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DETERMINATION OF POTENTIAL IMPURITIES OF NAPROXEN SODIUM IN SOFT GELATIN CAPSULES DOSAGE BY USING HPLC

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ABSTRACT

A simple, sensitive, and rapid RP-HPLC method was developed and validated for the quantification of seven potential impurities in naproxen sodium soft gelatin capsules. The separation of impurities from the drug sample matrix was achieved using an Acquity BEH C18 (100 mm × 2.1 mm, 1.7 µm) column. The optimized mobile phase consisted of 0.1% ortho-phosphoric acid (OPA) in water, pH adjusted to 3.0 with diluted NaOH (mobile phase A), and acetonitrile (mobile phase B). Gradient elution at a flow rate of 0.5 mL/min, with UV detection at 230 nm, successfully separated the impurities.

The column temperature was maintained at 50°C, with an injection volume of 3 µL and a total run time of approximately 13 minutes. The method was validated in accordance with ICH Q2(R1) guidelines for linearity, specificity, accuracy, LOD, LOQ, precision, robustness, ruggedness, and solution stability. The validated method is stability-indicating and robust, making it suitable for determining impurities that may arise during the shelf life of the drug product. This method is beneficial for quality control laboratories, providing precise results with a shorter run time, enabling faster analysis.

Keywords: Naproxane Sodium, Validation, Stability Indicating, Soft Gelatin Capsules, RP-HPLC.

I. INTRODUCTION

Analytical chemistry, a scientific discipline, is employed to understand the composition and structure of matter via the acquisition, practice, and dissemination of knowledge. It is not limited to specific substances or reactions and encompasses the examination of both natural and synthetic materials. Geometric characteristics such as molecular structures and species identification are inherent in the qualities of analytical chemistry [1]. The advancement of its diverse concepts and theories encompasses food, pharmaceutical, and water safety and quality, environmental monitoring, biomedical applications, as well as aiding legal processes (forensics) and disease diagnosis.

Chromatography (CG):

Gas chromatography (GC) is a prominent and established technique for the separation of multi-component mixtures into their separate constituents, applicable in both quantitative and qualitative analyses. However, additional techniques such as IR spectroscopy, NMR and mass spectrometry are necessary for definitive identification and confirmation.

Method:

Aim: The objective of this analytical technique validation research is to develop robust and accurate methodologies for assessing isomeric impurities in NAN utilizing high-performance liquid chromatography (HPLC).

Sample solution preparation:

Carefully removed and collected the medicinal ingredient from at least ten soft gelatin capsules, then transferred the contents into a dry, clean glass beaker. After weighing and adding around 10 mg of NAN sodium to a 100 mL volumetric flask, about 70 mL of diluent was added. The mixture was then sonicated for 15 minutes while being shaken occasionally. filtered using a 0.22 µm or finer porosity filter.

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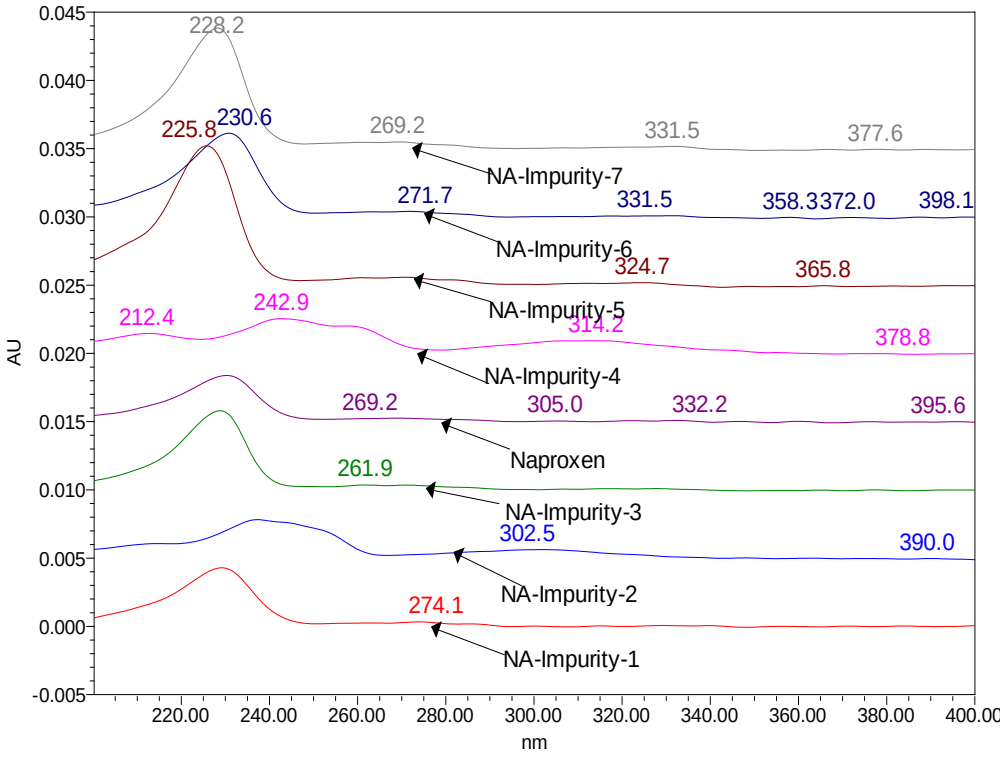

Fig 1: Spectra of NAN and its IMP

II. RESULTS AND DISCUSSION

HPLC conditions:

The table displays the final HPLC chromatographic conditions.

The table showed the respective Rt of the IMP . Finalized chromatographic specifications

Table 1:

Chromatographic Parameter	Condition			
Column	Acquity BEH C18 (100 × 2.1) mm, 3 ⍰m.			
MOP A	A diluted sodium hydroxide solution is used to bring the pH down to 3.0 ± 0.05 after 1 milliliter of orthophosphoric acid is dissolved in 1000 milliliters of water. Use a 0.22µ membrane filter to filter.			
MOP B	Acetonitrile			
Flow Rate	1 mL/min			
Column Temperature	50°C			
Wavelength	230 nm			
Injection Volume	10 µL			
Gradient Programme	Time (min)	Flow rate (mL/min)	MOP -A (%)	MOP -B (%)
	0.0	1.0	65	35
	3.0	1.0	65	35
	10.0	1.0	30	70
	10.5	1.0	65	35

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	13.0 1.0 65 35
Rt	13 minutes
concentration	100 ppm
Retention time of NAP	3.90 minutes

Table 2: Rt of NAP IMP

Name of the impurity	RRT
Imp - 1	0.34
Imp - 2	0.68
Imp - 3	0.74
Imp - 4	1.21
Imp - 5	1.70
Imp - 6	1.83
Imp - 7	2.33

