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Kinetics Spectrophotometric determination of Ranitidine based on its Inhibitory effect on the Oxidation Rate of Malachite green by N-bromosuccinide

Ashraf M. Taha*, Alaa Eldin Mokhtar Abdel-Hady

Sinai University, Faculty of Pharmacy, Pharmaceutical Chemistry Department, Areesh City, Cairo, Egypt

Abstract : A simple and sensitive kinetic spectrophotometric method is described for the determination of ranitidine. The method is based on the inhibiting effect of ranitidine on the rate of oxidation of malachite green (MG^+) with N-bromosuccinimide (NBS) The oxidation reaction was followed spectrophotometrically by measuring the rate of change of the absorbance of malachite green with time at λ=617nm in the presence of different concentrations of ranitidine using the recommended procedure. Ranitidine can be determined from 0.08 to 2.40 μg ml^{-1} with a linear calibration graph and detection limit of 0.026 μg ml^{-1}. The method was successfully applied for the determination of ranitidine in pure ranitidine samples and in ranitidine tablets. The recovery of the analyzed samples were 97-100% with relative standard deviation, sr (%) =1.14 x 10^{-4} indicating high accuracy and precision of the suggested method. The interference of various cations and anions in the determination of ranitidine was studied.

Keywords : Malachite green, N-bromosuccinimide reactions, Kinetics, Ranitidine, Spectrophotometry.

Introduction

N-haloimides have been used as effective oxidizing/brominating agents for the spectrophotometric determination of many pharmaceutical compounds. N-bromosuccinimide (NBS), being the most versatile, is the most commonly used N-haloimide [1, 2]. The analysis involving NBS was based on direct measurement of the chromogenic derivative of the drug, or indirectly by measuring the remaining NBS with color - producing reagents susceptible to oxidation or bromination with NBS. It was reported that p-amino-phenol (PAP) is easily susceptible to oxidation with NBS and gives a violet chromogenic product of lmax at 552 nm. Malachite green (4-[(4-dimethylaminophenyl)-phynylmethyl]-N, N-dimethylanaline) is a basic organic dye for wool, silk or for suitable mordanted cotton. It is also widely used as dye materials such as jute, leather, ceramics and paper[3], as a cytochemical staining agent[4] and as antimicrobial [3,5,6]. It has, in fact, been widely used as the most efficacious antifungal agent in the fish

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farming industry [5,6] Its worldwide use in aquaculture will probably continue due to its relatively low cost, ready availability and efficiency; therefore potential human exposure to malachite green result from the consumption of treated fish [7]. The dye can also be used as a detection method for latent blood in criminalistics and for spot detection of cerium and sulfurous acid [8]. Malachite green (MG^+) an intensely colored dye that is used as a biological strain to differentiate between various bacteria, has a sharp absorption peak in the visible region, λ_{max}= 617nm. Malachite green when discharged into receiving streams will affect the aquatic life and causes detrimental effects in liver, gill, kidney, carcinogenesis, mutagenesis, intestine, gonads and pituitary gonado-trophic cells [9]. Also malachite green is employed in medical diagnoses of occulted blood detection of micro-estimation of glucose, hemoglobin, and other heme compounds [10]. Oxidation reaction of MG^+ by Mn (II) diphosphate complex [11], Cr (VI) [12], permanganate ions [13] and periodate have been reported [14]. The MG-periodate reaction, which was catalyzed by Mn (II), has been suggested as a kinetic method for determination of Mn (II) [14]. Oxidation of malachite green by Fe(III) in aqueous and micellar medium was studied spectrophotometrically by monitoring the absorbance change at 618 nm[15]. Ranitidine (RNH), 2-[[[5-(dimethylamino) methyl-2-furanyl]methyl] thio] ethylamino-2-methylamino-1-nitroethene, is the active compound of the pharmaceutical formulation of Zantac. It competitively inhibits the action of histamine on the H_2-receptors of parietal cells, and reduces gastric acid secretion under daytime and nocturnalbasal conditions. Several methods have been reported for the determination of ranitidine HCl including chromatography [16-18], HPLC [19-21], polarography [22, 23], voltammetry [24], potentiometry[25-26],and spectrophotometrically[27-32], however, spectrophotometric methods suffer from disadvantages such as have low sensitivity, taking long reaction time for color development >30 min. and require prior extraction of the colored products. In our study, a simple, sensitive and accurate kinetic spectro- photometric method for determination of ranitidine has been developed. The method is based on the inhibiting effect of ranitidine on the rate of oxidation of malachite green by N-bromosuccinimide.

