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ASSAY OF CLEMASTINE FUMARATE AND PROPRANOLOL HYDROCHLORIDE BY NEW METHODS BASED ON ION PAIRS FORMATION

Ioana Clementina CONSTANTINESCU* and Alexandra Filareta NEAGU

University of Medicine and Pharmacy, Carol Davila, Department of Analytical Chemistry, Faculty of Pharmacy, 6th Traian Vuia str, Bucharest 2, 020956, Roumania

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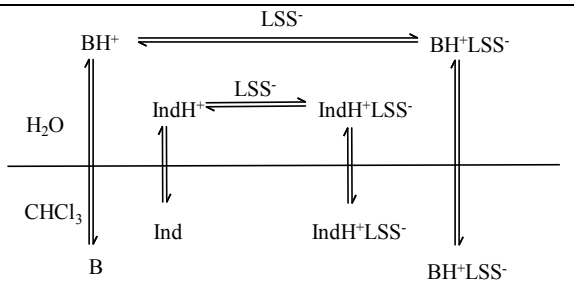
Two simple and rapid titrimetric methods in heterogeneous system (water / chloroform) for the assay of clemastine fumarate and propranolol hyhrocloride by ion association titration are proposed. Sodium lauryl sulfate was used as a titration reagent. The titrations were carried out in acidic medium, in the presence of sulfuric acid. The indicator for titrations was dimethyl yellow. The reactions stoichiometry was found to be 1:1 for both drugs. These methods were successfully applied to the assay of clemastine fumarate and propranolol hydrochloride in bulk and pharmaceuticals, with good accuracy and precision and without detectable interference by excipients. Results are in good agreement with those of pharmacopoeial methods.



INTRODUCTION

Clemastine fumarate (CF), chemically known as (*2R*)-2-[2-[(*R*)-1-(4-chlorophenyl)-1-phenyl ethoxy] ethyl]- 1-methylpyrrolidine (*E*) – butenedionate (Fig. 1),[1] is an antihistamine drug used for decreasing the effects of histamine at H_1 receptors.[2] CF is used to decrease the symptoms associated with upper respiratory allergies or to relief the allergic skin manifestations. Propranolol hydrocloride (PCl), (2 *RS*) – 1 - [(1 – methyl ethyl) amino] – 3 - (naphthalene -1- yl oxy) propan -2 - ol hydrochloride (Fig. 2),[1] is a beta adrenergic receptor antagonist being widely used as standard therapy for many diseases (hypertension, angina pectoris, myocardial infarction, cardiac arrhythmias, migraine and anxiety).[2]

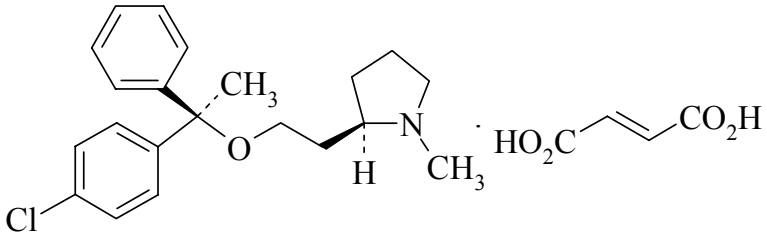


Fig. 1 – Chemical structure of clemastine fumarate.

* Corresponding author: constantinescu_clementina@yahoo.com

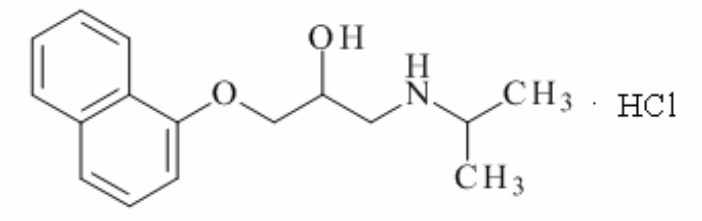


Fig. 2 – Chemical structure of propranolol hydrochloride.

