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Original Scientific Article

Spectrophotometric Determination of Isoxsuprine Hydrochloride as Base Form in Pharmaceutical Formulation through Charge Transfer Complexation

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Abstract. Two simple and selective spectrophotometric methods are described for the determination of isoxsuprine hydrochloride (ISX·HCl) as base form in bulk drug and in injections and tablets. The methods are based on the molecular charge-transfer complexation of ISX base (ISX) with either *p*-chloranilic acid (PCA) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The intense colored radical anions formed on dissociation, are quantitated at 520 nm (PCA method) or 600 nm (DDQ method). The optimum assay conditions were optimized. Beer's law is obeyed in the concentration ranges 5.28×10^{-5} to 42.2×10^{-5} mol dm^{-3} in PCA method and 0.79×10^{-5} to 10.6×10^{-5} mol dm^{-3} in DDQ method, with respective molar absorptivity values of 1.32×10^{3} and 6.55×10^{3} dm^{3} mol^{-1} cm^{-1}. The reaction stoichiometry in both methods was evaluated by either Job's method or limiting logarithmic method and was found to be 1:1 (ISX: PCA, ISX: DDQ). Developed methods were validated according to ICH guidelines and found to be accurate and precise.

Keywords: isoxsuprine hydrochloride, *p*-chloranilic acid, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, spectrophotometry, injection, tablets

INTRODUCTION

Isoxsuprine hydrochloride (ISX) is chemically known as 4-hydroxy-α-[1-[(1-methyl-2-phenoxyethyl) amino] ethyl] benzenemethanol hydrochloride (Figure 1). The main pharmacodynamic effects of ISX are induced by three mechanisms of action:[1] a) stimulation of β-adrenergic receptors, largely predominant in the myometrium, connected with the inhibitory relaxation responses of the smooth muscle fibres; b) inhibition of α-adrenergic receptors prevalent in some arteries, connected with excitatory and vasoconstrictive responses; and c) direct, papaverine-like spasmolysis of smooth muscles and the myometrium. The US pharmacopoeia[2] recommends UV spectrophotometric measurement of aqueous solution of ISX at 300 nm, while the British pharmacopoeia[3] recommends potentiometric titration using 0.1 M NaOH as titrant.

Different techniques are available for the determination of ISX in both pharmaceuticals and biological matrices, and include UV spectrophotometry,[4,5] ion selective electrode-potentiometry,[6] chemiluminescence spectrometry,[7] high performance liquid chromatography (HPLC),[8–10] gas chromatography (GC)[11], GC-MS,[12] LC-MS,[13] affinity chromatography,[14] polarography,[15] and fluorimetry.[16]

The presence of multi functional groups in ISX, *viz.* phenol, secondary amine and hydroxyl have resulted in a number of color formation reactions for its spectrophotometric determination utilizing different reagents. The comprehensive review on the spectrophotometric methods reported until 2010 for the determination of ISX HCl or ISX was reported.[17] Non-selectivity, multi-step reactions and strict pH control are some of the major disadvantages of the existing visible spectrophotometric methods. The spectrophotometry continues to be most preferred technique for the assay of different classes of drugs in pure form, pharmaceutical formulations and body fluids, because of its simplicity, reasonable selectivity, accuracy and precision and cost-effectiveness. Hence, a modest attempt has been made to develop spectrophotometric methods which would overcome some of the problems faced in most existing methods.

Acetonitrile is the choice of the solvent in many charge transfer reaction.[18–22] Acetonitrile is produced as a coincidental byproduct in the manufacture of acrylonitrile, which is used in the production of plastics and resins. A recent downturn in plastic production has resulted in severe shortages and escalating costs for

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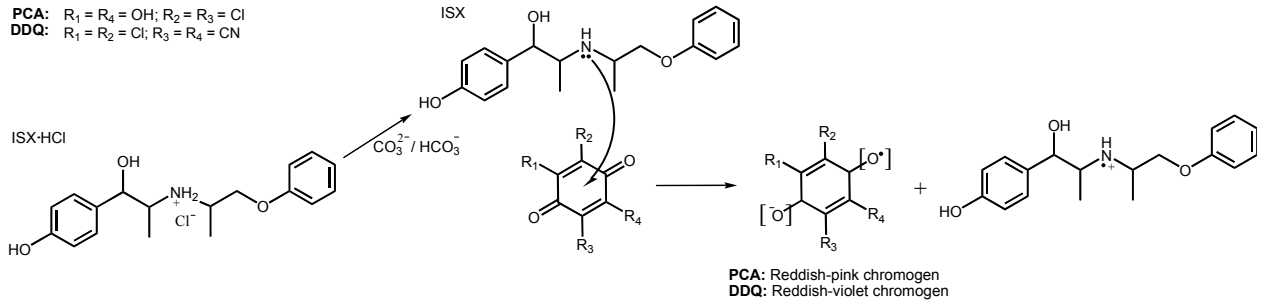


