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Spectrophotometric determination of dabigatran etexilate mesylate using 1, 2-napthoquinone-4-sulfonate (NQS) reagent in bulk and capsules

Barla Karuna Devi*[1], Manasa Somireddy[2], Swathi Naraparaju[1], Pani Kumar D Anumolu[2], Soujanya Chaganti[1]

[1]*Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad-500 090, Telangana, India*

[2]*Department of Pharmaceutical Analysis, Gokaraju Rangaraju College of Pharmacy, Hyderabad-500 090, Telangana, India*

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ABSTRACT:A simple, sensitive and cost-effective spectrophotometric method has been established to determine Dabigatran etexilate mesylate present in bulk and in capsules.The method involvesmeasurement of absorbance of orange coloured chromogen formed by the reaction between Dabigatran etexilate mesylate and 1, 2-napthoquinone-4-sulfonate reagent at 454 nm.The methodology shown abeyance of Beer's law in 1-10 µg/mL concentration range. Good linear relationship between the absorbance and corresponding concentrations of dabigatran was observed and it was evidenced by correlation coefficient of 0.999. The methodology was evaluated for accuracy and precision and the results were found to be within the acceptance criteria. The % assay of dabigatran was computed as 101%, which is in accord with its labelled claim. The limit of detection and quantification were determined as 0.048 and 0.147 µg/mL, respectively for the recommended spectrophotometric method.The assay of the formulation indicated that there is no significant interference from the excipients with the assay procedure.The established methodology is uncomplicated, sensitive and extraction-free and can be adopted effectively in the analytical practices of dabigatran in pharmaceutical dosage forms.

KEYWORDS: Dabigatran etexilate mesylate, 1, 2-Napthoquinone-4-sulfonate reagent, visible spectroscopy, capsule dosage form.

I. INTRODUCTION:

Dabigatran etexilate mesylate (DEM) is chemically known as ethyl 3-(1{2[({4 [amino({[(hexalogy)carbonyl] imino}) methyl] phenyl} amino) methyl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-(pyridin-2-yl) formamido) propanoate (**Figure 1**). It is used as anticoagulant[1]. DEM is a prodrug, which is transformed to dabigatran, the active form, in the plasma and liver by esterase-catalysed hydrolysis[2]. From the extensive literature review it is observed that there are a few spectrophotometric, spectrofluorimetric and many reverse phase high performance liquid chromatography (RP-HPLC) methods available to quantify dabigatran. The spectrophotometric methods were developed using hydrochloric acid[3-5], methanol [6,7] , acetonitrile[8] as solvents. The spectrofluorimetric methods were developed using eosin dye [9] and dimethyl sulfoxide [10]. RP-HPLCmethods were developed using solvent mixtures of 0.1% triethylamine and acetonitrile[11], acetonitrile: phosphate buffer of pH 2.5 (33:67 v/v)[12], acetonitrile: water (70:30 v/v)[13], triethylamine phosphate buffer (pH 3.0): acetonitrile (40:60 v/v) [14], methanol: eater (70:30 v/v) [15], methanol: ammonium acetate buffer (90:10 v/v) [16], toluene: ethyl acetate: methanol: formic acid (3:4:3:0.2, v/v/v/v) [17], triethyl ammonium phosphate (pH 2.0): methanol: acetonitrile (30:30:40 v/v/v)[18], orthophosphoric acid (pH 2.6): acetonitrile (60: 40 v/v)[19], hexane-1-solfonic acid sodium salt monohydrate and methanol [20], methanol: phosphate buffer 0.01M (pH 3) (60:40 v/v) [21], methanol: acetonitrile: water (80:15:5 v/v/v) [22], of phosphate buffer of pH 4.5 and acetonitrile (50:50 v/v) [23], acetonitrile and triethylamine (65:35 v/v) [24], methanol :water (70:30 v/v) [25]. A few hyphenated methods, such as Ultra Performance Liquid Chromatography-Mass Spectroscopy (UPLC-MS/MS) method [26] and Liquid Chromatography-Mass Spectroscopy (LC-MS/MS) method [27] were also reported. From the above literature survey, it is observed that there is no spectrophotometric method reported with NQS

