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Extractive Spectrophotometric Method for the Determination of Some Antipsychotic Drugs Using Eriochrome Black T

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ABSTRACT

Simple, accurate, precise, and rapid extractive spectrophotometric method was developed for the determination of four antipsychotics drugs, namely sulpiride (SUP), olanzapine (OLP), clozapine (CLP) and aripiprazole (ARP) both in tablets and in biological fluids. The method was based on the formation of red colored ion-pair complex between the studied drugs and eriochrome black T (EBT) with absorption maxima at 514 nm. The stoichiometry of the complexes in either case was found to be 1: 1 and the conditional stability constant (K_f) of the complexes have been calculated. Reaction conditions were optimized to obtain the maximum color intensity. Beer's law was obeyed in the concentration ranges of 4-30, 4-20, 2-18 and 4-26 µg/ml with SUP, OLP, CLP and ARP, respectively. Various analytical parameters have been evaluated and the results have been validated by satistical data. The proposed method was successfully applied to the analysis of commercial tablets containing the drugs and the results were in good agreement with those obtained with reported methods. The proposed method was further applied to the determination of the studied drugs in spiked human serum and urine. A proposal for the reaction pathway was postulated.

INTRODUCTION

Sulpiride (SUP), olanzapine (OLP), clozapine (CLP) and aripiprazole (ARP) are structurally related a typical antipsychotics. They are used in the treatment of schizophrenia and other psychotic syndromes. It is reported that they are effective in the treatment of both positive and negative symptoms of schizophrenia, and that they are less likely to produce extra pyramidal side effects when compared with classical antipsychotics. The advantages of the therapeutic profile of the four drugs have led to increasing use of them in treatment of schizophrenic patients (Li, 2002 and Li, 1996). However, high doses of these atypical antipsychotics are suspected to pose an increased risk for extra pyramidal side effects or other side effects (Li, 2002; Davis *et al.*, 1999; Raggi 2002; Yoshimura *et al.*, 2001; Gerlach, 2002). Sulpiride (SUP), 5-(Aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl) methyl]-2-methoxy-benzamide, (Fig. 1a). A review of the literature revealed that several analytical methods have been described for the determination of sulpiride in pharmaceuticals or biological fluids, including spectrophotometric (El Walily *et al.*, 1999; Attia *et al.*, 2003; Radwan, 2003; Zayed, 2005), fluorimetric (Buna *et al.*, 1996), chromatographic (Naguib and Abdelkawy, 2010; Chiba *et al.*, 2011; Huang *et al.*, 2001; Kirchherr *et al.*, 2006), electrophoretic (Xu and Stewart , 2000; Liu *et al.*, 2002; Li *et al.*, 2006), voltammetric (Farghaly, 2000) and chemiluminometric (Aly *et al.*, 2001); however, the methods proposed for the analysis of biological fluids suffer the inconvenience of time-consuming procedures and expensive instrumentation. Olanzapine (OLP), 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine (Fig. 1b). In the literature, there are only a few methods described for the determination of olanzapine in pharmaceutical formulations and include non-aqueous titrimetry and UV-spectrophotometry (Firdous *et al.*, 2005), visible spectrophotometry (Upadhyay *et al.*, 2013; Rajendraprasad and Basavaiah, 2010; Mohamed, 2008) and flow injection spectrophotometry (Jasinska and Nalewajko, 2004). A few methods have also been reported using HPLC (Reddy *et al.*, 2007; Shen *et al.*, 2002). Clozapine (CLP), (8-chloro-11-(4-methyl-piperazin-1-yl)-5H-dibenzo[b,e][1,4]-diazepine; (Fig. 1c) is an atypical antipsychotic drug. Different methods for the analysis of clozapine have been reviewed.

