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Spectrophotometric Assay of some Nitrogen Containing Drugs in Pharmaceutical Formulations using p-Chloranilic Acid Reagent

Mahmood A. Hasan, Huda A. Ibrahim and Theia'a N. Al-Sabha

Department of Chemistry, Faculty of Science, University of Duhok, Iraq
Mahasan54@gmail.com
Department of Chemistry, Faculty of Science, University of Duhok, Iraq
Huda.mh81@yahoo.com
Department of Chemistry, College of Education, University of Mosul, Iraq
dr_theiaa@yahoo.co.uk

Abstract

A spectrophotometric method is developed for the determination of some drugs containing amino groups (sulfacetamide sodium, lidocaine and terbutaline sulfate) based on their reaction with *p*-chloranilic acid reagent in an organic medium forming colored charge transfer complexes. The complexes have maximum absorptions at 530 and 527 nm for sulfacetamide sodium and lidocaine respectively, but terbutaline sulfate gave two maximum absorptions at 529 and 319 nm. Beers law is obeyed over the concentration range of 10-60 µg.ml^{-1} for sulfacetamide sodium and lidocaine and 5-70 µg.ml^{-1} for terbutaline sulfate. The molar absorptivity values are 0.940×10^3, 0.913×10^3 L.mol^{-1}.cm^{-1} for sulfacetamide sodium and lidocaine respectively while terbutaline sulfate gave 0.987×10^3 L.mol^{-1}.cm^{-1} at 529 nm and 7.407×10^3 L.mol^{-1}.cm^{-1} at 319 nm with accuracy range between 100.20% and 101.42% and RSD better than 3.15% for all drugs. The method is applied successfully for determination of these drugs in pharmaceutical formulations and compared favorably with British Pharmacopeia standard methods. F and t tests are less than the tabulated values at 95% confidence level.

Keywords

Spectrophotometry; *p*-Chloranilic acid; Sulfacetamide sodium; Lidocaine; Terbutaline sulfate.

Academic Discipline And Sub-Disciplines

Analytical chemistry, Drugs, Charge transfer complexes, pharmaceutical formulations

SUBJECT CLASSIFICATION

Chemistry, Analytical chemistry

TYPE (METHOD/APPROACH)

Spectrophotometric determination of some drugs

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Introduction

Sulfa drugs are among the first pharmaceutical agents used in veterinary practice. These drugs are widely used in the treatment of infections, especially for patients intolerant to other antibiotics [1,2] Sulfacetamide (I) is active against Gram positive bacteria, Gram negative bacteria, Chlamydia and Mode of resistance [3].

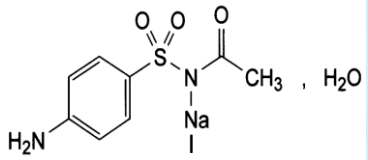
Terbutaline sulfate (II) is widely used as a prophylactic drug as well as to prevent acute exacerbations of asthma, chronic bronchitis, emphysema and other lung diseases. It relaxes muscles and opens air passage in the lungs, making them easier to breathe [4,5]. It is a short-acting bronchorelaxant which can be given orally [6]. It is readily metabolized in the gut wall and liver when given orally. It has a short duration of action [7].

Lidocaine (III) is a common local anesthetic [8] and antiarrhythmic drug used to treat burning and pain from skin inflammations. Lidocaine patches are used to relieve the pain of post-herpetic neuralgia (the burning, stabbing pains or aches that may last for months or years after a shingles infection) [9].

Viscous lidocaine is used to relieve pain and discomfort from a sore throat/mouth. It is also used to numb the lining of the mouth and throat before certain medical/dental procedures (e.g., dental impressions) [10].

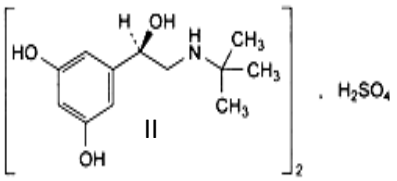
Different analytical techniques have been described for determination of sulfacetamide sodium, lidocaine and terbutaline sulfate, such as HPLC [11-13], voltammetry [14-16], GC [17,18] and Spectrofluorimetry [19]. These methods are often time-consuming, expensive, and cumbersome. Spectrophotometry continues to be very popular, because of its simplicity, versatility and low cost. Several spectrophotometric methods using different reagents have been reported for determination of sulfacetamide sodium, lidocaine and terbutaline sulfate. Diazotization coupling method using 8-hydroxyquinoline [20], iminodibenzyl [21], Phloroglucinol [22] and 3-Aminophenol [23] as coupling agents for determination of sulfacetamide. 4-Aminoantipyrine in the presence of potassium ferricyanaide [24], Fe (III) in the presence of potassium ferricyanide [25] and sodium periodate in the presence of acetylacetone [26] are used for determination of terbutaline sulfate. Phenol red or chlorophenol red [27], Bromocresol purple [28] and Sodium nitroprusside in the presence of hydroxylamine [29] are used for determination of lidocaine.