The present work was devoted to study the possibility of the kinetic determination of ranitidine depending on its inhibitory effect on the rate of oxidation of malachite green by N-bromosuccinmide.

Material and Methods

Materials

All chemicals were of analytical-reagent grade and used without any further purification. Doubly distilled water was used throughout. Freshly prepared solutions of N-bromosuccinimide and malachite green were prepared daily. The working solutions were prepared by diluting the stock solutions as needed. Buffer solutions were prepared from Na_2HPO_4 and citric acid of known concentrations. $NaNO_3$ was used to adjust the ionic strength in the different buffered used.

Apparatus

A Shimadzu UV-1700 spectrophotometer was used to follow the oxidation reaction. The pH of the reaction mixture was measured using 3505Jenway pH-meter. NE5D digital shaking water bath was used to thermostat the reaction at the required temperatures.

Recommended procedure

The catalytic reaction was monitored spectrophotometricall by measuring the change in absorbance of malachite green at 617 nm where the absorption is maximal at the pHs used. Malachite green and N-bromocussinimide solutions in the required buffer were thermostated in water bath separately at the reaction temperature for ca. 20 min before the reaction was initiated; the reactants were thoroughly mixed and then transferred to an absorption cell. The reaction was carried out under pseudo-first order conditions by using a large excess concentrations of NBS (at least10 fold) over MG^+ concentrations.

Results and Discussion

Absorption spectra

The progress of the oxidation reaction of MG^+ by NBS in the required buffer at constant ionic strength, pH, and temperature was followed spectrophotometrically by measuring the decrease of the absorbance of malachite green with time at λ = 617 nm Fig.1 using a Shimadzu1700 uv-visible p.c. spectrophotometer. The initial rate method was used to calculate the rate of oxidation of malachite, d[A]/dt, where A is the absorbance of malachite green with time from the slope of the initial tangent of the absorbance versus time plots. The rate of oxidation of malachite was affected by addition of different concentrations of ranitidine Fig.2 which indicates that the rate of reaction was inhibited by increasing the ranitidine concentrations in the reaction mixture. This fact has been attributed to the reduction of [NBS] available in the reaction mixture due to its consuming for the ranitidine oxidation.

