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Original Article

EXTRACTIVE SPECTROPHOTOMETRIC DETERMINATION OF SOME ANTIHISTAMINIC DRUGS FROM PHARMACEUTICAL FORMULATIONS USING ROSE BENGAL

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ABSTRACT

Objective: Simple and sensitive an extractive-spectrophotometric method have been developed for the determination of four important antihistaminic drugs, namely desloratadine (DSL), chlorpheniramine maleate (CPM), diphenhydramine hydrochloride (DPH) and fexofenadine (FXO).

Methods: This method is based on the formation of colored ion-pair complexes between the basic nitrogen of the drugs and halofluorescein dyes, namely rose bengal (RB) dye in weak acidic medium. The formed complexes were extracted with dichloromethane measured spectrophotometrically at 550 nm.

Results: The reaction conditions were optimized to obtain the maximum color intensity. Beer's law was obeyed with a good correlation coefficient (0.9963-0.9975) in the concentration ranges 1-6, 4-18, 6-16 and 2-22 µg/ml for DSL, CPM, DPH and FXO, respectively. The composition ratio of the ion-pair complexes was found to be 1:1 as established by Job's method.

Conclusion: The proposed method was successfully extended to pharmaceutical preparations. Excipients used as additive in commercial formulations did not interfere in the analysis. The proposed method can be recommended for quality control and routine analysis where time, cost effectiveness and high specificity of analytical technique are of great importance.

Keywords: Desloratadine, Chlorpheniramine maleate, Diphenhydramine hydrochloride, Fexofenadine, Rose Bengal, Ion-pair complexes, Spectrophotometry.

INTRODUCTION

Desloratadine (DSL, fig. 1), 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta [1,2b]pyridin-11-ylidene)-1-piperidine. DSL is a selective peripheral H1 receptor antagonist, devoid of any substantial effect on the central and autonomic nervous systems [1, 2]. Desloratadine exhibits qualitatively similar pharmacodynamic activity with a relative oral potency in animals, two to three-fold greater than its parent analogue loratadine, probably due to a higher affinity for histamine H1 human receptors [3].

Several analytical methods have been reported for the determination of DSL in biological samples and applied in pharmacokinetics studies. These methods include liquid chromatography [4-6] and High-performance liquid chromatographic method [7]. However, DSL was determined in pharmaceutical preparations using a spectrophotometric and spectrofluorometric [8-12].

Chlorpheniramine maleate (CPM, fig. 1), ((3-(4-chloro-phenyl)-N,N-dimethyl-3-(2-pyridyl)propylaminemonomaleate) 1), chemical structure is showed in (fig. 1c). Chlorpheniramine maleate is an antihistamine drug that is widely used in phamarceutical preparations for symptomatic relief of common cold and allergic diseases [13]. Chlorpheniramine maleate was determined in pharmaceutical dosage forms and plasma samples by chromatographic [14-24], spectrophotometric [25-28] and electrochemical methods [29, 30].

Diphenhydramine hydroch loride (DPH, fig. 1), is an antihistamine drug having the chemical name 2-(diphenylmethoxy)-N,N-dimethylethylamine hydrochloride. It is usually administered orally and may be used by intramuscular or intravenous injection in severe allergies and applied topically for local allergic reactions. Several published methods have been developed for the determination of DPH in pharmaceutical preparations and in biological fluids including: spectrophotometry [31–34], flow injection analysis [35], gas chromatography [36], atomic absorption spectrometry [37], high performance liquid chromatography [38], Liquid chromatography [39] and capillary electrophoresis [40–42].

Fexofenadine (FXO, fig.1) is, chemically, 2,2-dimethyl-4(1-hydroxy-4-{hydroxy diphenylmethyl-1-piperidinyl}butyl)benzoaceticacid. FXO is a highly selective peripheral histamine H1 receptor antagonist used in the treatment of allergic diseases such as allergic rhinitis and chronic urticaria. Fexofenadine is the active derivative of the antihistamine terfenadine, with no antichrolinergic or alpha 1-adernergic receptor-blocking effects and without severe cardiac side effects of terfenadine [43, 44]. Several methods for the determination of fexofenadine hydrochloride in pharmaceutical formulations and biological fluids have been reported including chromatographic methods [45–52], spectrophotometry [53–58], spectrofluorometry [59], potentiometry [60], and capillary electrophoresis [61].

