Green approach towards the determination of hydroxyzine dihydrochloride in pure and pharmaceutical dosage forms

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Abstract: A simple eco-friendly method has been developed for detection of hydroxyzine dihydrochloride in pure and pharmaceutical dosage forms. Both conventional system and microwave assisted procedures are used for the development of color. The blue coloured complex is measured spectrophotometrically at 750nm. Peak shift in FT-IR spectra also indicated the formation of complex. The reaction obeys Beer's law over the concentration range of 50-250µg/ml of hydroxyzine dihydrochloride. The precision value (intra-day and inter-day RSD) for the drug is not greater than 0.79% and recoveries were found to be in range of 99.01-99.99%. The designed method is applicable for periodic determination of hydroxyzine dihydrochloride in pure and pharmaceutical dosage forms.

Keywords: Hydroxyzine dihydrochloride, potassium ferrocynide, microwave, FT-IR, spectrophotometry.

INTRODUCTION

The reduction or elimination of chemical process or methods that leads the generation of hazardous and toxic chemical substances into environment causes pollution. So the need of time is to implement such process or methods which are eco-friendly as well as economical. So attempts are being made to fulfill the basic principles of green chemistry. The innovation in method development by using green chemicals and solvents is the biggest challenge for chemist.

Hydroxyzine dihydrochloride (HDH), a piperazine derivative, is a sedative antihistamine with antimuscarinic and significant sedative properties. Its main use is as an anxiolytic and also used as an adjunct to pre and postoperative medication. The other uses are in the management of pruritus, urticaria and an adjunct to opioid analgesic (Seth 2007).

Considering the importance of this drug various efforts had been put in to define methods for its analysis which range from simplest to complex e.g. USP (2005), titrimetric (Basaviah *et al*., 2002, Sanrick *et al*., 1966, Dembinski *et al*., 1993, Rajendraprasad *et al*., 2010), high performance liquid chromatography (Menon *et al*., 1981, Dragana *et al*., 1999, Pehoursq *et al*., 2004), gas chromatography (Kintz *et al*., 1990), thin layer chromatography (Ackermann *et al*., 1977), micellar liquid chromatography (Martinez-Algaba *et al*., 2006), capillary zone electrophoresis (Capella-Peiro *et al*., 2006), voltammetry (Beltagi *et al*., 2008), LC-MS (Zhou *et al*., 2007), potentiometry (Bouklouze *et al*., 2002), gravimetry (Pasich *et al*., 1962) and spectrophotometry (Basaviah *et al*., 2002, Kurzawa *et al*., 1999, Basaviah *et al*., 2003, Aboul-Kheir *et al*., 2002, Rajendraprasad *et al*., 2010).

The literature revealed that titrimetric procedures except Hg(II) are indirect, laborious, time consuming and responsible for decrease in accuracy. The method described by K. Basavah involves the determination of drug hydrochloride salt through chloride (Basaviah *et al*., 2002). The drug has also been estimated by precipitation of the drug using cadmium nitrate for onward estimation of residual cadmium using EDTA after separation of complex (Sanrick *et al*., 1966).The drug has been estimated potentiometrically after precipitating it with help of sodium tetraphenylborate (Dembinski *et al*., 1993). Chromatographic techniques also remained the method of choice for most of the researchers but these techniques are based on long and tedious procedure e.g. LC-MS requires skillful operator and expensive instrumentation. In addition to that these techniques are known to have high RSD value (upto 8%) (Zhou *et al*., 2007). Relatively better RSD values are observed when spectrophotometric methods are used. Few spectrophotometric procedures had been depended on coupling, charge transfer, ternary and ion-pair complexes need extraction in organic solvents before absorbance measurements (Basaviah *et al*., 2002, Kurzawa *et al*., 1999, Basaviah *et al*., 2003, Aboul-Kheir *et al*., 2002, Rajendraprasad *et al*., 2010). The reported methods have poor sensitivity and complicated due to time consumption, extraction and utilization of expensive or objectionable chemicals.