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reagent to our knowledge. Unlike chromatographic methods, spectrophotometric methods are comparatively simple, rapid involving quick sample preparation and cheaper. They are more responsive and specific[28] since they involve selective chemical reaction of the analyte with a reagent to yield colored chromogen. The reagent 1, 2-napthoquinone-4-sulfonate (NQS) is used for estimation of drugs containing primary and secondary amines by derivatization method[29]. Dabigatran contains primary amine group; thus, it is a suitable candidate for derivatization with NQS reagent. In view of the above facts, dabigatran was estimated by using NQS reagent in the present investigation. Further the suggested methodology was justified as mentioned in International Counsel for Harmonization (ICH) specifications and the same adopted with success in marketed formulation containingDEM.

Figure 1. Structure of Dabigatran Etexilate Mesylate

II. MATERIALS AND METHODS

Chemicals

Dabigatran Etexilate Mesylate (DEM) was provided as gift sample by Neuland Laboratories Limited, Hyderabad. NQS Reagent was purchased from Sd fine-Chem Ltd., Mumbai. Capsules containing labelled claim 110 mg DEM (Pradaxa 110 mg) was procured from a pharmacy in the neighbourhood. Potassium hydroxide and methanol were obtained from Sd fine-Chem Ltd., Mumbai. Analytical grade reagents and solvents were used and they were utilized without any further purification.

Instrumentation

UV-Visible spectrophotometer, Shimadzu UV-1800, Japan is used for absorbance measurement. Analyte samples were weighed by using analytical balance, Shimadzu AUX 220.

Chemicals and reagents

Preparation of 0.5 % w/v NQS reagent

Precisely weighed NQS (0.5 g) was disintegrated in sufficient distilled water. The volume was made to 100 mL using the same.

Preparation of 2% w/v potassium hydroxide solution

An accurately weighed about 2 g potassium hydroxide (KOH) pellets were dissolved in enough distilled water and further diluted with the same to produce 100 mL.

Preparation of dabigatran standard stock solution

In a 10 mL volumetric flask, accurately measured DEM (10 mg) was transferred and diluted with methanol in order to get 1000 µg/mL solution. Transferred 1 mL of this solution in to another 10 mL flask and the volume was made with methanol to get standard solution of DEM having final concentration of 100 µg/mL.

Selection of suitable wavelength

Dabigatran (10 µg/mL) was produced by taking 1 mL of drug solution from standard solution,1 mL of 0.5% NQS solution, 1 mL of 2% KOH and final volume was made using distilled water. Resulting solution was scanned between 400 and 800 nm.

Analysis of dabigatran using NQS reagent

Aliquots of standard drug solutions of dabigatran ranging from 0.1-1 mL were transferred into a group of 10 mL volumetric flasks containing NQS reagent (0.5 % w/v, 1 mL), potassium hydroxide (2% w/v, 1 mL) and shaken for 5 min. The volume was adjusted with water. The absorbance of the orange-coloured complex was recorded after 15 min at 454 nm for dabigatran against corresponding reagent blank. The linear response of DEM (absorbance vs concentration) was verified and various statistical parameters were validated.

Method optimization

Current analytical procedure was optimized for the concentration of NQS and KOH, reaction time and mole ratio of the reaction and the particulars were given in results and discussions.

Method validation

The developed methodology was justified in terms of linearity, accuracy, precision, limit of detection and quantification.

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Linearity

The linearity of calibration curve in standard solution of DEM was examined over 1-10 µg/mL concentration range. By plotting absorbance against concentration of DEM, calibration line was obtained and from that various statistical parameters were computed.

Accuracy

Recovery experiments were performed to assess the method's accuracy. Reference standards of the drug were added to the formulation at distinct levels (80, 100 and 120%). The percentage recovery and percentage relative standard deviations (%RSD) of the same were calculated statistically for triplicate samples at each level.