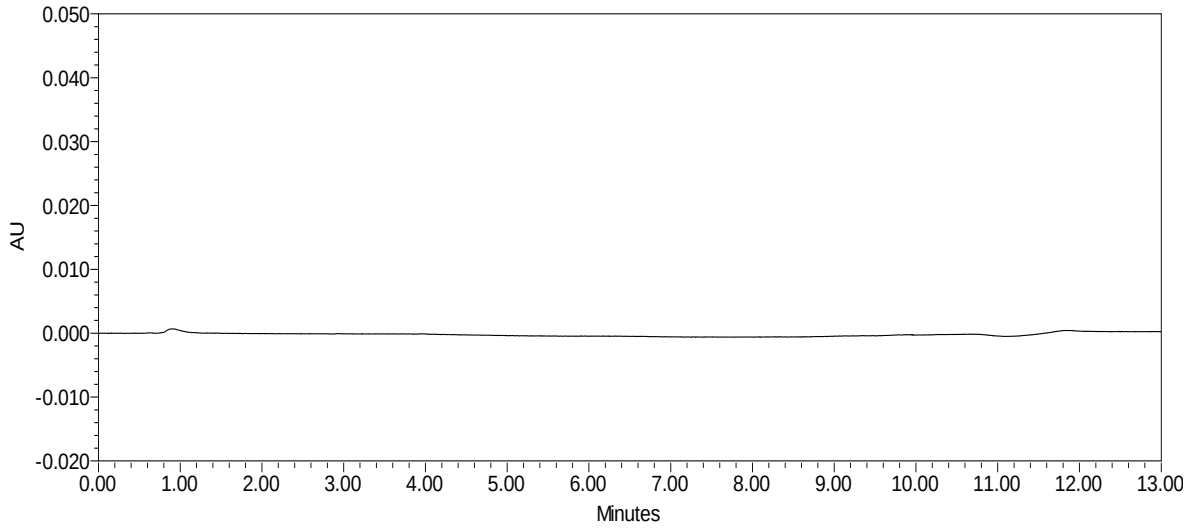

Fig 2: DILUENT CGM

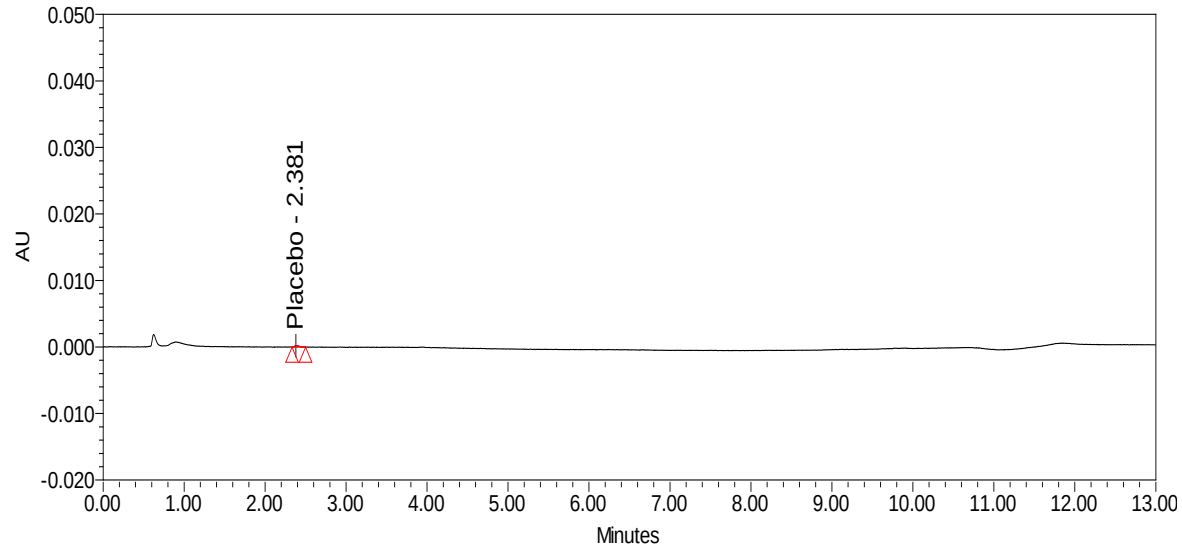

Fig 3: PLACEBO CGM

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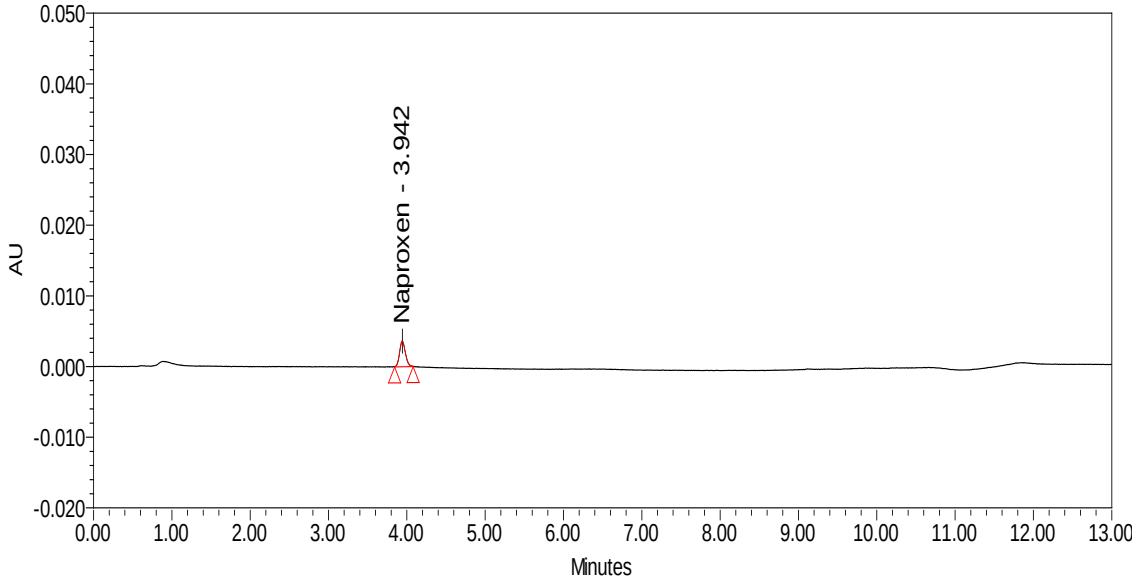

