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Spectrophotometric Method Development and Validation for Estimation of Nabumetone Using Hydrotropic Agent

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ABSTRACT

Various techniques are employed to enhance the aqueous solubility of poorly water-soluble and water-insoluble drugs and the hydrotropic solubilization technique is one of them. In the present investigation, a hydrotropic solution of 20% sodium Benzoate and 20%Phenol was employed as a solubilizing agent to solubilize the water-insoluble drug. Nabumetone shows its absorbance at 330.40 nm and Beer's law was obeyed in the concentration range of 10-70 µg/ml. The percentage recovery of Nabumetone was 99.51% and all the analytical validation parameter was determined and found within the limit as per ICH guidelines, which indicate the validity of the method. The proposed method is new, simple, safe, environmentally friendly, accurate, and cost-effective and can be successfully employed in routine to analyze Nabumetone tablets. Hydrotropic agents and commonly used tablet additives did not interfere with the analysis.

INTRODUCTION

Nabumetone (NAB), 4-(6-methoxy-2-naphthyl)-2-butanone is a non-steroidal anti-inflammatory drug from the class of 2,6 disubstituted naphthyl-alkanes. It is used for the treatment of osteoarthritis and rheumatoid arthritis. Which is practically insoluble in water and soluble in acetone and methyl alcohol.

It is well documented that concentrated aqueous solutions of a large number of hydrotropic agents viz. sodium acetate, niacinamide, urea, sodium benzoate, sodium salicylate, sodium ascorbate, and sodium glycinate have been employed to enhance the aqueous solubilities of poorly water-soluble drugs. The primary objective of the present investigation was to employ a hydrotropic solution to extract the drug from the fine powder of Nabumetone tablets, precluding the use of costlier organic solvents for spectrophotometric analysis. Costlier organic solvents are more often employed to solubilize poorly water-soluble drugs for spectrophotometric analysis. Volatility and pollution are drawbacks of such solvents. Various techniques are employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydrotropic solubilization is one of them. In the present investigation, a hydrotropic solubilizing agent, 20%Sodium Benzoate, and 20%Phenol solution were employed to solubilize Nabumetone from the fine powder of its tablets to carryout spectrophotometric analysis.

MATERIALS AND METHODS

Instruments:

Double Bean UV spectrophotometer (Model No. UV2401 PC), Shimadzu Corporation, Koyto, Japan, Orbital Flask Shaker (Model No. HM8), Spectralab Instruments Pvt. Ltd., Centrifuge (Model No. R-8C), Remi Instrument Ltd, Mumbai, India, Digital pH Meter (Model No. 335), Systronics, Ahmadabad.

Material and Reagent:

A pure gift sample of Nabumetone from Divi's Lab. Ltd., Nalgonda (A.P.), India, and IPCA Lab. Ltd., Ratlam (M.P.), India. Sodium Benzoate and Phenol were purchased from Loba chemicals, Mumbai, India. Commercial tablets of Nabumetone were purchased from the local market.

Approximate Solubility Determination Method

20ml of distilled water/hydrotropic solution was taken in a 50 ml glass bottle and gross weight (including the cap) was noted. Then, a few mg (by visual observation) of fine powder of the drug was transferred to the bottle. The bottle was shaken vigorously (by hand). When the drug got dissolved, more drug (a few mg. by visual observation) was transferred to the bottle and again the bottle was shaken vigorously. The same operation was repeated till some excess drug remained undissolved (after constant vigorous shaking for 10 minutes). Then, again gross weight was noted. From the difference in two readings (of weight), an approximate solubility was determined and solubility enhancement ratios (solubility in hydrotropic solution/solubility in distilled water) were calculated.

Preparation of 20%Sodium Benzoate (SB) and 20%Phenol (PH) Solution

20g SB and 20 ml PH were taken in a 100 ml volumetric flask, the volume was made up to the mark with distilled water.

Determination of wavelength

An accurately weighed quantity of NAB equivalent to 50 mg was taken in a 10ml volumetric flask and dissolved in a sufficient quantity of phenol and volume was made up to mark with the phenol. Then 1 ml pipetted out and diluted up to 500 ml with distilled water (10 μg/ml).

The solution was scanned in the range of 400–200 nm in 1cm cell against blank.

Preparation of Calibration Curve

50mg bulk drug was accurately weighed and transferred to a 50 ml volumetric flask, 25 ml of 20% sodium benzoate and 20%Phenol solution were used to dissolve the drug, and the flask was shaken vigorously. Heating was carried out to avoid the crystal formation of phenol. After the complete dissolution of the drug, sufficient distilled water was used to make up the volume.