These substances were the subject of many researches. Several methods have been published for the assay of CF in bulk, pharmaceuticals dosage forms and biological fluids.[3-6] Different chemical or physicochemical methods have been reported for the assay of PCl.[7-11] CF and PCl are official in European Pharmacopoeia, which describes two potentiometric methods for their assay.[1]

Many of published methods involve several steps which are not simple for routine analysis from bulk or pharmaceutical formulations and required expensive instruments and reagents. Expanding the use of CF and PCl requires the existence of simple analytical methods, sensitive and readily available for their determination in pure form or in pharmaceutical forms.

Therefore, we considered the possibility of developing such fast and simple methods, but also with high analytical performances. Due to its advantages, visual titrimetry may serve as an alternative to many instrumental methods. It is known the capacity of the protonated cations of the organic basis to form with voluminous anions ion pairs, some with low solubility in water and other soluble in water. These reactions were studied by a large number of researchers for the titration of drugs or surfactants. The ion pairs were used to develop new methods for the separation and quantitative determination of basic drugs.[12-14]

This paper reports two new titrimetric methods for the assay of CF and PCl, methods based on ion pairs formation with sodium lauryl sulfate (LSS). These simple and rapid methods allowed the determination of CF and PCl in bulk and pharmaceutical forms.

EXPERIMENTAL

Material and reagents

All chemical and reagents were of analytical grade and water has been always distilled water.

Pharmaceutical grade CF and PCl were supplied by Promedic S.A., Roumania. Substances purity was verified by the determination of melting point and registration of IR spectrum. A 10^{-2} M LSS standard solution was prepared by dissolving 2.84 g LSS (Acros Organics, UK) in 1000 ml of distilled water. The LSS solution standardization was performed on papaverine hydrochloride (Sigma Aldrich, Germany) using dimethyl yellow (DY) as indicator. A 10^{-3} M LSS standard solution was prepared by diluting of the 10^{-2} M LSS standard solution. DY acid alcoholic solution was prepared as follow: an alcoholic solution of DY was obtained by dissolving 0.1 g DY (Merck, Germany) in alcohol (Merck, Germany); then 10 ml of this alcoholic solution and 50 ml of 100 g/l sulfuric acid (prepared by diluting of an appropriate volume of sulfuric acid (Merck, Germany) with distilled water) were mixed. 2 M sulfuric acid solution was prepared by diluting of an appropriate volume of sulfuric acid (Merck, Germany) with distilled water. Chloroform (Merck, Germany) was used without purification.

A Mettler Toledo AT 261 Delta Range analytical balance was used for weighing.

Methods

Procedure for the assay of drugs in pure form: Samples of drugs (0.05-0.10 g CF and 0.02-0.04 g PCl) were accurately weighed; CF samples was dissolved in 30 ml chloroform and 5 mL of 2 M sulfuric acid, 20 mL water were added; PCl samples were dissolved in sulfuric acid, then 50 ml chloroform were added; 1 ml DY solution was added to each samples. The two-phase mixture was vigorously shacked until the aqueous solution became colorless and the chloroformic phase turns yellow and then was titrated with 10^{-2} M LSS standard solution. The titration was performed under continuous stir and the end point was reached when the color of the organic phase became pink.

Procedure for the assay in tablets: Twenty tablets (Clemastin, 1.34 mg CF - Promedic, Roumania, respectively, Propranolol, 10 mg PCl - Pharmascience, France) were weighed and grounded into a fine powder. Amounts of homogeny powder of Clemastin (equivalent to 1.34 mg CF), respectively Propranolol (equivalent to the 0.02 – 0.04 g PCl) were accurately weighed and transferred into a 200 ml volumetric flask. The powders were vigorously shacked with 30 ml chloroform (CF), respectively 20 ml sulfuric acid solution (PCl). The suspensions were treated with the same reagents described for pure form and titrated in the same conditions with 10^{-3} M LSS standard solution (CF) or 10^{-2}M LSS standard solution (PCl).

