Development and Optimization of Green Method for Antihistamine Using Ecofriendly Reagent in Pure and Pharmaceutical Formulations by Microwave Assisted Spectrophotometry

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Summary: Synthetic substances and solvents utilized in investigation of drugs crumble the earth as well as human health. So attempts should be made to minimize or eliminate the utilization of obnoxious chemicals and solvents. The objective of study is to develop the green spectroscopic method using new ecofriendly chromogenic reagent for the evaluation of antihistamine *i.e*. desloratadine in pure and commercial dosage forms. Both heating systems (conventional and microwave assisted procedures) are used for the development of color. The method is based on formation of stable blue coloured complex with ammonium molybdate in the presence of acid having λ_{max} at 732nm respectively. All the reaction conditions and different statistic parameters for the proposed methods have been studied. The method is found to be rapid, precise and accurate and can be successfully used for the determination of antihistamines in bulk and commercial tablet formulations.

Key words: Environment, Desloratadine, Microwave, Ammonium molybdate, Spectrophotomerty.

Introduction

The biggest challenge for chemist is to development new methodologies by following the principles of green chemistry. So time demands to implement such techniques which safe the environment as well as money. The advancement in strategy improvement by utilizing green synthetic substances and solvents must be arranged with the end goal to ensure the earth from pollution.

Desloratadine is the major active metabolite of loratadine. It is a non-sedative antihistamine used for the treatment of allergies like rhinitis and chronic urticaria [1]. Based on number of reports, the antihistamine (loratadine, cetirizine, fexofenadine and acrivastine) have low sedation effect *i.e*. cetirizine > acrivastine > loratadine. The studies showed that loratadine and fexofenadine show no difference in"sedation [2].

Considering the importance of antihistamines various efforts had been put in to define different methods for its analysis, whether in pharmaceutical preparations or in biological fluids [3]. These methods include High Performance Liquid Chromatography [4-6], Ultra Performance Liquid Chromatography [7], Liquid Chromatography [8], Tandem mass spectrometry [9-12], Densitometry [13], Voltammetry [14] and Spectrophotometry [15-20].

Conventional methods for the quantification of pharmaceuticals in dosage form possessed potential environmental hazards. Use of mobile phases in separation and chromatographic techniques employ variety of organic solvents which are not only carcinogenic but also when disposed off in the surroundings deteriorate the environment. Spectrophotometric methods are usually require UV reagent or coloring reagents *i.e*. organic compounds or dyes (2,3-dichloro-5,6-dicyno-1,4-benzoquinone, 2,4-dichloro-6-nitrophenol, 2,4-dinitrophenol, 2,4-dinitrofluorobenzene); all of these resulted in release of many toxic degradation products in waste. Hence, the need of time is the development of such methodologies which are eco-friendly and have lesser environmental hazards. This approach open a path in the development of greener methodologies for pharmaceutical analysis by using inorganic salts which have less effect on the environment as well as economical. In any case, Chromatographic systems likewise remained the strategy for decision for a large portion of the specialists yet these methods depend on long and dull methodology e.g. LC-MS requires technical experts and costly instrumentation. These methods have high RSD value (upto 15.1%).

Viewing the importance of desloratadine and reliability of spectrophotometric methods, a study was initiated in order to overcome the existing disadvantages of the already developed

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spectrophotometric methods like extraction, more time consuming, reduced sensitivity etc. Hence, spectrophotometric methods, in general, are far more convenient and economical. The losses of analyte, time reduction and atmospheric contamination are questionable when conventional procedures are adopted.

Microwaves are radiation energy that performs heating in non-ionizing form. The energy produced does no harm to chemical bonds but selectively transfers to specific substances [21].To maintain temperature for stabilized colored complex the pulse is given by microwaves. The microwave heating energy is uniform and increases the rate of color development procedure .This fastest and stabilized color development is associated with superheating effect of microwave [22].

Much work has been done to use microwave technology in the field of organic synthesis. Present study presented an effort to use this technology in field of analytical chemistry for the first time. For this purpose focus has been driven on microwave (MW) in order to overcome these problems and its application in various areas with different samples. In addition this method can be used in laboratories where modern and expensive instruments are not available.