From the above solution, a 5ml pipette out in a 50ml volumetric flask, and the volume was made up to the mark with distilled water (Stock Solution,100ug/ml).

The stock solution was further diluted with distilled water to get different standard solutions containing 10, 20, 30, 40, 50, 60, and 70 µg /ml of the drug. The absorbance of the solutions was noted at 330.40 nm against the blank.

Equilibrium Solubility Determinations at Room Temperature

Sufficient excess amounts of drugs were added to 100ml conical flasks containing 20ml distilled water, buffer solution having pH 8.1 (prepared as per IP), and the hydrotropic solutions separately. The flasks were shaken mechanically for 8 hrs. at room temperature in an Orbital Flask Shaker. Then the solutions were allowed to equilibrate for the next 24hr and centrifuged for 5 min at 2000 rpm using a centrifuge. The supernatants of each tube were filtered through Whatman filter paper # 41. Filtrates of saturated solutions of NAB in distilled water, buffer solution, and hydrotropic solution were appropriately diluted with distilled water and the absorbance was noted against respective reagent blanks at 330.40nm.

Solubility was determined by using the following formula,

$$Enhancement\ ratio = \frac{Solubility\ in\ hydrotropic\ solution}{Solubility\ in\ distilled\ water}$$

Analysis of tablet formulation of Nabumetone(Nilitis^{R}) by the proposed method

Standard Preparation

An accurately weighed quantity of about 50mg of NAB standard was transferred in a 50 ml volumetric flask, 25 ml of 20% Sodium benzoate and 20% Phenol solution was used to dissolve the drug, and the flask was shaken vigorously. Heating was carried out to avoid the crystal formation of phenol. After the complete dissolution of the drug, sufficient distilled water was used to make up to mark. Further dilution was carried out for the preparation of stock solution (100µg/ml).

2ml of the above standard stock solution was diluted up to 10ml with the help of distilled water (20µg/ml). The absorbance of the solution was noted at 330.40 nm against the blank.

Sample Preparation

Twenty tablets of NAB were weighed and ground to a fine powder. An accurately weighed tablet powder equivalent to 50 mg of NAB (as per the labeled claim) was transferred to a 50 ml volumetric flask. Then 25ml of 20% Sodium benzoate and 20% Phenolsolution was used to dissolve the drug and the flask was shaken vigorously to solubilize the drug present in tablet powder. Heating was carried out to avoid crystal formation of phenol and the volume was made up to the mark with distilled water. After shaking the volumetric flask to mix the contents, filtration was done through Whatman filter paper No. 41. Further dilution was carried out for preparation of stock solution (100µg/ml).

2ml of the above stock solution was diluted up to 10ml with the help of distilled water (20µg/ml). The absorbance of the solution was noted at 330.40 nm against the blank.

The content of NAB in each sample was calculated by comparing the absorbance of the sample with that of the standard using the following formula.

$$\%\ Labelclaim of NAB = \frac{A(sample)}{A(std)} \times \frac{Wt.(std)}{Wt.(sample)} \times \frac{Avg.Wt.}{LabelClaim} \times 100$$

Validation of Proposed Method

The method was validated for accuracy, precision, linearity, the limit of detection, and the limit of quantitation as per ICH guidelines.

The accuracy of the method was determined by the recovery studies in the tablet formulations of Nabumetone. Recovery studies were carried out by the addition of known quantities of the standard drug to a pre-analyzed sample at three different concentrations. Also, the experiment was repeated three times within a day to determine intra-day precision and on three different days to determine inter-day precision. The value of LOD and LOQ were calculated from the linear regression equation.

RESULT

Various hydrotropic solutions in different concentrations were tried for Nabumetone. Based on Approximate Solubility Determination Method 20%Sodium Benzoate and 20%Phenolsolution were selected for the drug sample.

The spectra of the Hydrotropic Solution were shown in Figure No.1 and the pH Study of the Hydrotropic Solution was shown in Table No.1.