Precision

Repeatability studies were carried out to determine the method's intra-day and inter-day precision. Three different concentrations (2, 6, 10 µg/mL) were utilized to study the same. In the intra-day studies, three different concentrations of the DEM solutions were analysed thrice in the same day. To check the inter-day variation, analysis of three different concentrations of the drug was performed on three different days and corresponding data was represented as %RSD.

Limit of Detection (LOD) & Limit of Quantification (LOQ)

Samples containing very low concentrations of analyte were utilized to determine the limit of detection (LOD) and limit of quantitation (LOQ) as mentioned in ICH guidelines. The LOD and LOQ values were computed from the linearity data using the given formulae.

$$LOD = \frac{3.3\,\sigma}{S}$$

σ = standard deviation of the response
S = slope of the calibration curve of the analyte.

$$LOQ = \frac{10\,\sigma}{S}$$

σ = standard deviation of the response
S = slope of the calibration curve of the analyte.

Assay of DEM in capsules

The average weight of ten capsules holding 110 mg of Dabigatran was calculated. The contents of capsules were taken out and average weight of powder was determined. Powder weight analogous to 10 mg of DEM was shifted and dissolved in methanol in a 10 mL flask. Resulted solution was screened and 1 mL of the clear filtrate was taken and diluted with methanol to 10 mL to give standard solution of 100 µg/mL concentration. An aliquot of the clear filtrate (1 mL) was added to NQS (0.5% w/v, 1 mL) and potassium hydroxide (2% w/v, 1 mL) contained in a 10 mL volumetric flask. The solutions diluted with water and rested for 15 min were utilized to record absorbance against the corresponding reagent blank. The outcome was validated statistically and provided in the following sections.

III. RESULTS AND DISCUSSION

Analytical method optimization

The reaction of NQS with DEM in alkaline medium is the basis for the development of present spectrophotometric method. NQS when treated with primary or secondary amine containing compound, the sodium sulfonate group in NQS is replaced with the aromatic amine group. The resulted orange-coloured chromogen showed absorption maxima at 454 nm (**Figure 2**). The expected mechanism of reaction was illustrated in **Figure 3**.

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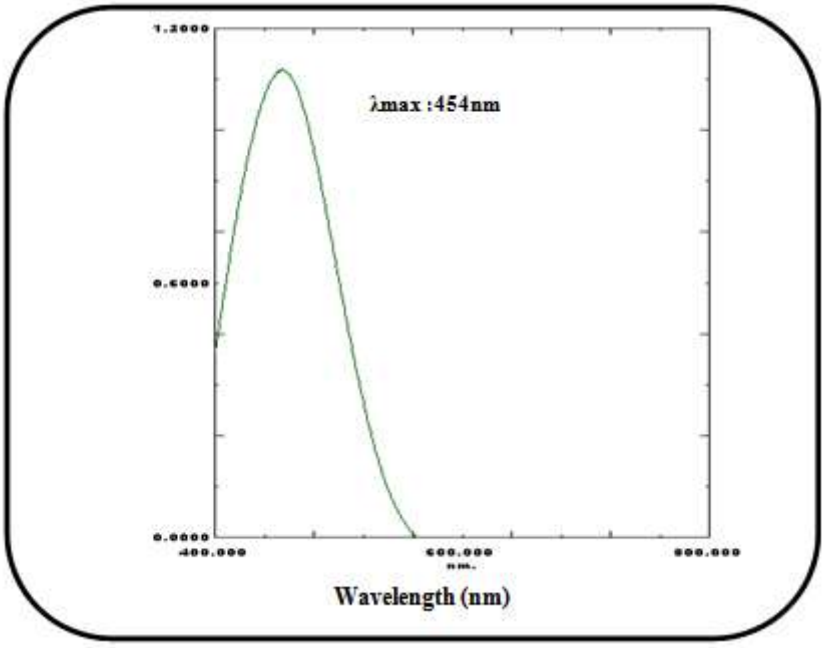