Figure 1. Probable reaction scheme.

acetonitrile.[23] Hence, we exploited the similar chemical properties of 1,4-dioxane for charge transfer reaction with DDQ instead of acetonitrile. DDQ in 1,4-dioxane was found to be stable for 4 days. The concentration of DDQ used in charge transfer reaction[18–22] is 4.4×10^{-3} or 8.8×10^{-3} mol dm^{-3} in acetonitrile which is monetarily quite costly, where as, we found that a 2.2×10^{-3} mol dm^{-3} DDQ in 1,4 dioxane was sufficient. Further, DDQ charge transfer complex in acetonitrile absorbs maximally between 458–588 nm as reported,[18–22] but the same reaction in 1,4-dioxane exhibited a bathochromic shift towards 600 nm, leading to improve sensitivity and selectivity.

EXPERIMENTAL

A Systronics model 106 digital spectrophotometer provided with 1 cm matched quartz cells was used for absorbance measurements. All chemicals were of analytical reagent grade of make from Merck or Loba Chemie, Mumbai, India, and distilled water was used to prepare the solutions.

A 4.8×10^{-3} mol dm^{-3} PCA and 2.2×10^{-3} mol dm^{-3} DDQ solutions were prepared separately in 1,4-dioxane. Carbonate-bicarbonate buffer of pH = 9.48 ± 0.01 was prepared by dissolving 1.325 g of Na_2CO_3 and 1.050 g of $NaHCO_3$ in water and made up to the mark with same solvent in a 25 cm^3 standard flask. 20 mg of pure ISX·HCl (99.85 % purity, Juggat Pharma, India) was dissolved in 10 cm^3 water in a 125 cm^3 separating funnel, 5 cm^3 of carbonate-bicarbonate buffer of pH = 9.48 ± 0.01 was added followed by 20 cm^3 of ethylacetate. The content was shaken for 15 minutes. The lower aqueous layer was discarded and the upper organic layer was collected in a beaker containing anhydrous sodium sulphate. The water-free organic layer was transferred into a dried beaker and the solvent evaporated on a hot water bath. The residue was dissolved in acetone, transferred to a 100 cm^3 calibrated flask and diluted to volume with the same solvent. The resulting solution was diluted to get ISX concentrations of 5.3×10^{-4} mol dm^{-3} and 1.3×10^{-4} mol dm^{-3} for PCA method and DDQ method, respectively.

Procedures

PCA Method

Different aliquots of a standard ISX solution (0.5–4.0 cm^3, 5.3×10^{-4} mol dm^{-3}) were transferred into a series of 5 cm3 calibrated flasks using micro burette and the total volume was adjusted to 4.0 cm^3 with acetone. To each flask was added 1 cm^3 of 4.8×10^{-3} mol dm^{-3} PCA solution. The absorbance of the resulting redish-pink chromogen was measured against the reagent blank at 520 nm.

DDQ Method

Into a series of 5 cm^3 calibrated flasks, 0.3–4.0 cm^3 of 1.3×10^{-4} mol dm^{-3} of standard ISX solution were added using micro burette and the total volume was made up to 4.0 cm^3 with acetone. To each flask was added 1 cm^3 of 2.2×10^{-3} mol dm^{-3} DDQ solution. The absorbance of the resulting redish-violet product was measured against the reagent blank at 600 nm.

In either case, the calibration graph was obtained for the absorbance *vs*. concentration of ISX and the concentration of the unknown was read from the calibration or computed from the regression equation.

Formulations

Twenty tablets (Tidilan, Juggat Pharma, Bangalore-560074, India) were weighed accurately and ground into a fine powder. A portion of the powder equivalent to 20 mg of ISX was accurately weighed and transfer into 125 cm^3 separating funnel. The procedure extraction of ISX from the formulations was followed as done for pure ISX. The contents of ten injection tubes each containing 2 cm^3 of inject able product (5 mg ISX·HCl cm^3) were pooled in a dry beaker. An aliquot equivalent to 20 mg of ISX·HCl was accurately measured into a separating funnel, and the steps described for tablets were followed.