The present method is based on the charge transfer complex formation reaction of above drugs as n-donors with *p*-chloranilic acid as π-acceptor without any derivatization or catalysis.



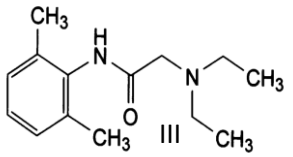
Sulfacetamide sodium

M.Wt=254.24 g.mol^{-1}



Terbutaline sulfate

M.Wt= 548.7 g.mol^{-1}



Lidocaine

M.Wt= 548.7 g.mol^{-1}

Experimental

Apparatus

All spectral absorption measurements are made on a Jenway 6800 U.V- visible double beam and 6305 U.V- visible single beam spectrophotometers, with 1-cm matched quartz cuvettes. Heating of solutions is carried out on a water bath (SWBD) product by Bio Cote Company. Weighing is carried out on a sensitive balance type of DENVER balance Tp-214 with four digitals.

Reagents

All chemicals used are of analytical or pharmaceutical grade.

p-Chloranilic acid (p-CA) reagent (Fluka)(1×10^{-3}M) Solution: It is prepared by dissolving 0.0209 g of 2,5-dichloro-3,6-dihydroxy-1,4-p-benzoquinone (*p*-CA) in absolute ethanol (99.9%) in 100 ml volumetric flask. The solution is prepared daily and used immediately.

Standard solutions of pure forms drugs (250µg.ml^{-1})**(SDI, Sammara-Iraq)**

A 0.025g of sulfacetamide sodium and lidocaine are dissolved separately in ethanol and terbutaline sulfate dissolved in 10ml methanol. The volumes were completed to 100ml with absolute ethanol. These solutions are prepared daily and used immediately.

Sulfacetamide sodium eye drops (100 mg/ml)/ (Amman pharmaceutical industries, Jordan)

A volume of 0.5 ml of 100 mg.ml^{-1} sulfacetamide is diluted by absolute ethanol to 50 ml in a volumetric flask and filtrated through Whattman filter paper no.4 containing anhydrous sodium sulfate to remove the water content, then 12.5ml portion from the filtrate is diluted to 50ml by absolute ethanol, and this gave a solution containing 250 µg.ml^{-1} sulfacetamide sodium.

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Lidocaine gel (2% w/w)/ (Sina-Darou Tehran-Iran)

An amount equivalent to 5.0 g of lidocaine hydrochloride gel is weighed accurately and dissolved in 5ml of 36 % hydrochloric acid and heated in water bath for 10min to increase the solubility, then allowed to cool and transferred to a 250 ml separating funnel. 20 ml distilled water was added followed by addition of 5M sodium hydroxide until the solution became alkaline [12], then extraction with three portions of 10ml chloroform is performed. The chloroform extracts filtered through 2g anhydrous sodium sulphate and the filtrate is completed to 100ml by absolute ethanol; a solution containing 1000µg.ml-1 lidocaine has been obtained. From this solution 12.5ml was taken and diluted to 50ml by absolute ethanol, the final concentration was 250µg.ml^{-1}lidocaine.

Terbutaline sulfate tablets (5mg)/ (Mediotic Labs, Homs – Syria)

An accurately weighed portion of the powder equivalent to 0.025g terbutaline sulfate is dissolved in 20 ml methanol, heating with stirrer to increase the solubility, filtered into 50ml volumetric flask completed to the volume with absolute ethanol (the solution was equivalent to 500 µg.ml^{-1} terbutaline sulfate). From this solution a 250µg.ml^{-1} terbutaline sulfate solution was prepared

General procedure

An increased volumes of 250µg.ml^{-1} working solutions of sulfacetamide sodium, lidocaine and terbutaline sulfate were transferred to a series of 5 ml volumetric flasks to cover the concentration range 10 – 60 µg.ml^{-1} for sulfacetamide sodium and lidocaine and 5 – 70 µg.ml^{-1} for terbutaline sulfate solutions, followed by the addition of 1.4, 1.6, and 0.8 ml of 1×10^{-3}M of *p*-CA respectively, diluted to the mark with absolute ethanol and the absorbance was measured at 530 and 527nm for sulfacetamide sodium and lidocaine respectively and terbutaline sulfate was measured at 529 and 319 nm against their respective blank after 5 min at room temperature.

