

Validated Spectrophotometric Method for the Determination of Nitrofurantoin in Pure and in its Dosage Form

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Abstract: A simple, precise, rapid sensitive and accurate spectrophotometric methods have been developed for the estimation of Nitrofurantoin UV in pure form and its pharmaceutical formulations based on oxidative coupling reaction UV with 2, 2, Bipyridine reagent at P^H - 4 which is extractable at 520 nm. Beer's law is obeyed in the concentration range 0.4 - 2.4 ml (4 - 24 μgml^{-1}). The developed method was applied directly and easily for the analysis of the pharmaceutical formulations. RSD was found to be 0.1473% and recovery 99.31%. The method was completely validated and proven to be rugged. The interferences of the ingredients and excipients were not observed. The repeatability and the performance of the proved method were established by point and internal hypothesis and through recovery studies.

Keywords: Spectrophotometry, Nitrofurantoin, 2, 2, Bipyridine, Oxidative coupling

1. Introduction

Several materials have been tested toward this aim, including solid amalgam electrodes (SAE), carbon paste electrodes (CPE), nanotube carbon paste electrodes (NTCPE), glassy carbon electrodes (GCE), solid composite electrodes (SCE) and boron - doped diamond film electrodes (BDDFE). Several reviews illustrating the use of these materials in the electroanalytical field have been published in recent years¹⁻¹¹.

Among these materials, BDDFE has attracted the attention of electro analytical researchers as a candidate for the electrochemical determination of pharmaceutical compounds, since BDDFE presents a stable background current, wide potential window for aqueous and non - aqueous electrolytes, high thermal conductivity, high hardness, high electrochemical stability, low organic molecule adsorption and high sensitivity for analytical purposes^{5, 8, 9, 12-14}.

However, little attention has been given in the literature concerning the influence of different boron - doping levels on the electrochemical response of the pharmaceutical compounds.

In addition, some reports have been published showing that nitrofurazone, which is in the group of nitrofurantoin, has a good electrochemical response on the BDDFE^{15 and 16}. This enables the application of this electrode for the electrochemical detection and quantification of compounds belonging to the nitrofurantoin group. Among them, nitrofurantoin [NFT; 1 - ((5 - nitro - 2 - furfurylidene) - 1 - amino) hydantoin] is a drug synthesized from nitrofurantoin that is very useful in the treatment of urinary tract diseases. Depending on its concentration at the inflammation site, this drug may act as a bacteriostatic or bactericidal agent¹⁷. As pointed out by Hamman¹⁷, this drug can act against various gram - negative bacteria, as well as some gram - positive bacteria, including Citrobacter, Corynebacterium, Enterobacter, Escherichiacoli, Klebsiella,

Neisseria, Salmonella, Staphylococcus aureus and Enterococcus faecalis. It is efficient against these bacteria in the concentration range of 1-32 $\mu\text{g mL}^{-1}$. However, this drug is partially metabolized, and 24 h after the application of a single oral dose, 30-50% of this drug is excreted in its original form and 1% is excreted as Aminofurantoin in the urine¹⁷. Thus, this drug can become a water contaminant, which can be dangerous for human health.

On the other hand, electro analytical techniques are increasingly used to detect organic compounds. These techniques have several advantages, including that they are quick and reproducible, present low limits of detection and quantification and have relatively low cost compared with the more traditional techniques⁸. The two initial reports about the use of electro analytical techniques to determine NFT came from the sixties and seventies years, when Jones et al.²⁴ and Mason and Sandmann²⁵ reported the use of the Polarographic method and the reductive Voltammetric method using a rotating platinum electrode, respectively. Recently, three reports have been published that demonstrate the use of square wave Cathodic adsorptive stripping Voltammetry for the detection on mercury electrodes^{17&23} and on activated carbon fiber microelectrodes²⁶. In these works, this technique was shown to be a very sensitive and selective methodology for NFT analysis^{17, 23&26}. Resolution of ternary mixtures of Nitrofurantoin, Furaladone and Furazolidone by partial least - square analysis to the Spectrophotometric signals after Photo - decomposition²⁷⁻³⁰.