Procedures for Method Validation

Three different concentrations of ISX were analyzed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision) to study the method accuracy and precision. Selectivity was evaluated by both placebo blank analysis and re-

covery studies. A placebo blank, the commonly employed tablet excipients, consisting of 20 mg sodium alginate, 30 mg magnesium stearate, 20 mg lactose, 20 mg acacia, 50 mg talc and 30 mg starch, but without ISX was prepared as described in paragraph above. Following the similar extraction procedure, synthetic mixture was prepared by adding 10 mg of ISX·HCl to 50 mg of placebo blank.

RESULTS AND DISCUSSION

PCA and DDQ are π acceptors. They form n-π type complex with n-electron donors. This is an intermediate molecular association complex which dissociates in to corresponding radical anions depending upon the polarity of the solvent used.

The basis of the proposed methods is the transfer of n-electrons from secondary amine of ISX to π acceptor such as *p*-chloranilic acid (PCA method) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ method) resulting in the formation of CT complexes which dissociate to form intensely colored radical anion. The transfer of non-bonding electrons is restricted in hydrochloride salt of isoxsuprine, *i.e.* ISX. HCl, hence hydrochloride was neutralized with buffer of pH = 9.48 ± 0.01 and ISX was extracted into ethyl acetate before assay. The effort to skip extraction step by neutralizing HCl using methanolic KOH and NaOH prior to charge complex formation failed, because the methanolic KOH or NaOH gave yellow color product with both PCA and DDQ. Therefore, sample pretreatment by extraction of ISX into immiscible organic solvent is an inevitable step.

Instead of acetonitrile, solvents such as acetone, methanol and chloroform were unsuitable because DDQ itself was found to be unstable in these solvents. PCA exists in unionized form in 1,4-dioxane.[24] Further, owing to low dielectric constant, 1,4-dioxane, does not compete or shield the charge-transfer process from donor to acceptor which is necessary for instant and stable color formation at room temperature (about 25 °C).[25] The solution of PCA in 1,4-dioxane stored in an amber-glass bottle was found to be stable for at least 6 weeks.[25] Due to the structural similarity between PCA and DDQ, similar properties of PCA in 1,4-dioxane was observed in DDQ in 1,4-dioxane.

The reddish-pink chromogen of PCA radical anion exhibits absorption maximum at 520 nm (Figure 2b) with negligible blank absorption (Figure 2a). The charge transfer complex between DDQ and ISX shows two absorption maxima at 440 nm and 600 nm (Figure 2d), with negligible blank absorption at either wavelength (Figure 2c). Some authors[18,21,22] have considered analytical wavelength between 458–467 nm. When the same chromogen was measured against reagent blank, it exhibited absorption maximum at 600 nm (Figure 2e). Therefore, all absorbance measurements were made at 600 nm in DDQ method.

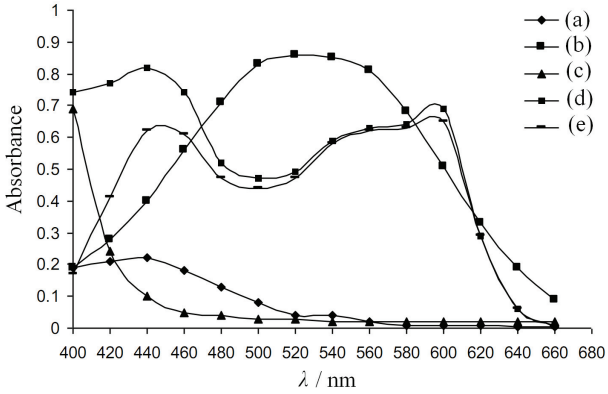


Figure 2. Absorption spectra of: (a) blank *vs*. acetone – PCA method; (b) sample *vs*. acetone (ISX = 1.85×10^{-4} mol dm^{-3}) – PCA method; (c) blank *vs*. acetone; DDQ method; (d) sample *vs*. acetone (ISX = 9.24×10^{-5} mol dm^{-3}) – DDQ method; (e) sample *vs*. reagent blank (ISX = 9.24×10^{-5} mol dm^{-3}) – DDQ method.

