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Development and Validation of UV-Spectroscopic Methods for Determination of Nabumetone in Bulk and Tablet Formulation.

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Abstract
Nabumetone is a non steroidal anti-inflammatory drug with good analgesic and anti-rheumatic properties. Various methods for analysis of the same are available but are time consuming and expensive. Two simple, precise, accurate and economical UV spectrophotometric methods have been developed and validated for the routine estimation of Nabumetone in bulk drug and pharmaceutical preparations. The drug shows maximum absorption at 229.0 nm and obeyed Beer-Lambert's law in the concentration range of 1-5µg/ml. The same spectrum was derivatised into second order derivative the amplitude of trough at 230.0 nm and creast 236.8nm for D_2 were measured. In D_2 method the drug showed linearity in the concentration range of 1-5 µg/ml. The linear regression equations were calculated to be y=0.02071x+0.0561 (R^2=0.9942) for D_0 at 229.0 nm, y=-0.0012x+0.0002 (R^2=0.9931) for D_2 at 230.0 nm and y= 0.0005x+8E-05 (R^2=0.9987) for D_2 at 236.8 nm The results of estimation of marketed tablet formulations were found to be 99.538±0.1546-99.762±0.1181 with their standard deviation less than 2.0. Recovery studies were carried out by addition of known amount of standard drug (80,100 and 120% of labeled claim of a tablet) to the preanalysed tablet solution. The percentage recovery was found to be 98.024-99.984, which indicates accuracy and reliability of the validated method as well as non-interference from excipients to the developed method. The intraday and inter day assay was within 2.0%. The methods were then validated statistically as per the ICH guidelines which yielded good results concerning range, precision, accuracy, specificity and repeatability.

Key Words
Nabumetone, UV–Vis Spectrophotometry, Derivative spectroscopy, Validation.

Introduction
Nabumetone, 4-(6-methoxy-2-naphthyl)-butan-2-one, is a non-steroidal anti-inflammatory drug (NSAID) of naphtylalkanone class. The drug has proved to be effective in the treatment of rheumatoid arthritis, osteoarthritis and acute soft tissue injuries[3,4]. Nabumetone is a prodrug which undergoes extensive first pass metabolism to 6-methoxy-2-naphthylacetic acid (6-MNA), the major circulating metabolite. 6-MNA is largely responsible for the therapeutic efficacy of nabumetone. It decreases prostaglandin synthesis via inhibition of cyclooxygenase, an enzyme involved in the arachidonic acid conversion pathway[1]. It is official in United States Pharmacopoeia, British Pharmacopoeia. Several analytical techniques like colorimetric liquid chromatography spectrophotometric, high performance liquid chromatography[5,6,9], micelle-stabilized room temperature phosphorescence[7], flow injection analysis[10] and voltametric[12] have been reported for the determination of nabumetone. However some of these methods are costlier and time consuming. To overcome these difficulties spectrophotometric analysis serves to be the quickest, promising and reliable method for routine analytical needs. The aim of the present study is to develop a new simple, rapid, reliable and precise UV spectrophotometric method for analysis of nabumetone from tablet formulation; method is based on measurement of UV absorbance of nabumetone in phosphate buffer pH 6.8.

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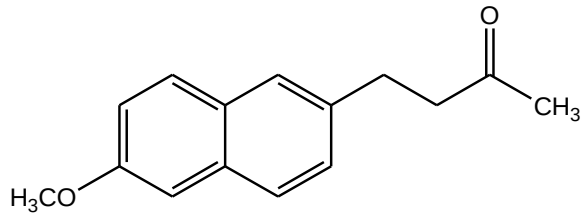

Nabumetone

Materials and Methods

Materials

UV-visible double beam spectrophotometer, JASCO-V-630 with spectral bandwidth of 1 nm, wavelength accuracy of ± 0.3 nm and a pair of 10 mm matched quartz cells were used. Nabumetone pure drug was obtained as a gift sample from zydus cadila health care, Ahemadabad, Gujarat, India. The tablet of nabumetone (Nabuflam, Label claim Nabumetone 500 mg) was procured from local market.

Selection of solvent

After assessing the solubility of drugs in different solvents phosphate buffer pH 6.8 has been selected as solvent for developing spectral characteristics.

Preparation of phosphate buffer pH 6.8

13.872 gm of potassium hydrogen phosphate and 35.084 gm disodium hydrogen phosphate was accurately weighed and transferred to 1000ml volumetric flask. Dissolved in distilled water and volume was made up to the mark with distilled water pH of final solution was adjusted to 6.8 by addition of 0.1 N sodium hydroxide solution.