M. C Mahedero et. al. has described Liquid Chromatographic and Spectrophotometric Determination of Phenazopyridine Hydrochloride, Ampicilline Trihydrate, and Nitrofurantoin in Pharmaceutical Preparations³¹⁻³⁵. Essam Hammamet al Determination of nitrofurantoin drug in pharmaceutical formulation and biological fluids by square - wave cathodic adsorptive stripping voltammetry³⁶.

Stability of Nitrofurantoin in Extemporaneously Compounded Suspensions Mary H. H. Ensomet al Differential Effects of Chrysin on Nitrofurantoin

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Pharmacokinetics Mediated by Intestinal Breast Cancer Resistance Protein in Rats and Mice Atsushi Kawase, et al³⁷⁻³⁸.

The empirical formula for Nitrofurantoin UV is $C_8H_6N_4O_5$ and the molecular weight is 238.16 g. It has the following structure.

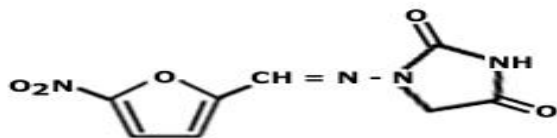


Figure 1: Chemical Structure of Nitrofurantoin

There is however no reported UV - Visible Spectrophotometric method for the analysis of Nitrofurantoin in its technical grade and formulations. This describes a validated UV - Visible Spectrophotometric method for the quantitative determination of Nitrofurantoin. Functional group used for color development of Nitrofurantoin was nitro group, which is undergoes reduction in presence of Conc. HCl and Zn to form amino group. The results obtain in this method was based on and Oxidative coupling reaction with 1, 10 - phenanthroline Oxidative complex formation reaction.

An attempt has been made to develop and validate a method to ensure their accuracy, precision, repeatability, reproducibility and other analytical method validation parameters as mentioned in the various guidelines

6.4: Method (D): (Visible Spectrophotometric method by 2, 2 - Bipyridine reagent).

2. Experimental

2.1 Preparation of Standard Calibration curve of pure drug.

a) Solvent

Dimethyl Formamide was used as Solvent.

b) Preparation of Calibration curve

Fresh aliquots of Nitrofurantoin ranging from 0.4 to 2.4ml were transferred into a series of 10 ml volumetric flasks to provide final concentration range of 4 to 24 $\mu\text{g ml}^{-1}$. To each flask 1ml of (0.01M) 2, 2 - Bipyridine solution was added followed by 1ml of (0.2%) Ferric chloride solution and resulting solution was heated and finally 1ml (0.2M) Orthophosphoric acid solution was added. The solutions were cooled at room temperature and made up to mark with

Dimethyl Formamide. The absorbance of orange red colored chromogen was measured at 520 nm against the reagent blank. The color species was stable for 24 h. The amount of Nitrofurantoin present in the sample solution was computed from its calibration curve

c) Procedure for formulations

Twenty tablets containing Nitrofurantoin were weighed and finely powdered. An accurately weighed portion of the powder equivalent to 100 mg of Nitrofurantoin was dissolved in a 100 ml of Dimethyl Formamide and mixed for about 5 min and then filtered. The Dimethyl Formamide was evaporated to dryness. The remaining portion of solution was diluted in a 100 ml volumetric flask to the volume with Dimethyl Formamide up to 100 ml to get the stock solution A. 10 ml of aliquots was pipette out into 100 ml volumetric flask and the volume was made up to the mark with Dimethyl Formamide to obtain the final concentration of $100 \mu\text{g ml}^{-1}$ (Stock solution).

Subsequent dilutions of this solution were made with Dimethyl Formamide to get concentration of 4 to 24 $\mu\text{g ml}^{-1}$ and were prepared as above and analyzed at the selected wavelength, 520 nm and the results were statistically validated

d) Procedure for blood sample

After collection of Blood sample it will be centrifuged. For isolation of Nitrofurantoin from plasma sample, Dimethyl Formamide was used for protein precipitation. Liquid - Liquid extraction was performed with plasma by alkalization with 1M NaOH, followed by extraction with 30% dichloromethane in Hexane. The upper organic layer was evaporated to dryness, the dry residue 100 mg was dissolved in 100 ml of Dimethyl Formamide ($1000 \mu\text{g ml}^{-1}$). From the above solution 10 ml is taken into a 100 ml of Volumetric flask and made up to the mark with Dimethyl Formamide. ($100 \mu\text{g ml}^{-1}$)

