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METHOD DEVELOPMENT AND VALIDATION OF STABILITY-INDICATING RP-HPLC METHOD FOR DETERMINATION OF NABUMETONE

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Abstract: An easiest, precise, accurate and isocratic RP-HPLC stability-indicating method was developed and validated for determination of Nabumetone. RP-HPLC separation was achieved on Agilent Zorbax Bonus RP (5µ, 250 mm X 4.6 mm) column using mobile phase comported of methanol: water (35:65, % v/v) at flow rate of 1 ml/ min. Forced declination studies were performed on bulk sample of Nabumetone using acid (1 N Hydrochloric acid), base (1 N Sodium hydroxide solution), oxidation (3% Hydrogen Peroxide Solution), Dry heat (80˚C). Good resolution between the peaks corresponds to declination products. The estimation angles of Nabumetone showed good linearity in the attention range 60-140 µg/ ml with UV discovery (270 nm). The correlation portions were better than 1.000. With limit of discovery and quantification 0.61 ug/ml and 1.86 µg/ml, independently. The system has the needful delicacy, selectivity, perceptivity and perfection to assay declination products performing from the stress studies didn't intrude with assay is therefore stability- indicating.

Keywords: Stability-Indicating method, Nabumetone, Recovery studies, Stress studies.

1. INTRODUCTION

Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) belonging from naphtylalkanone class, 4-(6-methoxynaphthalen-2-yl) butan-2-one and structure is shown in figure 1. The drug is used to treat various arthritis like rheumatoid arthritis, osteoarthritis and acute soft tissue injuries. Nabumetone is a prodrug which undergoes wide-ranging first pass metabolism to 6-methoxy-2-naphthylacetic acid (6-MNA), the major flowing metabolite; 6- MNA is largely responsible for the satisfying NSAID efficiency of nabumetone. [1, 2, 3, 4]

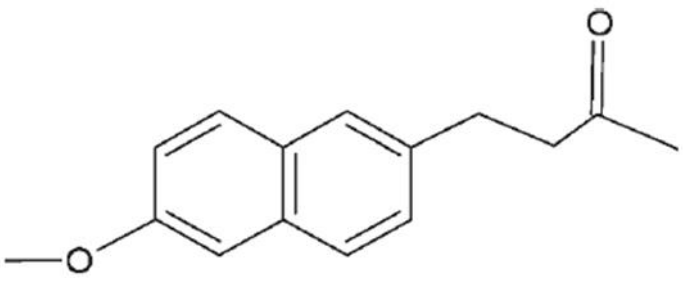

Figure 1: Structure of Nabumetone

Some literature review revealed various analytical techniques for nabumetone in human plasma and determination of the active metabolite of nabumetone in biological fluids by heavy atom-induced atmospheric temperature phosphorescence [6], synchronized estimation of COX-2 inhibitors in pharmaceuticals dosage form [7], in human plasma by liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry [8], by micellar—stabilized room temperature phosphorescence [9], by high-performance liquid chromatography with photodiode array and mass spectrometric detection [10].

Based on current good manufacturing practices (GMPs), all drugs must be checked by a stability-indicating assay technique before proclamation. Stress degradation studies of the drug element can be helpful into recognize the likely mortified products have ability to turn in helping to establish the degradation ways and the fundamental constancy of the molecule and validate the stability-indicating power of the analytical system used. The class of the stress study is depend upon the individual drug ingredient and the class of drug product to be checked. Considering the sensitivity of Nabumetone under differential conditions, it was sensed that a RP-HPLC method of analysis that split up the drug from the mortified products generated under ICH guideline situations (hydrolysis, oxidation and thermal stress) would be of general interest. These testing delivers precious statistics on drug's intrinsic strength and beneficial in the authentication of analytical system to be used in stability testing of the taken drug. Attempts were made to develop a acceptable single stability indicating HP-LC system [9] which will be used to estimate the affiliated substances and also the assay of bulk samples of Nabumetone. The International Conference on Harmonization (ICH) guideline Q1A (R2) for parent drug (API) stability testing suggests that stress testing on the drug substance should be performed to ascertain stability characteristics and to support the felicity of the proposed analytical system. [1, 12,13]