Results and Discussion

Absorption spectra

The spectrum of *p*-CA, as π-acceptor, in absolute ethanol exhibits an absorption band at 460 nm. The addition of sulfacetamide sodium, lidocaine or terbutaline sulfate, as n-donors, to this solution cause an immediate shift with new characteristic bands at 530 nm for sulfacetamide, 527 nm for lidocaine where as terbutaline shows two absorption bands at 529 and 319 nm when measured against their respective blank (Fig.1). These bands may be attributed to the formation of *p*-CA radical anions and the band at 319 nm may be attributed to the interaction of *p*-CA with the hydroxyl group present in terbutaline forming n-π charge transfer complex.

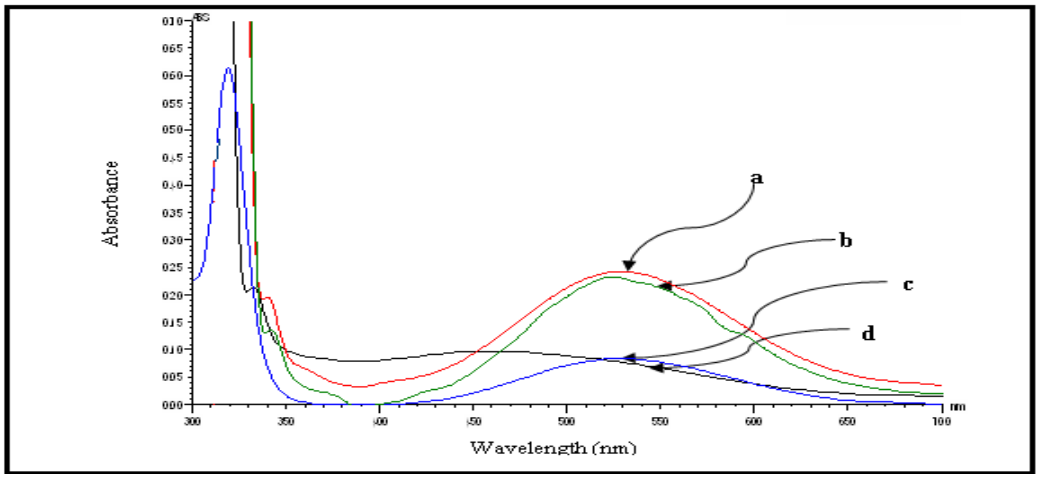

Fig. 1: Absorption spectra of a) 50 µg.ml^{-1} sulfacetamide sodium versus blank, b) 50 µg.ml^{-1} lidocaine versus blank, c) 60 µg.ml^{-1}terbutaline sulfate versus blank and d) reagent blank versus ethanol.

Optimization of conditions

Effect of solvent

It was observed that p-CA react with water (electron-rich agent) to form charge-transfer complex giving a violet colored product according to the following mechanism, scheme (1) [30]:

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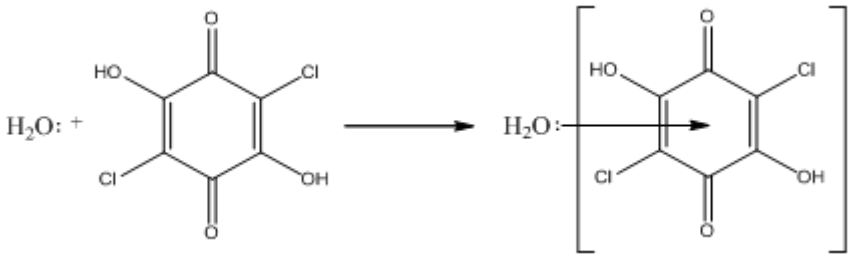

Scheme 1: Reaction of water with *p*-CA

Therefore water was canceled in all the subsequent experiments in this work. Different organic solvents like methanol, ethanol, acetone, acetonitrile, propanol and butanol are examined. It was observed that using absolute ethanol, as solvent for both *p*-CA and drugs and also for dilution, gave maximum absorbance intensity at respective λ_{max}. Therefore; this solvent was used in all subsequent experiments.

Effect of temperature and developing time

The effect of temperature on the rate of reaction between *p*-CA and drugs is studied by mixing of 1 ml of each sulfacetamide sodium, lidocaine and terbutaline sulfate respectively and separately with 1 ml of 1×10^{-3} M *p*-CA in 5 ml volumetric flasks. The results indicate that complexes are formed after addition of reagent immediately at room temperature (25°C). The complexes remain constant for more than 24 hr. However, 5 minutes as developing time is recommended in subsequent experiments.