Figure 2. UV –Visible spectrum of Dabigatran (10 µg/mL)

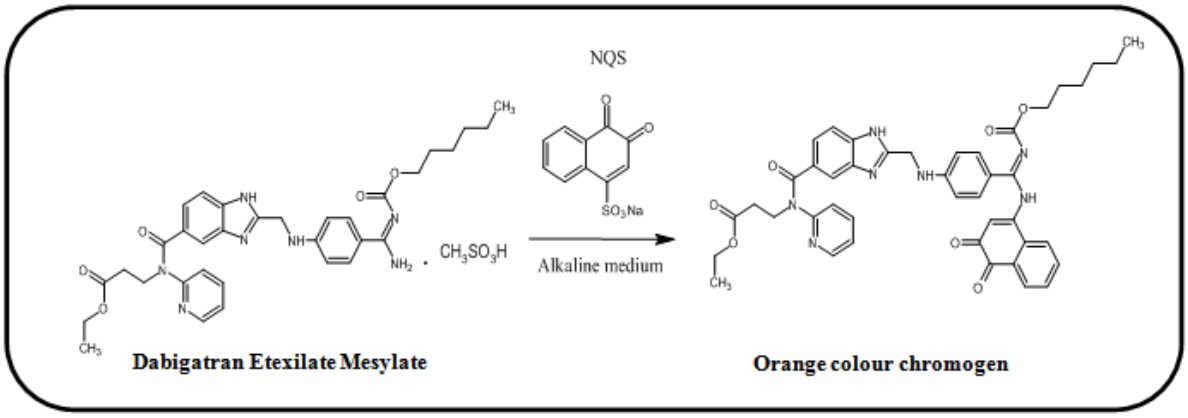

Figure 3. Reaction of Dabigatran with NQS reagent

The method was optimized for the concentration of NQS, KOH, time for colour development to attain maximum absorbance and stability and mole ratio of the reaction. The effect of concentration of chromogenic reagent was determined by using dissimilar concentrations (0.125, 0.25, 0.5, 0.75 and 1.00% w/v). The maximum absorbance (**Figure 4**) was observed with 0.5% w/v of NQS reagent. So, the same was selected for the determination of DEM. The effect of concentration of KOH was determined by taking divergent concentrations (1.0, 1.5, 2.0, 2.5, and 3.0% w/v) and maximum absorbance (**Figure 5**) was observed with 2.0% w/v of KOH. So, the concentration 2% w/v of KOH was selected for the determination of DEM. The effect of reaction time was determined at different time points (0, 15, 30, 45 and 60 minutes). Maximum absorbance (**Figure 6**) was observed after reaction time of 15 min and the coloured chromogen was stable for over a period of 30 min. Continuous variation method was used to study the stoichiometry of the reaction. The drug and the chromogenic reagent were varied to produce dissimilar mole ratios (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 and 0.9), while other reaction variables were maintained as mentioned earlier. Equimolar solutions of dabigatran and NQS (0.5:0.5) shown maximum absorbance, the stoichiometric relationship shown in **Figure 7** indicates the same.

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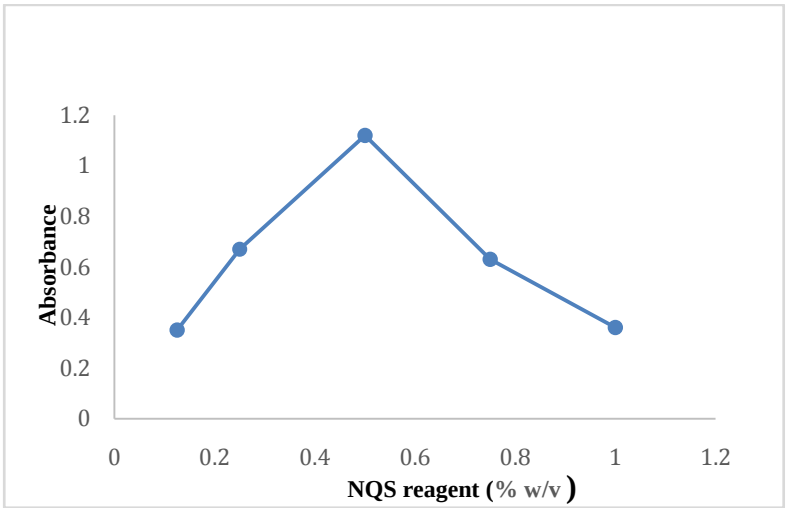

