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RESEARCH ARTICLE

Characterization of a mixed-reagent ion-pair complex

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Abstract

A method has been proposed for the determination of drug containing amino group phenylephrine hydrochloride (PHP) in pharmaceutical dosage forms. The method is based on the ion pair reaction of this drug with reagent (egg yellow) in alkaline medium to give intense orange colored product (λmax at 470 nm of PHP) with molar absorptivity values of 1.67×105L.mol-1.cm-1 (r = 0.9995) and 5.60 ×105 L.mol-1.cm-1 (r = 0.9996), limit of detections of 0.0252 mg/L and 0.0236 mg/L and Limit of quantification of 0.0831 mg/L and 0.0708 mg/L respectively with concentration rang of (0.2-6.0) mg/L for drug. The experimental data underwent statistical analysis, which demonstrated the approaches' accuracy and precision. Excipients that are employed in pharmaceutical formulations as additives did not obstruct the suggested methods. Ion pairs are distinct chemical entities, electrically neutral, formed between ions of opposite charge and held together by Coulomb forces, without formation of a covalent bond.

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1. Introduction

The majority of commercial pharmaceutical products containing phenylephrine and marketed by different producers are in a sachet format that is dissolved into a hot drink. Phenylephrine hydrochloride (PHP), [(R)-1-(3-hydroxyphenyl) 2- (methylamino) ethanol hydrochloride], is a white crystalline powder, freely soluble in water, melts at 143°C [1,2] and its chemical structure is: It belongs to a group of drugs named sympathomimetics [3]. It stimulates alpha receptors in certain areas of the body. It is used locally, as decongestant, for non-specific and allergic conjunctivitis, sinusitis, and nasopharyngitis [4]. Phenylephrine nasal drops are used for treating symptoms such as runny nose, sneezing, itching of the nose, and throat [5]. PHP is normally used to increase the blood pressure in unstable patients with hypotension, especially resulting from septic shock [5]. Various methods reported in literature for analysis of phenylephrine hydrochloride. Examples of these methods are conductometric titration [6], voltammetry [7-9], thin-layer chromatography [10], high-performance liquid chromatography (HPLC) [11-14], flow injection [15-17], and fluorescence [18]. Among the different techniques, the most popular and simple method for rapid and trace analysis of drugs is spectrophotometry [19-26].

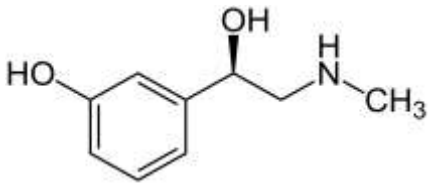

Figure 1: Structure of Phenylphrine hydrochloride

Ion receptors have reached by now an elaborate design, [27–30] yet when coordinating a single ion, the corresponding counter-ion affects both binding strength and selectivity. To also control the binding of the counter-ion, ion-pair (IP)

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receptors, which have cation and anion recognition moieties in the same molecular scaffold, have become the focal point of recent ion sensing studies [31–33]. Ion-pair spectrophotometry refers to analysis methods based on the optical properties of the ion pairs. Infrared, nuclear magnetic resonance and Raman spectrometry are the methods generally used to investigate the structure of the ion pairs and molecular and atomic absorption, fluorimetry and resonance light scattering are used as assay methods. The described spectrophotometric methods are based on interactions of phenylephrine with 1-nitroso-2-naphthol [34], ninhydrin in sulfuric acid [35], p-aminophenol [36], hematoxylin [37], nitrobenzene derivate [38], or alizarin [39, 40]. Recently, several multivariate methods have been applied for the determination of phenylephrine in mixtures with other drugs in pharmaceutical formulations, namely, spectrophotometric [41–44], and spectrofluorometric [45, 46] methods. Flow injection analysis (FIA) with spectrophotometric [47], or chemiluminescence [48] detection, was also used for determination of phenylephrine in pharmaceutical dosage forms. Some of the FIA methods utilized, for example, the condensation reaction of the analyte with 4-aminoantipyrine in the presence of potassium ferricyanide, leading to formation of a product with strong absorptivity at 500 nm [49]. Classical and modern as well, ion-pair–based spectrophotometric methods had a dynamic evolution over the time. On the one hand, this is due to the elucidation of the mechanisms underlying the formation of ion pairs, and thus, the setting of the experimental conditions, which allow the obtaining of ion pairs for all types of substances, is easier; in this regard, com putational chemistry is a very useful tool. On the other hand, the synthesis of new pharma cologically active molecules at very low concentrations requires sensitive analysis methods. Among them, less used spectrophotometric techniques, such as resonance light scattering, have found interesting applications when ion pairing was taken into account.