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These methods include high performance liquid chromatography (Mosier *et al.,* 2003; Liu *et al.,* 2001; Hariharan *et al.,* 1996), liquid chromatography (Vardakou *et al.,* 2010; Zhou and Li, 2004), gas chromatography (Jin *et al.,* 2000), capillary zone electrophoresis (Mashhadizadeh MH, Afshar, 2013; Arvand *et al.,* 2012) and linear scan voltammetry (Mohamed and Al-Ghannam, 2004; Sastry *et al.,* 1998). Few photometric (Gfeller GC and Frey, 1978; Liang *et al.,* 2012) and fluorimetric (Bhanotu *et al.,* 2012) methods have been reported for the analysis of clozapine.

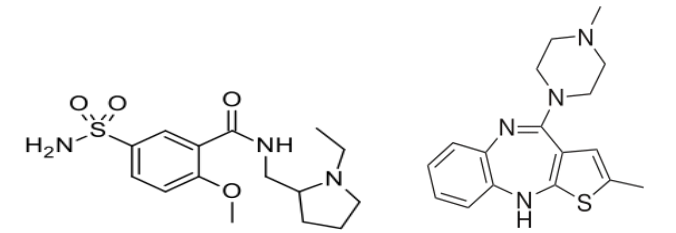

Fig. 1: Chemical structure of the studied drugs.

Aripiprazole (ARP), chemically 7-[4-[4-(2, 3-dichlorophenyl) piperazin -1- yl] butoxy] - 3, 4-dihydro-1H-quinolin-2-one (Fig. 1d). A survey of pertinent literature revealed that few analytical methods reported for determination of aripiprazole in pharmaceutical dosage forms and biological samples include chromatographic (Thakkar *et al.,* 2011; Akamine *et al.,* 2010; Lancelin *et al.,* 2008; Patel *et al.,* 2014; Ravinder *et al.,* 2012) and spectrophotometric (Helmy *et al.,* 2012; Sandeep *et al.,* 2013) methods. Most of the reported methods (except spectrophotometric methods) are either not appropriately sensitive or tedious and utilized expensive instruments that are not available in most quality control laboratories and the procedures are not simple to perform. Therefore the aim of the present work is to develop a simple, accurate, sensitive and low-cost spectrophotometric method for the quantification of four antipsychotic drugs, namely sulpiride, olanzapine, clozapine and aripiprazole. The proposed method is based on the ability of the studied drugs to form ion-pair complex with EBT.

MATERIALS AND METHODS

Apparatus

All the absorbance spectral measurements were made using spectroscan 80 D double-beam UV/Visible spectrophotometer (Biotech Engineering Ltd. (UK), with wavelength range 190 nm ~ 1100 nm, spectral bandwidth 2.0 nm, with 10 mm matched quartz cells.

Reagents and Solutions

All of the chemicals used were of analytical or pharmaceutical grade and used without further purification. Double distilled de-ionized water was used to prepare all solutions.

i. A 5×10^{-3} M of eriochrome black T (EBT) was prepared by dissolving the accurate weighed amount of 230.68 mg in 100 ml water.
ii. Series of buffer solutions of KCl-HCl (pH 1.0-2.2), NaOAc-HCl (1.99-4.92) and NaOAc-AcOH (3.4-5.6) pH were prepared by standard methods.
iii. Pharmaceutical grade of SUP, OLP, CLP and ARP certified to be 99.85% pure was obtained as gift were kindly supplied from Egyptian International Pharmaceutical Industries Company (EIPICo), Egypt. Stock solutions of pure SUP, OLP, CLP and ARP were prepared separately by dissolving accurately weighed 10 mg of each drug in 1.0 ml of concentrated sulphuric acid and finally the volume was made up to 100 ml with distilled water (100 µg/ml).

General Recommended Procedures

Procedure for Calibration Curve

Into a series of separated funnels, accurately measured aliquots of SUP, OLP, CLP and ARP, in the concentration range shown in (Table 1) were pitted out. A volume of 2.0 ml of 5×10^{-3} M EBT were added. Then, 1.0 ml of KCl-HCl buffer solution (pH 2.0 for SUP and ARP) while NaOAc-HCl of (pH 4.6 for OLZ and CLP) were added and the volume was completed to 10 ml with distilled water.

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 20 min of extraction at 514 nm against reagent blank prepared in the same manner except addition of drugs.