Figure 4. Effect of NQS concentration

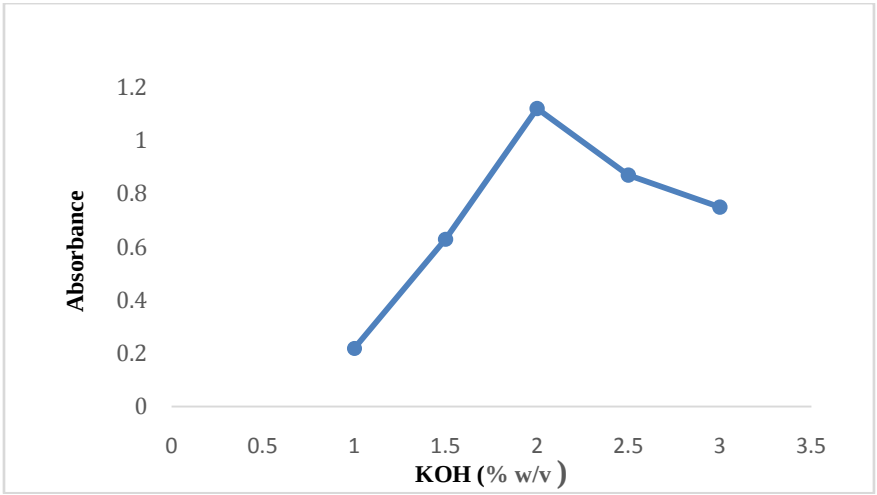

Figure 5. Effect of KOH concentration

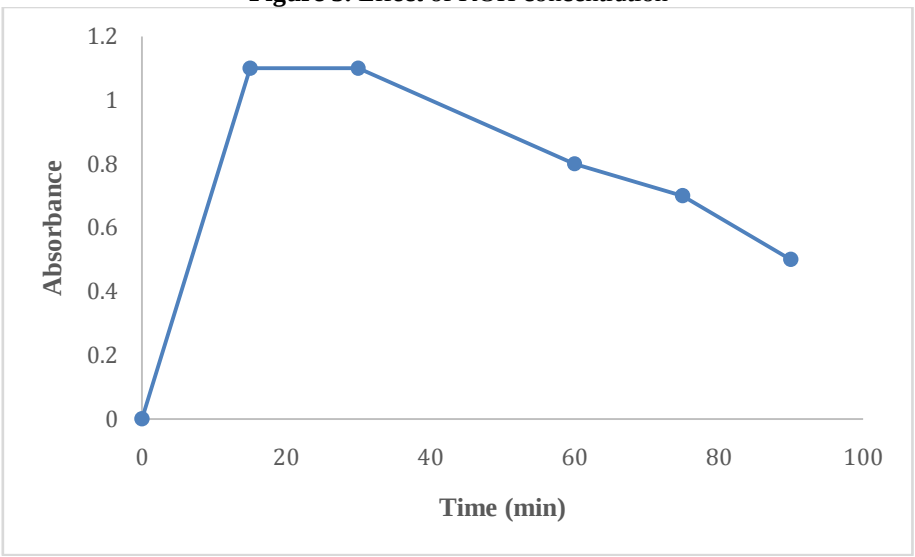

Figure 6. Effect of reaction time

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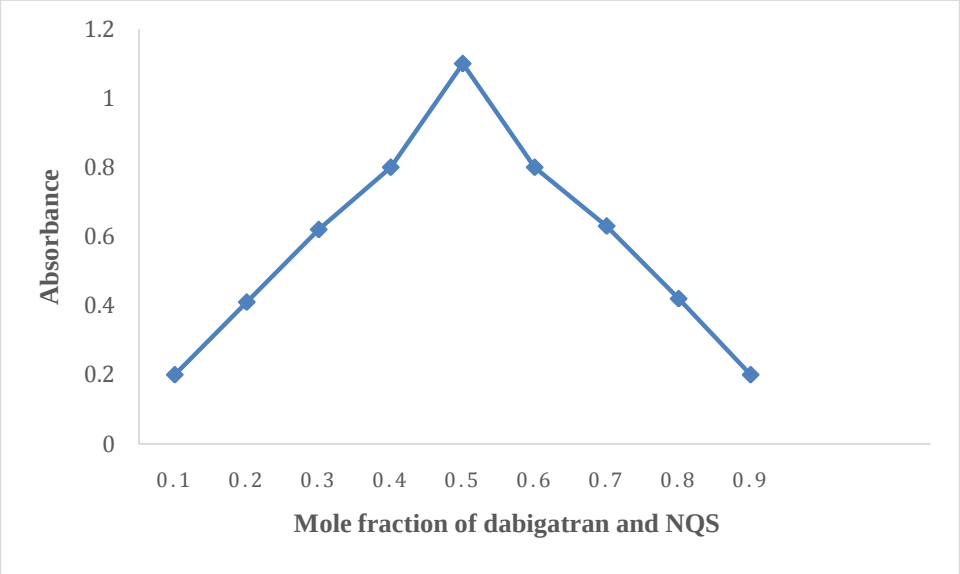

Figure 7. Job's continuous variation plot for the analytical method

Analytical method validation

Linearity

The abeyance of Beer's law over 1.00 - 10.00 µg/mL concentration range by suggested methodology was shown in **Figure 8**. The equation of the regression analysis was obtained as y = 0.0682x+0.4402 and the correlation coefficient was found to be 0.9993. The results indicated that the absorbance is increased as the concentration of DEM increases.

Accuracy (recovery studies)