2. Experimental Apparatus

Spectrophotometric studies were carried out with Spectronic 20D+ (Thermo-Spectronic) visible spectrophotometer. A Mettler balance H 51AR (Ner-Parma instrument Corp. L.C. = 0.01mg) was used for weighing purpose.

2.1 Materials and reagents

All chemicals and reagents used were of analytical grade. Phenypherine was obtained from ZIM laboratories. Egg Yellow, chloroform, ethanol was obtained from LOBA Chemie. Preparation of solutions Stock solutions of phenylpherine was prepared as 0.1M in D.W. whereas 0. 1M Egg Yellow solution was prepared in D.W. The solutions were further diluted as per requirement.

2.2 Mole ratio method

The mole ratio method was applied to study the nature of colored product, this method was conducting by adding fixed volume of drug solution $1*10^{-3}$ M for Phenylpherine, with variable volume of reagents from (0.2-2.0) mL in 10 mL volumetric flask and add PH 8.

2.3 Procedure for calibration curve

A solutions are prepared, containing increasing concentration of drug Phenylpherine (1 ml) of $1*10^{-3}$M with (0.25, 0.5, 1,2,3,4,6,7) of 2.5-70 µg/mL of reagent, and added (1ml of PH8). Then drug is measured spectrophotometrically at maximum wavelength against a blank solution prepared under the similar conditions without drug.

2.4 Application of the proposed method on pharmaceuticals formulation

The solutions of the pharmaceutical formulation were prepared under the conditions. The proposed method of Cloud Point was applied for the determination of phenolic drug in Drop with different concentrations of a solution for each samples under optimal conditions.

3. Results and Discussion

This study provides a new concept in devising of novel analytical methods for the estimating the studied phenolic drug Phenylpherine. This study includes methods used new coupling reaction in visible region using new analytical reagents. The reaction was separated and pre-concentrated from aqueous solution by using cloud point extraction method. The results obtained from the optimum experimental conditions for the physical and chemical experimental parameters obtained for the different of the studied drugs spectrophotometrically and the discussion of these results, then showing the possible application of the suggested methods for the different on research drugs in real samples in various pharmaceutical preparation.

3.1 Study of optimization of cloud point extraction for drugs

The different factors were affected on the absorption intensity of colored cloud point extraction, such as volume of Triton X-114, volume of cationic surfactant, type of electrolyte salt, concentration of salt, equilibration temperature and incubation.

3.2 Effect volume of (10% v/v) Triton X-114

Different volumes of 10% v/v Triton X-114 (0.25-2) mL were used, completed the addition, keeping other conditions constant. It is clear the absorbance was increase with increased the volume of Triton X-114, but suddenly decreased at excess the volume of Triton X-114, probably due to the increase in surfactant-rich phase volume at which the analyte become more diluted resulting in poor sensitivity and thus valueless extraction efficiency. This volume of Triton X-14 fixed in subsequent studies.

3.3 Effect volume of THM

Different volumes of 0.01M THM (0-3) mL were studied, completed the addition, keeping other conditions constant. Cloud point extraction improve the efficiency to separation, therefore improving the enrichment factor and pre-concentration factor. It is clear the absorbance increase with increase the volume of THM but suddenly decrease at increase the volume of THM. The extraction efficiency is low, probably due to the increase in surfactant-rich phase volume at which the analyte become more diluted resulting in poor sensitivity and thus valueless extraction efficiency. This volume of THM fixed in subsequent studies.

3.4 Effect of salt type

It is known that the behavior of some electrolyte salt solutions lie in increasing the extraction percent during Cloud point extraction process due to their act in increasing the dehydration of surfactant-rich phase. Various type of salt such as NaCl, KCl, Na_2SO_4 and CH_3COONa 5% w/v, were studied, completed the addition, keeping other conditions constant. Evident from studied best salt was Na_2SO_4 that gave a higher absorbance of dye and higher efficiency, the Na_2SO_4 fixed in subsequent studies

3.5 Effect of volume of electrolyte salt Na_2SO_4

The different volumes (0-3) mL used from the Na_2SO_4 to find the best volume used to give higher separation and extraction of the phenolic drug, and complete the addition, keeping other conditions constant, the 2 mL volume of Na_2SO_4 was given a higher absorbance that fixed in subsequent studies.