Considering the environmental mandates and green chemistry norms; the microwave technology is introduced for the rapid assay of Hydroxyzine dihydrochloride in pure and pharmaceutical formulation by employing

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spectrophotometry. Spectrophotometric methods are known for their ease of determination and simplicity in addition to the reliability of the method. This method also offers advantages over the previous existing methods in terms that it doesn't require tedious extraction procedures, long colour development time, analyte losses and atmospheric contamination.

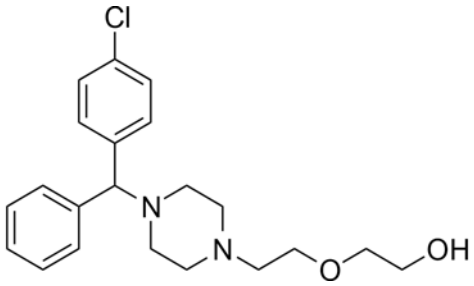

Fig. 1: Structure of hydroxyzine dihydrochloride.

MATERIALS AND METHODS

Chemicals and reagents

All the reagents employed in this study were of analytical grade. Hydroxyzine dihydrochloride was obtained from AGP (Pvt.) Ltd., B-23, S.I.T.E., Karachi, Pakistan and potassium ferrocynide was purchased from BDH. Analytical grade concentrated hydrochloric acid used in this study was supplied by E. Merck. Doubly distilled water and ethanol (BDH) was used throughout the study where applicable.

Instruments

Orient Microwave, FT-IR and Cecil spectrophotometer (CE-2041) along with 1cm quartz cell was used for absorbance measurement.

Preparation of stock, standard and working solutions

The preparation of stock solution of hydroxyzine dihydrochloride (w/v) was done using ethanol to the concentration of 1mg/ml and stored in refrigerator. Standard solutions were prepared from this stock solution as per requirement by further dilution. 1.0% (w/v) solution of potassium ferrocynide (BDH) and 0.1 N hydrochloric acid (Merck) was prepared in distilled water.

Preparation of pharmaceutical preparations

Tablets containing 10mg and 25 mg hydroxyzine dihydrochloride were weighed and powdered .The powder was dissolved in ethanol and filtered using Whattman paper No.40 to get 1mg/ml solution of hydroxyzine dihydrochloride.

General procedure

Aliquot of hydroxyzine dihydrochloride were transferred into series of calibrated flasks. To each flask 1.5 ml of 1.0% (w/v) potassium ferrocynide solution and 2.0ml of 0.1 N hydrochloric acid were added. After that the contents were given pulse for 5min in MW at 500W, allowed to cool to room temperature and dilute to 10ml with ethyl alcohol. The absorbance measurement of blue colour was carried out with spectrophotometer at 750nm. A similar experiment was repeated without hydroxyzine dihydrochloride referred as blank.

The above study was conducted using conventional heating in water bath in order to determine the effectiveness of MW. In this case color was produced after heating for 30min when temperature is 100°C which show low absorbance as compared to the one developed using MW. Thus, MW heating considerably improved the reaction rate and hence, colour development.

For preparation of calibration curve, different concentrations of hydroxyzine dihydrochloride were taken and above experiment was repeated (fig. 2). The results show that color reaction obeys Beer's law in concentration range of 50-250µg/ml of hydroxyzine dihydrochloride.

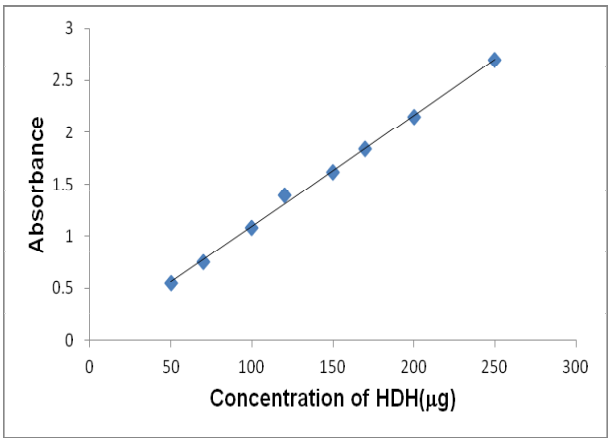

Fig. 2: Calibration curve of HDH.