Procedure for Tablets

At least ten tablets of the drugs were weight into a small dish, powdered and mixed well. A portion equivalent to 10 mg of SUP, OLP, CLP and ARP were weight and dissolved in distilled water with 1.0 ml of concentrated sulphuric acid, filtered into a 100 ml calibrated flask and diluted to volume with water. Solutions of working range concentration were prepared by proper dilution of this stock solution with water and followed the above procedure for calibration curve.

Procedure for Human Serum and Urine

Human serum samples were thawed at room temperature and mixed well. A 4.0 ml aliquot of serum was added and mixed briefly with 4.0 ml of acetonitrile. After centrifugation at approximately 3000 rpm for 3.0 min, filtration then dilution into 100 ml in calibrated flask was done. Aliquots of 5.0 ml of each serum sample spiked with different concentrations levels of drugs,

0.5 ml of 1.0 M sodium hydroxide, was added and mixed briefly, samples were extracted by addition of 10 ml of dichloromethane followed by rotation for approximately 2.0 min. After centrifugation at approximately 3000 rpm for 10 min, the organic layer was quantitatively transferred to a separating funnel, then proceeds as described for calibration curve.

Human urine samples were thawed at room temperature and mixed well, centrifugation at approximately 3000 rpm for 3 min followed by filtration process. A 5.0 ml aliquot of each sample was placed into a screw cap culture tube then spiked with different concentrations levels of drugs, the medium turned to alkaline with 0.5 ml of 1.0 M sodium hydroxide. Samples were extracted by addition of 10 ml of dichloromethane followed by rotation for approximately 2.0 min. After centrifugation at approximately 3000 rpm for 10 min; the organic layer was quantitatively transferred to a separating funnel, then proceeds as described for calibration curve.

RESULTS AND DISCUSSION

Absorption Spectra

The studied drugs have amino groups which are protonated in acidic medium and form with eriochrome black T (EBT) ion-pair complexes, forming a red chromophore. The ion-pair complexes were quantitatively extracted with dichloromethane.

The absorption spectra were shown in (Fig. 2) which revealed that the ion-pair complexes absorbed maximally at 514 nm. Several parameters such as pH and buffer type, reagent volume, sequence of addition and effect of extracting solvent were optimized to achieve high sensitivity, stability, low blank reading and reproducible results. The optimum conditions were established by varying one variable and observing its effect on the absorbance of the colored product.

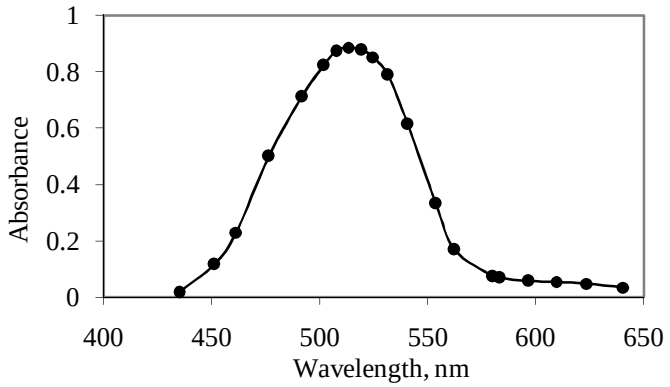

Fig. 2: Absorption spectra of OLP–EBT ion-pair complex (concentration of OLP was 16 µg/ml).

Effect of Buffer Type and pH

It was observed that the effective extraction of the complex depends on the type of buffer used and its pH. The effect of pH was studied by extracting the colored complexes in the presence of various buffers such as KCl–HCl (pH 1.0-2.2), NaOAc–HCl (pH 1.99-4.92) and NaOAc–AcOH (pH 3.6-5.6). It was noticed that the maximum color intensity and constant absorbances were observed in KCl–HCl buffer of (pH 2.0 for SUP and ARP) and NaOAc–HCl buffer of (pH 4.6 for OLZ and CLP). 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 1.0 ml of buffer solutions.