Preparation of standard stock and calibration curve

The standard stock solutions of nabumetone was prepared by dissolving 10 mg of drug in phosphate buffer pH 6.8 in 100mL volumetric flask, final volume was adjusted with phosphate buffer pH 6.8 and sonicated for about 30 min to get 100 µg/mL. Working standard solutions of 5µg/mL were scanned in the entire UV range of 400-200 nm to obtain the absorbance spectra. (Fig. 1) The drug shows maximum absorption at 229 nm. Five working standard solutions for drug having concentration 1, 2, 3, 4 and 5 µg/mL were prepared in phosphate buffer pH 6.8 from stock solution. The absorbance of resulting solutions were measured at respective λ max and plotted a calibration curve against concentration to get the linearity and regression equation. The same spectrum was derivatised into second order derivative, the amplitude of trough at 230nm and creast 236.8 nm for D_2 (Fig. 2) were measured. In Do drug shows linearity in the range of 1-5µg/ml at 229.0 nm while in D_2 1-5µg/ml at 230.0nm and 236.8 nm. The linear regression equations were calculated to be y=0.02071x+0.0561 (R^2=0.9942) for D_0 at 229nm (Fig. 3), y=0.0012x+0.0002 (R^2=0.9931) for D_2 at 230.0 nm (Fig. 4), and y= 0.0005x+8E-05 (R^2=0.9987) for D_2 at 236.8 nm (Fig. 5).

Analysis of tablet

Twenty tablets were weighed accurately and reduced to fine powder, drug equivalent to 10 mg of Nabumetone was weighed and dissolved in phosphate buffer pH 6.8 in a 100ml volumetric flask, final volume was made with phosphate buffer pH 6.8 and sonicated for about 30min. The above solution was filtered by using Whatmann filter paper No.:41. From the above filtrate 0.5 mL of solution was diluted to 10 mL with distilled water to get 5 µg/mL of Nabumetone. Analysis procedure was repeated six times with tablet formulation. Aliquot was scanned in the UV range (200-400nm). The same spectrum was derivatised into Second order, amplitude of the trough at 230.0 nm and crests 236.8 nm for D_2. The amount of drug present in the tablet was calculated from the standard graphs (Table No.2)

Method Validation

Linearity

Appropriate concentration of stock solution was assayed as per developed methods. Beer-Lambert's concentration range was found to be 1- 5µg/ml. The linearity data for both methods are presented in Table No.1

Accuracy

The accuracy of the methods was determined by performing recovery studies on tablet formulation and for prepared solutions containing known amount of drug by standard addition method in which preanalyzed samples were taken and standard drug was added at three different levels 80%.100% and 120% as per ICH guidelines. The recovery study performed three times at each level. The results are shown in Table No. 2.

Precision

To check the degree of repeatability of methods, suitable statistical evaluation was carried out. Repeatability was performed for six times with tablets formulation. The standard deviation, coefficient of variance and standard error was calculated. The results of statistical evaluation are shown in Table No.2.

Intermediate Precision (Interday and Intraday precision)

The experiments were repeated three times in a day to determine intraday precision and on three different days to determine interday precision. The results of the same are presented in Table No. 3.

Selectivity

The selectivity of the methods was checked by monitoring a standard solution of Nabumetone in presence of excipients at the same concentration level as used in tablet using the method described in the procedure for calibration curve in pharmaceutical tablets.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of Nabumetone by proposed methods were determined using calibration standards. LOD and LOQ were calculated as 3.3□ /S and 10σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response. The results of the same are shown in Table No.3.

Results and Discussion

The proposed methods are simple, rapid and precise and do not suffer from any interference due to excipients of tablet. Various optical characteristics are shown in the Table No.1. The proposed spectrophotometric methods were found to be linear in the range of 1- 5µg/ml at 229 nm in D_o with correlation coefficients (R^2) 0.9942 while in D_2 1-5 µg/ml at 230.0nm, and 236.8 nm with correlation coefficients (R^2) for D_2were found to be 0.9931 and 0.9987 respectively. The methods were validated in terms of accuracy, precision, repeatability and the results are recorded in Table No.2 and 3.The accuracy of the method was determined by performing recovery studies by standard addition of method in which preanalyzed samples were taken and standard drug was added at three different levels. Values of recovery greater than 98.0% indicate that proposed method is accurate for the analysis of the drug. The precision of the proposed method was estimated in terms of interday precision and intraday precision wherein the method was repeated on three different days and repeated for three different time periods in the same day respectively. The results shown in Table No.3. SD less than 2% at each level clearly indicate that the proposed method is precise enough for the analysis of the drug. The selectivity of the method was checked by monitoring a standard solution of nabumetone in presence of excipients at the same concentration level as used in tablet using the method described in the procedure for calibration curve in pharmaceutical tablets. The excipients did not show any effect on the estimation of nabumetone. Hence, the determination of nabumetone in the tablet is considered to be free from interference due to the excipients. Rigorous analysis of the results indicates that the presence of excipients in tablet formulation did not interference with the final determination of the active component. This reveals that the potential utility of this method for the routine analysis of nabumetone in pharmaceutical preparations.