The study of the effect of different solvents was restricted since the solubility of ISX is limited to acetone, ethanol, methanol, DMF and DMSO. Acetone was found to be an ideal solvent as it afforded maximum sensitivity in both the methods. Effect of varying volumes of 9.5×10^{-3} mol dm^{-3} PCA and 4.4×10^{-3} mol dm^{-3} DDQ was studied on a fixed concentration of ISX. It was found that 0.5 cm^3 each of 9.5×10^{-3} mol dm^{-3} PCA and 4.4×10^{-3} mol dm^{-3} DDQ was sufficient to yield maximum sensitivity. Therefore, 1.0 cm^3 each of 4.8×10^{-3} mol dm^{-3} PCA and 2.2×10^{-3} mol dm^{-3} DDQ were used in actual procedure.

Reaction Stoichiometry

Job's method of continous variations of equimolar solutions was employed to establish the stoichiometry of the PCA method. The solutions of ISX and PCA equivalent to 1.66×10^{-3} mol dm^{-3} were prepared in acetone and 1,4-dioxane, respectively. The solutions were mixed in various proportions; the volume was completed to the mark with both acetone and 1,4-dioxane keeping the volume ratio of the two solvents as 1:1 in each flask. The resulting graph (Figure 3) shows that the interaction occurs on an equimolar basis (1:1 reaction stoichiometry), owing to the presence of one basic nitrogen containing group. The Job's continuous variations technique failed in DDQ method. Therefore, the stoichiometry of the reaction was studied adopting the limiting logarithmic method.[26] Two straight lines were obtained upon using increasing concentrations of DDQ while keeping the concentration of ISX constant (Figure 4a) and upon using increasing concentrations of ISX while keeping the concentration of the DDQ constant (Figure 4b). The

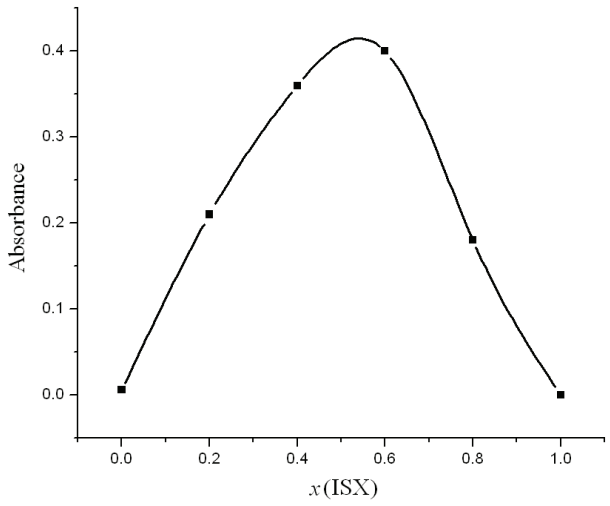


Figure 3. Job's continous variation plot, PCA method.

slopes of the two lines are 1.20 and 1.17. This means that the reaction proceeds in a molar ratio of 1.20:1.17 *i.e.* in a ratio of ≈ 1:1. Hence, based on 1:1 (ISX:PCA, ISX:DDQ) reaction stoichiometry, a probable reaction scheme has been proposed (Figure 1).

METHOD VALIDATION

Analytical Data

The linear regression equations were obtained by the method of least squares and the Beer's law range, molar absorptivity, correlation coefficient, variance, confidence limits for slope and intercept for both methods are summarized in Table 1.

The detection limit (LOD) and quantification limit (LOQ) were calculated by using the following equations:[27]

$$\mathrm{LOD} = \frac{3.3S}{R}, \qquad \mathrm{LOQ} = \frac{10S}{R}$$

Table 1. Regression and analytical parameters

Parameter	PCA method	DDQ method
λ_{max} / nm	520	600
Beer's law limits / (10^{-5} mol dm^{-3})	5.28–42.2	0.79– 10.6
Molar absorptivity / (10^3 dm^3 mol^{-1} cm^{-1})	1.32	6.55
Limit of detection / (10^{-6} mol dm^{-3})	4.20	0.38
Limit of quantification / (10^{-5} mol dm^{-3})	1.27	0.11
Regression equation;[(a)] intercept, a slope, b	 –0.0085 0.0138	 –0.0086 0.0687
Correlation coefficient, R	0.9994	0.9993
Standard deviation of intercept, S_a	0.0067	0.0095
$\pm tS_a / \sqrt{n}$ [(b)]	0.0066	0.0088
Standard deviation of slope, S_b	6.0×10^{-5}	2.9×10^{-4}
$\pm tS_b / \sqrt{n}$ [(c)]	5.8×10^{-5}	2.7×10^{-4}

[(a)] $y = a + bx$, where y is the absorbance and x is concentration in mol dm^{-3}.
[(b)] Confidence limit for intercept.
[(c)] Confidence limit for slope.