The proposed method is dedicate to study the formation of a ion-pair complex between each of the studied drugs and rose bengal dye in an attempt to develop a simple, sensitive and accurate extraction-free spectrophotometric method for the determination of DSL, CPM, DPH and FXO drugs in their pharmaceutical preparations.

MATERIALS AND METHODS

Equipments

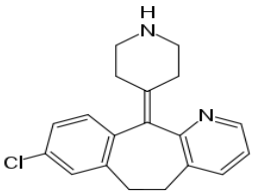
All the absorbance spectral measurements were made using spectroscan 80 D double-beam UV/Visible spectrophotometer (Biotech Sedico, Scientific Equipment Distribution, Ltd. Nicosia, Cyprus), with wavelength range 190 nm ~ 1100 nm, spectral bandwidth 2 nm, with 10 mm matched quartz cells. An Orion Research Model 601 A/digital analyzer, pH-meter with a combined saturated calomel glass electrode was used for pH measurements, water bath and hot plate.

Materials

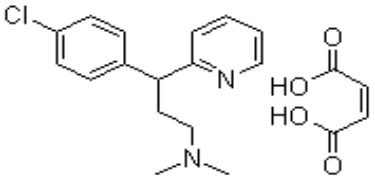
All chemicals and reagents were of pharmaceutical or analytical grade and all solutions were prepared fresh daily. They are included drugs under investigation: desloratadin (DSL) chlorpheniramine

(CPM), diphenhydramine (DPH) and fexofenadine (FXO) that supplied from Egyptian International Pharmaceutical Industries Company (EIPICo) 10th of Ramadan City, Egypt. Rose bengal was supplied from (Aldrich), sodium acetate and methylene chloride were supplied from (Egyptian, Adewic).

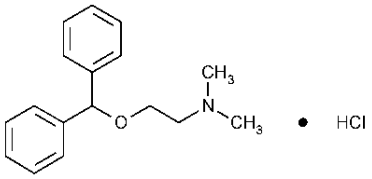
Tablets containing the drugs were obtained from the local market. The pharmaceutical preparations of desloratadine pharmaceutical preparations were delarex tablets 5 mg/tab produced by (global napi Pharm. Cairo–Egypt). The chlorpheniramine maleate pharmaceutical preparations were anallerge tablets 4 mg/tab (Kahira Pharm. Cairo–Egypt). Diphenhydramine hydrochloride is sultan tablets, 50 mg/tab produced by Pharaonia pharmaceuticals. The fexofenadine hydrochloride pharmaceutical preparations were allerfen tablets 60 mg/tab produced by (Amoun Pharm. Cairo–Egypt).



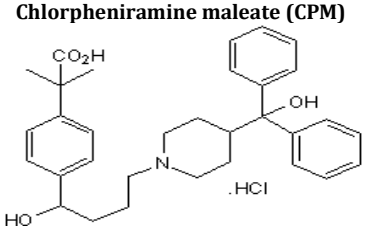
Desloratadine (DSL)



Chlorpheniramine maleate (CPM)



Diphenhydramine hydrochloride (DPH)



Fexofenadine hydrochloride (FXO)

Fig. 1: Chemical structures of the studied drugs

Reagents and solutions

All chemicals and reagents used were of analytical-reagent grade and distilled water was used throughout the investigation.

Pure drugs

An accurately weighed quantity of the investigated drugs (20 mg) was dissolved in distilled water in a 100 ml measuring flask. Aliquots of the above prepared stock solution were further diluted to obtain 100 µg/ml working standard solutions.

Buffer solution

Citrate–phosphate buffer was prepared by adding 0.20 M disodium hydrogen phosphate (Fisher Scientific Co., Pittsburgh, PA) to 50 ml 0.1 M citric acid (Sigma Chemical Co., St. Louis, MO) to adjust the pH to 2–7 and the volumes were diluted to 100 ml with distilled water.