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents:

The reference standard of Nabumetone (Nabumetone) was purchased from Aadhar Life Sciences Pvt. Ltd. All chemicals such as MEOH and water used were of HPLC grade bought from Merck Specialities Pvt. Ltd., Shiv Sagar Estate 'A' Worli, Mumbai. Potassium dihydrogen phosphate, Triethylamine and Orthophosphoric acid, Tetra butyl ammonium hydroxide sulphate (TBAH) as having HPLC grade of Avantor Performance cloth India Ltd. Thane, Maharashtra were used for chromatographic procedure. was used to prepare solutions. Tablet dosage form manufactured by Ipca laboratory; NILTIS 500 mg was used.

2.2. Selection of Wavelength:

The pattern changed into scanned from 200-400 nm with DAD detector. The Wavelength on which the evaluation selected changed into 270 nm on foundation of suitable depth of Nabumetone.

2.3. Instrumentation & Chromatographic conditions:

Agilent 1260 Infinity II system consisting of Compatible with conventional and ultrahigh performance LC: 1260 Infinity II Quaternary Pump and 1260 Infinity Binary Pump operate up to 600 bars, a perfect match for our Infinity Lab Poroshell 120 columns. The peaks were quantified by means of PC based Lab Advisor software. A reverse phase Agilent Zorbax Bonus-RP (250 x 4.6 mm, 5 µ) column equilibrated with mobile phase Methanol: Water (35:65 % v/v) was used. Mobile phase flow rate was maintained at 1 ml/min and effluents were monitored at 270 nm. The temperature of the system was maintained at 300 C. The sample was injected using a 10 µl fixed loop, and the total run time was 5 min.

2.4. Preparation of Standard Solution:

Prepare a Standard Stock Solution (SSS-I) of by adding 10 mg of Nabumetone in 10 ml volumetric flask & add 5 ml diluent (methanol: water, 50: 50 %v/v), mix for 2 minutes and make the volume to 10 ml with diluent. (Conc. of Nabumetone = 1000 µg/ml). Then add 1.0 ml of ASSS-I in 10 ml volumetric flask and add 5 ml diluent and vortex and make up the volume with diluent. (Conc. of Nabumetone = 100 µg/ml).

2.5. Drug Product Sample Preparation for Assay:

10 Tablets were weighed and average weight was calculated and Tablets was crushed & mixed in mortar and pestle. Powder weight equivalent to 10 mg Nabumetone was weighed into 10 ml volumetric flask & add 5 ml diluent, sonicate for 10 minutes and make the volume to 10 ml with diluent. (Conc. of Nabumetone = 1000 µg/ml).

2.6. Forced Degradation Studies:

To determine whether the analytical approach was stability-indicating, Naphthyl acetic acid derivative (Nabumetone) active pharmaceutical ingredient (API) powder was tensed under numerous situations to accomplish forced degradation studies. Purposeful declination was struggled to pressurize conditions of acidic hydrolysis (using 1 N HCl), alkaline hydrolysis (using 1N NaOH), oxidative degradation (using 3.0% H2O2) and dry & wet thermal treatment (heated at 80 °C and 45 °C) with reflux condition respectively. After completion of the degradation procedures, the resolutions were neutralized and diluted with mobile phase. Stress degradation conditions were categorical on the basis of unobjectionable pH range of the column. The resolution peak within drug and its degradants should be more than 1.5. Attempt become made to decompose 10-30% of the drug by introducing drug to strained situations and then milder conditions were used. This becomes executed to decrease the time period of degradation. The tolerable pH range of column is 2.5-8.5 therefore higher basic stress surroundings cannot be used.