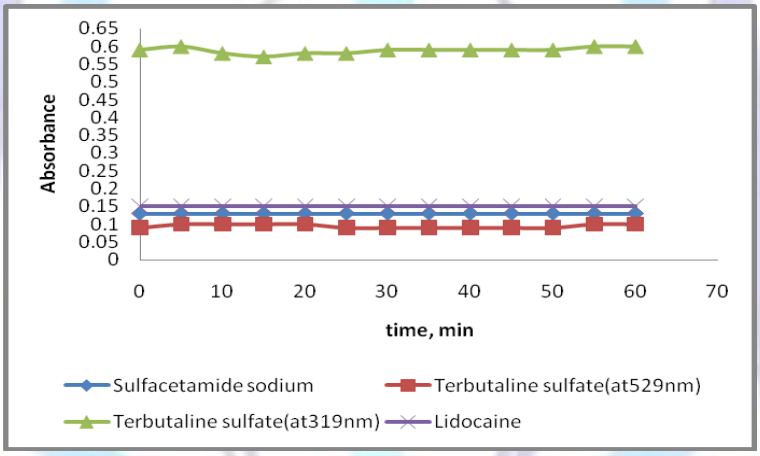

Fig.2: Effect of time on the absorbance of drug-p-CA complexes

Effect of p-CA reagent concentration

The effects of changing the volume of 1×10^{-3} M *p*-CA is studied over the range of 0.0-2.0 ml in a solution containing 50 µg.ml^{-1} sulfacetamide sodium, terbutaline sulfate and lidocaine. The results, as shown in Fig. 3, reveal the fact that 1.4, 0.8 and 1.6 ml of *p*-CA respectively is required to achieve the maximum intensity of the color in final dilution with ethanol.

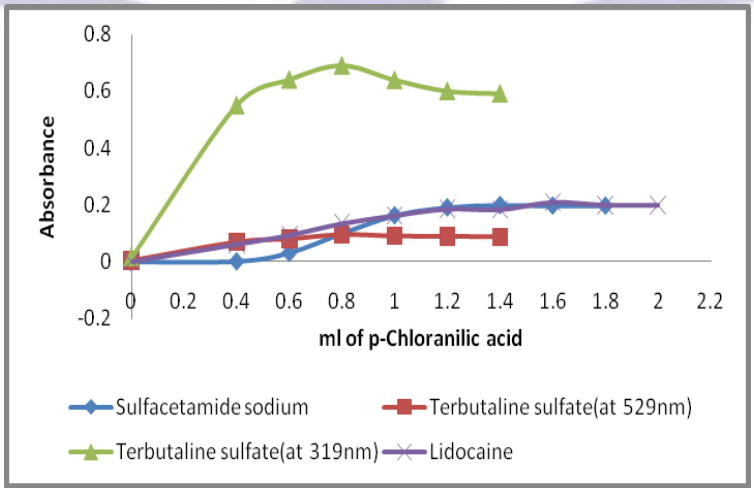

Fig.3: Effect of *p*-CA reagent on the absorbance of drug complexes

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Effect of surfactants

The effect of various surfactants including SDS, CTAB, Tween-80 and Triton x-100, of 0.1% concentration, on the absorption intensity of the *p*-CA-drugs complexes are investigated. Tween-80 has no effect on the absorbance, other surfactants have negative effects.

However; the optimum conditions for the reaction of *p*-CA with the intended drugs are summarized in Table (1).

Table (1): Optimum reaction conditions for the determination of drugs

Compound	λ_{max} (nm)	Temp.	*p*-CA 1×10^{-3}M (ml)	Development time (min.)	Stability period (min.)	Final pH
Sulfacetamide sodium	530	R.T*	1.4	5	60	3.65
Lidocaine	527	R.T	1.6	5	60	4.02
Terbutaline sulfate	529 319	R.T	0.8	5	60	2.68

*R.T = Room temperature (25 ºC)

Quantitation

In order to investigate the range in which the colored complexes adhere to Beer's law, the absorbance of the complexes were measured at their corresponding λ_{max} value after developing the color by following the general procedure for individual calibrations for a series of solutions containing increasing amounts of each drug (Figure 4). The Beer's law limits, molar absorptivity and Sandell's sensitivity values were evaluated and given in Table 2. The linearity was represented by the regression equation and the corresponding correlation coefficient for the studied determined drugs by the proposed method represents excellent linearity. The relative standard deviation (RSD) and accuracy (average recovery %) for the analysis of four replicates of each three different concentrations for each drug indicated that the method is precise and accurate. Limit of detection (LOD) and limit of quantitation (LOQ) are in the accepted range below the lower limit of Beer's law range (Table 3).