Fig 4: DILUTED STANDARD CGM

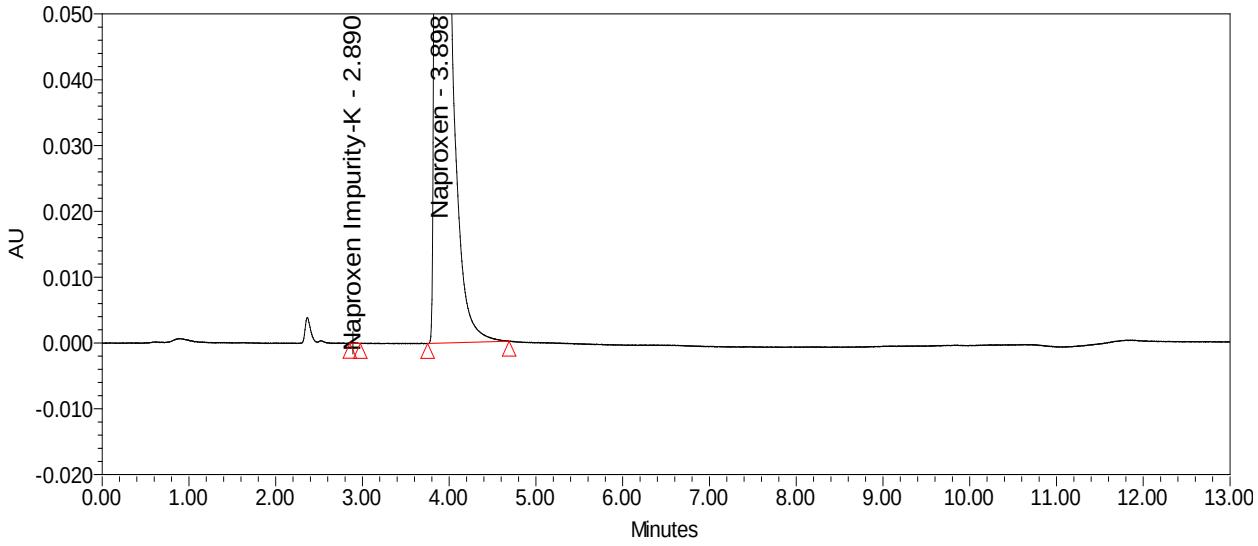

Fig 5: Control Sample CGM

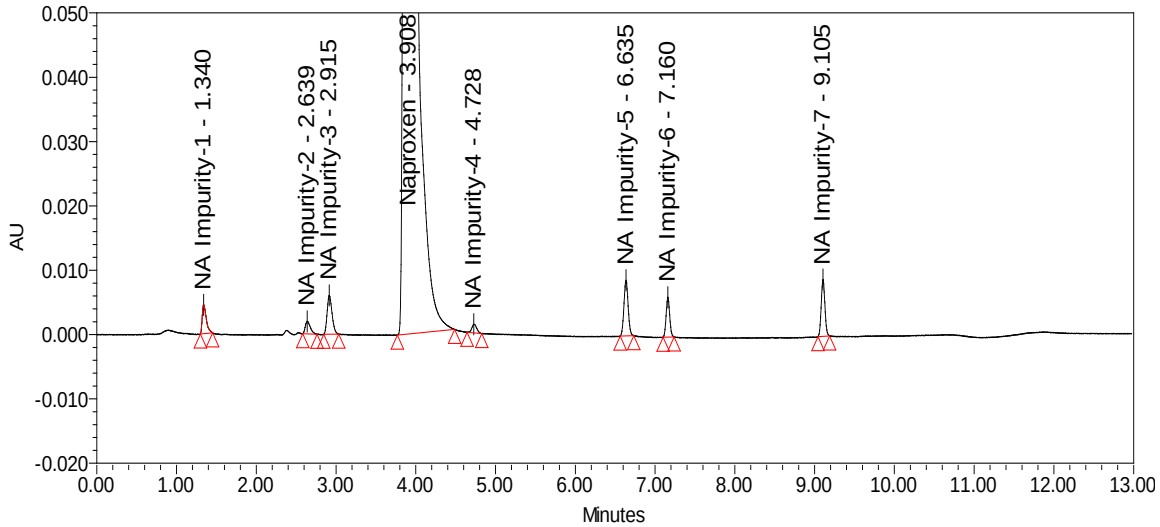

Fig 6: Spike Sample CGM

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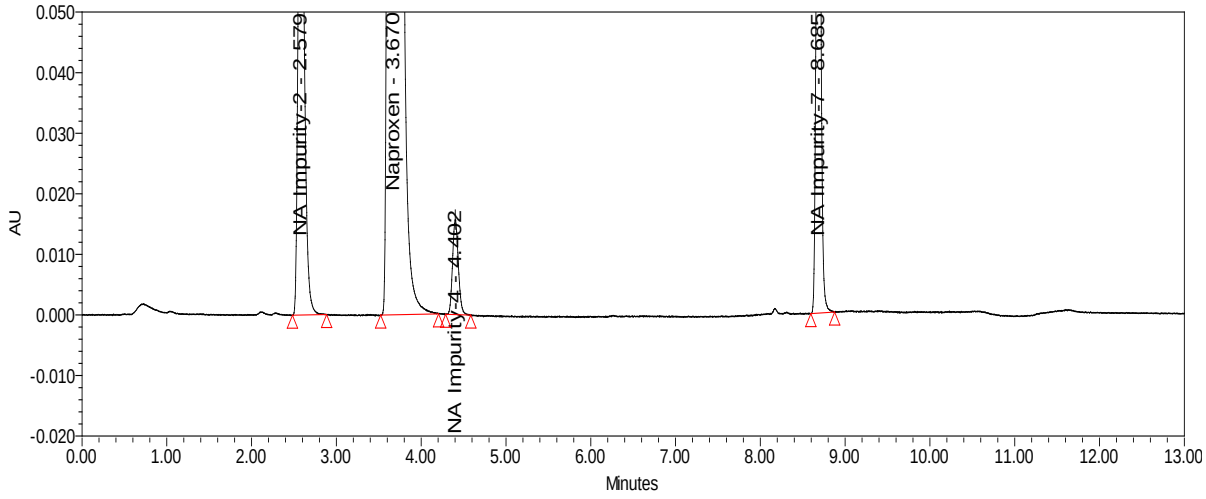

Fig 7: CGm of Acid degradation sample

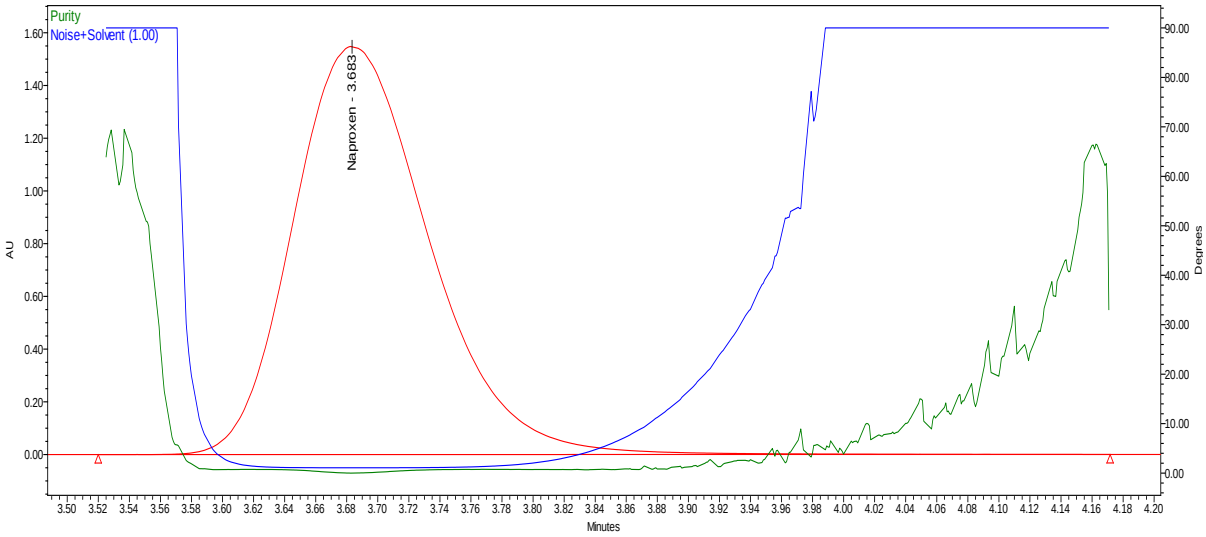

Fig 8: Purity plot of NA in Acid degradation

Purity Angle: 0.414;

