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A new method for spectrophotometric determination of paracetamol

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ABSTRACT

A new and simple spectrophotometric method for determination of paracetamol is reported. The method is based on conversion of the drug into copper complex, which is green in colour and its resultant absorbance is correlated to concentration of the drug.

KEYWORDS

Paracetamol;
Schiff-base;
Copper complex;
Spectrophotometer.

INTRODUCTION

There are concerns about presence of pharmaceutical products in water bodies and their possible harmful effects on aquatic life and on humans. It is feared that long term and synergistic effect of low concentration of pharmaceutical products in water may cause hormonal imbalance and health hazard in aquatic life and hence on human health. Since concentrations of these compounds in water are very low, sophisticated analytical methods like GC-MS, LC-MS are used for determination. These methods are expensive[1,2]. Hence need is to develop simpler and less costly analytical methods for such determinations.

It was thought worthwhile therefore to study this aspect and develop a new method of determination of paracetamol in water. There are many reported methods of spectrophotometric analysis of paracetamol based on oxidation of paracetamol with potassium hexacyanoferrate (III) [3], nitration of paracetamol with $NaNO_2$[4], hydrolysis of paracetamol to p-aminophenol and then treatment of the resultant solution with copper (II) solution[5], reduction of Fe(III) to Fe(II) by the paracetamol in the presence of 2,2'–bipyridyl (bpy)[6], microwave assisted alkaline hydrolysis of paracetamol to p-amino phenol that reacts with S^{2-} in the presence of Fe^{3+} as oxidant[7], reaction of paracetamol with sodium hypochlorite forming N-acetyl-p-benzoquino neimine which then reacts with sodium salicylate in sodium hydroxide solution yielding a blue indophenol dye[8].

The present work describes a new and simple spectrophotometric method for determination of paracetamol. The method is based on acid catalyzed hydrolysis of paracetamol in aqueous medium. This results into formation of 4-aminophenol; the resultant primary amine is then condensed with salicylaldehyde to form a schiff base. Schiff base is then complexed with copper(II) ion which gives a green coloured complex. The concentration of the complex measured spectrophotometrically is then correlated to concentration of the drug.

EXPERIMENTAL

A spectrophotometer (ELCO) equipped with 1cm quartz cell and wavelength range of 340-1000nm was used for all absorbance measurements. Salicylaldehyde, ethanol (EtOH), $CuSO_4 \cdot 5H_2O$, concentrated HNO_3,

HCl, ammonium hydroxide were all analytical reagent grade and were used as such. Commercially available paracetamol tablets were used to extract the API. (Extraction from powdered tablets was carried out using absolute ethanol, resultant suspension was filtered through Whatman no. 1 filter paper and filtrate evaporated to get API.) IR spectrum was recorded as KBr disc using Perkin Elmer model spectrum RX1.

Solution preparations

Paracetamol solution

0.151gm of paracetamol was dissolved in 1:1 EtOH:H_2O and was diluted to 100ml to get 0.01M stock solution. The stock solution was consumed within three days.

Salicylaldehyde solution

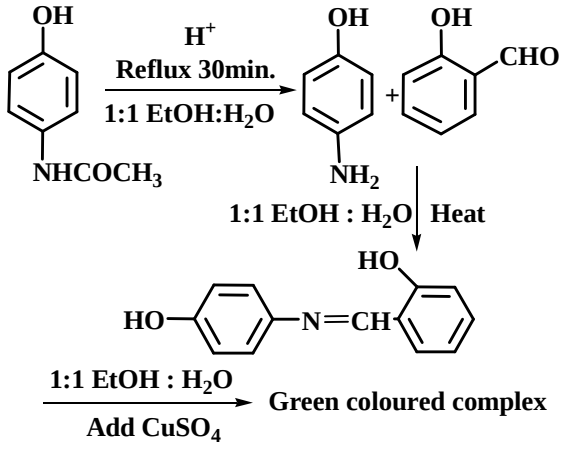
0.1ml of salicylaldehyde was dissolved in 1:1 EtOH :H_2O and it was diluted to 100ml to get 0.01M solution.

Copper sulphate solution

0.249gm of copper sulphate pentahydrate was dissolved in 1:1 EtOH:H_2O and diluted to 100ml to get 0.01M solution.

Standard procedure

To 25ml of freshly prepared 0.01M paracetamol solution in a 250ml round bottom flask, 3-4 drops of 1N hydrochloric acid was added, a few boiling chips were dropped and a water cooled reflux condenser was attached. The solution was refluxed for 30 minutes in hot water bath. After 30 minutes, refluxing was stopped, solution cooled and the pH of the solution was adjusted to 6- by adding 2M ammonium hydroxide. To this mixture, 25ml of 0.01M salicylaldehyde solution was added and refluxed for 30minutes. The clear, colourless solution turned yellow in colour, and then it was cooled to room temperature. To this, 25ml of 0.01M $CuSO_4.5H_2O$ was added followed by 30 minutes of refluxing to get a clear green coloured solution. For this solution, maximum absorbance(λ_{max}) was obtained by absorbance measurements in the wavelength range of 400-700nm. Following scheme shows various steps involved.



