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Development of Kinetic Spectrophotometric Determination of pipenzolate methyl bromide in Pharmaceutical Preparations

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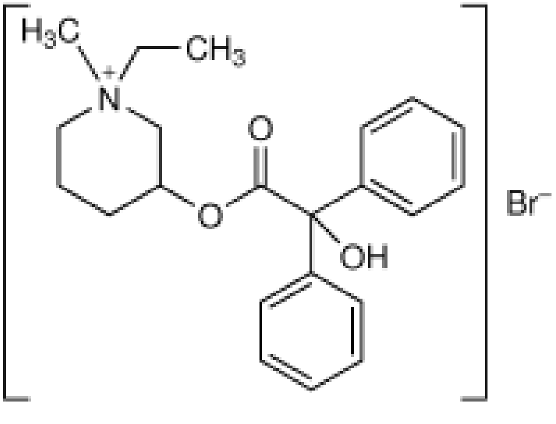
ABSTRACT

A simple kinetic spectrophotometric method has been developed for the determination of pipenzolate methyl bromide in pure and dosage forms. The method depends on oxidation of pipenzolate methyl bromide with alkaline potassium permanganate in presence of sodium hydroxide at room temperature (25 ± 1°C) to produce abluish- green colored species(manganite ions).The increase in absorbance of colored manganite ions was measured at 610 nm. All experimental variables affecting the development of the color were investigated and optimized. The initial rate and fixed time (at 20 minute) were adopted for determining the drug concentration.. The calibration graphs were linear in the concentration ranges of 2-28 μg mL^{-1} and 2-24 μg mL^{-1}, using the fixed time and initial rate methods, respectively. The method was successfully applied to the determination of pipenzolate methyl bromide in pure form and commercial dosage forms (spastal oral drops).

Keywords: pipenzolate methyl bromide , Spectrophotometric, kinetic, potassium permanganate.

INTRODUCTION

Pipenzolate methyl bromide ;1-ethyl-3-(2-hydroxy-2,2-diphenylacetoxy)-1-ethylpiperidinium bromide is a quaternary ammonium antimuscarinic (cholinergic) receptors on smooth muscles with peripheral actions similar to those of atropine and prevents the effect of Acetylcholine.. It has been used as an adjunct in the treatment of gastrointestinal disorders characterized by smooth muscle spasm and cramp[1,2]. Pipenzolate methyl bromide is not official in any pharmacopoeia.



Molecular formula:$C_{22}H_{28}BrNO_3$ =434.4

Chemical Structure of Pipenzolatemethyl bromide

The literature revealed that Pipenzolate methyl bromide has been determined by means of a few analytical methods. These include: HPLC [3,4], ratio spectra derivative spectrophotometry[5] Kinetic spectrophotometric methods use in chemical and pharmaceutical analysis has gained special interest as they offer many advantages over regular analytical techniques. These advantages include improved selectivity and a decrease of interferences caused by colored or turbid samples during testing [6]. However, noattempts were cited in the literature for the determination of Pipenzolate methyl bromide using kinetic spectrophotometric methods. The present work describes the development of simple and sensitive kinetic spectrophotometric methods for the determination of Pipenzolate methyl bromide in pharmaceutical formulations.

EXPERIMENTAL

Spectrophotometer UV / Visible double beam spectrophotometer [UVS-2700, Labomed, INC] with 1.0 cm quartz cells was used for all absorption measurements.

Reagents

All chemicals used were of analytical or pharmaceutical grade and high-purity water was used throughout. Pipenzolate methyl bromide was obtained from: AL-Hokamaa Company for pharmaceutical industries (HPI) Mosul-Iraq. A standard solution of Pipenzolate methyl bromide [$2.3X10^{-4}$M (100 ppm)] was prepared by dissolving 0.01g of pure drug in 100 ml distilled water. Potassium permanganate 0.01M. This solution was prepared by dissolving 0.16 g in 100 ml distilled water, and then the solution was heated to boiling and then filtered through asbestos. The filtered solution should be kept in the dark and standardized immediately before use [7]. Sodium hydroxide (1N). This solution was prepared by dissolving 4 g of pure NaOH in 100 ml distilled water.