RESULTS AND DISCUSSION

LSS is known as one of the most used anionic surfactants. It presents in its structure a hydrophobic chain of 12 carbon atoms and the

other end a sulfone group, ionized (hydrophilic end) that causes negative charge of the lauryl sulfate ions (LSS^-).

Clemastine is structurally related to ethanolamine and it is a basic substance due to pyrrollidine nucleus. Propranolol is derived from aryl oxy propanol amine, with basic character (pKa = 9.42).[15] In acidic medium clemastine and propranolol are protonated cations (BH^+) and with lauryl sulfate anion (LSS^-) they form uncharged ion pairs ($BH^+ \cdot LSS^-$). They are colorless and extractable in organic solvents like chloroform.

The determination of studied substances by titration with LSS is based on the different stabilities of the two ion pairs: the stability of $BH^+ \cdot LSS^-$ is higher than the stability of ion association formed between protonated indicator DY ($IndH^+$) and lauryl sulfate anion ($IndH^+ \cdot LSS^-$). That allows the detection of the end point. During of the titration, the mixture was vigorously shacked to allow the formation of ion pairs $BH^+ \cdot LSS^-$ and their extraction into the organic phase. Since the beginning of the titration and to the end point, the molecular form of the indicator, Ind, chloroform extractible, colors the organic phase in yellow. The titrant, LSS^{--}, added in excess at the end point, changes the color of the choroformic phase from yellow to pink, because of the extraction of $IndH^+ \cdot LSS^{--}$ ion pair formed in aqueous phase. The general scheme of the processes that occur in the titration of a base (B) with sodium lauryl sulfate (LSS) in the presence of the indicator Ind is shown in Fig. 3.

The calculations are based on a 1:1 (reagent titrant: drug) molar-ratio determined by the presence of one the basic nitrogen atom nitrogen atom in the atom in the structure of the two analytes. We take into account that 1 ml 10^{-2} M LSS solution reacts with 0.004600 g CF or 0.002958 g PCl and 1 ml 10^{-3} M LSS solution corresponds to 0.000460 g CF.

Analytical performances testing

The methods were validated according to the ICH regulations Q2 (R1).[16]

Accuracy of the proposed methods was evaluated. For this purpose, nine amounts (within the range of study) of each studied drug, accurately weighted, were subjected to analysis using the procedures mentioned previously. The results expressed in percent of recovery are compiled in Table 1 and prove a good accuracy for both methods (mean recovery 99.88% for CF and 99.87 for PCl).

Precision of the assay was determined by repeatability and intermediate precision. Three different series of samples of CF or PCl were analyzed in three replicates in the same day and three consecutive days. The relative standard deviations were calculated and were found to be 0.06 % for CF, respectively 0.01 for PCl (repeatability) and 0.10% for CF, respectively 0.09 for PCl for intermediate precision (Table 1).

Robustness of the methods was evaluated by making small changes in volumes of reagents (sulfuric acid 5 ± 0.5 mL for CF assay and 20 ± 2 mL for PCl assay; DY 1 ± 0.2 mL for CF and PCl assay and chloroform 30 ± 3 mL for CF assay and 50 ± 5 mL for PCl assay). Robustness was studied at three different drug levels (0.05, 0.07, 0.10 g of Cl and 0.02, 0.03, 0.04 g of PCl). The results indicate that proposed methods are robust (RSD % within limits (0.70 – 1.55 for CF, 0.79 – 1.70 for PCl) (Table 2).