Purity Threshold: 1.173

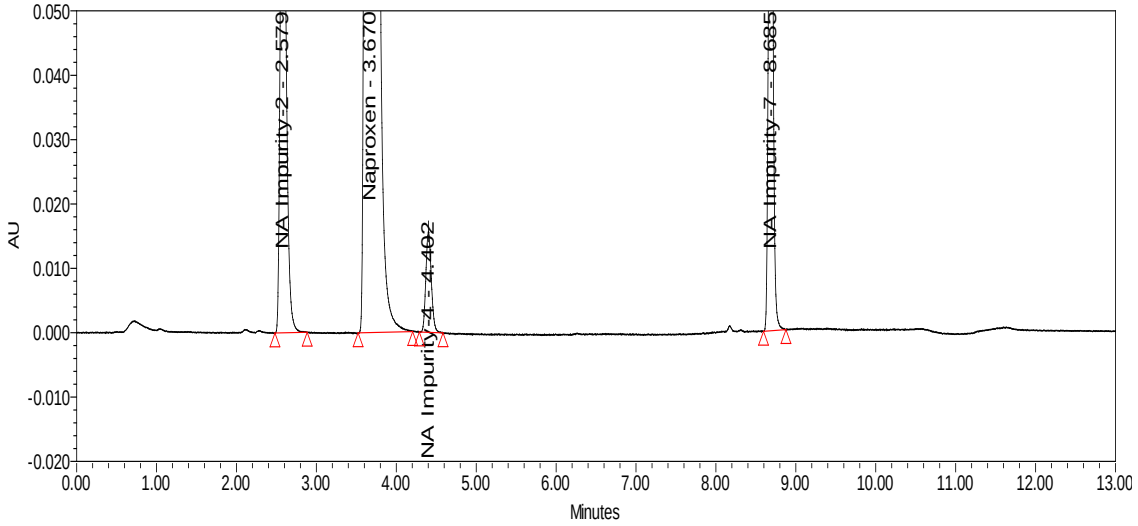

Fig 9: CGm of Base degradation sample

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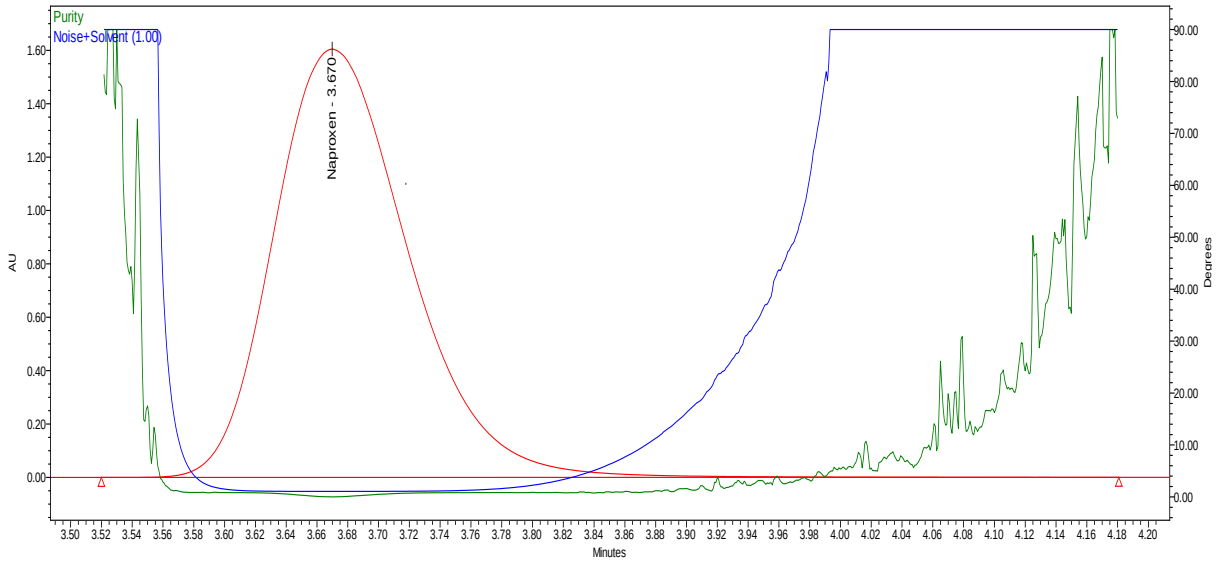

Fig 10: Purity of NA in Base degradation

Purity Angle: 0.453;

Purity Threshold: 1.127

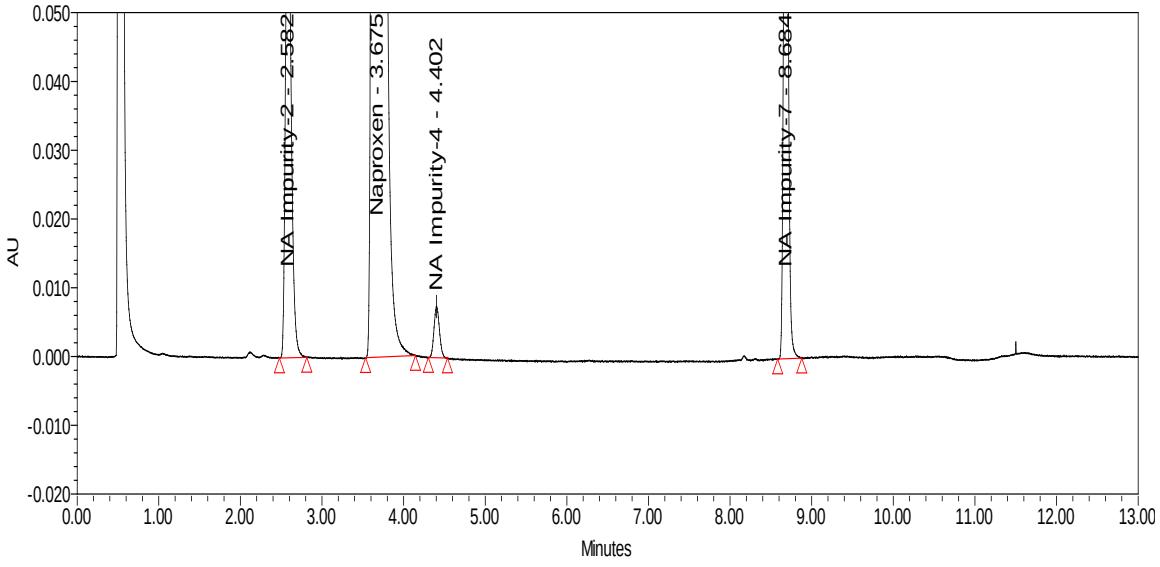

Fig 11: CGm of Peroxide degradation sample

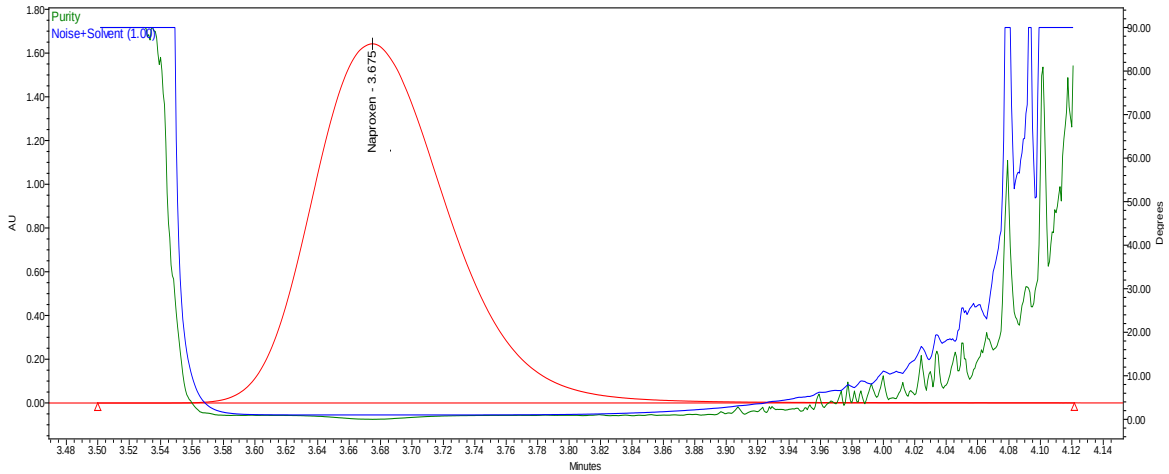

Fig 12: Purity of NA in Peroxide degradation

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Purity Angle: 0.497; Purity Threshold: 1.014