From the above solution ranging from 0.5 - 3 ml ($5 - 30 \mu\text{g ml}^{-1}$) were transferred in to 10 ml Volumetric flask and to the each flask 1ml of (0.5%) 2, 2 - Bipyridine solution was added followed by 1ml of (0.2%) Ferric chloride solution and made up to the mark with Dimethyl Formamide. Then the resulting solution was heated and finally 1ml (0.2M) Orthophosphoric acid solution was added. The solutions were cooled at room temperature and made up to the mark with distilled water. The absorbance of orange red colored chromogen was measured at 520 nm against the reagent blank. The color species was stable for 24 h. The amount of Nitrofurantoin present in the sample solution was computed from its calibration curve.

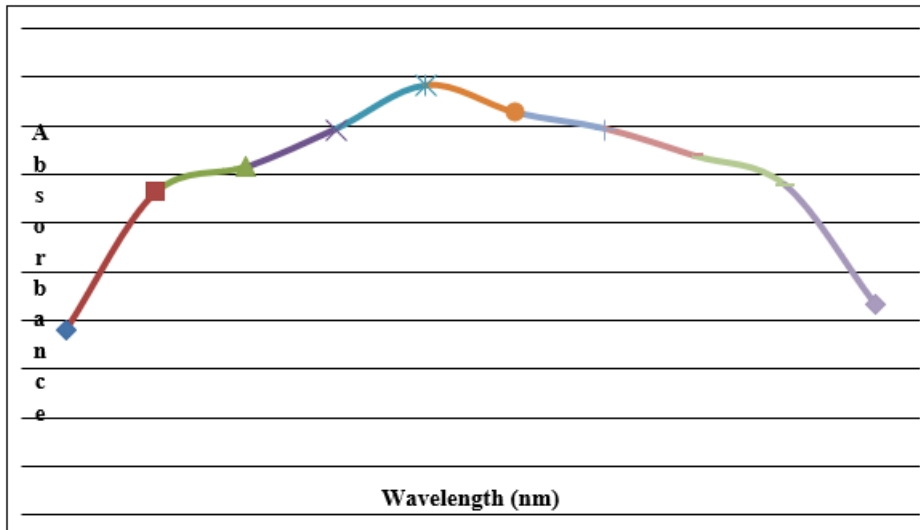


Figure 6.11: Absorption spectrum of Nitrofurantoin with 2, 2 - Bipyridine/FeCl₃

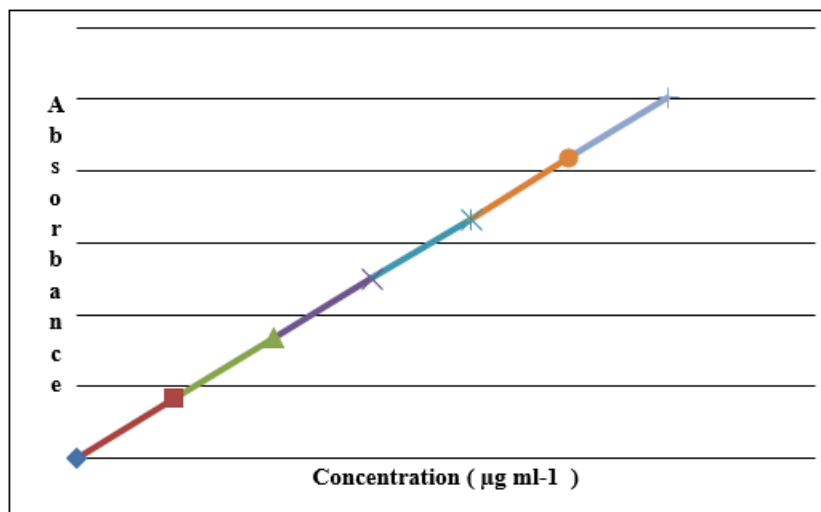


Figure 6.12: Beer's law plot of Nitrofurantoin with 2, 2 - Bipyridine/FeCl₃

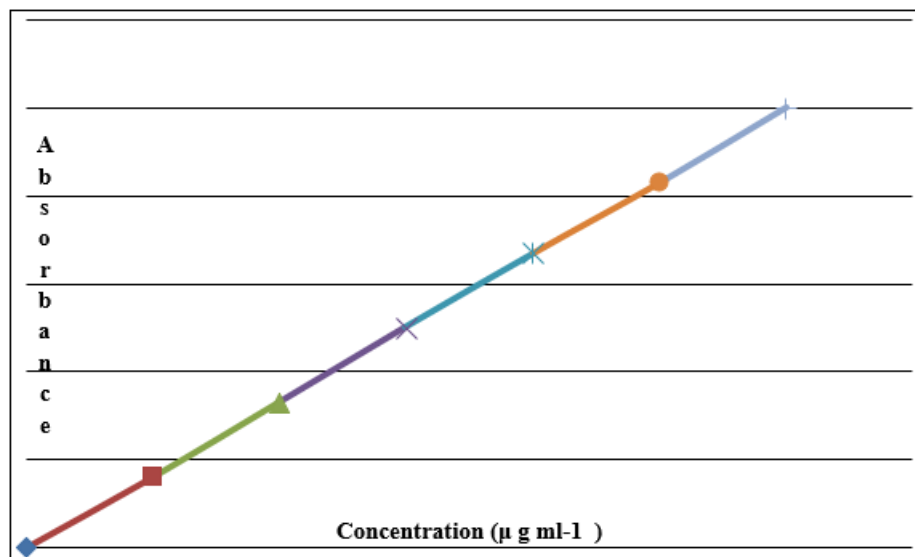


Figure 6.13: Beer's law plot for Nitrofurantoin in Blood sample

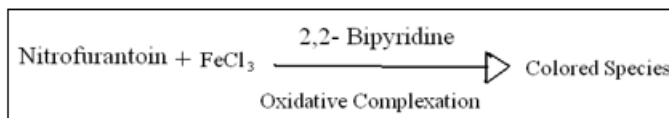


Figure 6.14: A Schematic reaction Mechanism of Nitrofurantoin with

Table - 6.22: Optical characteristics and precision by (2, 2 - B. P)

Parameter	Visible method
Absorption maxima (nm)	520
Beer's law limits ($\mu\text{g ml}^{-1}$)	4 - 24
Molar absorptivity ($1 \text{ mol}^{-1} \text{ cm}^{-1}$)	1.012×10^4
Sandell's Sensitivity ($\mu\text{g cm}^{-2}$)	0.0235
Regression equation (Y*)	
Slope (b)	0.0419