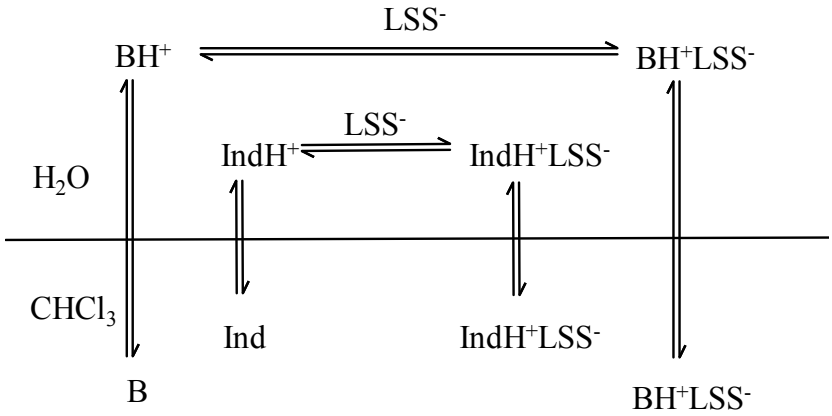


Fig. 3 – Schematic representation of the processes at the titration of a base (B) with sodium lauryl sulfate (LSS) in the presence of the indicator (Ind).

Table 1

Analytical results for the assay

Drug	Mean recovery* (%)	RSD (%)		Confidence interval**
		Repeatability	Intermediate precision	
Clemastine fumarate	99.88	0.06	0.10	99.88 ± 0,05
Propranolol hydrochloride	99.87	0.01	0.09	99.87 ± 0.01

* Mean of 9 determinations, ** at 95% confidence level

Table 2

Methods robustness

Drug	Amount taken (g)	Parameter varied		
		Volume of H_2SO_4 (RSD%), n = 3	Volume of DY (RSD%), n = 3	Volume of $CHCl_3$ (RSD%), n = 3
CF	0.05	0.95	0.81	1.01
	0.07	1.06	1.55	0.83
	0.10	1.25	1.03	0.70
PCl	0.02	0.79	1.21	1.38
	0.03	1.15	0.95	1.70
	0.04	0.99	1.08	1.19

The proposed methods were tested in order to assess their ***selectivity*** using artificial mixtures prepared from CF or PCl and excipients (in proportion from tablets). The suspensions were titrated using the procedures previously described for tablets. The replicate analysis (n = 6) have yielded the % CF recovery at 100.30 ± 0.84, respectively the % PCl recovery at 99.70 ± 0.34 and thus revealed that the inactive ingredients did not interfere with CF or PCl determination.

Application to pharmaceutical formulations

The methods were used for the assay of CF and PCl from tablets. The accuracy is good, the confidence intervals at 95% confidence level (99.81 ± 0.09 for CF assay and 99.97 ± 0.01 for PCl assay) are comparable to those obtained from assay drugs through pharmacopoeial methods (100.20 ± 0.60% for CL and 99.78 ± 0.40% for PCL (n = 6)). Low RSD% values obtained in each method (0.13% for CF assay and respectively 0.01% for PCl assay) indicate a good precision for the proposed methods.

For routine analysis of drug in pure form or from pharmaceutical formulations, methods based on stoichiometric reactions and suitable for the assay of drugs at milligram level are very important. The proposed methods allow the assay of CF and PCl at milligram level, by comparison with other methods for the determination of studied drugs, applicable only over the microgram or nanogram levels (Table 3).

Table 3

Comparison of the range of proposed method with other methods for the determination of CF and PCl

Drug	Method	Range	Reference
CF	GC (nitrogen-phosphorus detection)	0.1-12.8 ng/ml	3
	Spectrophotometry (Ion-pairs with eosin)	1.25-11.25 ng/ml	4
	Titrimetry	0.02 - 2 mg/ ml	Proposed method
PCl	RP-HPLC (UV detection)	5 -50 ng/ml	9
	Polarography	0.15-15 ng/ml	11
	Titrimetry	0.2 – 0.8 mg / ml	Proposed method

CONCLUSIONS

The proposed methods are simple, sensible, selective and rapid (free from rigid experimental conditions or difficult operations as separation). The chemicals used in the proposed methods are inexpensive and easily available, which are advantages over instrumentals methods. These new methods can be indicated for the routine analyze in quality control laboratories for quantitative determination of drugs both in the pure and formulations, as an alternative to the pharmacopoeial methods.

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