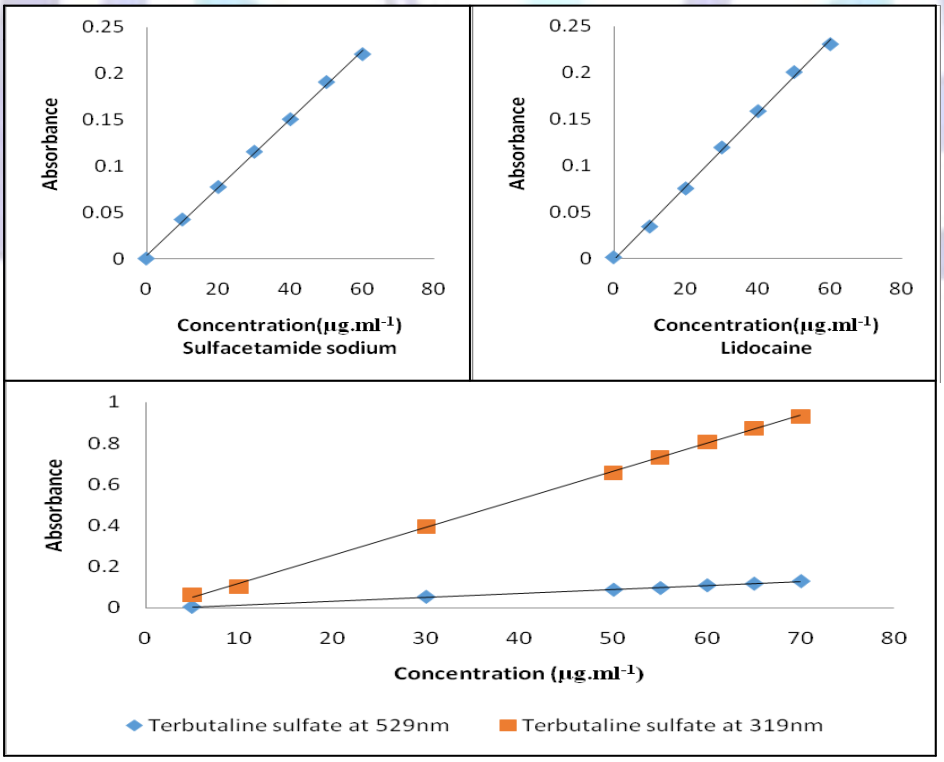

Table (2) Characteristics parameters for complexes of the studied drugs

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Parameter	Sulfacetamide sodium	Lidocaine	Terbutaline sulfate at 529 nm	Terbutaline sulfate at 319 nm
Linearity range ($\mu g.ml^{-1}$)	10 – 60	10 - 60	5 - 70	5 - 70
Molar absorptivity ($L.mol^{-1}.cm^{-1}$)	940.7	913.8	987.7	7407.5
Sandell's Sensitivity ($\mu g.cm^{-2}$)	0.27	0.25	0.55	0.07
LOD ($\mu g.ml^{-1}$)	0.97	1.35	1.89	1.03
LOQ ($\mu g.ml^{-1}$)	2.96	4.11	5.73	3.14
Average recovery* (%)	101.25	101.42	100.34	100.20
RSD*	≤3.11	≤3.44	≤3.51	≤0.69
Slope	0.0037	0.0039	0,0018	0.0135
Intercept	0.0042	0.0004	0.0005	0.0101
Correlation coefficient	0.9989	0.9982	0.9985	0.9992

* Average of four determinations.

Selectivity

In order to evaluate the selectivity of the proposed method for the analysis of pharmaceutical formulations, the effect of the presence of common excipients was tested for possible interference in the assay by placebo and synthetic mixture analyses.

Three different placebo contents, as described in Table 3, were prepared by mixing amounts of pure sulfacetamide sodium, terbutaline sulfate and lidocaine separately with different amounts of starch, acacia, lactose, methylpraben (MHB) and ethylparben (BHB). Mixed together and dissolved in 30 ml absolute ethanol (except for terbutaline sulfate dissolved in 20 ml methanol). The contents are shaken well for 20 min and filtered through filter paper and the filtrate is completed to 50 ml ethanol absolute in a volumetric flask. An amount equivalent to 50 $\mu g.ml^{-1}$ of each drug is measured under the optimum conditions by following the recommended procedure.

The analysis of synthetic mixture solution prepared as described earlier yielded percent recoveries which ranged between 95.34 and 101.58 for three different placebo (Table 4). The results of this study showed that the inactive ingredients did not interfere in the assay indicating the high selectivity of the proposed method.

Table (3): Placebo contents of exciepients

Placebo no.	Content (mg)				
	starch	acacia	lactose	methylpraben	ethylparben
1	10	15	10	10	10
2	15	20	15	15	20
3	5	10	5	20	15