3.6 Effect of equilibration temperature

Different temperature (25-75) ºC was studied. In series of 20 mL volumetric flask prepared the azo dye then transfers 1mL from the azo dye into 15 mL of centrifuge tubes and completes the addition. The absorption when keeping other factor constant, the results showed that the higher absorbance and efficiency of extraction of the drugs at temperature (40,50,60,60) ºC for phenylpherine, it is clear the absorbance increase in this temperature due to formed high number of micelles.

Table 1: Effect of equilibration temperature

Temperature ºC	Abs. phenylpherine λ max 460 nm
25	0.129
30	0.217
35	0.545
40	0.820
50	0.711
60	0.544
75	0.413

The absorbance decrease at higher temperature because the decomposition of the azo dye product that decrease the efficiency of extraction, this temperature is fixed used in subsequent studies. fixed used in subsequent studies.

3.7 Effect of incubation time

Extraction by cloud point requires sufficient time to obtain the equilibrium between the aqueous and the rich phase of the surface effective material by means of greater concentration of the micelles. This period represented the amount of heat accumulated in the solution which allows the Micelles to lose the water molecules to give a hydrophobic mass of small size and high viscosity entrap dye easily. The optimal incubation time was 50 min which give higher absorbance.

Table 2: Effect of incubation time

Incubation Time(min)	Abs.Phenyl phrine λ max 460 nm
10	0.225
20	0.341
30	0.452
40	0.677
50	0.824
60	0.322

After completing the study experimental conditions of cloud point extraction method and obtaining the best analytical data, the results of optimal conditions can be summed up for the drug.

Table 3: Optimal conditions for the cloud point extraction for drugs

Parameter Factor	Value phenylphrine λ max 460 nm
Volume of Triton X-114(mL)	1
Volume of CTAB(mL)	2
Volume of Na_2SO_4 5%(mL)[a]	2
Equilibration Temperature/ ºC	40
Incubation Time / min	50
a:Type of salt 5% Na_2SO_4	

3.8 Accuracy and Precision

The accuracy and precision were studied for the proposed method, under optimum conditions using three different concentrations and measured absorbance at a minimum for five readings per concentration. The accuracy was estimated by determination the relative error, percentage recovery. Precision estimate determination for the percentage relative standard deviation RSD%, Beer's law is obeyed in the concentration rang (0.25-2.5) µg /mL for phenylpherine.

4. Application the proposed method on pharmaceuticals formulation

The application of the proposed method of research for drug phenolic evaluation in pharmaceuticals that contain the functional group of drug. phenylpherine drop, European and

Jordan. The results are good and of high reliability in the analysis of samples in the pharmaceutical preparation.

Table 4: Characteristic parameter for the regression equation of the proposed CPE method

Parameter	Phenylephrine
λ max(nm)	460
color	Reddish yellow
linearity rangeμg/mL	(0.25-2.5)
Molar absorptivity ($L.mol^{-1}.cm^{-1}$) Ɛ	0.437×10^5
Sandell's sensitivity (μg/ cm^2)	0.0048
Correlation coefficient(r)	0.9997
Regression equation	Y=0.207×– 0.044
Slope(b)	0.207
Intercept(a)	-0.044
Analytical sensitivity μg/mL	0.505
Limit of detection μg/mL LOD	0.032
Limit quantification μg/mL LOQ	0.097
Enrichment Factor(EF)	11.43
Pre-concentration factor(PF)	25
Distribution coefficient(D)	265.03
C.L. for the slope($b\pm ts_b$)at 95%	0.207 ±0.010815
C.L. for the intercept($a\pm ts_a$) at 95%	-0.044±0.032515

5. Conclusions

The current study introduced cloud point extraction for the estimation of phenylpherine for the first time. The proposed spectrophotometric method is based on the chromatic intensity of the resulting dye in the determination of different CFD concentrations as well as the proposed spectrophotometric-CPE to estimate the CFD trace concentrations in dye produced by the diazotization-coupling method. This method is a qualitative detection of the CFD at the maximum wavelength of 460nm. This method proved its accuracy and acceptance is by measuring several different concentrations of several replicates and comparing them with the method reported.

References

[1] Council of Europe. European Pharmacopoeia. 3rd ed. Strasbourg: Council of Europe; 1996.