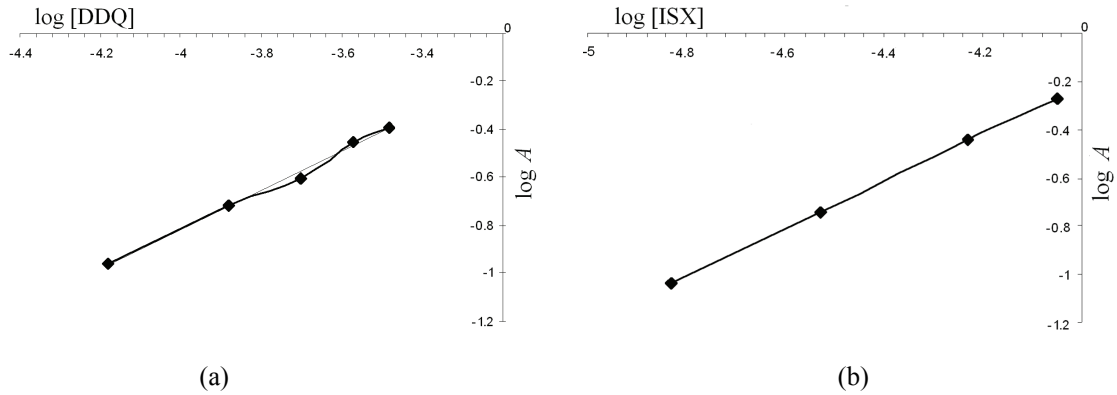
where S is the standard deviation of seven replicate determinations under the same conditions as for the sample in the absence of the analyte and R is the slope of the calibration graph.

Precision and Accuracy

The results obtained for the evaluation of precision and accuracy of the method is compiled in Table 2.

Selectivity

Upon analysis of placebo blank solution as shown under "*Formulations*", the resulting absorbance readings for



(a) (b)

Figure 4. (a) Limiting logarithmic plots for the molar reactivity of DDQ with ISX: logarithm of absorbance *vs*. log [DDQ] at which [ISX] is kept constant; (b). logarithm absorbance *vs*. log [ISX] at which [DDQ] is kept constant.

Table 2. Precision and accuracy

Method	ISX taken / (10^{-5} mol dm^{-3})	Intra-day (n = 7)		Inter-day (n = 5)	
		RSD / %	RE / %	RSD / %	RE / %
PCA	15.83	1.59	1.10	1.26	0.69
	26.40	0.89	1.85	1.11	1.51
	36.96	1.75	1.59	2.00	1.59
DDQ	3.96	2.05	2.78	1.33	4.04
	6.60	0.85	1.97	2.02	4.09
	9.24	1.60	1.08	1.76	0.65

both the methods were same as reagent blank, inferring no interference from the placebo. Non interference from placebo was further confirmed by carrying out recovery study from synthetic mixture prepared by adding 10 mg of ISX to 50 mg of the placebo blank. The percent recoveries of ISX were 100.93 ± 0.63 and 102.56 ± 0.26 for PCA method and DDQ method, respectively. Hence confirms the selectivity of methods in the presence of the commonly employed tablet excipients.

Application to Analysis of Formulations

The proposed methods were successfully applied to the determination of ISX in tablets and injections (Table 3). The results obtained were statistically compared with those of the official method[2] by applying the Students t-test for accuracy and F-test for precision. The official method consisted of extraction of ISX from the matrices into aqueous solution and absorbance measured at 300 nm. As can be seen from the Table 3, the calculated *t*- and *F*-value at 95 % confidence level did not exceed the tabulated values of 2.78 and 6.39, respectively, for four degrees of freedom. The results indicated that there is no difference between the proposed methods and the official method with respect to accuracy and precision. Accuracy of the proposed methods was further confirmed by standard-addition procedure. Pre-analyzed tablet powder (Tidilan 40 mg) and injection (Tidilan 5 mg cm^{-3}) was spiked with pure ISX at three different concentration levels (50, 100, and 150 % of the quantity present in the formulation) and the total was found by the proposed methods. The result of the recovery study is shown in Table 4.