Conclusion

Two new, simple precise, accurate and selective spectrophotometric methods were developed for the analysis of Nabumetone in bulk and in pharmaceutical formulation. The D_0 method is useful for tablet formulations where there is no interference of excipients in the absorbance of Nabumetone and method D_2 can be utilized for formulations containing any interfering excipients. The developed methods were also validated and from the statistical data, it was found that methods were accurate, precise, reproducible and can be successfully applied to the pharmaceutical formulations without interference of excipients.

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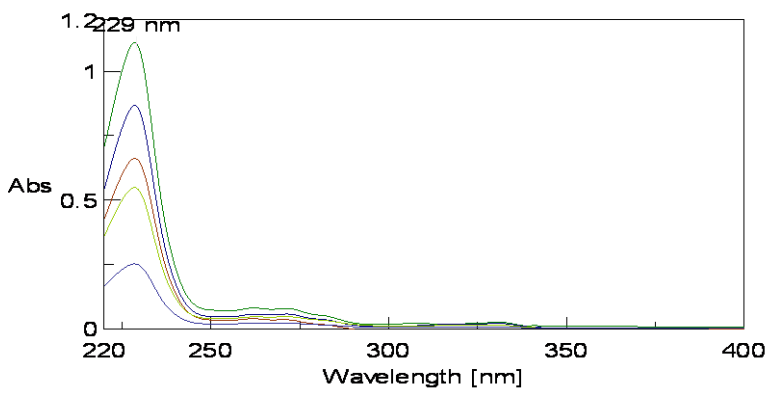

Figure 1: Overlain spectra of Nabumetone 1,2,3,4 and 5 µg/mL (D_0).

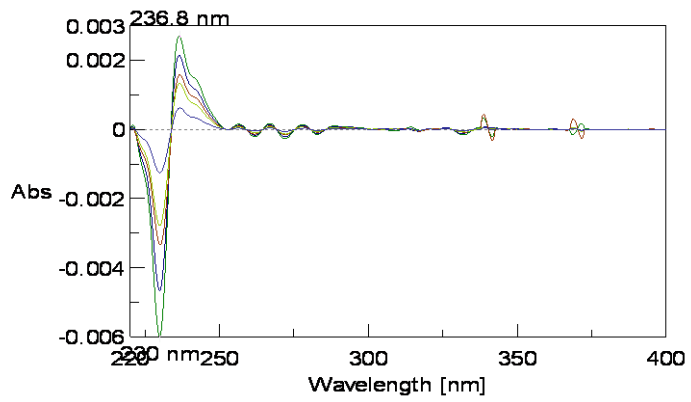

Figure 2: Overlain spectra of Nabumetone 1,2,3,4 and 5 µg/mL (D_2).

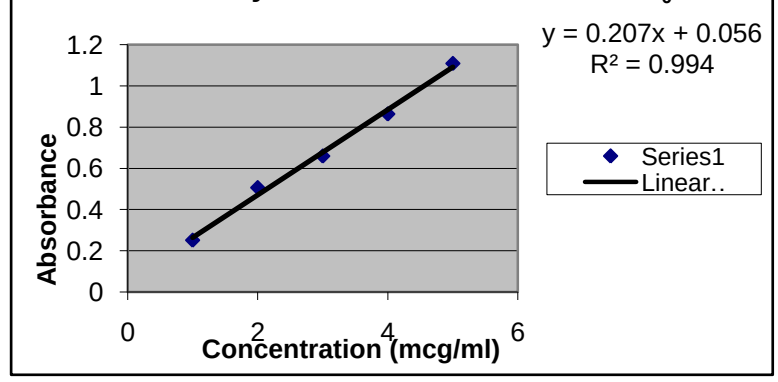

Figure 3: Linearity of Nabumetone at 229.0 nm (D_0).