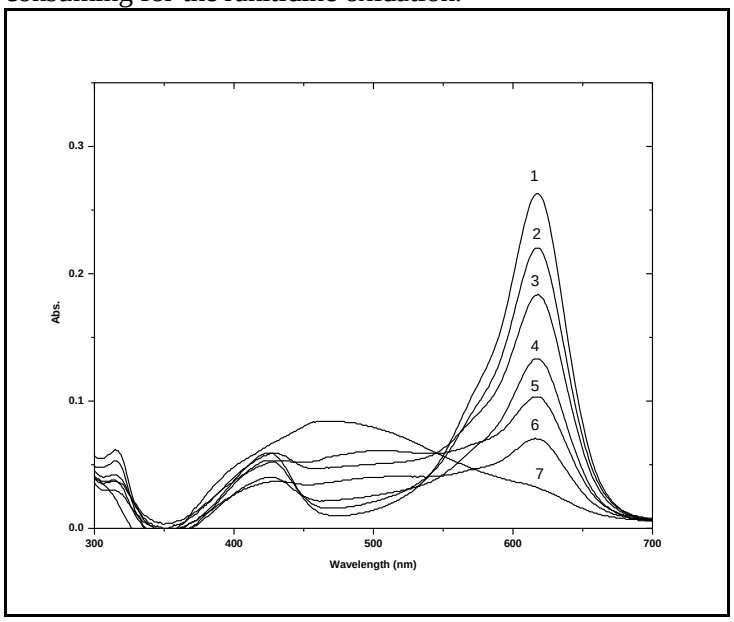

Fig. 1 Absorption spectra of the oxidation of malachite at different times. Peaks 1, 2, 3, 4, 5, 6, and 7 were measured at 0, 30, 60, 90, 120, 150 and 180 second from the time of initiation of reaction. [MG]=1.95 x10^{-6} moldm^{-3} [NBS] = 2.7x10^{-5} moldm^{-3}, pH = 4.0 and T = 25 ^{o}C.

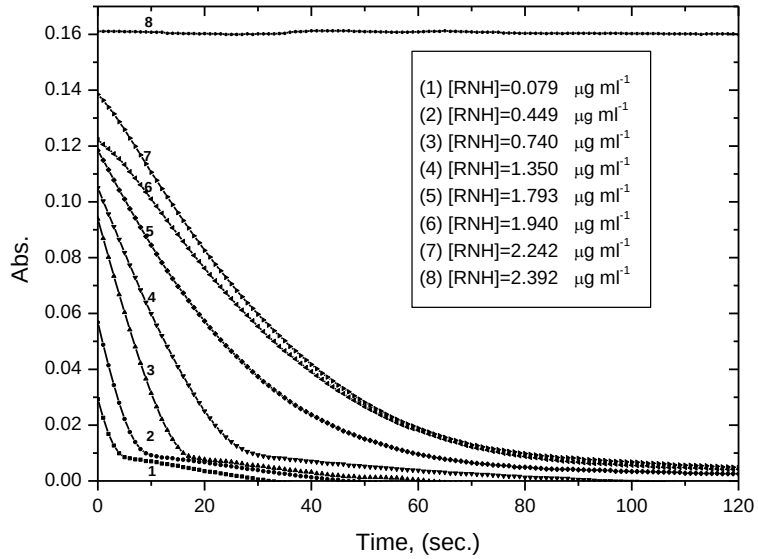

Fig. 2 Variation of absorbance of malachite green with time at different ranitidine concentrations. [MG]=1.95 x10^{-6} mol dm^{-3}, [NBS]= 2.7x10^{-5} mol dm^{-3}, pH = 4.0 and T = 25 ^{o}C

Optimization of the Effective Factors.

Effect of ranitidine concentrations

The rate of oxidation of malachite green by N-bromosuccinimide was studied under conditions of pH = 4.0, ionic strength = 0.1 mol dm^{-3},temp- erature =25°C,[NBS] = $2.70x10^{-5}$ mol dm^{-3} and [MG]=$1.95 x10^{-6}$ $moldm^{-3}$ over a range of ranitidine concentrations 0.08-2.24 µg ml^{-1} Table 1. Variation of the absorbance of MG^{+} with NBS with time in presence of different concentrations of ranitidine Fig.2 indicates that the rate of the oxidation was decreased gradually as the concentrations of ranitidine increased in the reaction mixture (peaks 1-7). At [RNH] = $6.81 x10^{-6}$mol dm^{-3}(2.39µg ml^{-1}, peak 8); there is no reaction between MG^{+} and NBS could be observed which indicated by the constancy of its absorbance with time. This phenomenon has been explained on the light of consuming of the total [NBS] by ranitidine oxidation due to its lower oxidation potential as compared to the oxidation potential of malachite. This indicates that the stochiometric ratio of NBS:RNH is 4:1 respectively.

Effect of pH

Under standard conditions of ionic strength (0.1 mol dm^{-3}), temperature, [MG]= $1.95 x 10^{-6}$ mol dm^{-3} [NBS] = $2.70 x10^{-5}$ mol dm^{-3} and ranitidine =$1.50 x 10^{-6}$ mol dm^{-3} (0.52µg ml^{-1}), the oxidation rate was studied at different pHs values (2.20-10.0). The kinetics data for the effect of pHs Fig. 3 indicate that the optimum pH of the reaction is 4.