2.6.1. Acidic Degradation

304 mg of Tablet powder was weighed in a 10 ml volumetric flask and 1 ml of 1 N Hydrochloric acid was added and kept at room temperature for 30 min. Later 5 ml of diluent was added and sonicated for 2 minutes and made up to the volume with diluent.

2.6.2. Alkaline Degradation

304 mg of Tablet powder was weighed in a 10 ml volumetric flask and 1 ml of 1 N Sodium hydroxide solution was added and kept at room temperature for 30 min. Later 5 ml of diluent was added and sonicated for 2 minutes and made up to the volume with diluent.

2.6.3. Oxidative Degradation

304 mg of Tablet powder was weighed in a 10 ml volumetric flask and 1 ml of 3% Hydrogen Peroxide Solution was added and kept at room temperature for 30 min. Later 5 ml of diluent was added and sonicated for 2 minutes and made up to the volume with diluent.

2.6.4. Photolytic:

304 mg of Tablet powder was weighed in a 10 ml volumetric flask and kept at 254 nm in UV Cabinet for 5 hours. Later 5 ml of diluent was added and sonicated for 2 minutes and made up to the volume with diluent.

2.6.5. Thermal Stress Studies/ Dry heat Degradation:

304 mg of Tablet powder was weighed in a 10 ml volumetric flask and kept at 80˚C in Hot Air Oven for 5 hours. Later 5 ml of diluent was added and sonicated for 2 minutes and made up to the volume with diluent.

3. RESULTS AND DISCUSSION

3.1. Optimization of analytical conditions:

Different columns having different sizes and chemical natures have been attempted for separation and resolution. The Agilent Zorbax (250mm X 4.5mm, 5u) column have become extra tremendous over the opposite columns. Individual drug solution turned into injected into column, each elution sample and determination parameters studied as a characteristic of pH, as a function of mobile phase component and their ratio. To develop an acceptable HPLC method for estimation of nabumetone in formulations, different mobile phases were employed to realize the simplest separation from degradant peaks. The chosen and optimized mobile phase was methanol: water (35:65 % v/v) and conditions optimized have been: flow rate (1.0 ml/min), detector wavelength (270 nm), run time was 5 min. Here the peaks were separated and confirmed higher resolution, theoretical plate count and asymmetry was found as 1.01 for Nabumetone. The proposed chromatographic conditions have been observed applicable and suitable for the quantitative determination of the drugs.

3.2. Results of forced degradation studies

Acidic declination of Nabumetone was executed in 304 mg equivalent marketed formulation powder in 0.1 N hydrochloric acid at temperature 30°C because it is insoluble in HCl. Hydrolytic degradation of Nabumetone was observed to be very gradual and less, for that reason better compelled conditions have been attempted to boost degradation process. Then in addition degradation meted out within the mixture of methanol and hydrochloric solution having strength of 1 N HCl with influx at 80°C. Drug were given degraded into degradants having RT of 4.4 and 2.88 min and approximately 10.36 % of drug degraded in 30 minutes. In case of

alkaline degradation, process was carried out for 30 minutes at ambient temperature in 1 N NaOH and gave one minor degradant peak height showing RT of 5.79 min. Approximately 8.53% of drug was degraded in 30 minutes. Progress of decay can't be judged, right here in oxidative declination nabumetone is veritably labile to experimental condition and degradant peak further suffer degradation thus incessantly degradant Rt changes. Initially retention time was obtained of 6.40 then change to 5.47 and finally 2.24 min and approximately 12.38% of drug was degraded in 30 minutes. Thermal degradation was carried out as dry heat. Dry heat shows minimal degradation among all forced condition, as 5.67 % of drug was degraded in 5 hours with degradant peaks as RT at 5.72 and 4.66 minutes. In case of photolytic degradation, roughly 11.36% of drug was degraded in 5 hour and the degradants peaks at retention time of 4.62 minutes. Degradants concentrations increase as time passes and the degraded products were well resolved from the parent drug for chromatogram vs time in min. The order of stability for Nabumetone was found to be dry heat <alkali <acid <photolytic < H2O2. Developed RP-HPLC method is able to separate all degradants, produced from all stress condition from drug peak by resolution of more than 1.5 min. Analytical data for evaluation are given in Table no. 01 and figures 01, 02, 03, 04 and 05 shows acidic, basic (alkaline), oxidative, photolytic and thermal (Dry Heat) degradation respectively.