Intercept (a)	0.00133
Standard deviation (SD)	0.00086
Correlation coefficient (r^2)	0.9999
%RSD (Relative Standard deviation) *	0.1473
Range of errors	
Confidence limits with 0.05 level	0.00064
Confidence limits with 0.01 level	0.00084
Limits of detection (LOD) ($\mu\text{g ml}^{-1}$)	0.0615
Limits of quantification (LOQ) ($\mu\text{g ml}^{-1}$)	0.2052

*RSD of 6 independent determinations.

Table 6.23: Assay results of Nitrofurantoin in formulations by visible method

Name of the Formulation	Formulation in (mg)	Amount found by the proposed method (mg)	Amount found by the reference method ^{39, 40} (mg)	% Recovery
NIFTAS 50	250	247.83 $t=0.0032^*$ $F= 6.3992^*$	245.66	99.11
Niftran	250	248.66 $t=0.0033^*$ $F= 6.3892^*$	246.98	99.31

*t and F - values refer to comparison of the proposed method with reference method.

*Theoretical values at 95% confidence limits $t= 0.0029$ and $F= 5.7043$.

Table 6.24: Determination of accuracy of Nitrofurantoin

Amount of NFT in formulation (mg)	Amount of Standard NFT added (mg)	Total amount found (mg)	% Recovery
247.83	200	446.09	99.13
248.66	200	447.59	99.46
248.19	200	446.74	99.27
249.44	250	498.88	99.77
249.33	250	498.66	99.73
248.77	250	497.54	99.50
249.44	300	548.76	99.77
248.95	300	547.69	99.58
247.5	300	544.5	99.00

Table 6.25: Statistical data for accuracy determination

Total amount found (mean)	Standard deviation	% RSD
248.22	0.4162	0.1676
249.18	0.3593	0.14419
248.63	1.0088	0.4057

The results are the mean of five readings at each level of recovery.