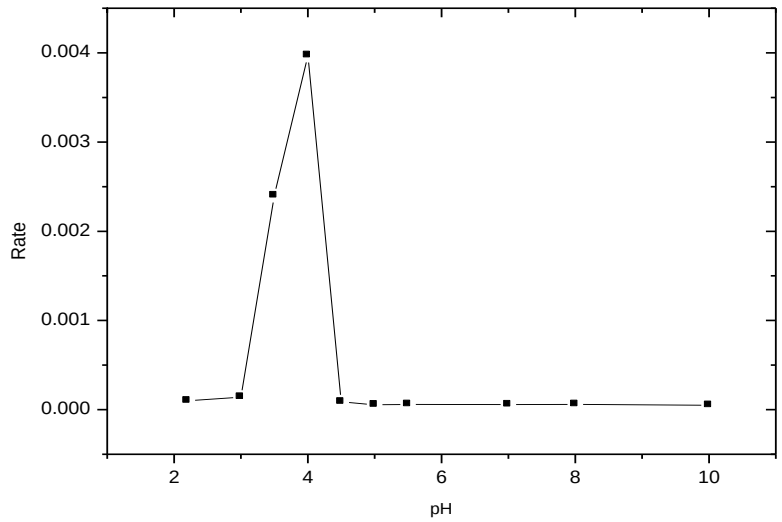

Fig. 3 Effect of pH on the oxidation of malachite with NBS. [MG]=$1.95x10^{-6}$ mol dm^{-3}, [NBS]= $2.7x10^{-5}$ mol dm^{-3} and [RNH] = $1.5\ 10^{-6}$ and T=25°C

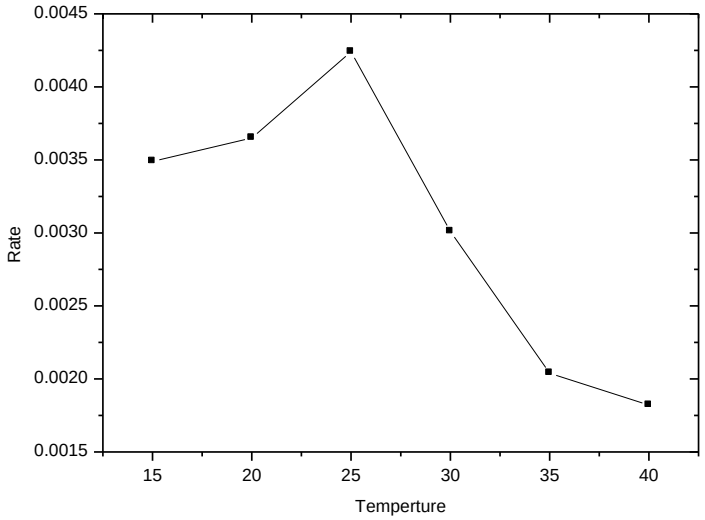

Fig.4 Effect of temperature on the oxidation of malachite with NBS. [MG]= 1.95x10^{-6} mol dm^{-3}, [NBS]= 2.7x10^{-5} mol dm^{-3} and [RNH] =1.5 10^{-6} mol dm^{-3} and pH 4.

Effect of Temperture

The effect of temperature on the rate of inhibited reaction (MG-NBS-RNH) was studied over the range (15-40) °C at the optimum reagent concentration. The results in Fig.4 show that, 25°C is the best temperature for the determination of ranitidine.

The effect of malachite green concentration

The effect of malachite green concentrations on the rate of the oxidation reaction was studied over the range (0.80- 2.72) x10^{-6} mol dm^{-3} and keeping the other parameters constant. As shown from Fig.5, 1.95 × 10^{-6} mol dm^{-3} of [MG^{+}] was regarded as the best concentration for MG-NBS reaction. At higher concentrations the reaction rate was decreased due to the dye aggregation. Thus, 1.95 × 10^{-6} mol dm^{-3} of MG was selected as optimum concentration for further studies.