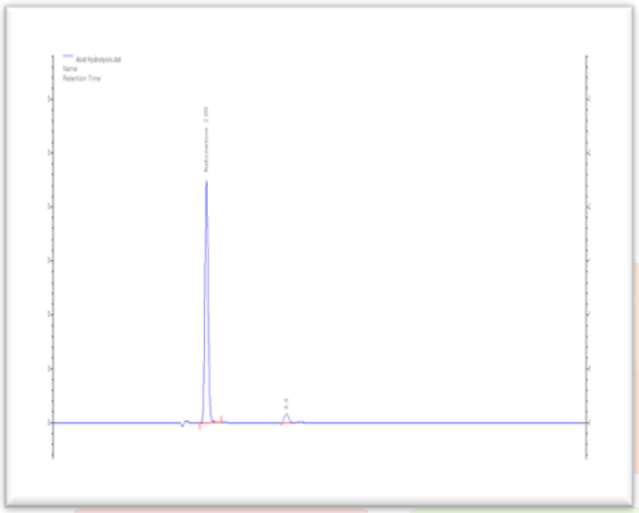

Fig. 01: Acidic Degradation of Nabumetone

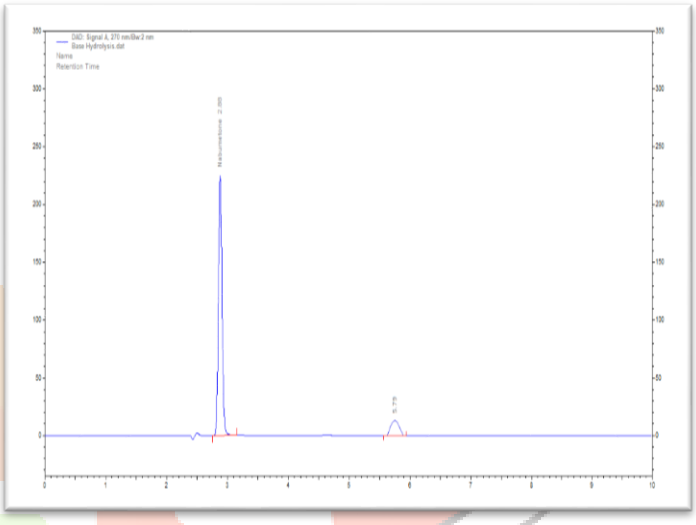

Fig. 02: Basic Degradation of Nabumetone

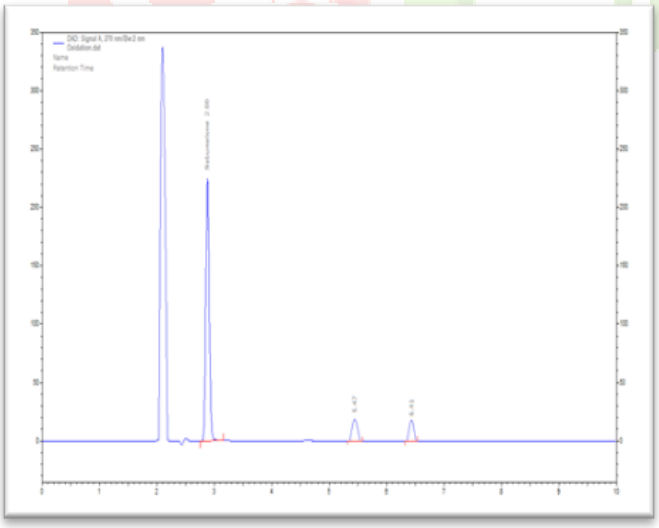

Fig. 03: Oxidative Degradation of Nabumetone

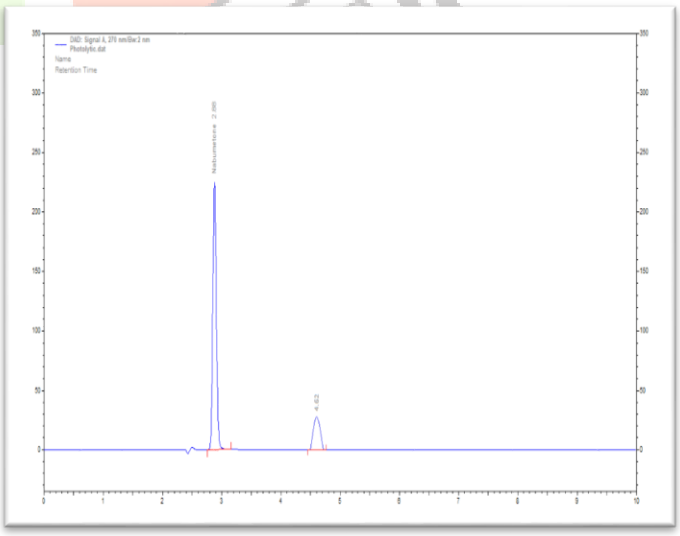

Fig. 04: Photolytic Degradation of Nabumetone

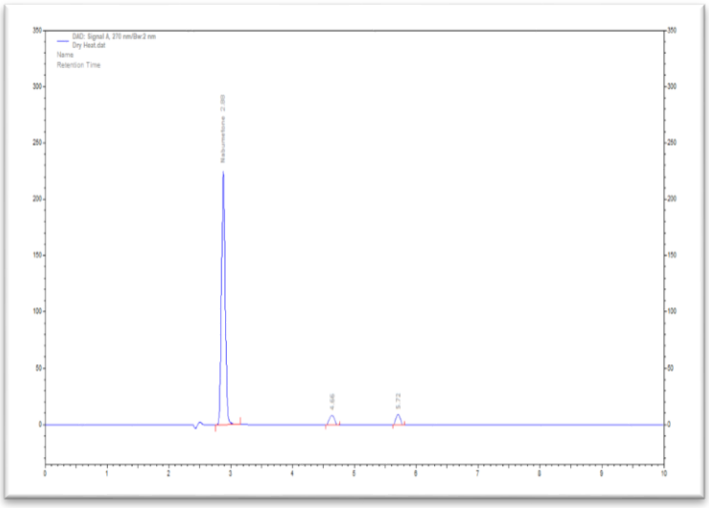

Fig. 05: Dry Heat Thermal Degradation of Nabumetone

Table No. 01: Analytical Data for Evaluation of Various Stress Degradation Conditions

Sample ID	Area	% Assay	% Deg
Working Standard	1525414	100.00	-
Acidic Degradation, 1 N HCl (reflux at 30°C)	1367381	89.64	10.36
Alkaline Degradation, 1 N NaOH *(At ambient temperature)*	1398347	91.67	8.33
Oxidative Degradation 3% hydrogen peroxide *(At ambient temperature)*	1336568	87.62	12.38
Dry heat Degradation (at 80 °C)	1438923	94.33	5.67
Photolytic Degradation	1352127	88.64	11.36

4. METHOD VALIDATION [15]

4.1. Specificity:

Specificity for the nabumetone as comparing to marketed formulation (Niltis 500mg Tablet, Ipca Laboratories Pvt. Ltd.) was found as mentioned in the following table no. 02 and mentioned figures 06 & 07. The % Assay of nabumetone for this developed technique was found to be 97.50.