[2] The Stationery Office. British Pharmacopoeia on CD-ROM. 3rd ed. London: System Simulation Ltd., The Stationery Office; 2000.

[3] Goodman A, Rall T, Nier A, Taylor P. The Pharmacology Bases of Therepeutics. New York: McGraw-Hill; 1996.

[4] H.M. Stationary Office. British Pharmacopaeia. London: H.M. Stationary Office; 2001.

[5] Goth A. Medical Pharmacology Principle and Concepts. 10th ed. St. Louis, MO: The Mosby C.V. Company; 1981.

[6] Hasan SH, Othman NS, Surchi KM. Determination of phenylephrineHCl using conductometric titration method. Curr Anal Chem 2016;12:330-4.

[7] Yagmur S, Ture M, Saglikoglu G, Sadikoglu M, Yilmaz S. The quantitative detection of phenylephrine in pharmaceutical preparations and spiked human urine by voltammetry. Russ J Electrochem 2018;54:741-6.

[8] Huang F, Jin G, Liu Y, Kong J. Sensitive determination of phenylephrine and chlorprothixene at poly(4-aminobenzene sulfonic acid) modified glassy carbon electrode. Talanta 2008;74:1435-41.

[9] Pourghobadi Z, Niazi A. Voltametric study and determination of phenylephrine hydrochloride at INP-Nafion-modified CPE sensor employing differential pulse voltammetry. J Pure Appl Chem 2014;30:219-27.

[10] Hegazy MA, Al-Ghobashy MA, Eltanany BM, Khattab FI. Purity indicating TLC method for quantitative determination of phenylephrine and dimethin dine maleate in presence of dimethin dine maleate impurity: 2-ethyl pyridine in nasal gel. J Pharm Res 2016;1:1-6.

[11] Bandelwar R, Nikam A, Sawant S. Analytical method development and validation of phenylephrine hydrochloride, chlorpheniramine maleate, paracetamol and caffeine in bulk drug and tablet dosage form by RP-HPLC. Indo Am J Pharm Res 2013;3:4330-8.

[12] Dewani AP, Dabhade SM, Bakal RL, Gadewar CK, Chandewar AV, Patra AV. Development and validation of a novel RP-HPLC method for simultaneous determination of paracetamol, phenylephrinehydrochloride, caffeine, cetirizine and nimesulide in tablet formulation. Arab J Chem 2015;8:591-8.

[13] Michal D, Petr G. Fast HPLC method using ion-pair and hydrophilic interaction liquid chromatography for determination of phenylephrine in pharmaceutical formulations. J AOAC Int 2010;93:1436-42.

[14] Patel DM, Chaudhary AB, Patel BD. Development and validation of RP-HPLC method for simultanous estimation of beclomethasone dipropionate, phenylephrine hydrochloride and lignocaine hydrochloride in cream. World J Pharm Pharm Sci 2018;7:829-41.

[15] Al-Abachi MQ, Abed SS. Flow injection-spectrophotometric determination of phenylephrine hydrochloride and amoxicillin trihydrate in pharmaceutical preparations. J Al-Nahrain Univ 2013;16:42-52.

[16] Rocha JR, Galhardo CX, Natividade MA, Masini JC. Spectrophotometric determination of phenylephrine hydrochloride in pharmaceuticals by flow injection analysis exploiting the reaction with potassium ferricyanide and 4-aminoantipyrine. J AOAC Int 2002;85:875-8.

[17] Mestre YF, Zamora YF, Lahuerta L, Martínez CJ. Determination of phenylephrine hydrochloride by flow injection analysis with chemiluminescence detection. J AOAC Int 2001;84:13-8.

[18] Salem YA, Hammouda ME, Abu El-Enin MA, El-Ashry SM. Application of derivative emission fluorescence spectroscopy for determination of ibuprofen and phenylephrine simultaneously in tablets and biological fluids. Spectrochim Acta A Mol Biomol Spectrosc 2019;210:387-97.

[19] Fawzy MA, Ekram AE, Essam MH, Mohamed FK, Hamdy MA. Spectrophotometric analysis of two eye preparations, vial and drops, containing ketorolac tromethamine and phenylephrine hydrochloride binary mixture and their ternary mixture with chlorphenirmaine maleate. Bull Fac Pharm Cairo Univ 2018;56:91-100

[20] Al-Sabha TN. Spectrophotometric assay of phenylephrine hydrochlorideSci 2017;9:1.