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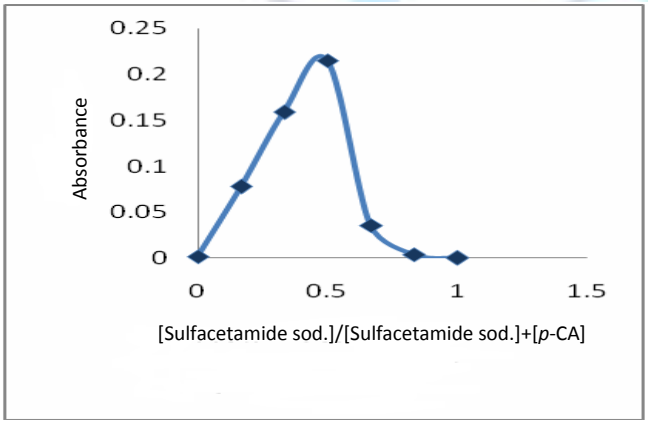
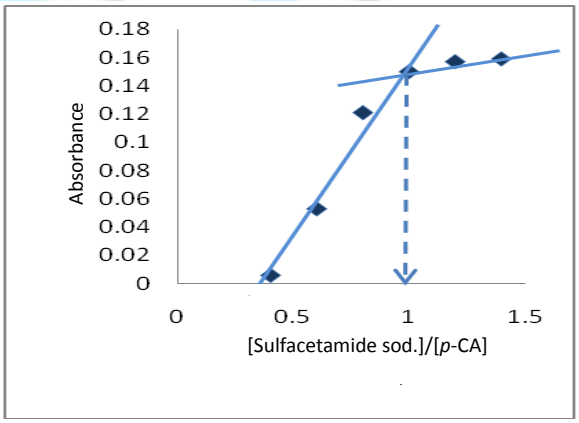
Table (4): Effect of exciepients on the determination of 50µg.ml^{-1}of drugs.

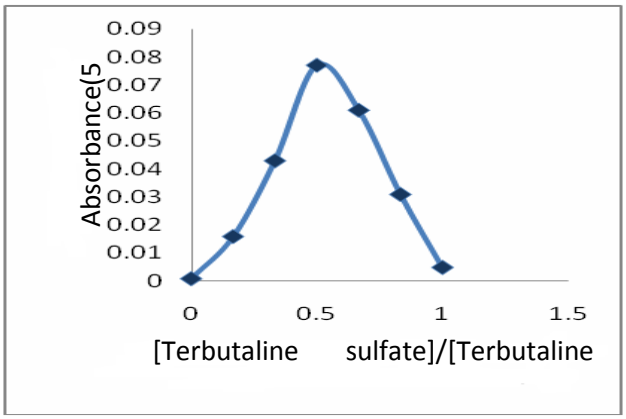
No. of placebo	Recovery%			
	Sulfacetamide sodium	Terbutaline sulfate		Lidocaine
		at 529nm	At 319nm	
1	101.5791	98.6111	99.2908	96.1966
2	99.1872	100.2541	100.8511	95.3419
3	100.1953	100.4717	95.3192	96.1966

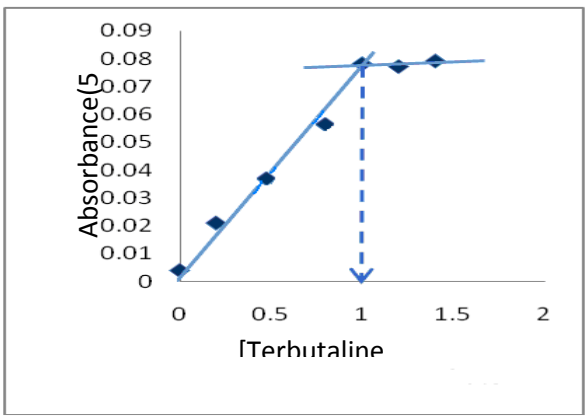
Composition and stability constant (K_{st}) of the complexes

The compositions of all charge transfer complexes are found to be 1:1 by both Job's and mole ratio methods. The results are shown in the Figures (5).