Table 6.26: Repeatability data for NFT at 520 nm

Conc. ($\mu\text{g ml}^{-1}$)	Abs 1	Abs2	Abs3	Mean	Std. deviation	(%) RSD*
4	0.167	0.168	0.169	0.168	0.001	0.5952
8	0.334	0.335	0.336	0.335	0.001	0.2985
12	0.508	0.509	0.505	0.507	0.002	0.3944
16	0.666	0.665	0.669	0.666	0.002	0.3003
20	0.838	0.837	0.839	0.838	0.001	0.11933
24	1.006	1.005	1.007	1.006	0.001	0.0994

*RSD of six independent determinations

Table 6.27: Color stability data for 2, 2 - Bipyridine Method

Conc. in $\mu\text{g ml}^{-1}$	Time in Hours							
	4	8	12	16	20	24	28	32
16	0.667	0.667	0.668	0.669	0.669	0.669	0.612	0.513

Table 6.28: Assay results of Nitrofurantoin in Blood sample

Name of the Formulation	Formulation in (mg)	Amount found by the proposed method in (mg)	Amount found by the reference method ^{39, 40} (mg)	% of Recovery
NIFTAS 50	50	39.99 $t=0.00296^*$ $F=4.5959^*$	38.89	97.17
Niftran	50	39.96 $t=0.00295^*$ $F=4.5659^*$	38.72	96.79

*t and F values refer to comparison of the proposed method with reference method.

*Theoretical values at 95% confidence limits $t=0.00196$ and $F=4.0156$.

Table 6.29: Determination of accuracy of Nitrofurantoin

Name of the Formulation in (mg)	Amount of Drug in Blood sample (mg)	Amount of Standard Drug added in (mg)	Total amount found (mg)	% Recovery
50	39.88	50	79.76	79.76
50	39.84	50	79.68	79.68

The results are the mean of five readings at each level of recovery.

Table 6.30: Repeatability data for Nitrofurantoin at 520nm

Concentration in ($\mu\text{g ml}^{-1}$)	Abs1	Abs2	Abs3	Mean	Std. Deviation	(%) RSD*
5	0.016	0.017	0.019	0.0173	0.00015	0.867
10	0.033	0.034	0.036	0.0343	0.00015	0.4373
15	0.05	0.051	0.052	0.051	0.0001	0.1960
20	0.067	0.066	0.068	0.067	0.0001	0.1492
25	0.083	0.084	0.085	0.084	0.0001	0.1190
30	0.101	0.11	0.12	0.11	0.001	0.9090

*RSD of 6 independent determinations

3. Results and Discussion

1) Optical parameters

In order to ascertain the optimum wavelength of maximum absorption (λ_{max}) formed in UV spectrophotometric method (Reference method – A) and of the colored species formed in each so the four visible spectrophotometric methods, specified amount of Nitrofurantoin in final solution $10 \mu\text{g ml}^{-1}$ (Reference method), and $4 \mu\text{g ml}^{-1}$ (method) were taken and the colors were developed following the above mentioned procedures individually. The absorption spectra were scanned on spectrophotometer in the wavelength region of 200 - 400 nm (for reference method) and 380 - 800 nm (for Method) against corresponding reagent blanks. The reagent blank absorption spectrum of each method was also recorded against distilled water /Dimethyl Formamide. The results are graphically represented in. fig.

2) Parameters fixation

In developing these methods, a systematic study of the effects of various relevant parameters in the methods concerned were under taken by verifying one parameter at a time and controlling all other parameter to get the maximum color development (for method) reproducibility and reasonable period of stability of final colored species formed. The following studies were conducted.