Recommended procedures

Initial rate method

Aliquots of 1-5 mL of 100ppm pipenzolate methyl bromide were pipette into a series of 25 mL standard flasks. To each flask, 3.0 mL of 1 M NaOH and 1ml of 0.01 M potassium permanganate were added successively and then diluted with distilled water. The contents of each flask were mixed well, and the increase in absorbance as a function of time was measured at 610 nm. The initial rate of the reaction at different concentrations was evaluated by measuring the slope of the tangent to the absorbance- time plot. The calibration graphs were obtained by plotting the initial rate of reaction versus the molar concentration of the pipenzolate methyl bromide. The amount of the drug was calculated either from the calibration graph or the regression equation.

Fixed time method

Aliquots of .5-7 mL of (100 ppm) pipenzolate methyl bromide were pipette into a series of 25 mL standard flasks. To each flask, 3.0 mL of 1 M NaOH and 1ml of 0.01 M potassium permanganate were added successively and then diluted with distilled water. The contents of each flask were mixed well, and a fixed time of 20 min was selected for the fixed time method. At this preselected fixed time, the absorbance of each sample of drug solution was measured at 610 nm against a reagent blank prepared similarly except without the drug. The calibration curve was obtained by plotting the absorbance against the concentration of pipenzolate methyl bromide. The amount of the drug was computed either from a calibration curve or regression equation.

Procedures for pharmaceutical preparations

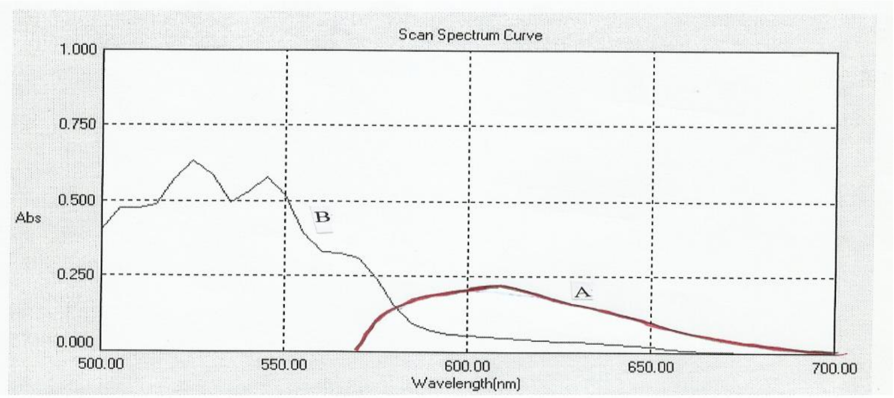
The contents of five bottles of oral drops were provided from AL-Hokamaa Company for pharmaceutical industries (HPI) Mosul-Iraq. (Containing 300mg of pipenzolate methyl bromide) were mixed. An aliquot corresponding to 10 mg of pipenzolate methyl bromide (2.5ml) was diluted to 100 ml with distilled water in a volumetric flask to obtain 100 $\mu g.ml^{-1}$ of pipenzolate methyl bromide . This solution was treated as described above under recommended procedure described above.

RESULTS AND DISCUSSION

The reaction between pipenzolate methyl bromide and KMnO4 in alkaline solution yields a green color as a result of magnate species, which have maximum absorption at 610 nm Fig. (1).at this wavelength, the various experimental parameters affecting the development and stability of the reaction product were carefully studied and optimized.

Optimization of reaction conditions

The factors affecting reaction condition (concentration of $KMnO_4$, alkalinity and temperature. A 12 $\mu g.m^{l-1}$ of pipenzolate methyl bromide was taken In a 25 ml final volume and the absorbance was measured at room temperature (25° C) for series of solutions by varying one and fixing the other parameters at 610 nm versus reagents blank after 20 min from the beginning of the reaction.



Fig(1):Absorption spectra of A :8 µg/ ml of Pipenzolate methyl bromide withKMnO$_4$ against reagent blank. B: blank against distilled water.

Effect of potassium permanganate concentration

The reaction increases substantially with increasing the concentration of $KMnO_4$. It was found that 1 ml of 0.01M $KMnO_4$ was adequate for the maximum absorbance for the dye formed.