Effect of Dye Concentration

Keeping other conditions unaltered, the effect of 5×10^{-3} M EBT dye concentration on the absorbance was investigated. The results appeared that the maximum absorbance was at using 2.0 ml of EBT dye. Excess of EBT dye did not have any effect either on the color of the ion-pair complexes or on the absorbance.

Choice of Organic Solvents

Different organic solvents as dichloromethane, carbon tetrachloride, chloroform and ether were tested as extractive solvents for the proposed method. Dichloromethane was preferred to other solvents for its selective and obtained highest absorbance with dichloromethane. It was also observed that only one extraction was adequate to achieve a quantitative recovery of the complexes and the shortest time to reach the equilibrium between both phases. Shaking time of 0.5-5 min provided constant absorbance and hence, 2.0 min was selected as the optimum shaking time.

Reaction Mechanism

Olanzapine forms ion-pair complexes with EBT dye, since it contains tertiary amino group which is protonated. In the ring of 1H-[1, 4] diazepine, protonation is very difficult due to resonance and steric effects. Therefore, the only site in OLP vulnerable for protonation is the nitrogen bonded to electron donating methyl group in the piperazine ring (Harikrishna *et al.*, 2008) and finally the protonated OLP forms ion-pair with the EBT dye. The suggested mechanism for the reaction product of OLP - EBT ion–pair complex formation for example, is given in Fig. 3.

Composition of the Ion-Pair Complexes

The composition of the ion-pair complexes formed between SUP, OLP, CLP and ARP drugs and the EBT dye were determined by Job's continuous variation method [Job, 1928]. In this method, a series of solutions were prepared in which the total volume of the drugs and reagent was kept at 2.0 ml and the procedures were completed as described under general procedures and calibration graphs. The absorbance of each solution was plotted against the mole fraction of drug. The plot reached a maximum value at a mole fraction of 0.5 (Fig. 4), which indicated that a 1: 1 (drug: dye) ion-pair are formed through the electrostatic attraction between positive protonated drugs and EBT anions.