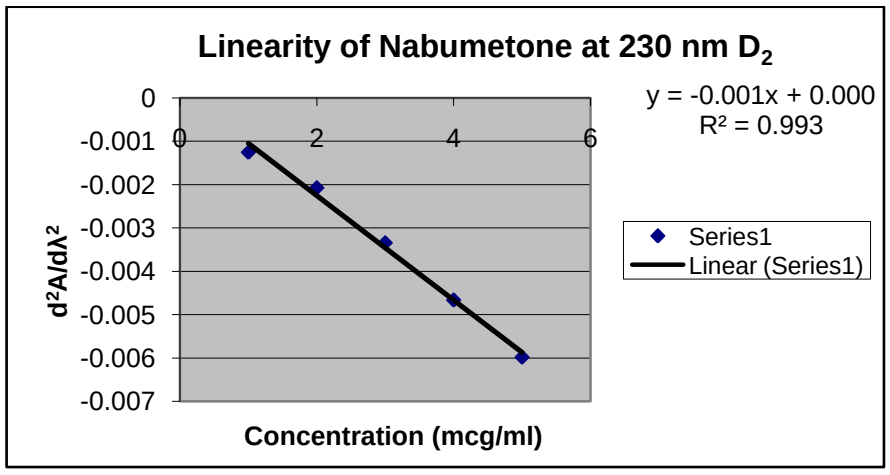

Figure 4: Linearity of Nabumetone at 230.0 nm (D_2).

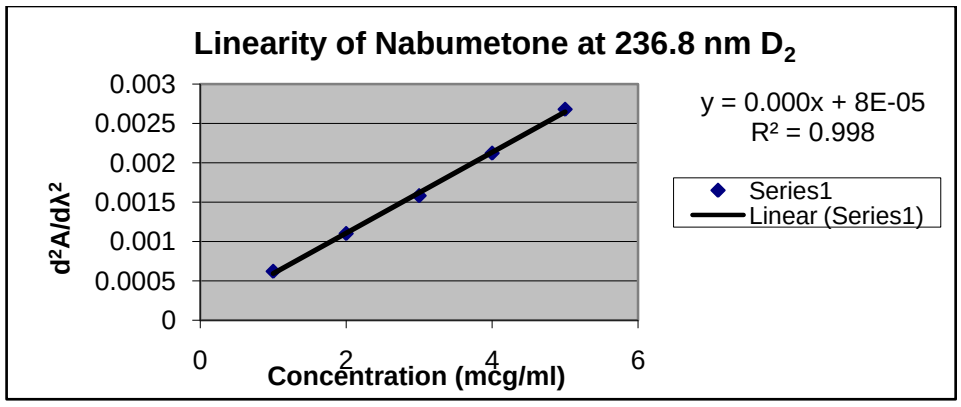

Figure 5: Linearity of Nabumetone at 236.8 nm (D_2).

Table 1: Optical Characteristic for Nabumetone.

Parameters	Values		
	(D_0)	**(D_2)**	
Working l max	229.0 nm	230.0 nm	236.8 nm
Beer's law limit (µg/ml)	1-5	1-5	1-5
Correlation coefficient*	0.9942	0.9931	0.9987
Intercept*	0.0561	0.0002	8E-05
Slope*	0.2071	-0.0012	0.0005

*Average of eight estimation.

Table 2: Analysis of Tablet formulation, Statistical Validation and Recovery studies.

Method		Label Claim mg/tab	Amount found mg/tab	Label Claim (%)	S.D.*	% COV	S.E.*	Amount Added		% Recovery #
								%	mg/ml	
D_0	**At 229.0 nm**	500	498.808	99.762	0.1181	0.1188	0.0484	80	400	99.045
								100	500	98.954
								120	600	99.984
D_2	**At 230.0 nm**		497.689	99.538	0.1546	0.154	0.0663	80	400	98.745
								100	500	99.458
								120	600	98.458
	At 236.8 nm		498.508	99.7016	0.1722	0.1717	0.0706	80	400	98.884
								100	500	99.485
								120	600	98.024

S.D.: Standard deviation, COV: Coefficient of variation, S.E.: Standard error *Average of six estimation of tablet formulation.
#Average of three estimation at each level.

Table 3: Validation Parameters.

Method		Precision(%COV)				LOD*	LOQ*
		Intraday n=3	Interday*				
			First day	Second day	Third day		
D_0	At 252 nm	0.1171	0.7781	0.1258	0.9431	1.188	0.571
D_1	At 238 nm	0.0941	0.9879	0.9065	0.8278	0.425	1.288
	At 259 nm	0.1249	0.1547	0.1893	0.1299	1.136	0.344

COV: Coefficient of variation.,LOD: Limit of detection, LOQ:Limit of Quantification *Average of six determination.

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