Effect of sodium hydroxide concentration

Trials were made to determine the drug through oxidation with $KMnO_4$ in neutral, acidic and alkaline media, oxidation of pipenzolate methyl bromide was observed in alkaline medium (NaOH) compared with neutral and acidic mediums. Maximum absorption was obtained when 2 ml of 1 M NaOH was used. Over this volume no change in absorbance could be detected obtained; 3ml of 1 M of NaOH was used as an optimum value.

Effect of temperature

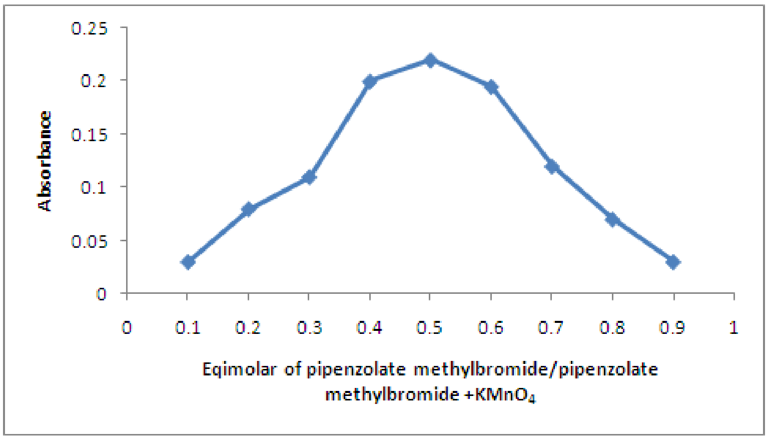
At room temperature the reaction rate increase substantially with time, while heating the solution was found to increase the rate of the reaction however MnO_2 was precipitated, therefore room temperature was elected as the optimum temperature.

Order of addition

To test the order of addition on the absorbance of the product, different orders were tested. The selected order was sample solution, NaOH followed by $KMnO_4$ solution which was gave high absorbance value.

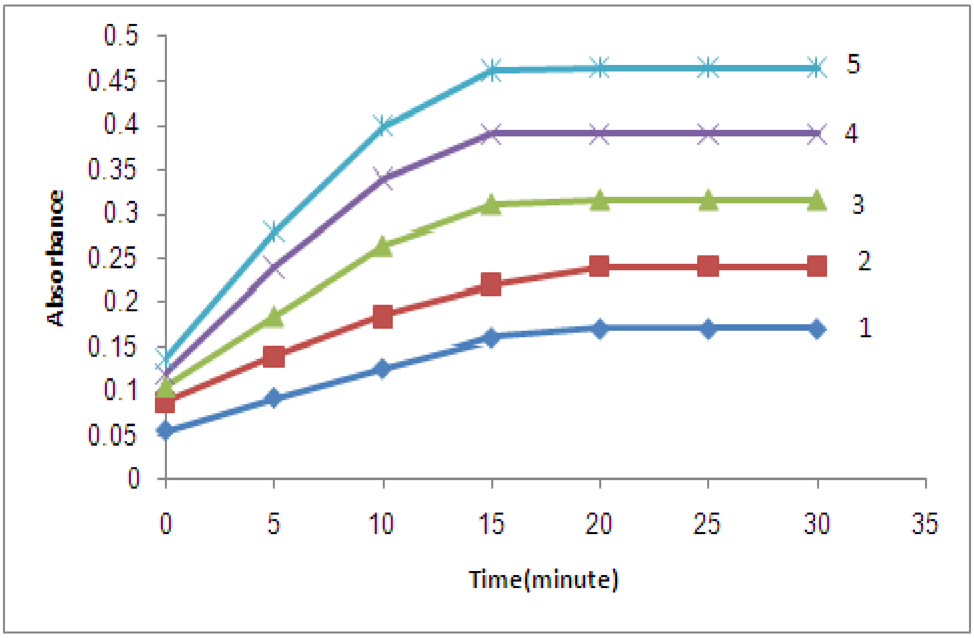
Stoichiometry of the reaction

The stoichiometric ratio between potassium permanganate and pipenzolate methyl bromide measured at 610 nm was determined by job's method of continuous variation of equimolar solution($2.3x10^{-4}$M), , the result obtained show that 1:1 $KMnO_4$ to drug, Fig(2).