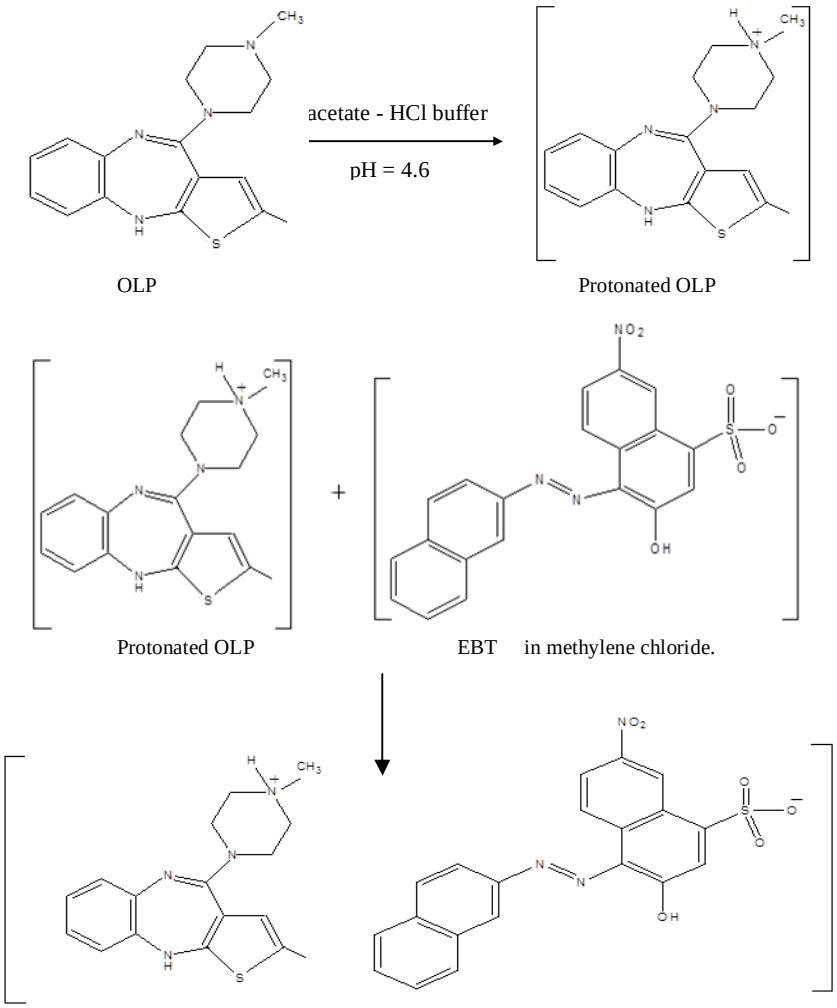

Fig. 3: The possible reaction mechanism for the formation of ion-pair complex OLP with EBT.

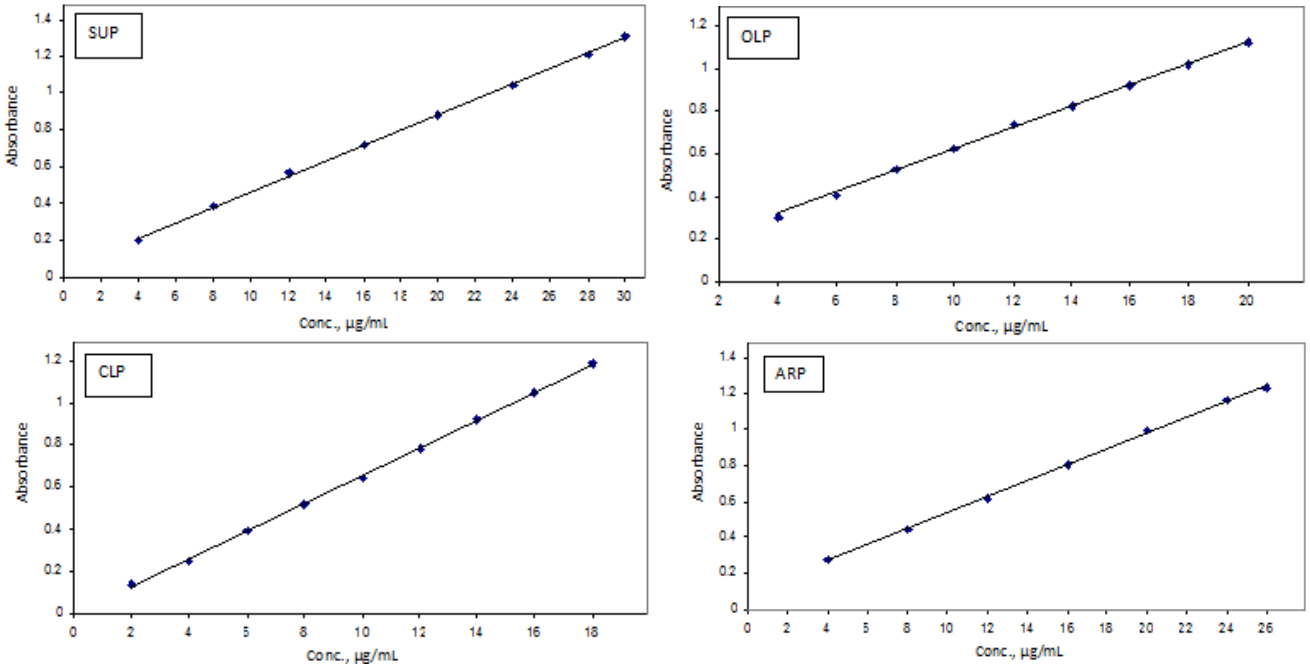

Fig. 4: Calibration curves of the studied drugs with EBT.

Effect of Temperature on the Colored Complexes

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 35 °C. At higher temperatures, the drug concentration was found to increase due to volatile nature of the dichloromethane. As a result, the absorbances of the colored complexes increased. Therefore all measurements were carried out at 25 ± 2 °C.