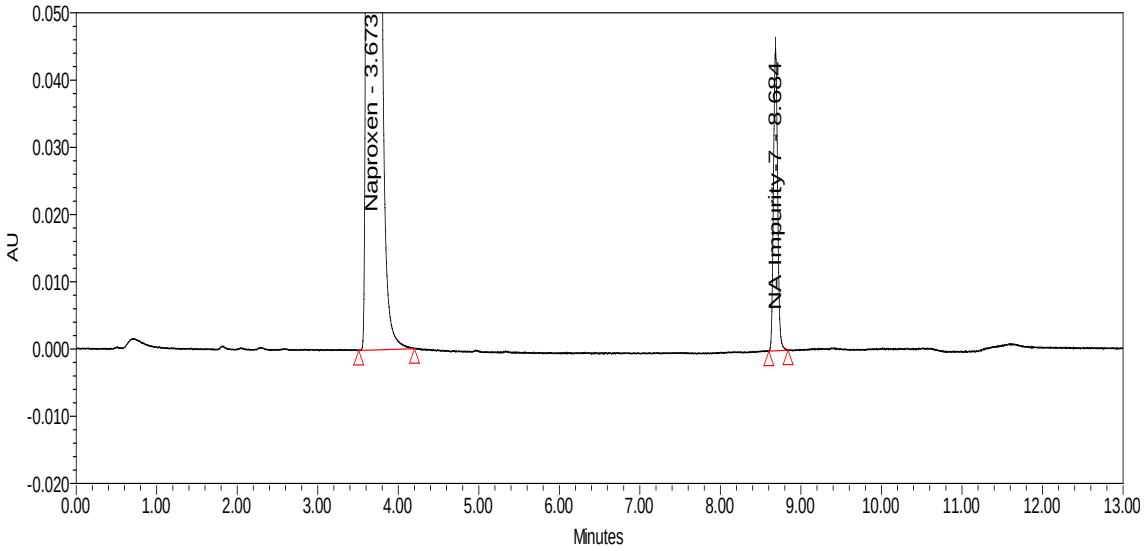

Fig 13: CGm of Thermal Stress sample

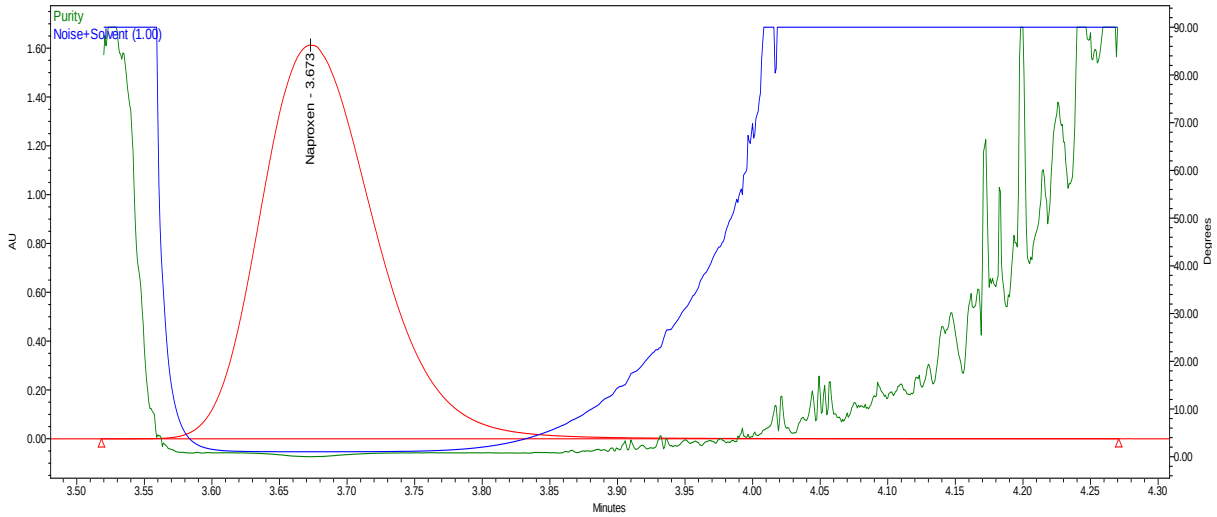

Fig 14: Purity plot of NA in Thermal degradation

Purity Angle: 0.448; Purity Threshold: 1.110

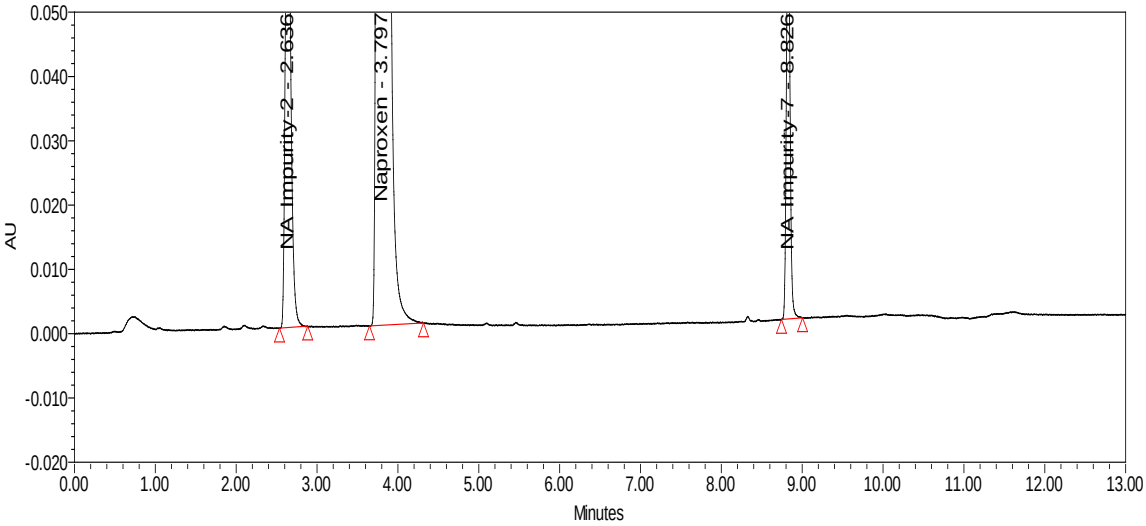

Fig 15: CGm of Humidity Stress sample

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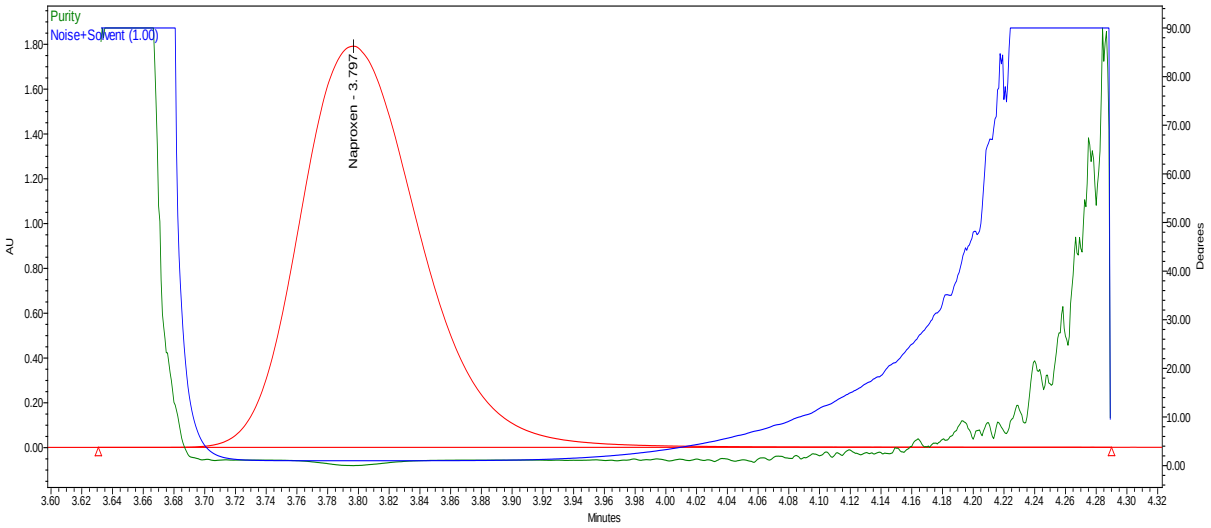

Fig 16: Purity plot of NA in Humidity degradation

Purity Angle: 0.638;