Fig(2) :Continuous variation plot for reaction of pipenzolate methyl bromide with KMnO$_4$ Kinetic of the reaction

Under the optimum conditions, the absorbance time curves of investigated pipenzolate methyl bromide with $KMnO_4$ were constructed (Fig. 3). The initial rate of the reaction was determined from the slope of tangents of the absorption time curves. Calibration graph was constructed by plotting the logarithm of the initial rate of the reaction versus the logarithm of the molar concentration of pipenzolate methyl bromide. (Fig.4).



Fig(3) : Absorbance–time curve for the reaction of pipenzolate methyl bromide withKMnO4.The concentrations of pipenzolate methyl bromide were 1-0.092 $\times10^{-4}$M,2- 0.184$\times10^{-4}$M ,3-0.27$\times10^{-4}$ M,4- 0.368$\times10^{-4}$ M, and 5- 0.46$\times10^{-4}$ M.

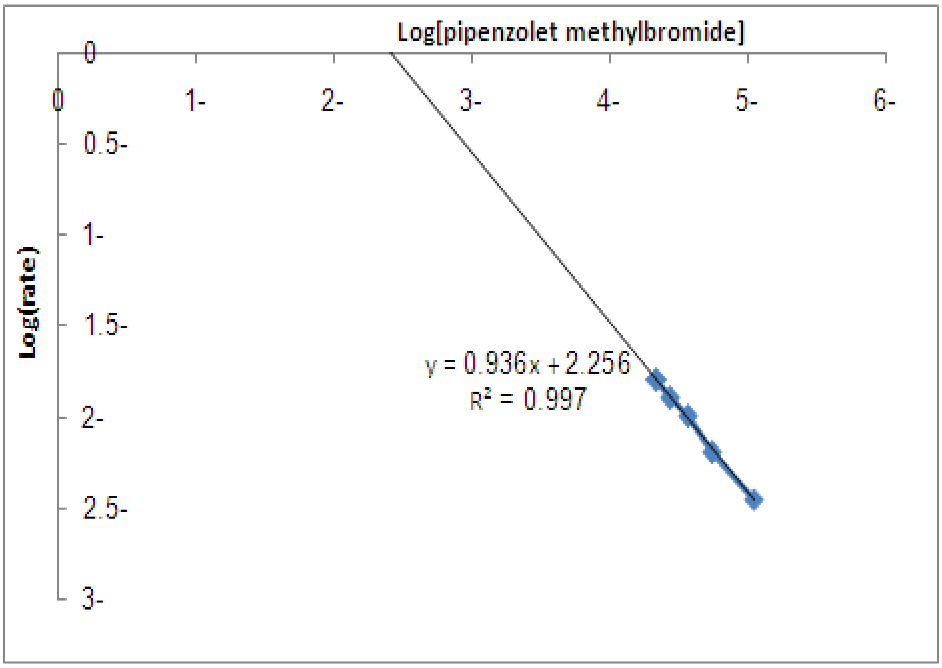


Fig. (4): log(rate)versus log(pipenzolate methyl bromide)graph

Reaction rates were determined for different concentrations of pipenzolate methyl bromide. At a pre-selected fixed time, which was accurately determined the absorbance was measured. Calibration graphs of absorbance versus initial concentration of pipenzolate methyl bromide were established at fixed time of 0, 5, 10, 15,20,25,30 and 20 min. It is clear that the slop increases with time and the most acceptable values of the correlation coefficient (r) and the intercept were obtained for a fixed time of 20 min, which was therefore chosen as the most suitable time interval for measurement. In the second procedures, the absorbencies measured at a fixed time of 20 min. were plotted against the final concentrations of pipenzolate methyl bromide. (Fig.5).