Study of linearity of calibration curve

Concentrations of 0.002M, 0.004M, 0.006M and 0.008M of paracetamol were prepared by diluting 5ml, 10ml, 15ml, and 20ml stock solution of 0.01M para cetamol solution respectively to final volume 25ml with 1:1 EtOH:H_2O.

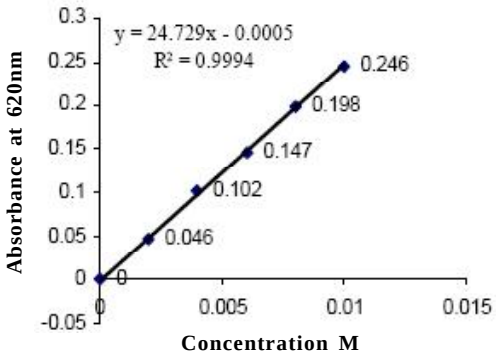
Then each 25ml of the above solutions were treated as per the standard procedure taking salicylaldehyde and copper sulphate solutions of concentrations corresponding to that of paracetamol so as to get the molar ratio 1:1:1(drug : aldehyde : metal salt).

The absorbance was measured at 620nm of the resultant clear green color solutions and the results are shown in Plot I.

Study of effect of concentration of salicyal dehyde and metal salt

Concentrations of 0.001M, 0.002M and 0.004M of paracetamol solution of 25ml each were prepared from stock solution of 0.01M paracetamol solution.

Then each 25ml of the above solutions were treated



Plot I : Calibration curve

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with the standard procedure keeping the concentration ratio 1:2:2(drug: aldehyde: metal salt).

The absorbance was measured at 620nm of the resultant clear green color solutions and the results expressed in plot III.

Study of effect of concentration of salicylaldehyde

Concentrations of 0.002M, 0.004M and 0.006M of paracetamol solution of 25 ml each were prepared from stock solution of 0.01M paracetamol solution.

Then each 25ml of the above solutions were treated with respective reagents as per the standard procedure keeping the concentration ratio 2:2:1(drug:aldehyde: metal salt).

The absorbance data were collected at 620nm for the resultant clear green color solutions and the results plotted (plot IV).

Study of effect of concentration of metal salt

Concentrations of 0.002M, 0.004M and 0.006M of paracetamol solution of 25ml each were prepared from stock solution of 0.01M paracetamol solution.

Then each 25ml of the above solutions were treated with salicylaldehyde and metal salt solution following the standard procedure, keeping the concentration ratio 2:1:2(drug: aldehyde: metal salt).

The absorbance was measured at 620nm for the resultant clear green colored solutions and the results are shown in plot V.

Determination of lowest concentration

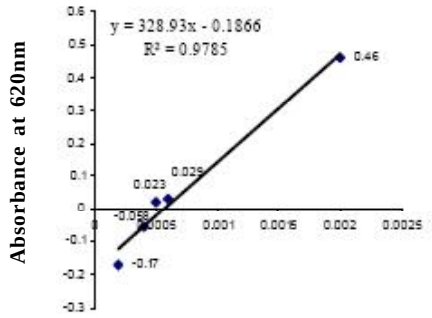
Concentrations of 0.0002M, 0.0004M, 0.0005M and 0.0006M of paracetamol solution of 25ml each were prepared from stock solution of 0.01M paracetamol solution.

Then each 25ml of the above solutions were treated as per the standard procedure keeping the concentration ratio 1:1:1(drug: aldehyde: metal salt)

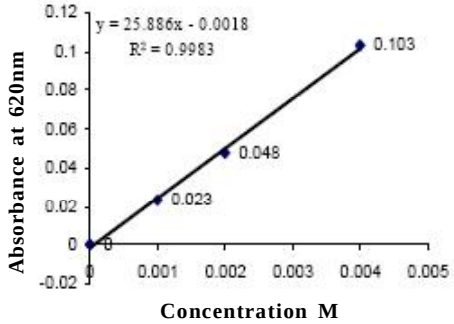
The absorbance was measured at 620nm of the resultant clear green color solutions and the results are depicted in plot II.