Purity Threshold: 1.021

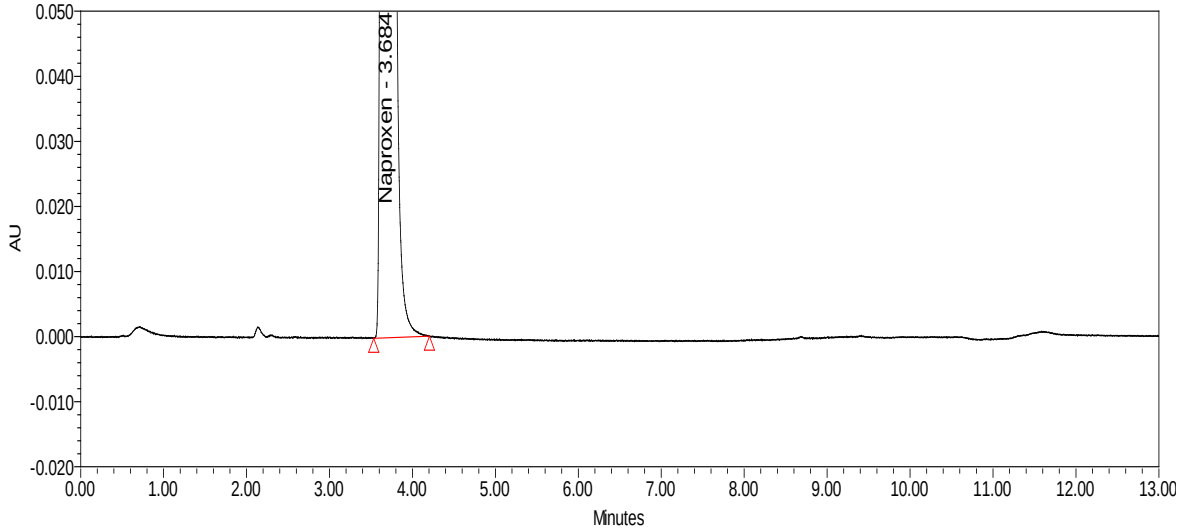

Fig 17: CGm of Photolytic Stress sample

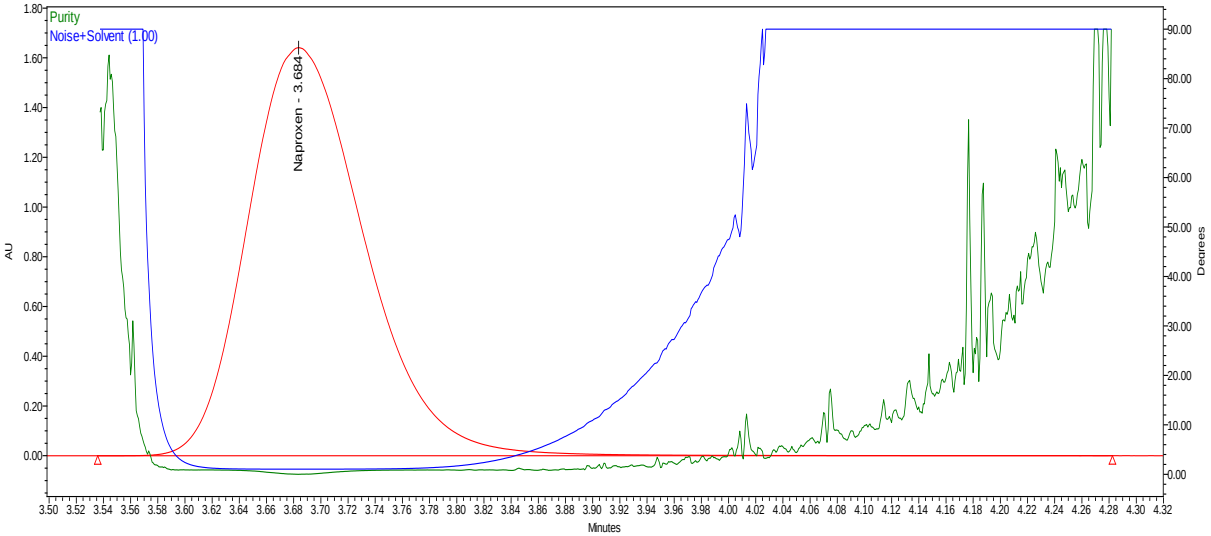

Fig 18: Purity of NA in Humidity degradation

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Purity Angle: 0.474;

Purity Threshold: 1.108

Table 3: Mass balance

Degradation condition	% Assay	% imps+ %Deg. products	Mass balance (%Assay+ %Imp+% Deg. products	Major IMP
Acid	87.6	11.8	98.1	Impurity-3, Impurity-4 and Impurity-7
Alkali	90.4	9.3	99.4	Impurity-3, Impurity-4 and Impurity-7
Oxidation	90.9	7.1	100.1	Impurity-3, NA Impurity-4 and Impurity-7
Thermal	97.1	1.2	99.6	Impurity-7
Humidity	94.0	4.6	99.7	Impurity-3 and Impurity-7
Photolytic	98.5	0.0	99.5	No degradation

PRECISION:

Method precision

Table 4:

Sample Name	Method precision		
	Avg	SD	%RSD
NA-imp-1	0.217	0.002	0.9
NA-imp-2	0.200	0.005	2.5
NA-imp-3	0.213	0.002	0.9
NA-imp-4	0.199	0.003	1.5
NA-imp-5	0.213	0.005	2.3
NA-imp-6	0.194	0.003	1.5
NA-imp-7	0.206	0.004	1.9

INTERMEDITE PRECISION

The procedure was assessed by various analysts utilizing different columns and HPLC instruments on separate days.

Table 5: Intermedite precision

Sample Name	Intermediate precision		
	Avg	SD	%RSD
NA-imp-1	0.210	0.003	1.4
NA-imp-2	0.198	0.004	2.0
NA-imp-3	0.211	0.003	1.4
NA-imp-4	0.192	0.003	1.6
NA-imp-5	0.210	0.002	1.0
NA-imp-6	0.192	0.004	2.1
NA-imp-7	0.201	0.003	1.5

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LOD & LOQ

Table 6:

Sample Name	LOD	LOQ
NAP	0.0023	0.0069
NA-Imp-1	0.0089	0.0268
NA-Imp-2	0.0021	0.0064
NA-Imp-3	0.0020	0.0059
NA-Imp-4	0.0098	0.0295
NA-Imp-5	0.0022	0.0065
NA-Imp-6	0.0020	0.0059
NA-Imp-7	0.0021	0.0063

LINEARITY AND RANGE

From the completed LOQ level to 150% of the IMP specified level, linearity solutions were performed. Plotting medication concentration against peak regions allowed for the creation of the curves. Using linear regression analysis, linear calibration curves were produced and acquired throughout the corresponding standard concentration range. The analytical method's range was defined as being between LOQ and 150% of the impurity specification values. The findings demonstrate a strong association between the peak area and NAP content as well as all other contaminants.