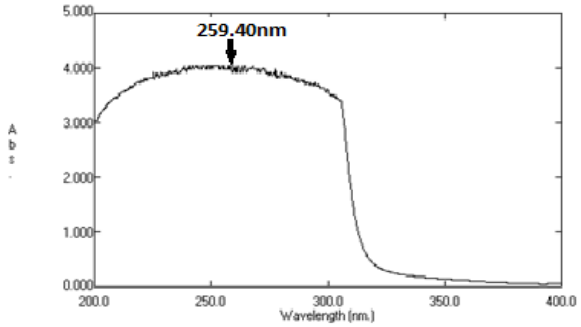

Figure No.1: Spectra of Hydrotrope Solution (λ max = 259.40nm)

Table No.1: Observation of pH Study

Hydrotropic Solution	Concentration	Day 1		Day 2		Day 3	
		Color	pH	Color	pH	Color	pH
SB & PH	20%	Colourless	8.121	Colourless	8.124	Colourless	8.128

By performing the Equilibriumsolubility studies, it was found that the solubility of Nabumetone in 20% Sodium benzoate and 20% Phenol solution was more satisfied compared to its solubility in other solvents like distilled water, buffer pH 8.1. (Table No.2) The wavelength for pure Nabumetone in 20% Sodium benzoate and 20% Phenol solution was found at 330.40 nm and the recorded graph was shown in Figure No.2.

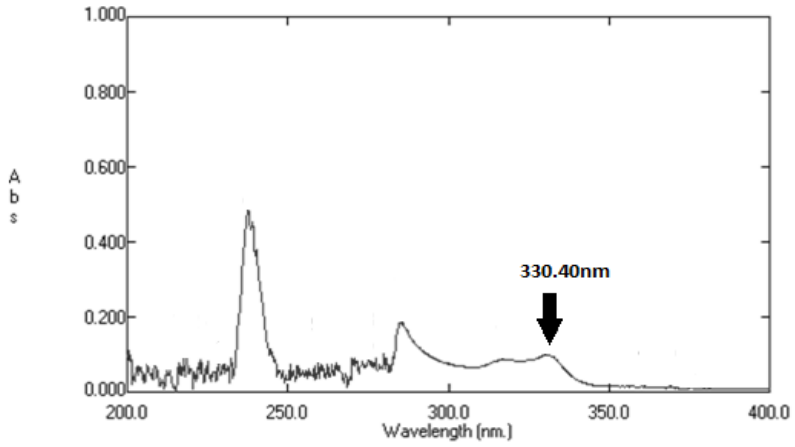

Figure No.2: Spectra ofNAB Showing Selected wavelength at 330.40 nm

Table No.2: Equilibrium Solubility of Nabumetone

Drug	Solvent System	Absorbance at 330.40nm	Temperature (^{o}C)	Solubility Enhancement ratio
NAB	DW	0.003	32 ± 1	-
NAB	Alkaline Borate Buffer (pH 8.1)	0.017	32 ± 1	5.67
NAB	DW + SB & PH	0.184	32 ± 1	61.33

SB- Sodium Benzoate, PH-Phenol, DW-Distilled water.

All the optical characteristics data and Validation parameters of Nabumetone are summarised in Table No.3. The calibration curve of Nabumetone was constructed by plotting the concentration (µg/ml)on X- axis and absorbance on Y –axis (Figure No.3).

Table No.3: Optical Characteristics data and Validation parameters of Nabumetone

Parameter	Nabumetone
Solvent System	Distilled Water + 25 ml 20% Sodium Benzoate and 20% Phenol solution
Wavelength (nm)	320.40
Beer's range (µg/ml)	10 –70
Regression equation (y = mx + c)	Y= 0.0074x + 0.0026
Slope (m)	0.0074
Intercept (c)	0.0026
Correlation coefficient (r)	0.9996
LOD (µg/ml)	1.1785
LOQ (µg/ml)	3.5714
Intra-day* (Coefficient of variation)	0.3882
Inter-day* (Coefficient of variation)	0.6261

*Average of three determinations.