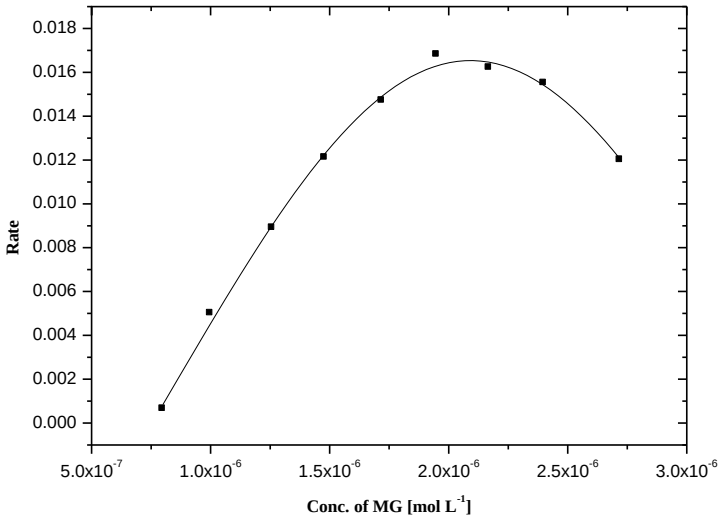

Fig. 5 Effect of [MG] on the oxidation rate. [NBS]= 2.7x10^{-5} mol dm^{-3} and [RNH]= 1.5 10^{-6} mol dm^{-3},T= 25^{o}Cand pH =4.

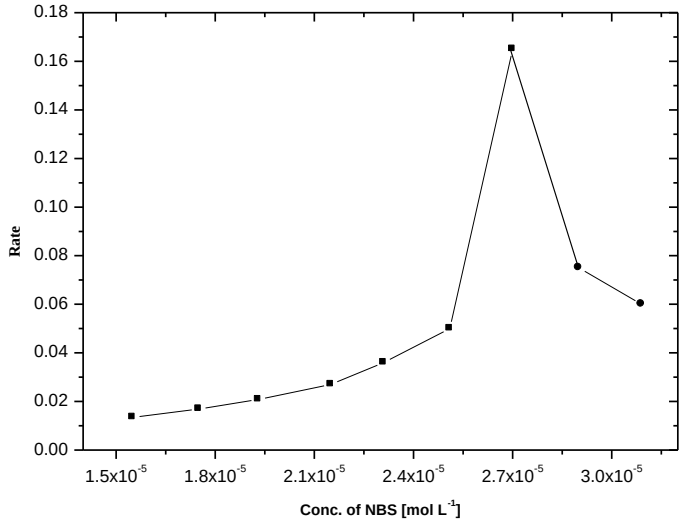

Fig.6 Effect of NBS on the oxidation rate. [MG]=1.95x10^{-6} mol dm^3,[RNH]= 1.5 10^{-6} mol dm^{-3} ,T=25^{o}C and pH=4.

Effect of N-bromosuccsinmide

The dependence of redox reaction rates on N-bromosuccsinmide concentrations was studied over the range (1.55-3.09)x10^{-5} mol dm^{-3}. As shown from Fig.6, the sensitivity of the redox reactions (ΔA) increased by increasing the NBS concentration to 2.7 x10^{-5}mol dm^{-3}, and then decreased. Thus, 2.7x10^{-5} mol dm^{-3} NBS was chosen for further experiments.