Procedure for determination of hydroxyzine dihydrochloride in tablets

An aliquot of tablet solution containing 50-250µg/ml was taken in test tube and colour was developed by following the general procedure. The absorbance of resulting colour was quantified at 750nm. The quantity of each tablet was evaluated from the standard calibration curve. The values found were in agreement with the reported ones.

RESULTS

Absorption spectrum of coloured complex

Hydroxyzine dihydrochloride reacts with potassium ferrocynide in presence of hydrochloric acid after giving pulse at 500W for 5min. This result a bluish green colored complex which is quantified at 750 nm under optimum conditions (fig. 3).

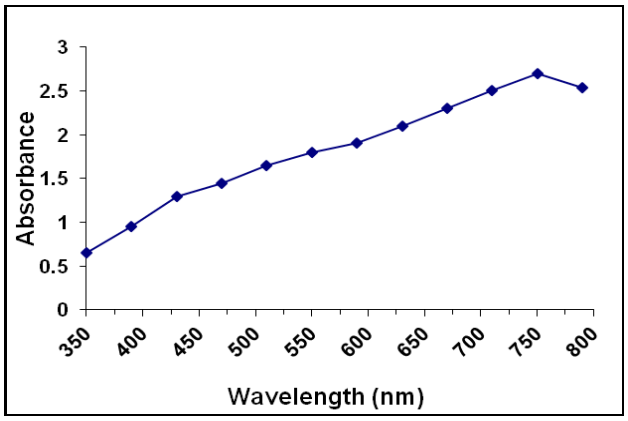

Fig. 3: Absorption spectra of HDH with showing λ_{max} at 750nm.

Optimization of parameters

Different parameters are adopted for the development of colour. In each of these parameters the contents of the test tube were cooled to room temperature prior to dilution and the measurement of absorbance. The study showed that the maximum absorbance of colour at 750nm when reaction conditions are optimized.

Effect of microwave power and conventional heating

To study the effect of MW power, 1.0ml of the hydroxyzine dihydrochloride standard solution was taken to which 2.0ml of 0.1 N hydrochloric acid was added followed by 1.5 ml of 1.0% (w/v) potassium ferrocynide solution were added. The contents were pulsed for 5min by varying the MW power over the range of 100-500W and maximum absorbance was recorded at 500W. For comparative studies, by using above-mentioned procedure the analysis were conducted in water bath at 10, 30, 50, 70, 90 and 110°C for 30 min and absorbance was taken at 750nm. The maximum absorbance was recorded at 100°C but the absorbance shown is comparatively less than the one shown by MW heating (fig. 4).

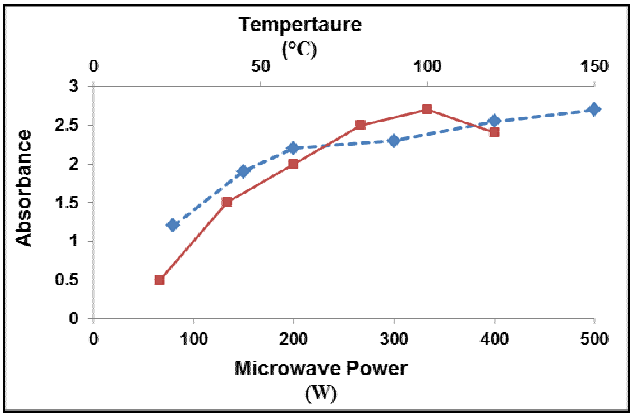

Fig. 4: Effect of conventional (—) and microwave (….) heating temperature on the color development.

Heating time

The effect of heating time for both MW and conventional was also studied between 1 to 10min by keeping the microwave power at 500W and 5-30min by maintaining temperature at 100°C, respectively. It was found that in case of MW, maximum absorbance was observed after 5min of heating while for conventional system, heating for 30 min is essential for complete reaction between the drug and reagent which results in maximum absorbance under the conditions studied (fig. 5). The stability of developed color was observed by measuring the absorbance after every hour by spectrophotometer at room temperature. The bluish green colored complex sustain for more than 24 h (fig. 6).