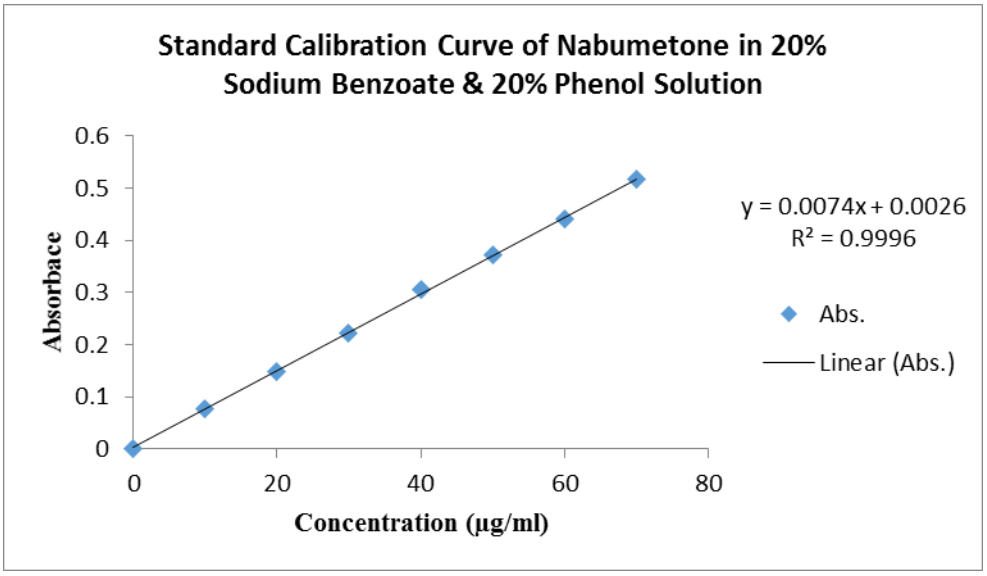

Figure No.3 Calibration curve of nabumetone

The percent label claim of Nabumetone tablet formulations estimated by the proposed method and values was summarized in Table No.4. The accuracy of the method was proved by performing recovery studies in the commercially available formulations (Table No.5). Values greater than 99%indicate that proposed method is accurate for the analysis of the drug.

Table No.4: Results of % Estimation of Nabumetone (n = 5) *

SN	Solutions	Weight took (g)	Absorbance at 330.40 nm	% Estimated*
1	**Standard**	0.0502	0.147	-
2	**Marketed Sample**	0.0656	0.145	99.03
		0.0653	0.144	98.80
		0.0657	0.146	99.57
		0.0650	0.143	98.67
		0.0652	0.144	98.95
			***Mean**	99.004
			± S. D	0.345369
			R. S. D	0.003488

n =No. of repetitions, SD = Standard deviation, RSD = Relative standard deviation

TableNo.5: Results of Recovery Study (n=3)

SN	Solutions	% Level of Recovery	Wt. of Powder Drug taken (g)	Amt. of Pure Drug added (g)	Absorbance at 330.40 nm	% Recovery
1	**Standard**	-	0.0500	-	0.148	-
2	**Marketed Sample**	20	0.0656	0.010	0.176	99.57
		40	0.0655	0.020	0.204	99.33
		60	0.0656	0.030	0.235	99.63
					Mean	99.51
					± SD	0.158745
					R. S. D	0.001595

n =No. of repetitions, SD = Standard deviation, RSD = Relative standard deviation

DISCUSSION

From the spectral study, 330.40nm wavelength was selected for Nabumetone for further studies. So their estimations were done by hydrotropic solubilization technique with respective selected wavelength.

From the spectral study of hydrotropic solutions, it is obvious that there was no interference of hydrotropic solutions in the estimation of drugs. Because for Nabumetone, the hydrotropic solution does not absorb above 260nm.

For Nabumetone, Beer-Lambert's concentration range was found to be 10–70 µg/ml at 330.40 nm.

For spectrophotometric estimations of Nabumetone, the regression equations were determined. The observed values of R^2 (correlation coefficient), were approaching 1, indicating good linear relationships.

Results of equilibrium solubility studies of Nabumetone show that, enhancements in aqueous solubility i.e. 61.33 fold in Sodium benzoate (20%) and Phenol (20%) solution as compared to solubility in distilled water.

The solubility of Nabumetone in the buffer of pH 8.1 was observed 5.67 fold, but its solubility in 20%Sodium benzoate and 20% Phenol solution (pH 8.1), was 63.33 fold as

compared to their solubility in water. This indicates that the enhancement in the aqueous solubility of Nabumetone was largely due to Hydrotropy not completely due to alteration in pH.

The proposed methods yielded very encouraging results for the estimation of the drug in marketed tablet formulation. The results of the recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. The recovery studies confirmed that nearly 100% of the drug can be recovered effectively by the proposed method as indicated by the results at three different recovery levels of 20%, 40%, and 60% respectively. The proposed method was validated for accuracy, precision, linearity, the limit of detection, and the limit of quantitation as per ICH guidelines.

So the proposed spectrophotometric methods can act as an alternative for the estimation of water-insoluble drugs, which can minimize the use of organic solvents. This method can be successfully adopted for routine analysis of Nabumetone in marketed formulations in quality control laboratories.

CONCLUSION

Hydrotherapy is one of the techniques for solubility enhancement of poorly water-soluble drugs. In the present study, the use of a hydrotropic agent shows enhancement in solubility and produces an appreciable result during the estimation of the drug. Hydrotropic agent avoids problem which is created by organic solvents like toxicity, high cost, and volatility.

The present study concludes that the proposed method using a hydrotropic agent is new, simple, cost-effective, safe, accurate, precise, and eco-friendly and can be successfully employed in the routine analysis of these drugs from bulk and pharmaceutical dosage forms.

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