4. Method

The results obtained in this method were based on oxidation followed by complex formation reaction of Nitrofurantoin with 2, 2 - Bipyridine, Ferric chloride and Orthophosphoric acid to form an orange red colored chromogen that exhibited maximum absorption at 520 nm against the corresponding reagent blank. The functional group used for the color development for this method was primary amine group. A schematic reaction mechanism of Nitrofurantoin with 2, 2 - Bipyridine reagent was shown in (fig) 2, 2 - Bipyridine and strength of acid order of addition of reagents, solvent for final dilution were studied by means of control experiments varying one parameters at a time.

1) Optical Characteristics

The reference method adhere to beer's law the absorbance at appropriate wave length of a set of solutions contains different amounts of Nitrofurantoin and specified amount of reagents (as described in the recommended procedure) were noted against appropriate reagent blank.

The beers law plot of the system illustrated graphically (fig:) least square regression analysis was carried out for the slope. Intercept and Correlation Coefficient. Beer's law limits, Molar absorptivity & Sandells sensitivity for Nitrofurantoin with each of mentioned reagents was calculated. The optical characteristics were present in the Table.

In order to test whether the colored species formed in the method here the beer's law the absorbance at appropriate wavelength of a set of solutions contain different amounts of Nitrofurantoin and specified amount of reagents (as described in the recommended procedure) were noted against appropriate reagent blanks or distilled water. The beers law plots of the system illustrated graphically (fig:) least square regression analysis was carried out for the slope, intercept and correlation coefficient, beer's law limits molar absorptivity Sandells sensitivity for Nitrofurantoin with each of mentioned reagents were calculated. The optical characteristics are presented in the Tables.

2) Precision

The precision of each one among the five proposed spectrophotometric methods were ascertained separately from the absorbance values obtained by actual determination of a fixed amount of Nitrofurantoin ($4 \mu\text{g ml}^{-1}$) in final solution. The percent relative standard deviation and percent range of error (at 0.05 and 0.01 confidence limits) were calculated for the proposed methods and presented in Tables.

3) Analysis of formulations

Commercial formulations of Nitrofurantoin were successfully analyzed by the proposed methods. The values obtain from the proposed and reference methods were compared statistically by the t and F tests and were found that those proposed methods do not differ significantly from the reported methods and they were presented in Tables. The proposed methods also applied for Biological Samples (Blood) for good recoveries are obtain which were recorded in Tables -

4) Accuracy

Recovery studies were carried by applying the method to Drugs sample present in formulations to which known amount of Nitrofurantoin of label claim was added (standard addition method) the recovery studies were carried by applying the method to Biological sample (Blood) to which known amount of Nitrofurantoin correspond to 2 mg Formulations taken by the patient. By the follow of Standard addition method 2 mg of label claim was added. After the addition of these standards the contents were transferred to 100 ml volumetric flask and dissolved in solvent. Finally the volume was made up to the mark with solvent. The solution was filtered through Whitman No.41 filter paper. The mixed sample solutions were analyzed and their absorbance value was determined. At each level of recovery five determinations were performed and present in Tables. The results obtained were compared with expected results and were statistically validated in Tables.

5) Linearity and Range

The linearity of analytical method is its ability to elicit test results that are directly proportional to the concentration of analyze in sample with in a given range. The range of analytical method is the interval between the upper and lower levels of analyze that have been demonstrated within a suitable level of precision, accuracy and linearity.

6) Specificity and Selectivity

Specificity is a procedure to detect quantitatively the analyze in the presence of components that may be expected to the present in the sample matrix. While selectivity is a procedure to detect the analyze qualitatively in presence of components that may be expected to present in the sample matrix. The excipient in formulations was spiked in a pre weighed quantity of drugs and then absorbance was measured and calculations were done to determine the quantity of the drugs

7) Repeatability

Standard solutions of Nitrofurantoin were prepared and absorbance was measured against the solvent as the blank. The observance of the same concentration solution was measure five times and standard deviation was calculated and presented in tables.

8) Interferences Studies

The effect of wide range of inactive, ingredients usually present in the formulations for the assay of Nitrofurantoin under optimum conditions was investigated. None of them interfered in the proposed methods even when they are present in excess fold than anticipated in formulations.

9) Solution Stability

The stability of the solutions under study was established by keeping the solution at room temperature for 48 Hours. The results indicate no significant change in assay values indicating stability of Drug in the solvent used during analysis. The results are recorded in Tables.

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