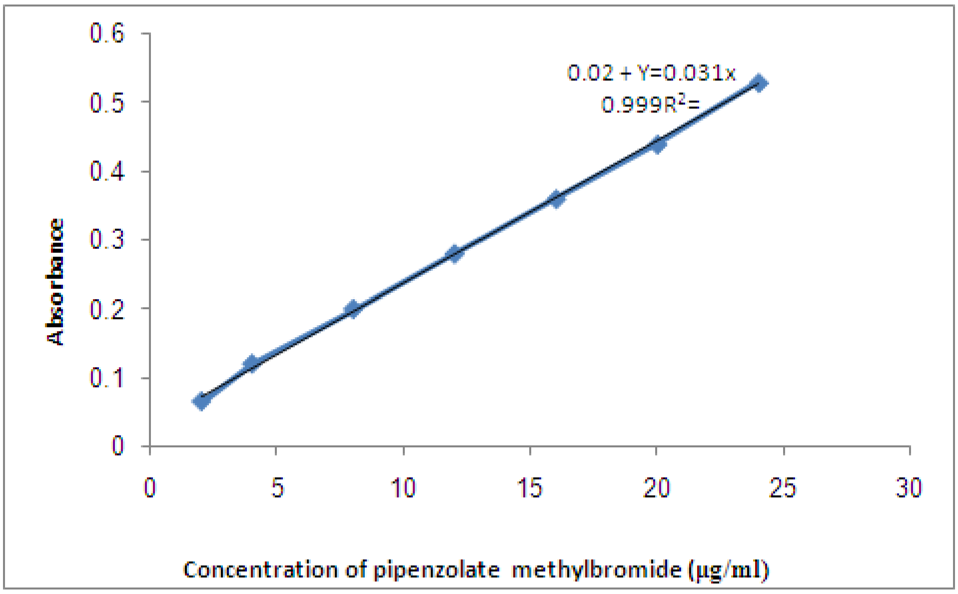


Fig (5): Calibration graph of pipenzolate methyl bromide at fixed time 20 min.

Evaluation of the kinetic methods

The rate of reaction was found to be dependent on pipenzolate methyl bromide concentration. The rates were followed at room temperature (25°C) with various concentration of pipenzolate methyl bromide in the range of (2-24) µg.ml^{-1} keeping $KMnO_4$ and NaOH concentrations constant. The reaction rate was found to obey the following equation: Rate = K` [Pipenzolate methyl bromide]^n(1)

Where K' is the pseudo-order rate constant and n is the order of the reaction. The rate of the reaction may be estimated by the variable-time method and differential initial rate method [8,9] as ΔA/Δt, where A is the absorbance and t is the time in minutes. Taking logarithms of rates and concentration, Eq. (1) is transformed into:

Log (rate) =log ΔA /Δt = log K' +n log [pipenzolate methyl bromide]   (2)

Regression of log (rate) versus log [pipenzolate methyl bromide] gave the regression equation: Log(rate)= 2.256 +0.936Log C (r=0.997)Hence K=180.3 min^{-1}=3 sec^{-1} and reaction is first order (n=0.936), with respect to pipenzolate methyl bromide concentration.

Accuracy and Precision

To evaluate the accuracy and precision of the method, a pure drug solution was analyzed at three different concentrations, each determination being repeated six times the relative error (%) and relative standard deviation (%) values were summarized in (Table1). It is clear that the relative error of less than 1.7% and the method was found to be precise with RSD value not more than 1.6%. for a better picture of reproducibility, a series of experiments were performed in which the standard drug solution was determined at three different levels each day for six days, with all solutions being prepared a fresh each day. The day-to-day relative standard deviation values were in the range of 0.8-1.6 % and represent the best appraisal of repeatability of the proposed method.

Table (1): Accuracy and precision of the method

pipenzolate methyl bromide taken (µg/ml)	**E_r (%)^a**	**RSD ^{a} %**
4	1.2	1.3
12	1.5	1.5
20	1.6	1.5

a: Mean of six determinations

Analytical applications

The proposed method was satisfactorily applied to the determination of pipenzolate methyl bromide in its pharmaceutical formulations were provided from AL-Hokamaa company for pharmaceutical industries (HPI) Mosul-Iraq). The results of the assay of the pharmaceutical formulations revels that there was closed agreement between the results obtained by the proposed method and the label claim as cited in (Table 2).

Table (2): Determination of pipenzolate methyl bromide in pharmaceutical formulations

Pharmaceutical formulation supplied by HPI	Amount of pipenzolate methyl bromide * Proposed method	Label claim	%Recovery
Oral drop	3.98mg/ml	4 mg/ml	99.5

*Mean of ten determinations.

CONCLUSION

The proposed method was simple, accurate, precise, sensitive and low economical cost. Furthermore, the proposed method doesn’t require elaboration of procedures, which are usually associated with chromatographic methods. The proposed method could be applied successfully for determination of pipenzolate methyl bromide in pure form as well as in different dosage forms.

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