The correctness of the methodology is confirmed by recovery studies and is proved to be significant under specification limits, with % recovery 99-101 %and % RSD < 2% for DEM. The results were summarized in the Table 1.

Precision

The repeatability (intra-day precision) and Intermediate precision of the procedure was established at three distinct levels (2, 6 and 10 µg/mL) and the outcome was summarized in the Table 2. The method was proved to be precise as the %RSD values less than 2.0 were observed in intra-day and inter-day studies.

Sensitivity

The sensitiveness in the procedure is verified in terms of LOD and LOQ and they were calculated as 0.048 and 0147 µg/mL, respectively. Sandell sensitivity was computed as 0.0089 µg/cm^2.

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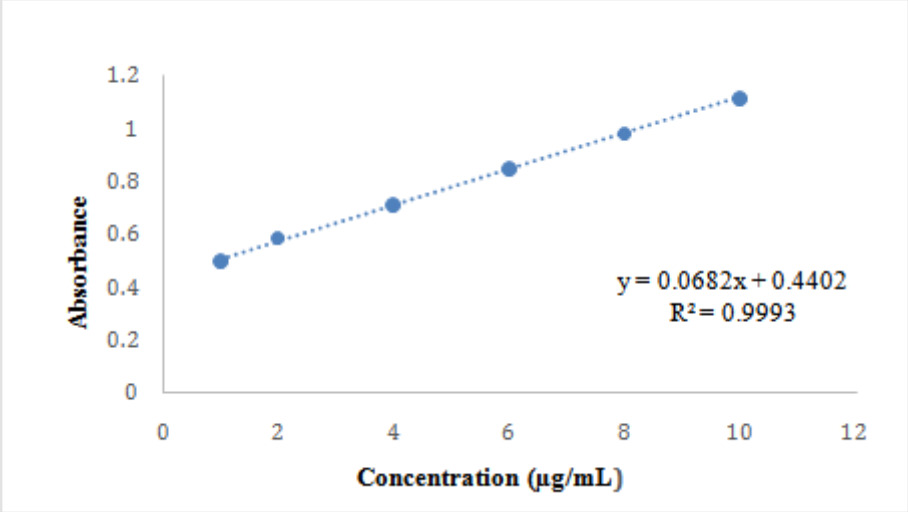