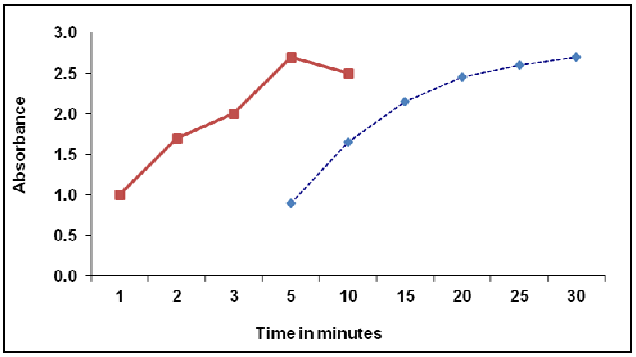

Fig. 5: Effect of conventional (…) and microwave (—) heating time and on the colour.

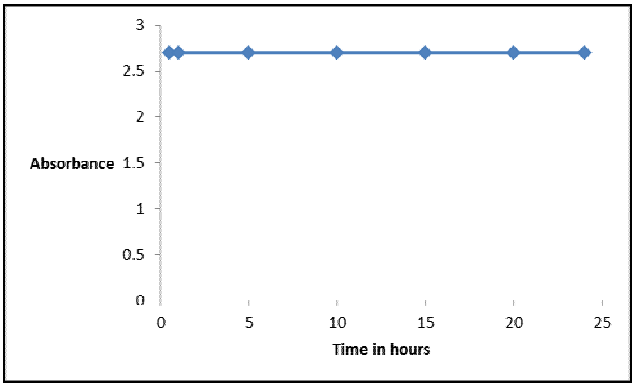

Fig. 6: Effect of color stability with time.

Effect reagent concentration

The influence of potassium ferrocynide, the colour producing reagent, concentration was studied using different amounts of w/v solutions. It was observed that 7.0 mg/ml of potassium ferrocynide is optimum for hydroxyzine dihydrochloride (fig. 7) and color stability above and below this concentration reduces. pH variations has appreciable effect on colour development as depicted in fig. 8. The maximum absorbance of color was observed at 3.0. Other acids, like sulphuric acid and nitric acid was also studied and it was found that the bluish green colour

developed in presence of these acids have low absorbance.

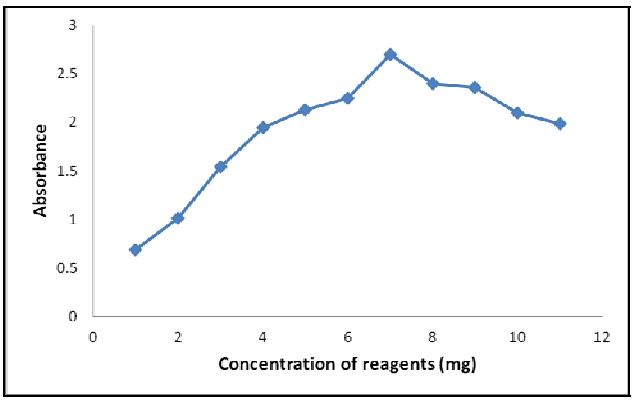

Fig. 7: Effect of reagent concentration on the color development.

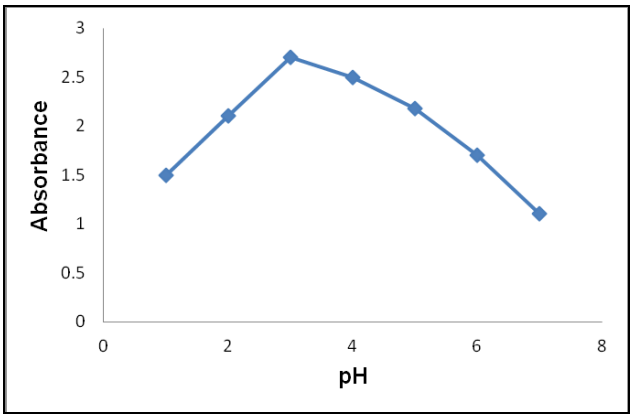

Fig. 8: Effect of pH.