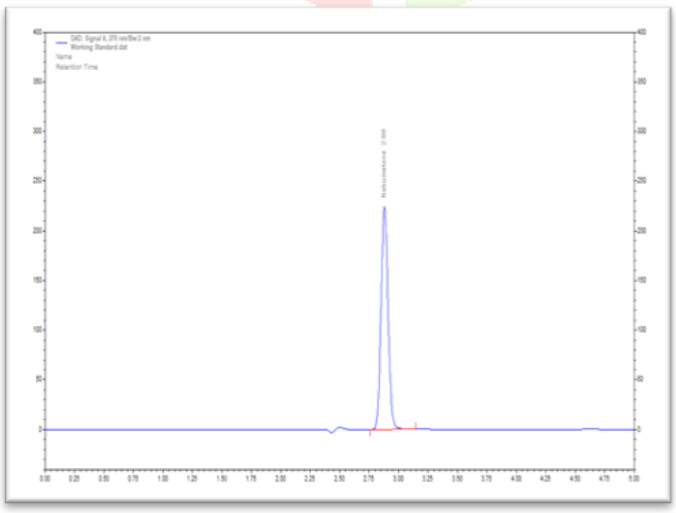

Fig. 06: Chromatogram of Working Standard

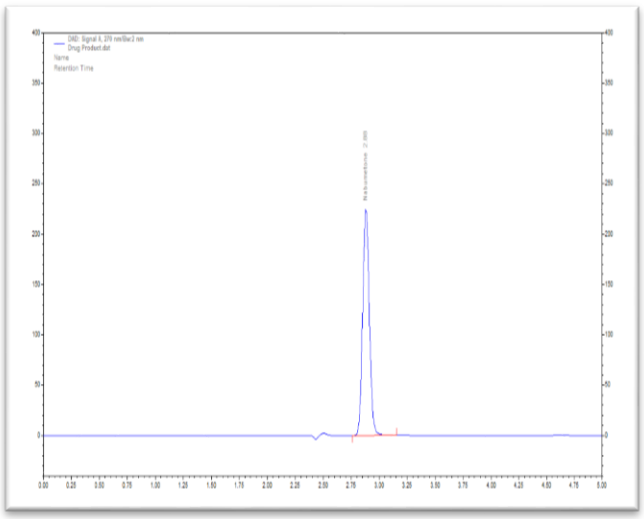

Fig. 07: Chromatogram of Drug Product

Table No. 02: Specificity and Assay:

Sample (API Name)	Nabumetone
Standard Solution	1525414
Marketed Formulation	1487272
% Assay	97.50

4.2. Linearity:

The data revealed a linear association between peak areas and concentrations in the ranges of 2-140 ug/mL for Nabumetone. The linear equation for Nabumetone was y = 15262x - 23.3, where x represents the concentration of the drug and y represents the peak area. The correlation coefficient was 1.000 and the calibration curve of Nabumetone is depicted in figure 8. Linearity data for the Nabumetone is represented in table no. 03.

Table No. 03: Linearity and range:

% Conc	Conc (ug/ml)	Nab AREA
60%	60.00	914382
80%	80.00	1224309
100%	100.00	1525733
120%	120.00	1827682
140%	140.00	2138925