Figure 8. Calibration plot of Dabigatran

Analysis of dabigatran in marketed formulation

The evolved methodology was employed in the marketed formulation to verify its reliability. The results are reported in Table 3. The %assay was determined as 99 – 101% (i.e., within 98–102%). The overall optimized characteristics for dabigatran are summarized in Table 4.

Table 1. Data for accuracy of Dabigatran

Analyte	Recovery level (%)	Conc of sample (µg/mL)	Conc of standard spiked (µg/mL)	Total amount (µg/mL)	Amount recovered (µg/mL) AM±SD (n=3)	% Recovery	RSD (%)
DEM	80	4	3	7	6.94±0.0015	99.1	0.164
	100	4	4	8	7.98±0.001	99.7	0.101
	120	4	5	9	9.09±0.001	101	0.961

Table 2. Data for precision of Dabigatran

Concentration (µg/mL)	Intra-day precision		Inter-day precision	
	Concentration estimated (µg/mL) AM± SD (n=3)	% RSD	Concentration estimated (µg/mL) AM± SD (n=3)	% RSD
2	2.04±0.002	0.336	2.07±0.002	0.336
6	6.03±0.002	0.234	6.06±0.004	0.468
10	10.12±0.015	1.32	9.97±0.01	0.880

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Table 3. Data for assay studies

Formulation	**Label claim (mg)**	**Amount found (mg) A.M± SD(n=3)**	**%Assay**	**% RSD**
Pradaxa 110 mg	110	111.4 ±0.15	101±0.12	0.98

Table 4. System suitability parameters for Dabigatran

Parameters	**Literature method**[7]	**Current method**
Reagent	MBTH	NQS
Reaction time (min)	60	15
Absorption Wavelength (nm)	632	454
Linearity range (µg/mL)	2-6	1-10
Correlation coefficient (r^2)	0.999	0.999
Slope (m)	0.1037	0.0682
Intercept (c)	0.0083	0.4402
Regression equation (y)	Y=0.1037x+0.0083	Y=0.0682x+0.4402
Limit of Detection (µg/mL)	0.0578	0.048
Limit of Quantification (µg/mL)	0.298	0.147
Molar absorptivity (L mol/cm)	0.00075	0.00074
Sandell sensitivity (µg/cm^2)	0.0083	0.0089

IV. CONCLUSIONS

A simple, sensitive and extraction-free spectrophotometric method using NQS as chromogenic reagent for the determination of dabigatran in bulk and capsules was developed. The assay data was in accord with the respective label claim. This indicates that formulation excipients were not interfering in actual analysis of the analyte. Further, the outcomes of the validation studies evidenced that the proposed method was sound scientifically. Further, less reaction time, appreciable linearity range, lower LOD and LOQ values in comparison to the method reported using 3-methyl-2-benzothiazoline hydrazone (MBTH) reagent, indicates the greater sensitivity of the established methodology. The developed

spectrophotometric method was proved to be better because of it does not involve additional extraction procedures, and no heating and cooling required, time saving, cost effective and involves very simple analytical procedures. Based on above mentioned advantages, the proposed methodology can be routinely used in the analytical practices of DEM in the pharmaceutical capsule dosage form.

ETHICS COMMITTEE APPROVAL

The Ethics Committee approval is not required for this research work, as it doesn't involve any human beings or animals.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

FINANCIAL DISCLOSURE

The authors declared that this study received no financial support.

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