Upon evolution [23], it was established that desloratadine and ammonium molybadate reacts in acidic media. Maximum absorbance of blue complex was observed at 732nm. This reaction obeys Beers Law in the range of 50 to 250µg/ml.

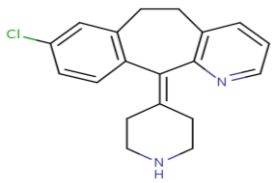

Fig-1: Structure of desloratadine.

Experimental

Chemicals and reagents

Analytical grade chemicals and solvents (E. Merck, BDH) were used throughout the experimental studies. Desloratadine was obtained from AGP Pvt. Ltd., B-23 S.l.T.E Karachi, Pakistan.

Instruments

For absorbance measurement Cecil CE-2041 spectrophotometer along with 1cm quartz cell were utilized. Orient Microwave was used for heating.

Preparation of stock, standard and working solutions

Stock solution of desloratadine (w/v) was prepared in ethanol to the concentration of 1mg/ml and stored in refrigerator. Standard solutions were prepared from this stock solution according to requirement by diluting. 1.0% (w/v) solution of ammonium molybadate (Merck) and 5.0 N hydrochloric acid (Merck) was used for studies.

General procedure

To an aliquot of desloratadine having 10-250µg/10ml, 2.0ml of 5.0N hydrochloric acid was added followed by 2.5 ml of 10% (w/v) ammonium molybadate solution. After that the contents were given pulse for 5min in MW at 500W, allowed to cool to room temperature and the volume was made up to 10ml with ethyl alcohol. The absorbance measurement was carried out at 732nm. A same procedure was used to conduct by omitting desloratadine labeled as blank.

A similar experiment was repeated by doing conventional heating in water bath in order to determine the effectiveness of MW. In this case color was produced after heating for 15min at 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 construction of calibration curve, the experiment was repeated with variable concentration of desloratadine (Fig. 7). The results show that color reaction obeys Beer's law in concentration range of 50-250µg/ml of desloratadine.

Procedure for determination of drug in dosage forms

Tablets having 10mg desloratadine were powdered, weighed and solubilize in ethanol. Then filtration was procedure by using Whatman 42 to get stock solution of desloratadine(1mg/ml) . The colour was developed by following above procedure. Standard calibration graph was used to calculate the quantity in dosage forms.

Results and Discussion

Visible Absorption spectrum of blue complex

The recation between desloratadine and ammonium molybadate was carried out in sulphuric acid at 500W for 5min. A bluish green colored

complex was assessed at 732nm after optimizing different parameters (Fig. 2)

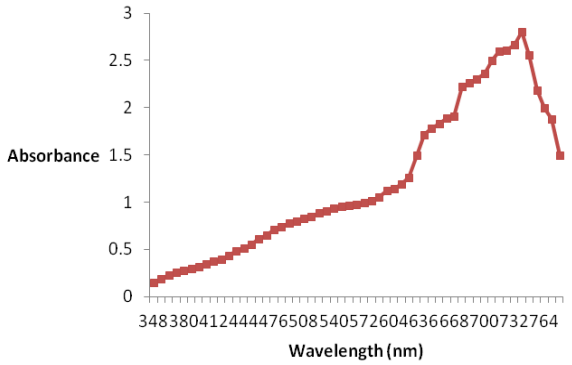

Fig. 2: Absorption spectra of desloratadine showing λ_{max} at 732nm.

Optimization of parameters

The development of colored complex of anti-histamine influence by certain physiochemical parameters like pH, heating temperature, heating time and concentration of color producing reagent as per general requirement of spectrophotometric analysis. In each parameter, dilution and the absorbance measurement are carried out at room temperature. According to data maximum absorbance was observed at visible region of spectrophotometer *i.e.*"732nm.