[21] Ahmed IS, Amin AS. Spectrophotometric microdetermination of phenylephrine hydrochloride in pure and in pharmaceutical formulations using haematoxylin. J Mol Liq 2007;130:84-7.

[22] l-Abachi MQ, Abed SS. Spectrophotometric determination of phenylephrine hydrochloride and salbutamol sulphate drugs in pharmaceutical preparations using diazotized metoclopramide hydrochloride. Baghdad Sci J 2015;12:167-77.

[23] Savić I, Nikolić G, Banković V. Development and validation of spectrophotometric method for phenylephrine estimation in nasal drops formulations. J Chem Chem Eng 2008;27:149-56.

[24] Othman NS, Fatah NT. Indirect spectrophotometric determination of phenylephrine hydrochloride in pharmaceutical preparations. Tikrit J Pure Sci 2011;16:74-82.

[25] Habibur R. Utilization of eosin dye as an ion pairing agent for determination of pharmaceuticals: A brief review. Int J Pharm Pharm.

[26] Sharma DK, Jasvir S, Pushap R. Spectrophotometric determination of propranolo hydrochloride and metopranol tartrate in pharmaceutical dosage forms, spiked water and biological fluids. Int J Pharm Pharm Sci 2018;10:107.

[27] J.-M. Lehn, Supramolecular Chemistry: Concepts and Perspectives, VCH, Weinheim, **1995**.

[28] Supramolecular Chemistry, Vol 1: Molecular Recognition, Receptors for Cationic Guests (Ed.: G. W. Gokel), Pergamon, Oxford, **1996**.

[29] A. Arduini, A. Casnati, A. Pochini, R. Ungaro, Curr. Opin. Chem. Biol. **1997**, 1, 467–474.

[30] P. D. Beer, P. A. Gale, Angew. Chem. Int. Ed. **2001**, 40, 486–516; Angew. Chem. **2001**, 113, 502–532.

[31] M. J. Langton, C. J. Serpell, P. D. Beer, Angew. Chem. Int. Ed. **2016**, 55, 1974–1987; Angew. Chem. **2016**, 128, 2012–2026.
[32] M. G. M. Antonisse, D. N. Reinhoudt, *Chem. Commun*. **1998**, 443–448.
[33] G. J. Kirkovits, J. A. Shriver, P. A. Gale, J. L. Sessler, J. Inclusion Phenom. Macrocyclic Chem. **2001**, 41, 69–75. Bhansali, K.G. (1979) Indian J. Pharm. Sci. 41, 247–251
[34] Muszalska, I., Zajac, M., Wrobel, G., & Nogowska, M. (2000) Acta Pol. Pharm. 57, 247–252
[35] Abbas, M.N., & Mostafa, G.A.E. (2001) Egypt. J. Chem. 44, 141–149
[36] Ahmed, I.S., & Amina, A.S. (2007) J. Mol. Liq. 130, 84–87
[37] El-Mossalamy, E.H. (2004) Spectrochim. Acta A 60, 1161–1167
[38] Shama, S.A. (2002) J. Pharm. Biomed. Anal. 30, 1385–1392
[39] Pavun, L., Malešev, D., & Veselinovi f , D. (2007) J. Serb. Chem. Soc. 72, 799–807
[40] Erk, N. (2000) J. Pharm. Biomed. Anal. 23, 1023–1031
[41] Collado, M.S., Mantovani, V.E., Goicoechea, H.C., & Olivieri, A.C. (2000) Talanta 52, 909–920
[42] Kazemipour, M., & Ansari, M. (2005) Iran. J. Pharm. Res. 4, 147–153
[43] Yao, B., Yi, J., Miao, K., & Lv, Q. (2005) Zhongguo Linchuang Yaoxue Zazhi 14, 384–385
[44] Nepote, A.J., & Olivieri, A.C. (2001) Anal. Chim. Acta 439, 87–94
[45] Arancibia, J.A., Nepote, A.J., Escandar, G.M., & Olivieri, A.C. (2000) Anal. Chim. Acta 419, 159–168
[46] Knochen, M., & Giglio, J. (2004) Talanta 64, 1226–1232
[47] Mestre, Y.F., Zamora, L.L., & Calatayud, J.M. (2001) J. AOAC Int. 84, 13–18
[48] Rocha, J.R., Galhardo, C.X., & Natividade, M.A. (2002) J. AOAC Int. 85, 875–878
[49] Beyene, N.W., & Van Staden, J.F. (2004) Talanta 63, 599–604.

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