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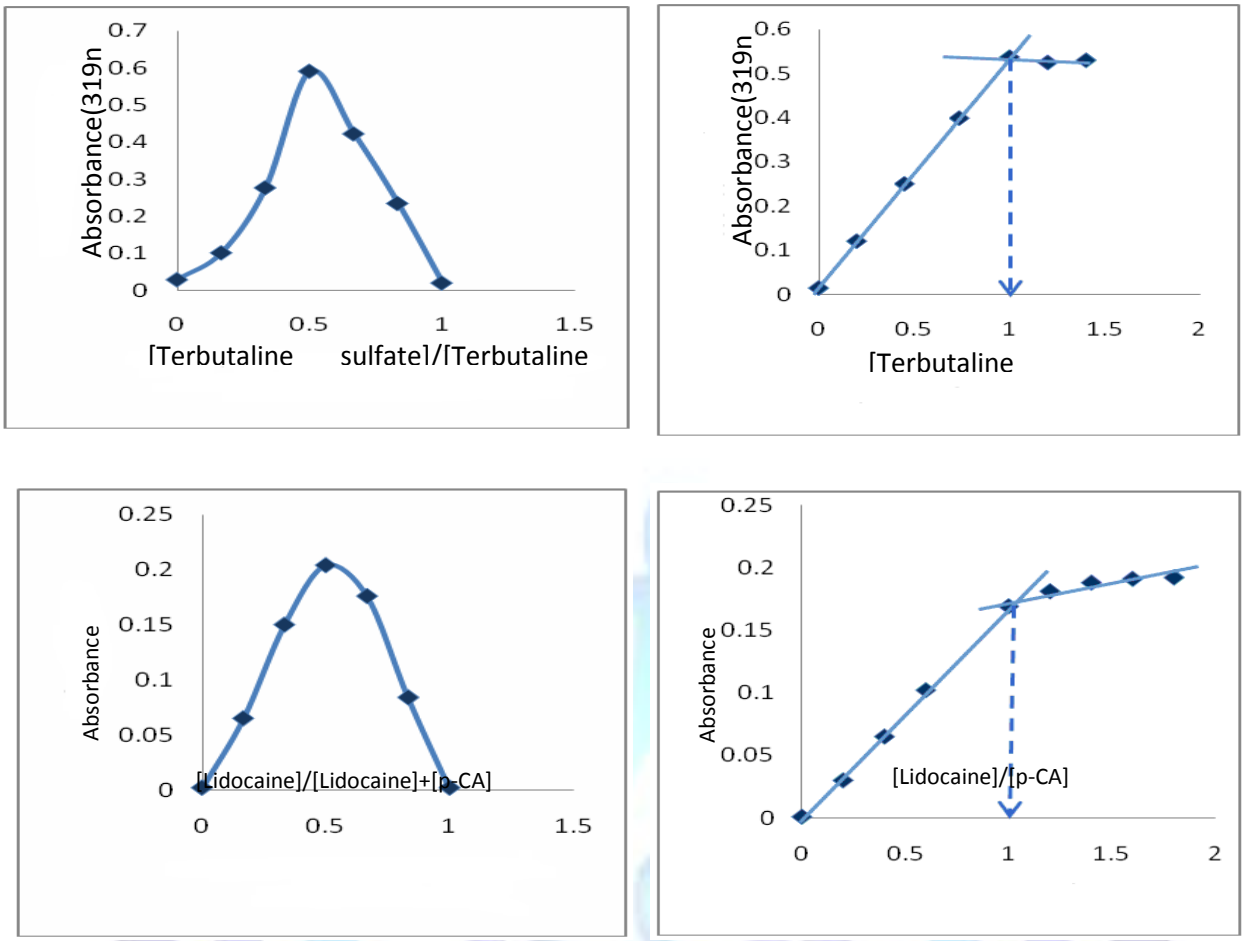

Fig. 5: Continuous variation and mole ratio plots of drug–*p*-CA complexes

The average stability constant (K_{st}) in ($L.Mol^{-1}$) for three different concentrations of each drug is 4.3×10^6 for sulfacetamide sodium, 3.2×10^6 for lidocaine, 2.1×10^6 for terbutaline sulfate at 529 nm and 4.8×10^5 for terbutaline sulfate at 319 nm indicating the high stability of complexes.

Reaction mechanism

The interaction of the studied drugs with *p-CA* in organic solvent, was a charge-transfer complexation reaction between the present amino group in the drugs as n-donor and *p-CA* as π-acceptor, followed by the formation of a radical anion. Complete electron transfer from the donor to the acceptor moiety took place with the formation of intensely colored radical ions (scheme 2)