Dye stuff

A stock solution of 1×10^{-3}M rose bengal {4,5,6,7-Tetrachloro-3',6'-dihydroxy-2',4',5',7'-tetraiodo-3*H*-spiro[isobenzofuran-1,9'-xanthen]-3-one}, was prepared by dissolving 97.367 mg from dye (99% purity) in distilled water and diluting to 100 ml in a measuring flask with distilled water.

Procedure for calibration curves

Into a series of separating funnels, accurately measured aliquots DSL, CPM, DPH or FXO in the concentration range shown in (table 1) were pitted out and then 2.0 ml of 1×10^{-3}M of RB dye was added. The solution was diluted to 10 ml with distilled water after the addition of 2.0 ml of acetate buffer of pH 6 for CPM, DPH or FXO but buffer of pH 6.8 for DSL was added. The ion-pairs were extracted with 10 ml of dichloromethane by shaking for 2.0 min and then, the combined dichloromethane extracts were dried over anhydrous sodium sulphate. The absorbance of colored ion-pair complexes were measured within 5.0 min of extraction against the reagent blank prepared in the same manner except addition of drugs.

Procedure for tablets

Ten tablets of each commercial pharmaceutical formulation were crushed, powdered, weighed out and the average weight of one tablet was determined. An accurate weight equivalent to 20 mg each drug and then active component was transferred into a 100 ml measuring flask. About 25 ml of distilled water was added and the mixture was shaken thoroughly for about 5 min. Then, it was diluted up to the mark with distilled water, mixed well and filtered using filter paper. An aliquot of this solution was diluted appropriately to obtain the working concentrations and analyzed as described under the standard procedure.

RESULTS AND DISCUSSION

Absorption spectra

The absorption spectra of the ion-pair complexes were measured in the range 525-630 nm against dichloromethane (blank). Antihistamine cations were found to react with anions of rose bengal dye in acidic buffer and gave an intense color with a maximum absorption at 550 nm as shown in fig. 2. Therefore, all the following measurements are carried out at 550 nm against blank where the investigated drugs, dyes, buffer and dichloromethane have no absorption in this region. The optimum conditions were established by varying one variable and observing its effect on the absorbance of the colored product.

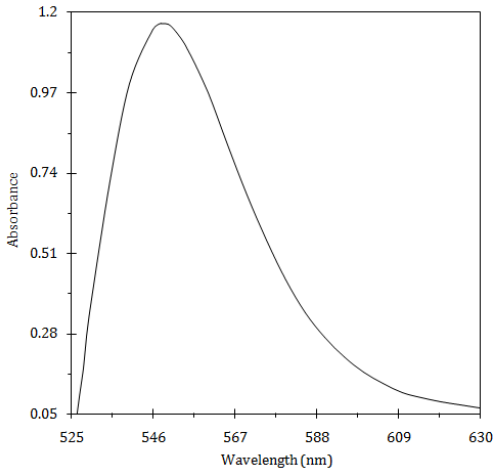


Fig. 2: Absorption spectra of 6 µg/ml DSL with RB dye at pH = 6.8

Effect of pH

The influence of pH on the ion-pair complex formations of DSL, CPM, DPH and FXO with RB dye has been studied using different types of buffers of different media. The optimum buffer associated with the maximum color intensity is disodium hydrogen phosphate-citric acid of pH=6 in case of DPH, CPA or FXO but pH=6.8 in case of DSL (fig. 3). Buffer volume was determined by applying the same experiment and variation the volume regularly (0.5-4.0 ml). The higher absorbance value obtained at using 2.0 ml.