Effect of Shaking Time for Extraction

Shaking time ranging from 0.5-3.0 min was tested to ascertain the extraction of the complex. Maximum and constant absorbance value was obtained when extracted after 1.5 min shaking. Therefore, shaking time of 2.0 min was maintained throughout the experiment.

Conditional Stability Constants (K_f)

The conditional stability constants (K_f) of the ion-pair complexes were calculated from continuous variation data using the following formula [Inczedy, 1976]:

$$K_f = \frac{A/A_m}{[1 - A/A_m]^{n+1} C_D^n}$$

Where A and A_m are the observed maximum absorbance and the absorbance value of all the drugs present is associated, respectively. C_D is the molar concentration corresponding to the maximum in absorbance and n is the stoichiometric constant with which dye ion associates with drugs. The log K_f values for SUP, OLP, CLP and ARP ion-pair complexes were 5.774, 5.642, 5.276 or 5.669, respectively.

Conformity to Beer's Law

Under the optimum conditions described above, the calibration graphs were constructed for the investigated drugs. The molar absorbtivity, Sandell's sensitivity, concentration range, regression equation and correlation coefficient for each drug are tabulated in (Table 1). A linear relationship was found between the absorbance at λ_{max} and the concentration of the drug substances within the range 2.0 - 30 µg/ml. Regression analysis of Beer's law plotted at λ_{max} reveals a good correlation (Fig. 5). The graphs showed a negligible intercept, which was calculated by the least-squares method's regression equation, A=a+bC (where A is the absorbance of 1.0 cm layer, b is the slope, a is the intercept and C is the concentration of the measured solution in µg/ml.

The high molar absorptivities of the resulting colored complexes indicated high sensitivity of the method (1.47×10^4 – 2.20×10^4). The ARP - EBT method was found to be the most sensitive of all these methods with high ε value. The limit of detection (LOD) and limit of quantitation (LOQ) are calculated according to ICH guidelines (Miller and Miller, 2005). The results are as shown in (Table 1).

Table 1: Optical characteristics and statistical data of the regression equations of the proposed method.

Parameters	SUP	OLP	CLP	ARP
λ_{max} (nm)	514	514	514	514
pH	2.0	4.6	4.6	2.0
Beer's law limit, µg/ml	4-30	4-20	2-18	4-26
Molar absorptivity, L mol^{-1} cm^{-}	1.47×10^4	1.74×10^4	2.16×10^4	2.20×10^4
Stability constant (K_f)	5.774	5.642	5.276	5.669
Sandell's sensitivity, ng cm^{-2}	23.226	17.956	15.131	20.581
Correlation coefficient (r)	0.9999	0.9998	0.9999	0.9999
Linear regression equation*				
$S_{y/x}$	1.64×10^{-3}	1.89×10^{-3}	1.76×10^{-3}	6.43×10^{-3}
Intercept (a)	0.0628	0.1353	-0.0069	0.0983
Slope (b)	0.0409	0.0492	0.0660	0.0441
S.D. of slope (S_b)	1.06×10^{-4}	2.28×10^{-4}	2.12×10^{-4}	4.18×10^{-4}
S.D. of intercept (S_a)	0.0004	0.0067	0.0053	0.0119
LOD, µg/ml	0.9779	0.6097	0.5303	0.9523
LOQ, µg/ml	3.2567	2.0304	1.7659	3.1714

*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.

Drug	Drug taken, µg/ml	Drug found[a], µg/ml	Recovery[a], %	RSD, %	RE[b], %
SUP	12	11.9	99.99	0.312	-0.833
	16	15.9	99.99	0.634	-0.625
	20	19.9	99.99	0.354	-0.500
OLP	10	9.99	99.99	0.694	-0.100
	14	13.9	99.97	0.355	-0.714
	18	17.9	99.99	0.822	-0.555
CLP	8	7.99	99.99	0.866	-0.125
	12	11.9	99.99	0.377	-0.833
	16	15.9	99.99	0.911	-0.625
ARP	8	7.99	99.99	1.008	-0.125
	12	11.9	99.99	0.428	-0.833
	16	15.9	99.99	0.278	-0.625

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

Table 3: Application of the proposed method for the analysis of the studied drugs in pharmaceutical formulations.