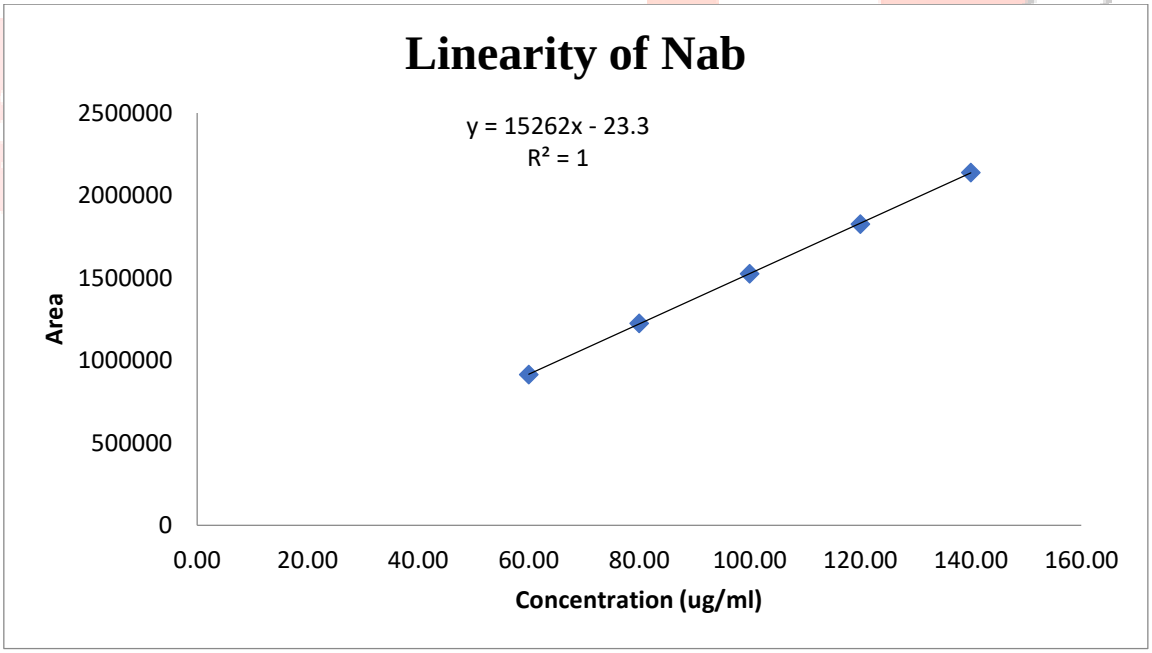

Fig. 08: Calibration curve (linearity) of nabumetone

4.3. System Suitability:

The system suitability was assessed by six replicate injections of the mixture containing as internal standard. The resolution, peak asymmetry, number of theoretical plates and HETP were calculated are represented in table no. 04.

Table No. 04: System Suitability:

Sr. No.	Parameters	Nabumetone
1	Theoretical Plates	23509
2	Retention Time	2.88
3	Asymmetry factor	1.01

4.4. Accuracy:

Validation of Recovery Studies which is done statistically is represented in table no. 05 which shows the effects of Nabumetone. Recovery studies were carried out to ensure that the developed approach was accurate. The solution which is previously analyzed means the specific standard drug concentration 80, 100, and 120 percentages were mixed and then allowed for the recovery analysis. Recovery experiments at various concentration levels are used to verify the accuracy of the RP-HPLC and UV Spectrophotometric methods. The recovery rate was determined to be between 98 and 101%.

Table No. 05: Accuracy of Nabumetone:

Level of Recovery	Sample No. (ug/ml)	Spiked Amount	Spiked Amount wrt Sample	Area ATV	Amount Recovered (ug/ml)	%Recovery	% RSD
80%	Reps1(80)	79.76	79.76	1229830	80.38	100.78	0.45
	Reps2(80)	79.76	79.76	1224309	80.02	100.33	
	Reps3(80)	79.76	79.76	1218782	79.66	99.87	
100%	Reps1(100)	99.7	99.70	1528732	99.92	100.22	0.10
	Reps2(100)	99.7	99.70	1525733	99.72	100.02	
	Reps3(100)	99.7	99.70	1527638	99.85	100.15	
120%	Reps1(120)	119.64	119.64	1828782	119.53	99.91	0.05
	Reps2(120)	119.64	119.64	1827682	119.46	99.85	
	Reps3(120)	119.64	119.64	1826783	119.40	99.80	

4.5. Precision:

Intraday and inter-day precision investigations on the RP-HPLC method for nabumetone demonstrate high precision percent amounts ranging from 97 to 101 percent, indicating an analytical procedure that was concluded. Table no. 06 shows the results of intraday and inter-day precision experiments on the RP-HPLC technique for Nabumetone.