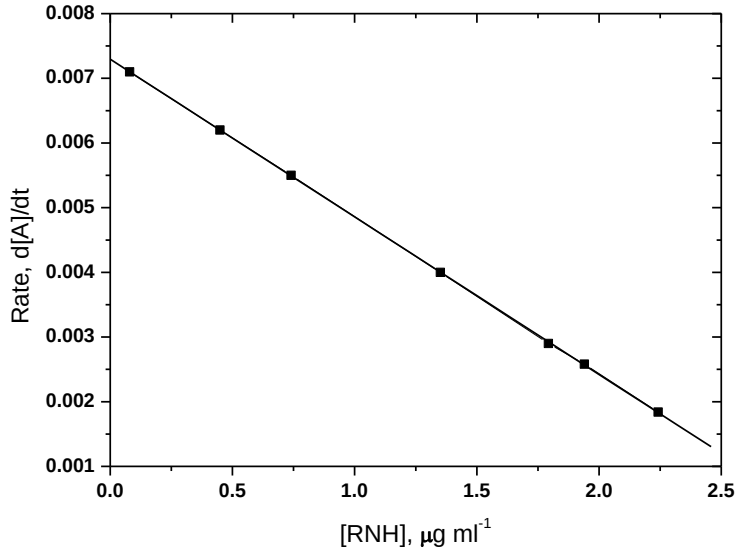

Fig. 7 Calibration curve of conc. of ranitidine. [MG]=1.95x10^{-6} mol dm^3, [NBS]=2.7x10^{-5} mol dm^{-3} ,T=25^{o}C and pH=4.

Analytical Parameters

Calibration graph and detection limit

As shown by Fig.7 and Table 1, a linear calibration graph over a range (0.08-2.24µgml^{-1}) of ranitidine concentrations was obtained using the recommended procedure. The calibration graph is best described by the equation y = mx + c, where y = the rate of change of absorbance of malachite with time, x = the concentrations of ranitidine as µg ml^{-1}, m = slope of calibration graph (0.00244), and c= the intercept obtained by least square fitting (0.00729). The limit of detection (LOD) was calculated using the formula, LOD = 3.3 σ / s, where σ is the standard deviation of five reagent blank determination, and s is the slope of the calibration graph as 0.019µgml^{-1}.

Table 1. Effect of ranitidine concentrations on the oxidation rate of MG^+ by NBS. [NBS]=2.70 x 10^{-5} mol dm^{-3} [MG^+] = 1.95 x10^{-6} mol dm^{-3}, I = 0.1 mol dm^{-3}, pH=4.0, and T = 25^{o}C

Sample No.	[RNH] (µg/ml)	Rate 10^2d[A]/dt
1	0.0796	0.710
2	0.4491	0.620
3	0.7403	0.550
4	1.3508	0.400
5	1.7928	0.290
6	1.9402	0.258
7	2.2420	0.184

Table 2. Kinetic determination of ranitidine in unknown samples using the recommended method

Sample No.	Prepared conc. µg ml^{-1}	Measured conc. µg ml^{-1}	error %
1	0.256	0.262	2.34
2	0.712	0.695	2.39
3	1.860	1.900	2.15
4	1.03	0.996	3.30
5	1.25	1.21	3.20
6	1.85	1.91	3.24

Precision and Accuracy

The error (%) for the determination of different unknown samples are shown in Table2. The samples (1-3) are different prepared concentrations of pure ranitidine samples and (4-6) are different ranitidine concentra- tions in ranitidine tablet (Medical Union Pharmaceuticales, Abu sultan Comp., Ismaillia Egypt). The reproducibility of the proposed method was tested by repeating.

Effect of interfering ions

The effects of foreign ions were investigated on the determination of 0.52µg ml^{-1} ranitidine using the recommended procedure. Experiments showed that there was no interference from additives and excipients, e.g. lactose, glucose, fructose, calcium hydrogen phosphate, magnesium citrate, talc, acacia and starch. Also, there was no interference from common degradation products of ranitidine by NBS.

Conclusion

A simple and sensitive kinetic spectrophotometric method for the determination of ranitidine over (0.079-2.24µg ml^{-1}) range was suggested. The method depends on the inhibitory effect of ranitidine on the rate of oxidation of malachite green with N-bromosuccinimide. A linear calibration graph obtained by a least square fit between the rate of change of the absorbance of malachite with time and ranitidine concentrations. The

suggested method was applied for determination of ranitidine in ranitidine tablets with acceptable standard deviation.

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