Isolation of complex

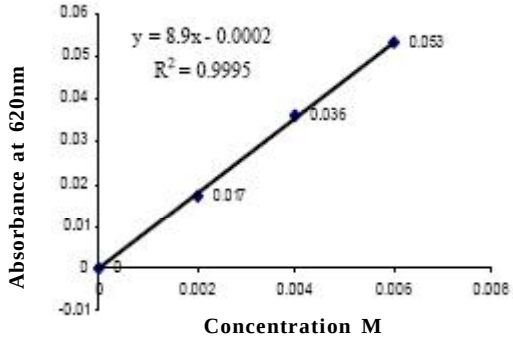
25ml of 1M solution of paracetamol solution was treated with appropriate reagents using the standard procedure in the 1:1:1 ratio. Refluxing the solution after adding metal salt solution resulted into precipitation of



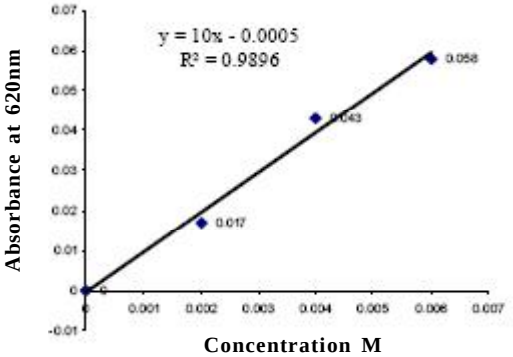
Plot II : Determination of lowest concentration of para cetamol



Plot III : Effect of salicylaldehyde and metal salt both



Plot IV : Effect of salicyladehyde only



Plot V : Effect of metal salt only

pale green coloured solid. This solid was filtered and washed with 1:1 EtOH:H_2O. It was air dried, weighed and then used for metal estimation. Determination of metal concentration in expected complex was carried out gravimetrically by decomposition of the ligand part of the complex using concentrated nitric acid and heating the residue to convert it into cupric oxide. 206mg of the green coloured complex was taken in cool, dry and pre-weighed porcelain crucible. Concentrated HNO_3 was added and it was digested and evaporated to dryness in fume cup-board. This treatment was repeated thrice and the residue was heated at high temperature for about one and half hour until the precipitate was completely free of carbon particles and black in color. It was cooled in desiccator and weighted to constant weight. Formation of the proposed complex was also verified by IR spectrophotometry.

RESULTS AND DISCUSSION

Characteristics of green solution

The λ_{max} of the clear green coloured solution was obtained at 620nm by scanning in the range 400-700nm. This is in agreement with similar spectra obtained for copper (II) complexes with Schiff base ligands. Plot I shows calibration curve for the green complex which is linear. Proposed structure of the green complex is shown in figure 1. Using the determined λ_{max}, lowest concentration of the drug that can be determined using this method was found to be 0.0005M as shown in plot II.

Formation of complex

Acid catalyzed hydrolysis of paracetamol is well documented[5]. Resultant primary amine is 4-amino phenol. On addition of salicylaldehyde to this solution and refluxing, the solution turns yellow indicating formation of Schiff base. Dilute solutions are taken so that the Schiff base does not separate out from the solution. To this solution, addition of metal salt solution results in to change in color of the solution to green. This indicates the formation of metal complex with Schiff base.

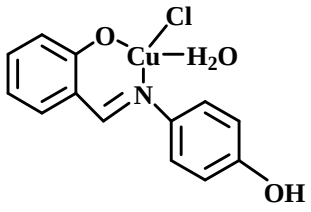


Figure 1: Proposed structure of green coloured complex

Literature studies of similar schiff base complexes of copper show that generally such complexes are green in colour. The most probable composition of the complex is $C_{13}O_8H_{11}NCuCl$, which was justified by IR, metal estimation and various experiments focused at studying concentration effect of different components needed for complex formation. Gravimetric determination of metal concentration indicates the percentage of copper to be 22.5%, which is close to theoretical value for the proposed structure of complex. IR spectrum of the isolated complex in KBr shows prominent band at 1736cm^{-1} indicative of C=N(an imine) function bonded to copper[6]. Further, presence of Cl^- in the complex was qualitatively confirmed by reaction with silver nitrate. To a mixture of metal complex and concentrated nitric acid, addition of silver nitrate solution results in formation of white precipitate of silver chloride.

Studies related to effect of varying proportions of various components also indicates 1:1:1 ratio of drug, salicylaldehyde and copper sulphate required for optimum results of absorbance. This also supports formation of the proposed complex. Thus, results in plot III show that for 0.0002M drug solution, increase in concentration of salicylaldehyde and copper does not cause any increase in the absorbance of green solution. This indicates that 1:1:1 complex is formed. Similarly, for 0.002M drug concentration and 0.002M copper ion concentration, (data in plot IV) taking half the concentration of aldehyde leads to decrease in absorbance of the green solution, indicating lesser concentration of the expected complex; this again indicates that a 1:1:1 proportion of the three is needed.

CONCLUSION

This new spectrophotometer method is simple and sensitive and can be used to determine a lowest concentration of paracetamol in aqueous medium up to 0.0005M. Though the method has several steps involved, viz., hydrolysis of drug, Schiff base formation and complex formation, all these steps are being carried out in a single pot. Hence errors resulting due to several steps of operation are minimized. The only dis-

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advantage of this method is that it is time consuming.

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