Influence of heating system

Solution of desloratadine (10-250µg/10ml) was taken in a round bottom flask, ammonium molybdat solution 2.5 ml of 10% (w/v) was added and the pulse of microwave at 100-500 w was given in presence of 2.0 ml of 5.0N hydrochloric acid. The mixture was allowed to cool at room temperature and volume made to 10ml with ethanol. The absorbance was taken at 732nm. Blank sample proceeded without adding desloratadine.

Effect of conventional reading was checked by adopting similar experiment and replacing heating of microwave with water bath at 20, 40, 60, 80 and 100°C. It has been observed that similar results were obtained in 15 minutes at 100°C. By comparing it has been found that time has been reduced from 15 minutes to 5 minutes by operating through microwave. The results can be obtained in less time, thus supports the procedure (Fig. 3).

Influence of Heating Time

The impact of time on heating systems (MW and conventional) was likewise examined between 1 to 10min by keeping the microwave control at 500W and 5-30min by keeping up temperature at 100°C, separately. The data obtained from results showed maximum absorbance after 5min by using microwave. While heating for 15 min is basic for finish reaction between desloratadine and ammonium molybdat which results in greatest absorbance under the conditions considered (Fig 4).

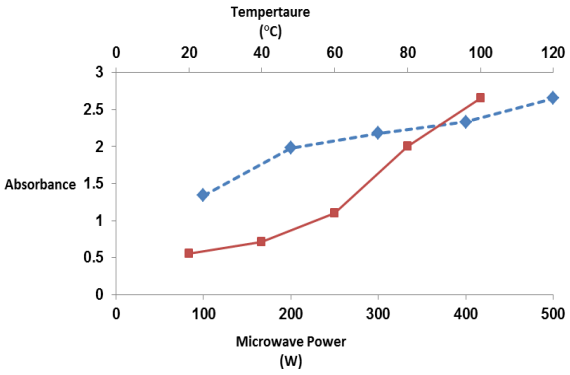

Fig. 3: Influence of conventional (—) and microwave (….) heating temperature.

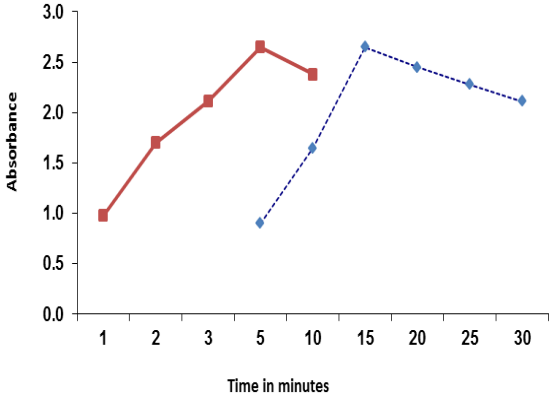

Fig. 4: Influence of conventional (…) and microwave (—) heating time.

Influence of reagent and acid concentration

The impact of ammonium molybadate was studied by utilizing different concentrations. It was seen that 250 mg/ml of ammonium molybadate showed intense color and ideal for the preparation of color complex of desloratadine (Fig 5). The absorption spectra of the reaction product were measured against blank in the visible region (350-800 nm). The maximum absorbance at 732nm was due to the reduction of ammonium molybdate (Mo^{+6}) into molybdenum blue (Mo^{+5}) by drug [24]. It was also observed that color dependability above and beneath this amount diminishes.

Fig. 6 demonstrates the intense color at pH 1.2. The intensity of blue green color was additionally checked by various aliphatic acids *i.e.* sulphuric acis, acetic acid and nitric acid. The lower value of absorbance was found by using above mentioned acids.

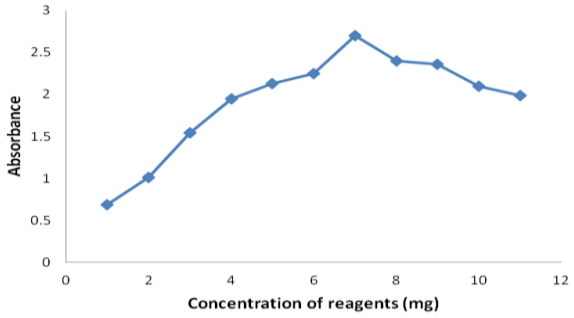

Fig. 5: Influence of reagent concentration.