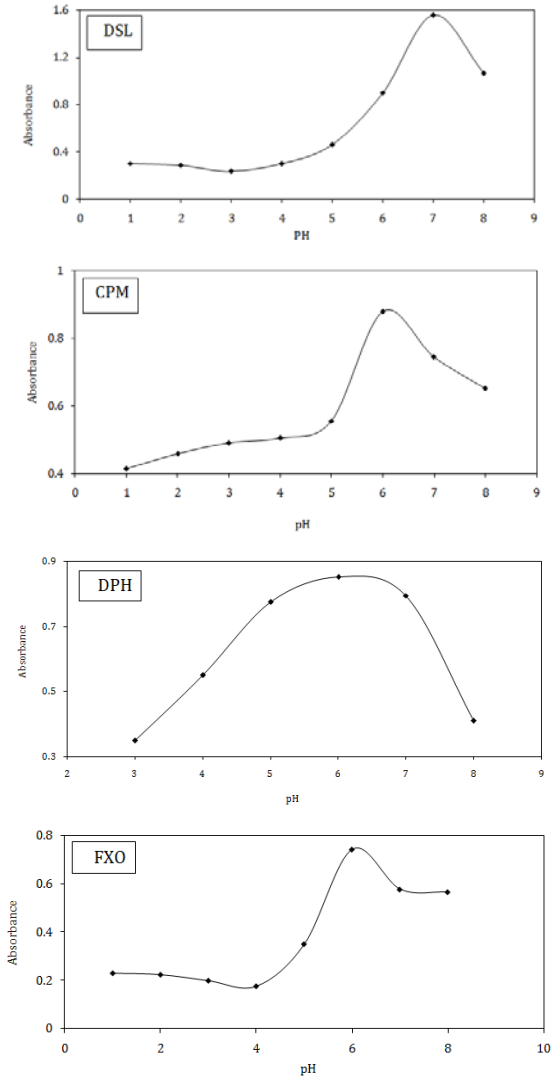


Fig. 3: Effect of pH on the formation of ion-pair complex between RB and the studied drugs at 550 nm

Choice of organic solvent

A number of organic solvents such as dichloromethane, chloroform, carbon tetrachloride, benzene and toluene were examined for extraction of the ion-pair complexes in order to provide an applicable extraction procedure. Dichloromethane was found to be the most suitable solvent for extraction of colored complex yielding maximum absorbance intensity and it was also, observed that only one extraction was adequate to achieve a quantitative recovery of the complex and very low absorbance of the reagent blank and shortest time to reach the equilibrium between both phases.

Effect of RB dye concentration

Keeping other conditions unaltered, the influence of 1×10^{-3}M RB dye concentration on absorbance was investigated. The results showed that the maximum absorbance was at using 3.0 ml from RB dye for DSL, CPM, DPH and FXO. After this volume, the absorbance remains constant by increasing the volume of RB dye. So any excess of reagents has no effect on the determination of the drugs.

Effect of shaking time

Shaking time of 1.0-4.0 min provided a constant absorbance and hence, 2.0 min was used as an optimum shaking time throughout the experiment. The ion-pair complexes were quantitatively recovered in one extraction only and were, also stable for at least 24 h without any change in color intensity.

Sequence of addition

The sequence of addition of drugs, buffer, and dye were studied via the formation of the colored complexes. The optimum sequence of addition was similar in all cases by starting with drug, then dye and at last buffer. Other sequences gave lower absorbance values under the same experimental conditions.

Effect of temperature and stability time

The effect of temperature on colored complexes was studied over the range 20-35 °C. It was found that the absorbance of the ion pair complex was constant up to 30 °C. At higher temperatures, the drug concentration was found to increase due to volatile nature of the dichloromethane. Therefore, the temperature chosen was 30 °C as the best temperature for micro-determination of the drugs under study in pure and pharmaceutical formulations. The stability time of the four extracted ion-pair complexes was more than 120 min.

Stoichiometric ratio

In order to establish the molar ratio between DSL, CPM, DPH, FXO drugs on one side and RB reagent used on the other, Job's method of continuous variation was applied [62]. In this method, 5×10^{-3} M solutions of drug and reagent were mixed in varying volume ratios in such a way that the total volume of each mixture was the same. The absorbance of each solution was measured and plotted against the mole fraction of the drug. This procedure showed that a (1: 1) complex was formed through the electrostatic attraction between the positively charged drug, D^+ions and negatively charged reagent, R^-, ions. The extraction equilibrium can be represented as follows:

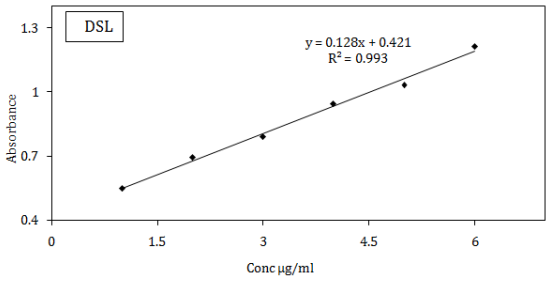
$$D^+_{aq} + R^-_{aq} \leftrightarrow D^+R^-_{aq} \leftrightarrow D^+R^-_{org}$$

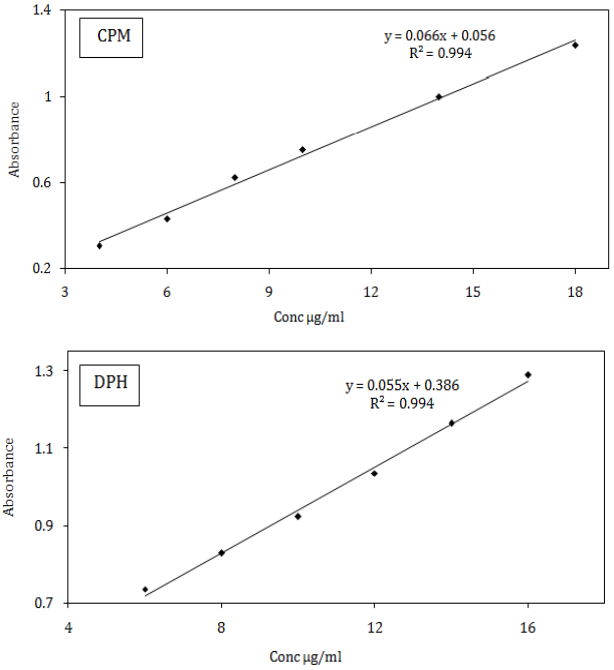
Where $D^+$and R^-represent the protonated drug and the anion of the reagent, respectively and the subscripts "aq" and "org" refer to the aqueous and organic phases, respectively.

Quantification

Under the optimum conditions described above, the calibration graphs for the investigated drugs were constructed by plotting absorbance versus concentration in µg/ml. (fig. 4). Conformity with Beer's law was evident in the concentration ranges cited in table 1. Regression equations, intercepts, slopes and correlation coefficients for the calibration data were presented in table 1.

The high molar absorptivities of the resulting colored complexes indicated high sensitivity of the method (2.35×10^4–6.28×10^4). The small values of Sandell's sensitivity indicate the high sensitivity of the proposed method in the determination of the drugs under investigation. The limit of detection (LOD) and limit of quantitation (LOQ) are calculated according to ICH guidelines [63] and the results are tabulated in (table 1).





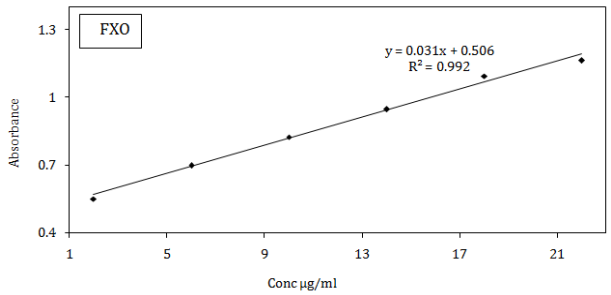


Fig. 4: Calibration curves for determination of: DSL (1–6 µg/ml), CPM (4–18 µg/ml), DPH (6–16 µg/ml) and FXO (2–22 µg/ml) under optimum conditions

Accuracy and precision

In order to determine the accuracy and precision of the recommended procedure five replicate determinations at three different concentrations of the studied drugs were carried out. Precision and accuracy were based on the calculated relative standard deviation (RSD, %) and relative error (RE, %) of the found concentration compared to the theoretical one, respectively and indicate that the proposed method is highly accurate and reproducible (table 2).