Linearity plot of Impurity-1

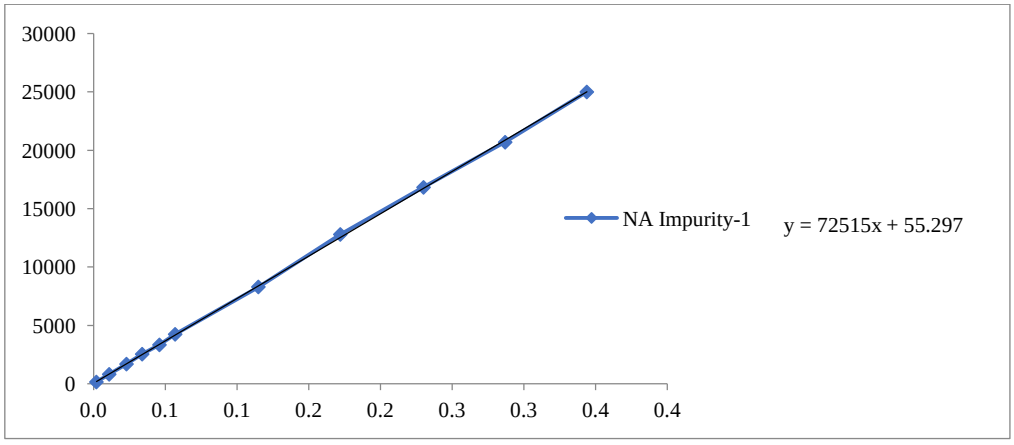

Fig 19: Linearity of Impurity-2

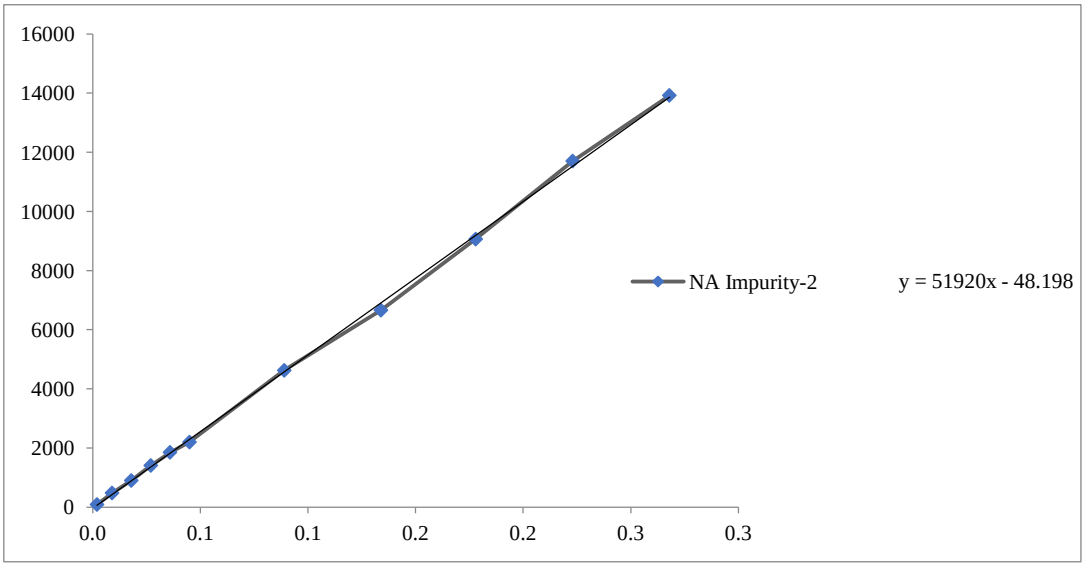

Fig 20: Linearity of Impurity-3

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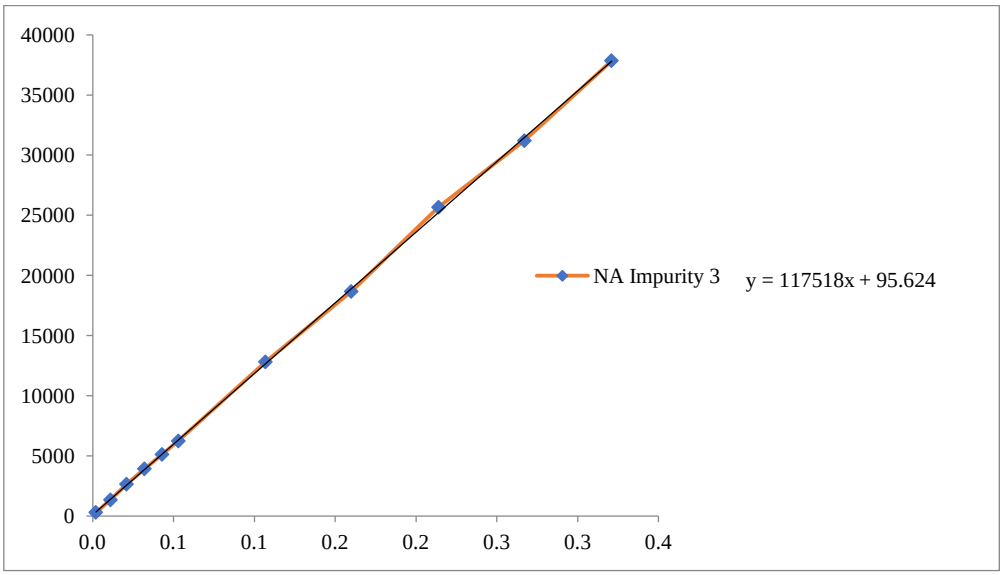

Fig 21: Linearity of Impurity-4

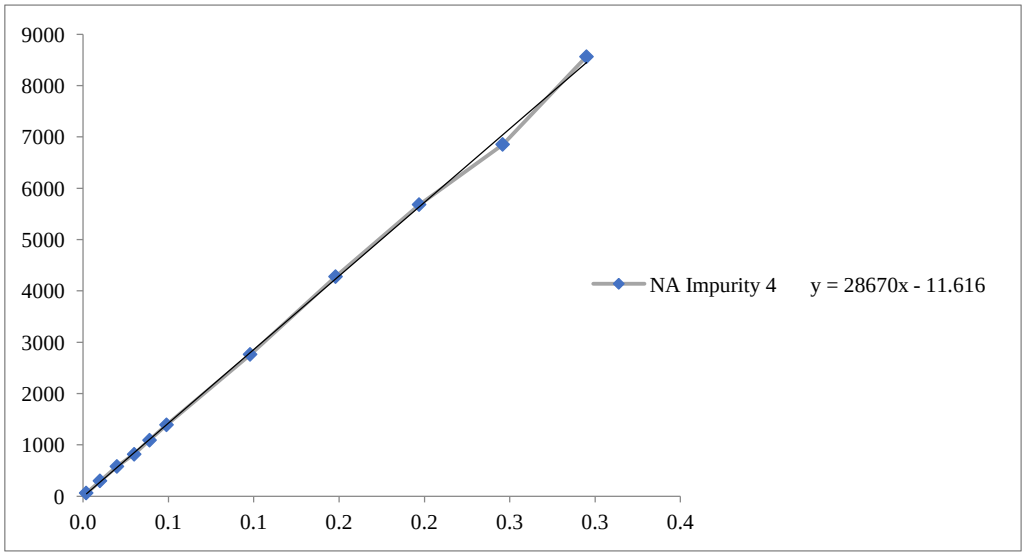

Fig 22: Linearity of Impurity-5

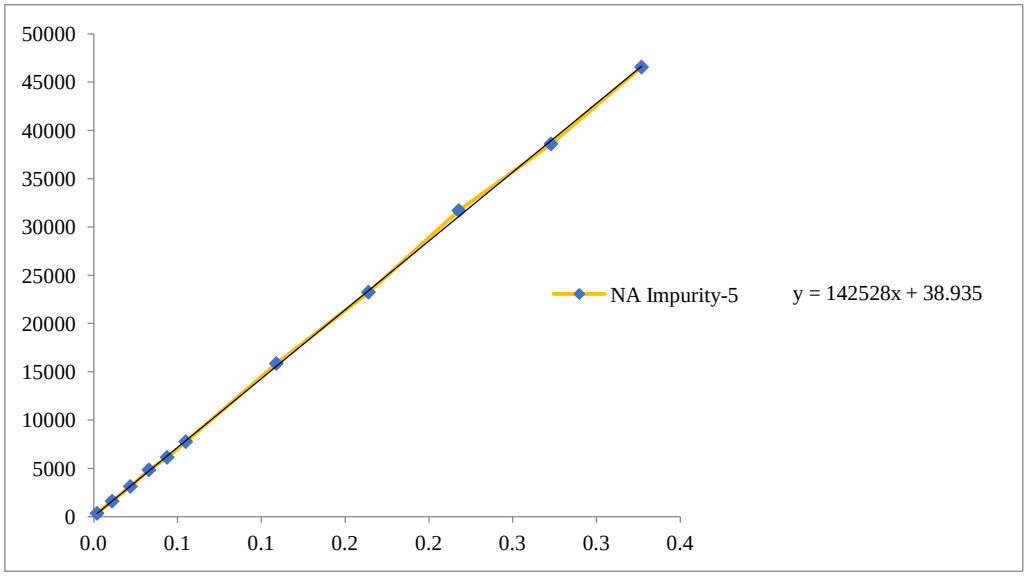

Fig 23: Linearity of Impurity-6

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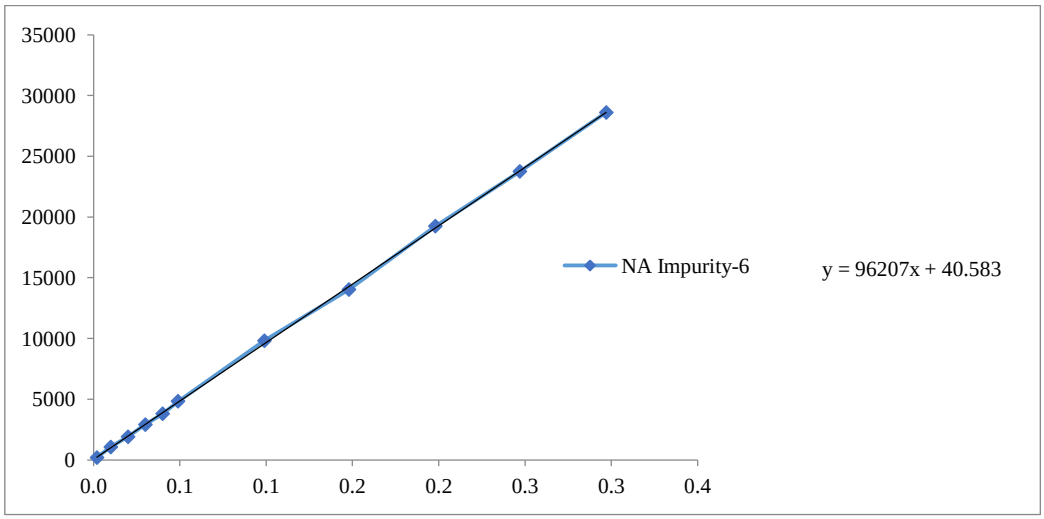