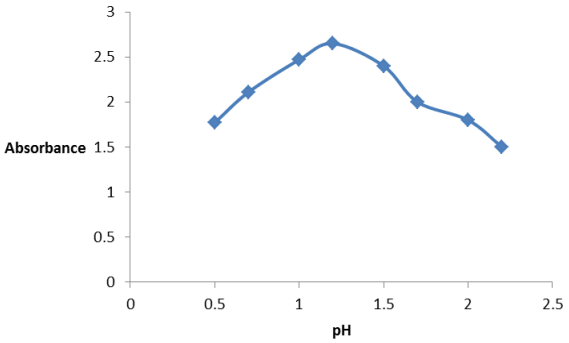

Fig. 6: Influence of pH.

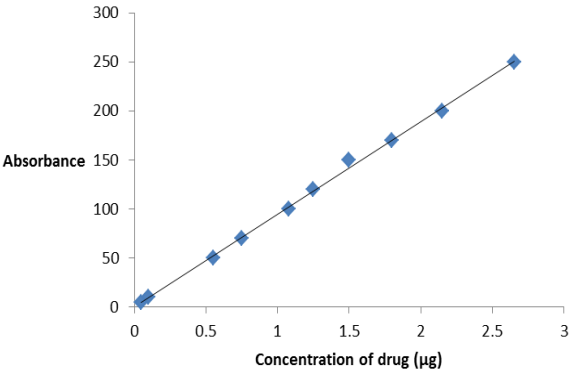

Fig. 7: Calibration curve of deslortadine.

Statistical studies of proposed Method

The method is optimized at lower analyte concentrations which shows the linearity of calibration curve in the range of 50-250µg/ml, calculated molar absorptivity 0.2900 x 10^4 (mol^{-1} cm^{-1}) and correlation coefficient (r^2) 0.998. Least square method is opted for regression calculation [25]. The results as presented in Table 1 and 2 depicted the developed method is sensitive, valid and repeatable with good relative standard deviation"(RSD 0.79%) (Table-1).

Table-1: Determination of desloratadine 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	29.8	0.27
60	59.1	0.13
90	90.5	0.39
100	99.0	0.36
140	139.50	0.25
200	210.50	0.17
250	250	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)	732
Molar absorptivity (mol^{-1} cm^{-1})	0.2900 x 10^4
Regression equation (Y*)	
Slope (b)	94.48
Intercept (a)	0.255
correlation coefficient of determination(r^2)	0.998
Relative standard deviation (RSD%)**	0.79
% range of error (confidence limit) at 95% confidence	4.9 ± 0.0011 %

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

Applications

According to the results it was found that the proposed method is efficiently used not only for the quality control but also for periodic analysis of pure desloratadine and in tablets. Low RSD value and study of interference of recipients also supports its suitability (Table-3).

Table-3: Determination of desloratadine in pharmaceutical preparations.

Drug (desloratadine)	Pharmaceutical Preparation	Amount present (Manufacturer's specifications) (mg)	Amount found* (mg)	Percentage Recovery (%)
Sample 1	Tablet	10	9.99 (± 0.81)	99.99
Sample 2	Tablet	10	9095(± 0.77)	99.95
Sample 3	Tablet	10	9.01 (± 0.83)	99.01
Sample 4	Tablet	25	24.9 (± 0.73)	99.60
Sample 5	Tablet	25	24.8 (± 0.68)	99.20

*Every reading is an average of five determinations.

Conclusions

Based on the utility of eco-friendly reagents for the evaluation of desloratadine, The developed novel green spectroscopic method is found simple, economical and sensitive in pharmaceutical quantification. The method limits the use of organic solvents and reagents for the quality assurance thus contributing a step towards pollution prevention. This technique is energy efficient and colored complex is formed in 5min, enabling quick and easy determination of the drug. Thus permits quantitative analysis to be carried out with good reproducibility in micro-determination of desloratadine in both pure and pharmaceutical"preparations.

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