Table 1: Analytical parameters and optical characteristics with RB dye

Parameters	Drugs			
	DSL	CPM	DPH	FXO
λ_{max} (nm)	550	550	550	550
pH	6.8	6	6	6
Beer's law limit, µg/ml	1-6	4-18	6-16	2-22
Molar absorptivity, l mol^{-1} cm^{-1}	6.28×10^4	2.69×10^4	2.35×10^4	2.84×10^4
Sandell's sensitivity, ng/cm^2	4.94	14.52	12.41	18.90
Correlation coefficient (r)	0.9938	0.9945	0.9947	0.9926
Linear regression equation*				
$S_{y/x}$	0.0214	0.0278	0.0167	0.0225
Intercept (a)	0.4214	0.0563	0.3860	0.5063
Slope (b)	0.1284	0.0668	0.0550	0.0312
S. D. of slope (S_b)	5.13×10^{-3}	2.38×10^{-3}	1.99×10^{-3}	1.34×10^{-3}
S. D. of intercept (S_a)	0.0440	0.0584	0.0538	0.0395
LOD, µg/ml	0.0155	0.0299	0.0363	0.0641
LOQ, µg/ml	0.0518	0.0997	0.1210	0.2134

*A= a+bC, where A is the absorbance and C is the concentration of drug in µg/ml.

Table 2: Evaluation of intra-day accuracy and precision of the proposed method

Drugs	Drug taken µg/ml	Drug found[a] µg/ml	Recovery, %	RSD, %	RE[b], %
DSL	1.0	0.999	99.994	3.410	-0.100
	3.0	2.999	99.996	2.104	-0.033
	5.0	4.999	99.994	1.152	-0.020
CPM	4.0	3.999	99.996	4.255	-0.025
	8.0	7.999	99.994	6.075	-0.012
	14	13.999	99.996	2.542	-0.007
DPH	2.0	1.999	99.994	4.214	-0.050
	6.0	5.999	99.994	1.401	-0.016
	10	9.999	99.996	1.759	-0.010
FXO	2.0	1.999	99.996	3.871	-0.050
	10	9.999	99.994	0.994	-0.010
	18	17.999	99.996	3.759	-0.005

[a]Mean value of five determinations, [b]RE: Relative error.

Analysis of dosage forms

To evaluate the validity and reproducibility of the method, known amounts of the DSL, CPM, DPH and FXO drugs were added to the previously analyzed pharmaceutical preparations and the mixtures were analyzed by the proposed method. The percent recoveries are given in table 3. Interference studies revealed that the common excipients and other additives such as lactose, starch, gelatin, talc and magnesium trisilicate, that are usually present in the tablet dosage forms did not interfere at their regularly added levels.

Table 3: Recovery of the studied drugs in pharmaceutical formulations using the proposed method

Drug formulations	Drug taken µg/ml	Drug found[a] µg/ml	Recovery, %	RSD, %	RE[b], %
sultan tablets,	2	1.999	99.994	1.232	-0.050
50 mg/tab	6	5.999	99.994	1.761	-0.016
	10	9.999	99.999	2.929	-0.010
anallerge tablets,	4	3.999	99.994	4.134	-0.025
4 mg/tab	8	7.999	99.996	2.910	-0.012
	14	13.999	99,994	1.579	-0.007
allerfen tablets,	6	5.999	99.994	4.762	-0.016
60 mg/tab	14	13.999	99.996	2.936	-0.007
	18	17.998	99.994	2.375	-0.011
delarex tablets,	2	1.999	99.994	4.377	-0.050
5 mg/tab	4	3.999	99.996	3.466	-0.025
	5	4.999	99.996	3.811	-0.020

[a]Mean value of five determinations, [b]RE: Relative error.

CONCLUSION

The proposed spectrophotometric method is simple, sensitive, and suitable for the determination of DSL, CPM, DPH and FXO drugs in bulk and pharmaceutical dosage forms. The proposed method offers the advantages of accuracy and time saving as well as simplicity of reagents and apparatus. The developed method may be recommended for routine and quality control analysis of the investigated drugs in pharmaceutical preparations.

CONFLICT OF INTERESTS

Declared None

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