DISCUSSION

Method validation and optimization

The optimization has been done at lower analyte concentration. The calibration graph is linear in the range 50-250µg/ml. The calculated value of molar absorptivity and coefficient of determination (r^2) are 0.405 x 10^4 and 0.999.For regression calculation, least squares method has been applied. (Christian 2004).

The results of hydroxyzine dihydrochloride are shown in tables (1-2), which confirm the sensitivity, validity and repeatability of the developed method. Results obtained from the analysis show that proposed procedure has good relative standard deviation (RSD 0.79%) (table 1).

Proposed mechanism

The probable mechanism of the formation of complex is that the acid proton will react with the chloride of benzene ring of hydroxyzine resulting in protonation of chloride ion leaving the positive charge on the benzene ring. This positive charge will attract the cyanide ion of the ferrocynide and thus lead the formation of -C-C=N – bond at *o*-position. The FT-IR shows peak at 1635 cm^- confirm the findings.

Table 1: Determination of hydroxyzine dihydrochloride from pure solution

Drug taken (µg/ml)	Drug found* (µg/ml)	Relative standard deviation (%)
10	10.27	0.79
20	19.95	0.41
30	29.80	0.27
60	59.10	0.13
90	90.50	0.39
100	99.00	0.36
140	139.50	0.25
200	210.50	0.17
250	250.0	0.14

*Every reading is an average of five independent measurements.

Table 2: Optical characteristics, precision and accuracy of the proposed methods

Parameters	Values
λ_{max} (nm)	750
Molar absorptivity (mol^{-1} cm^{-1})	0.4054×10^4
Regression equation (Y*)	
Slope (b)	0.0107
Intercept (a)	0.0255
correlation coefficient of determination(r^2)	0.9974
Relative standard deviation (RSD%)**	0.79
% range of error (confidence limit) at 95% confidence	9.92 $\pm$ 0.0248 %

*Y = a+ bc where c is the concentration of analyte (µg/mL $^{-1}$) and Y is the absorbance unit.

Applications

The proposed method is successfully applicable for the quality control and periodic analysis of pure hydroxyzine dihydrochloride and in the pharmaceutical dosage form without any interference of excipients as shown in table 3. The results of statistical analysis are in good agreement with that of reported potentiometric official British Pharmacopeia 2002 procedure as shown in table 4 (BP 2002).

CONCLUSIONS

The new green spectroscopic method using new ecofriendly reagent for the evaluation of hydroxyzine dihydrochloride is simple, reliable and sensitive. The color development took place five minutes using microwave which on other hand requires thirty minutes

Table 3: Determination of hydroxyzine dihydrochloride in pharmaceutical preparations by proposed method

Drug (hydroxyzine dihydrochloride)	Pharmaceutical Preparation	Amount present (Manufacturer's specifications) (mg)	Amount found* (mg)	Percentage Recovery (%)
Sample 1	Tablet	10	9.99	99.99
Sample 2	Tablet	10	9.95	99.95
Sample 3	Tablet	10	9.01	99.01
Sample 4	Tablet	25	24.9	99.60
Sample 5	Tablet	25	24.8	99.20

*Every reading is an average of five determinations.

Table 4: Determination of hydroxyzine dihydrochloride in pharmaceutical preparations by BP method

Drug (hydroxyzine dihydrochloride)	Pharmaceutical Preparation	Amount present (Manufacturer's specifications) (mg)	Amount found* (mg)	Percentage Recovery (%)
Sample 1	Tablet	10	9.99	99.99
Sample 2	Tablet	10	9.96	99.96
Sample 3	Tablet	10	9.20	99.20
Sample 4	Tablet	25	24.94	99.76
Sample 5	Tablet	25	24.91	99.64

*Every reading is an average of five determinations.

when conventional heating was used. Moreover the colour reaction needs unquestionable reagents and solvents hence contributing in protecting the environment. Nevertheless, this method has significantly advantages when compared with reported ones. It also provides a quick and economical quality tool for the micro-determination of hydroxyzine dihydrochloride. Hence this study is an innovation to develop the analytical method by following the principles of green chemistry.

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