Table 3. Results of assay of formulations and statistical evaluation

Tablets/ injections	Found[(a)] (percent of label claim ±SD)		
	Reference method	PCA method	DDQ method
Tidilan Tablet (100 mg)	100.7 ±0.78	99.85 ± 0.54 t = 2.03 F = 2.09	99.20 ± 1.56 t = 2.02 F = 4.00
Tidilan Injection (5 mg)	102.4 ± 0.63	101.7 ± 1.61 t = 0.99 F = 6.53	103.1 ± 1.41 t = 1.08 F = 5.01

[(a)] Mean value of 5 determinations ±SD; tabulated *t*- and *F*-value at 95 % confidence level are 2.78 and 6.39 respectively.

CONCLUSION

Formation of n-π complex between n-electron donor ISX and π-acceptor PCA or DDQ is highly selective. Beside simple steps in sample pretreatment, the methods are accurate, precise, reproducible and applicable over wide linear dynamic ranges. Among the two methods, DDQ method is more sensitive with LOD = 0.38 × 10^{-6} mol dm^{-3} whereas PCA method have LOD of 4.20 × 10^{-6} mol dm^{-3}. For the first time the charge transfer reaction with DDQ in 1,4-dioxane was used instead of commonly employed acetonitrile. Lower amount of DDQ for charge transfer complexation than normally used 4.4 × 10^{-3} to 8.8 × 10^{-3} mol dm^{-3} in other solvents, and its high stability in 1,4-dioxane are two major advantages. Both the methods are rapid taking less than one minute for analysis, excluding ten minutes for sample preparation. The advantageous over the existing visible spectrophotometry is that the proposed methods are free from rigid experimental conditions like strict pH control or boiling steps.

Table 4. Results of recovery study by standard addition method

Formulation studied	PCA method			DDQ method		
	ISX in tablet / (10^{-5} mol dm^{-3})	Pure ISX added / (10^{-5} mol dm^{-3})	Pure ISX recovered / %[(a)]	ISX intablet / (10^{-5} mol dm^{-3})	Pure ISX added / (10^{-5} mol dm^{-3})	Pure ISX recovered / %[(a)]
Tidilan Tablet	9.55	5.280	104.7 ± 0.01	1.37	1.32	102.3±2.10
	9.55	10.56	99.91 ± 0.23	1.37	2.64	98.48 ± 0.22
	9.55	18.48	95.77 ± 1.20	1.37	3.96	95.20 ± 1.35
Tidilan Injection	13.92	10.56	102.4 ± 0.12	3.08	2.64	101.4 ± 0.58
	13.92	15.84	99.4 ± 0.21	3.08	3.96	103.1 ± 0.51
	13.92	21.12	101.5 ± 0.36	3.08	5.28	100.8 ± 0.22

[(a)] Mean value ±SD; n = 3

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SAŽETAK

Spektrofotometrijsko određivanje baznog oblika izoksuprin hidroklorida pomoću kompleksa prijenosa naboja kod farmaceutskog oblikovanja

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U ovom radu opisane su dvije jednostavne i selektivne metode za određivanje baznog oblika izoksuprin hidroklorida (ISX·HCl) u sirovom lijeku u injekcijama i tabletama. Metode se baziraju na kompleksu prijenosa naboja između ISX baze (ISX) s *p*-kloranilnom kiselinom (PCA) ili 2,3-dikloro-5,6-dicijano-1,4-benzokinonom (DDQ). Intenzivno obojeni anioni radikala nastali disocijacijom, određeni su kavantitativno na 520 (PCA metoda) ili 600 nm (DDQ metoda). Lambert Beerov zakon vrijedi za područje koncentracija od 5.28×10^{-5} do 42.2×10^{-5} mol dm^{-3} kod PCA metode, te od 0.79×10^{-5} do 10.6×10^{-5} mol dm^{-3} kod DDQ metode uz vrijednosti molarne apsorptivnosti od 1.32×10^3 odnosno 6.55×10^3 dm^3 mol^{-1} cm^{-1}. Stehiometrija reakcije 1:1 (ISX: PCA, ISX: DDQ) kod obiju metoda određena je Jobovom ili graničnom logaritamskom metodom. Točnost i preciznost metoda okarakterizirana je prema ICH mjerilima.