Fig 24: Linearity of Impurity-7

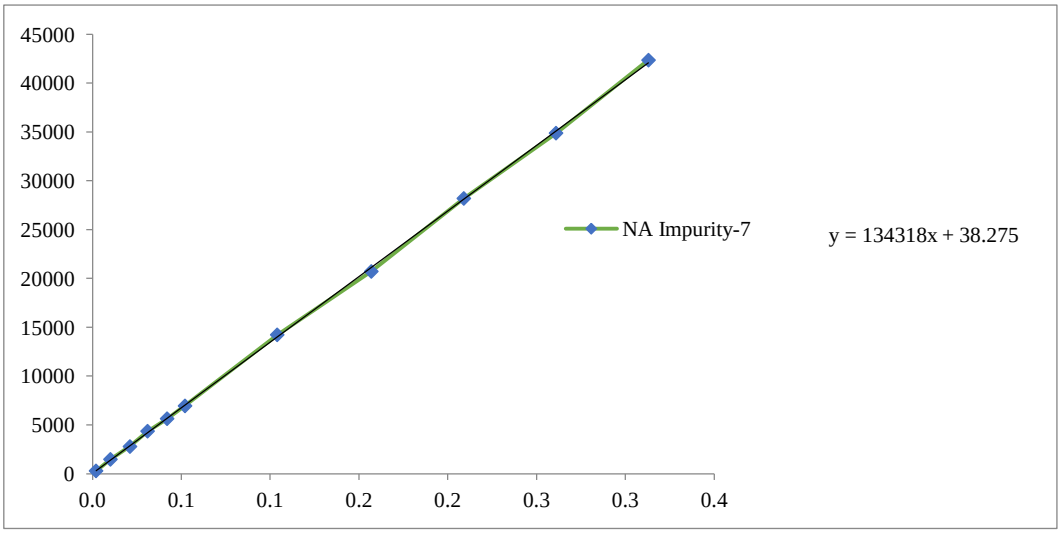

Fig 25: Linearity of NAP

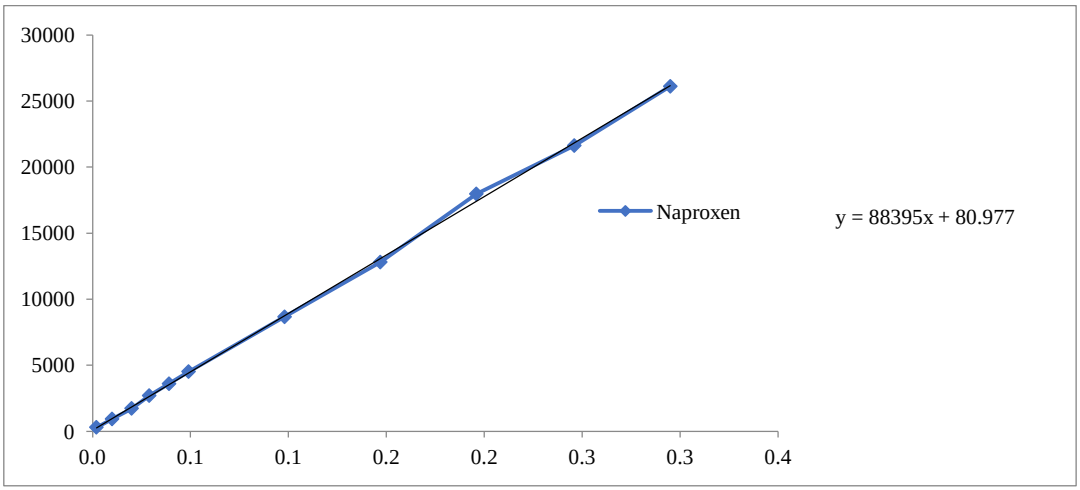

Fig 26:

ACCURACY

The method's accuracy was assessed by introducing known quantities of impurity stock solutions at concentration levels corresponding to the LOQ, 50%, 100%, and 150% of the analyte concentration into the samples. Triplicate preparations are conducted at each step. The recoveries for all IMP were computed.

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Table 7: Recovery for NAP IMP

Impurity Name	Avg recovery & RSD in triplicate preparation							
	LOQ Level		50% Level		100% Level		150% Level	
	Avg Recovery	% RSD	Avg Recovery	% RSD	Avg Recovery	% RSD	Avg Recovery	% RSD
NA-Imp-1	95.6	2.67	101.3	2.48	100.8	1.51	103.4	0.94
NA-Imp-2	99.0	2.24	94.8	1.78	97.0	2.71	102.5	2.06
NA-Imp-3	104.5	1.02	97.8	1.06	99.8	1.61	99.3	0.58
NA-Imp-4	94.2	1.92	93.3	1.67	93.9	1.57	93.1	1.28
NA-Imp-5	96.6	4.56	103.8	1.52	104.8	0.61	105.4	0.75
NA-Imp-6	100.6	3.52	95.2	0.61	93.8	1.09	94.7	0.37
NA-Imp-7	96.5	3.19	97.4	1.52	95.9	0.30	96.0	1.37

Solution Stability:

The experimental data on solution stability demonstrates that both normal and sample solutions were steady for up to 24 hours at ~25°C.

ROBUSTNESS

To assess the robustness of the approach, the experimental conditions were purposefully changed. In contrast to the preliminary temperature of 50°C, the belongings of column oven temperature are investigated at 45°C and 55°C. The starting pH of the MOP was 3.0, and its effects were evaluated at pH 2.8 and pH 3.2.The flow rate of the MOP is 0.5 mL/min. to examine the effects of a 0.1 unit change in flow rate, particularly between 0.4 and 0.6 mL/min. The composition of MOP -B was changed by ± 2% absolute in order to modify the gradient program. The wavelength was adjusted from the final value of 230 nm by ± 5 nm. In each case, all other conditions were left unchanged and only one parameter was changed. Table number provided the RRT requirements for the NAP impurity.

Table 8: Robustness for NAP IMP

Impurity Name	RRT's of the IMP										
	As per the method conditions	Flow rate		Column temperature		pH of the buffer		Gradient programme variation (±2% Absolute)		Wavelength (nm)	
		0.9 mL min^{-1}	1.1 mL min^{-1}	45°C	55°C	2.8	3.2	-2%	+2%	225	235
Impurity 1	0.34	0.35	0.34	0.34	0.35	0.34	0.34	0.32	0.38	0.34	0.34
Impurity 2	0.68	0.69	0.68	0.67	0.68	0.68	0.67	0.68	0.70	0.68	0.68
Impurity3	0.74	0.76	0.75	0.73	0.76	0.74	0.75	0.74	0.78	0.74	0.74
Impurity 4	1.21	1.17	1.25	1.19	1.23	1.21	1.22	1.15	1.27	1.21	1.21
Impurity 5	1.70	1.57	1.85	1.65	1.74	1.69	1.71	1.54	1.89	1.70	1.70
Impurity 6	1.83	1.67	2.04	1.77	1.88	1.82	1.85	1.65	2.05	1.83	1.83
NA Impurity 7	2.33	2.09	2.63	2.25	2.41	2.31	2.35	2.06	2.66	2.33	2.33

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III. CONCLUSION

To help separate potential NAP contaminants in NAN Sodium Soft Gelatin capsules, a gradient RP-HPLC technology was successfully developed. The established method is linear, accurate, exact, selective, and long-lasting. According to the ICH requirements, this method has been validated and establish to be linear, robust, rugged, precise, and specific. The stress testing shows that the method is stability-indicating and selective. UV detection at 230 nm worked well and showed no signs of excipient interference. The linearity calibration curves were used to get correlation coefficients greater than 0.995. The correctness of the procedure was confirmed by the recovery findings. The well-established RP-HPLC method is precise, accurate, and stability-indicating.

IV. REFERENCES

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