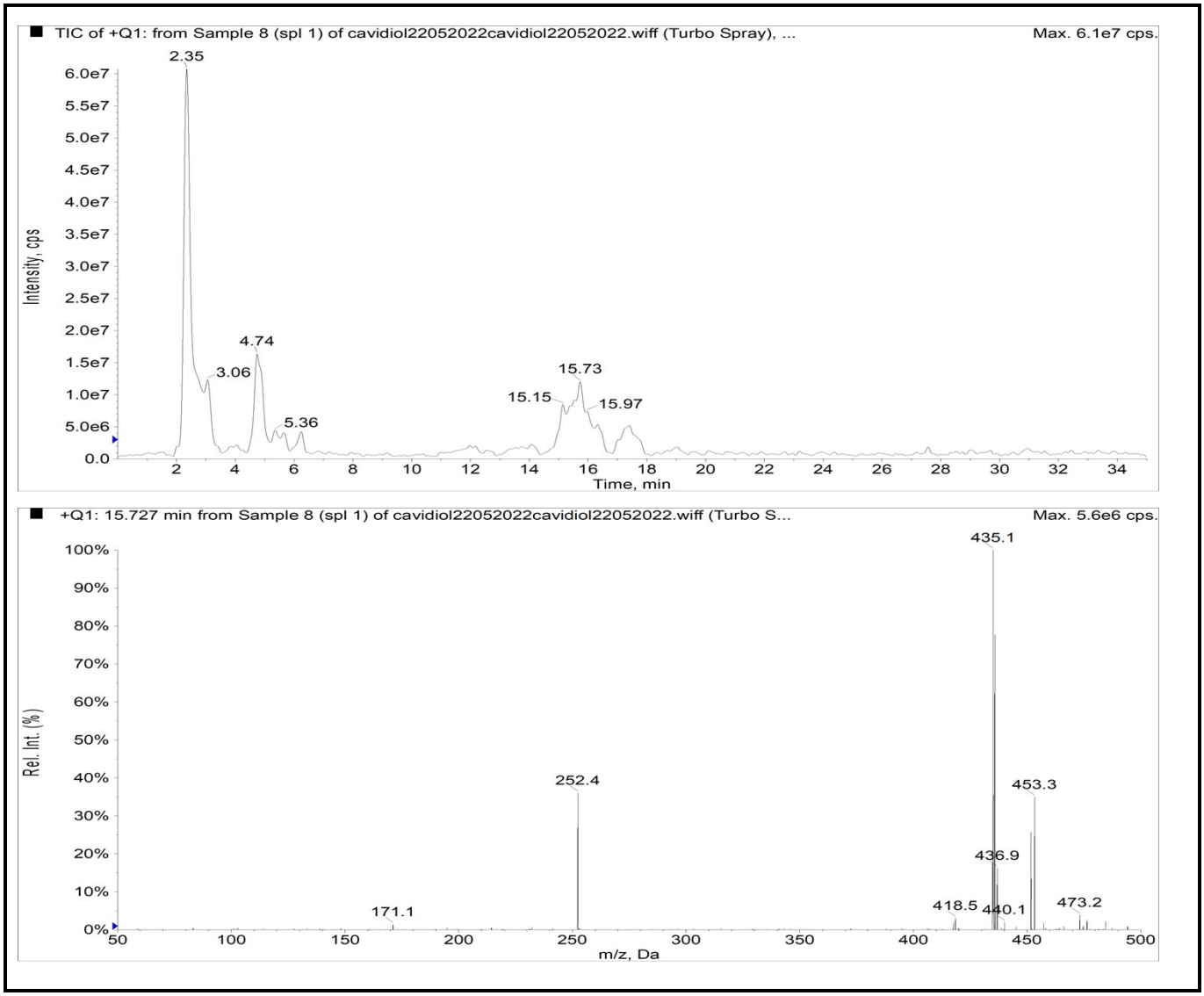


Figure 166S. LC/MS chromatogram of the degradant at RRT 3.7.