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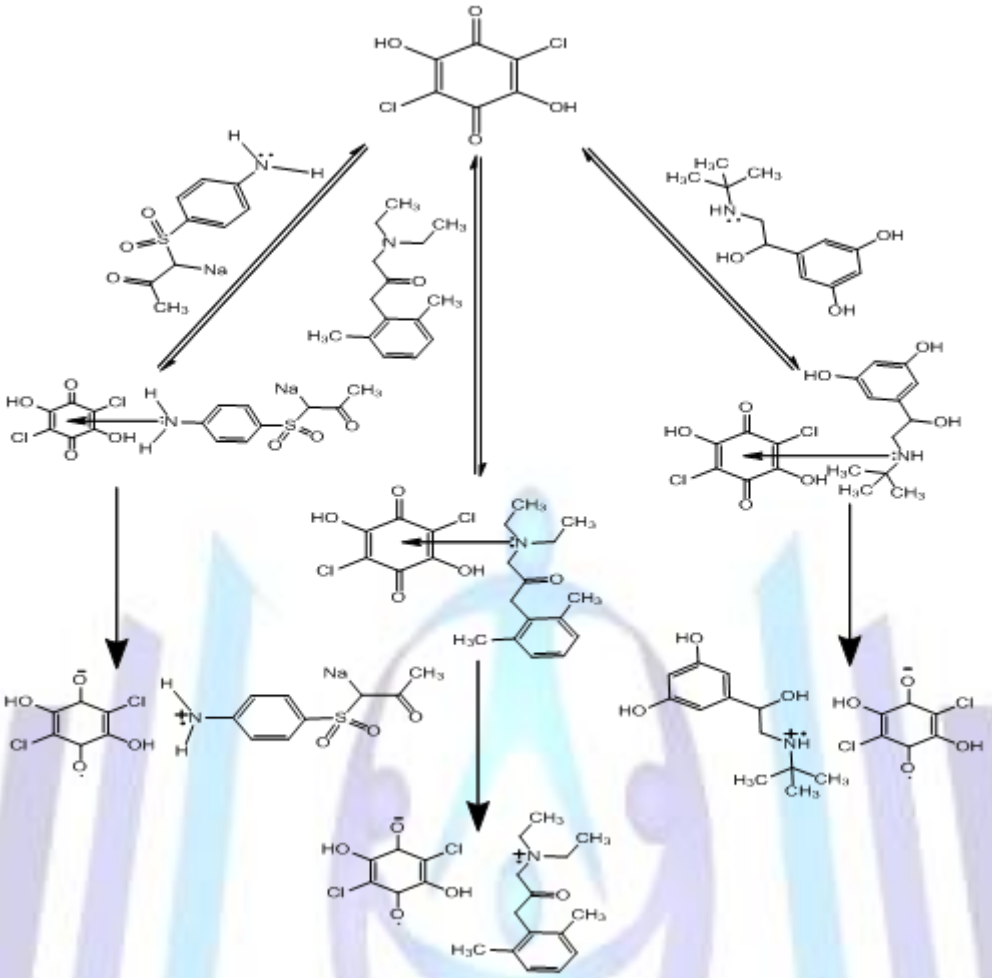

Scheme 2: Proposed mechanisms of charge transfer complex formation reaction for assay of the drugs by *p*-CA.

Application of the developed method on the pharmaceutical formulations

The proposed method was applied for estimation of the studied drugs in pharmaceutical formulations, three concentrations for each drug was used. The obtained average recovery% ranges between 95.05 and 97.99 indicates that the method is accurate and the RSD% is ≤ 4.75 indicate the method is precise, (Table 5). The method was compared with the British Pharmacopeia [31] procedures, which are depended upon the potentiometric titration. The obtained results were compared statistically by a Student's *t*-test for accuracy and a variance ratio *F*-test for precision at the 95% confidence level with six degrees of freedom, as cited in Table 5. The results showed that the experimental *t*-test and *F*-test were less than the theoretical value (*t*=2.45, *F*=6.39), indicating that there was no significant difference between the proposed method and official method.

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Table (5): Results of Assay of Assay of drug in pharmaceutical preparations using the proposed method.

Pharmaceutical preparation	Certified Value	Amount present ($\mu g.ml^{-1}$)	Drug content found*	Recovery* (%)	Average recovery (%)	RSD%
Sulfacetamide sodium eye drop	100mg.ml^{-1}	10	9.270	92.703	95.25	1.49
		30	28.392	94.64		0.88
		50	49.200	98.405		0.52
Terbutaline sulfate tablet (at 529 nm)	5mg	20	20.556	102.778	96.22	4.75
		40	37.5	93.75		2.73
		60	55.278	92.13		1.84
Terbutaline sulfate tablet (at 319 nm)	5mg	20	20.03	100.13	95.05	0.19
		40	36.026	90.065		0.27
		60	56.97	94.951		0.32
Lidocaine gel	2%	10	9.4	93.974	97.99	4.14
		30	30.17	100.556		1.28
		50	49.72	99.436		1.82

* Average of four determinations

Table (6): Comparison of the proposed method with official method:

Drug determined	Pharmaceutical formulation	Recovery(%) *		$t_{exp.}$	$F_{exp.}$
		Present method	Standard method		
Sulfacetamide sodium	Apisulfa-10 Sterile Eye Drops	95.249	99.44	1.806	1.677
Terbutaline sulfate at 529nm	Asmanol tablets	96.219	99.5	0.81	4.476
Terbutaline sulfate at 319nm	Asmanol tablets	95.049	99.5	1.6	4.07
Lidocaine	xylogel	97.986	94.3	1.67	2.57

* Average for six determinations

Conclusion

The proposed spectrophotometric method has been developed for the determination of microgram amounts of 10-60 $\mu g.ml^{-1}$ for each of sulfacetamide sodium and lidocaine and 5-70 $\mu g.ml^{-1}$ for terbutaline sulfate with a good accuracy and precision. The statistical analyses show that the data from the proposed method are in a good agreement with those of the official method. The method does not require stringent conditions nor any specific reagent or buffer solution and the color is stable more than 24 hours. The proposed method has been applied successfully for the assay of the pharmaceutical formulations of sulfacetamide sodium

(eye drops), terbutaline sulfate (tablets) and lidocaine (gel).

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