Table No. 06: Precision for Nabumetone:

Instrument Precision	**Peak Area**
Parameter	**ATV**
Rep 1(50 ug/ml)	1529432
Rep 2(50 ug/ml)	1527204
Rep 3(50 ug/ml)	1527273
Rep 4(50 ug/ml)	1524395
Rep 5(50 ug/ml)	1520934
Rep 6(50 ug/ml)	1523246
Average	**1525414**
SD	**3118.117701**
%RSD	**0.20**

4.6. Limit Detection:

Depending on the standard deviation of response and slope, the limit of detection means LOD is detected. The LOD is the lowest limit that can be detected. The value of LOD of Nabumetone was observed as 0.613600684 (ug/mL), the analytical method that concluded.

Limit of detection = 3.3X6032.658809/32444.185 =0.613600684 (ug/mL)

4.7. Limit Quantification:

The LOQ is that the lowest concentration which will be quantitatively measured. The value of LOQ for Nabumetone was observed as 0.613600684 (ug/mL) for the concluded method.

Limit of Quantitation = 10X12.80/177.8=1.85939601 (µg/mL)

4.8. Analysis of Tablet Formulation:

The quantity of Nabumetone in each tablet was estimated by the extrapolation method by taking the value of area from the calibration curve. The process of Analysis procedure was done repeatedly about five times by using tablet formulation. For calculation of % Label claim and %RSD, tablet assay was estimated. In Table no. 07 and figure 09, results are represented. Brand Name Niltis tablet 500 mg (IPCA laboratories) was used for the analysis. The average weight of the tablets was 1.5328 gms /Tab. Its equivalent weight for 10 mg nabumetone would be 100X 1.5328 / 500 =0.0304 grams. Hence, 167.6 mg in 10 ml water was taken and sonicated 10 min. Analysis of marketed formulation was analyzed and % Label Claim was observed as 100-101% which was concluded satisfactorily.

Table 07: Analysis of marketed formulation:

Assay	**Drug**	**mg**	**Potency**	**% Label Claim**	**S.D.**	**%R.S.D.**
RP-HPLC Method	Nabumetone	10	97.5	97.50	3118.117701	0.20

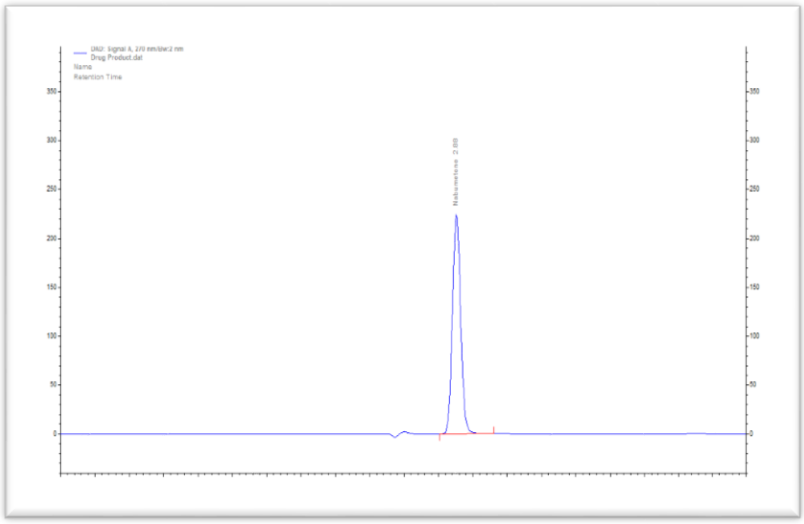

Fig. 09: Chromatogram for Marketed Formulation

4. CONCLUSION:

The data demonstrate that the RP-HPLC method we have developed showed acceptable linearity, specificity, accuracy, precision and LOD &LOQ in the concentration range of 2-140 µg/ml for Nabumetone as per the necessity of ICH guidelines. In this testing, firmness of drug was conventionally according to ICH-recommended stress conditions. There was no finding of interference any mortified products or excipients in the estimation of the API. In conclusion, the projected system could be regularly used for the analysis of API in pharmaceutical dosage form.

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