Drugs	Tablet brand name	Labeled mg content	Found, mg	Recovery[a], % ±SD,	t- and, F-test[b]	Reported methods
SUP	Dogmatil[1],	200 mg/tab	199.39	96.74 ±0.977	t = 0.59, F = 1.36	96.01 ±1.47
OLP	Olazine[2],	10 mg/tab	9.84	97.73 ±0.468	t = 1.56, F = 2.44	98.54 ±0.68
CLP	Clozapex[3],	100 mg/tab	98.79	97.95 ±1.198	t = 0.34, F = 1.27	98.21 ±0.25
ARP	Aripiprex[4],	10 mg/tab	9.92	98.64 ±0.765	t = 0.61, F = 1.45	101.62 ±0.16

*Produced by: [1]Sanofi- Aventis, S.A.E., El-Ameryia-Zeitoun, Egypt. [2]EIPICo, 10th of Ramadan City, Egypt. [3]APEX Pharma S.A.E.,10th of Ramadan City, Egypt. [4] S.P.I.for Al Andalous Medical Company, 6th of October City, Egypt. [a]Mean value of five determinations. [b]Theoretical value for t- and F-values for five degrees of freedom and 95% confidence limits are 2.57 and 5.05, respectively.

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 (Table 2) and indicate that the proposed method is highly accurate and reproducible.

Analysis of Dosage Forms

The proposed method was successfully applied to the analysis of SUP, OLP, CLP and ARP in commercial tablets. The results of analysis of pharmaceutical formulations (Table 3) were compared statistically by Student t- test and by the variance ratio F- test with those obtained by reported methods. The Student t-values at 95% confidence level did not exceed the theoretical value indicating that there was no significant difference between the proposed and reported methods. It was also observed that the variance ratio F-values calculated for p=0.05 did not exceed the theoretical value indicating that there was no significant difference between the precision of the proposed and reported methods (Zayed, 2005; Rajendraprasad and Basavaiah, 2010; Sastry *et al.*, 1998 and Helmy *et al.*, 2012).

Table 4: Application of the proposed method for the analysis of the studied drugs in spiked human serum.

Drug	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD, %	RE[b], %
SUP	6	5.93	97.42	2.995	-1.166
	10	9.87	96.96	3.506	-1.300
	14	13.83	97.04	3.464	-1.214
OLP	4	3.93	96.19	4.465	-1.750
	8	7.88	96.49	4.098	-1.500
	10	9.85	96.41	4.349	-1.500
CLP	4	3.93	95.93	4.710	-1.750
	6	5.93	97.22	3.209	-1.166
	10	9.87	96.77	3.735	-1.300
ARP	4	4.05	103.2	3.805	1.250
	8	8.13	104.1	4.816	1.625
	10	10.12	103.1	3.680	1.200

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

Analysis of Biological Fluids

The high sensitivity of the proposed method, also allowed the in vitro determination of SUP, OLP, CLP and ARP in spiked human serum and urine samples. Thus the proposed method is sufficient for routine estimation of the drugs in human serum and urine. A prior extraction step by the same organic solvent was adopted before application of the method. The results obtained in (Tables 4, 5) are satisfactorily accurate and precise.

Table 5: Application of the proposed method for the analysis of the studied drugs in spiked human urine.

Drug	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD, %	RE[b], %
SUP	12	11.8	97.19	3.366	-1.666
	16	15.7	96.74	3.768	-1.875
	20	19.7	96.48	4.074	-1.500
OLP	10	9.91	97.86	2.481	-0.900
	14	13.8	97.78	2.944	-1.428
	18	17.8	97.33	3.081	-1.111
CLP	6	5.92	97.01	3.522	-1.333
	8	7.90	96.93	3.607	-1.250
	12	11.8	96.10	4.522	-1.666
ARP	4	3.93	95.65	5.037	-1.750
	8	7.91	97.40	3.012	-1.125
	14	13.8	96.70	3.826	-1.428

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

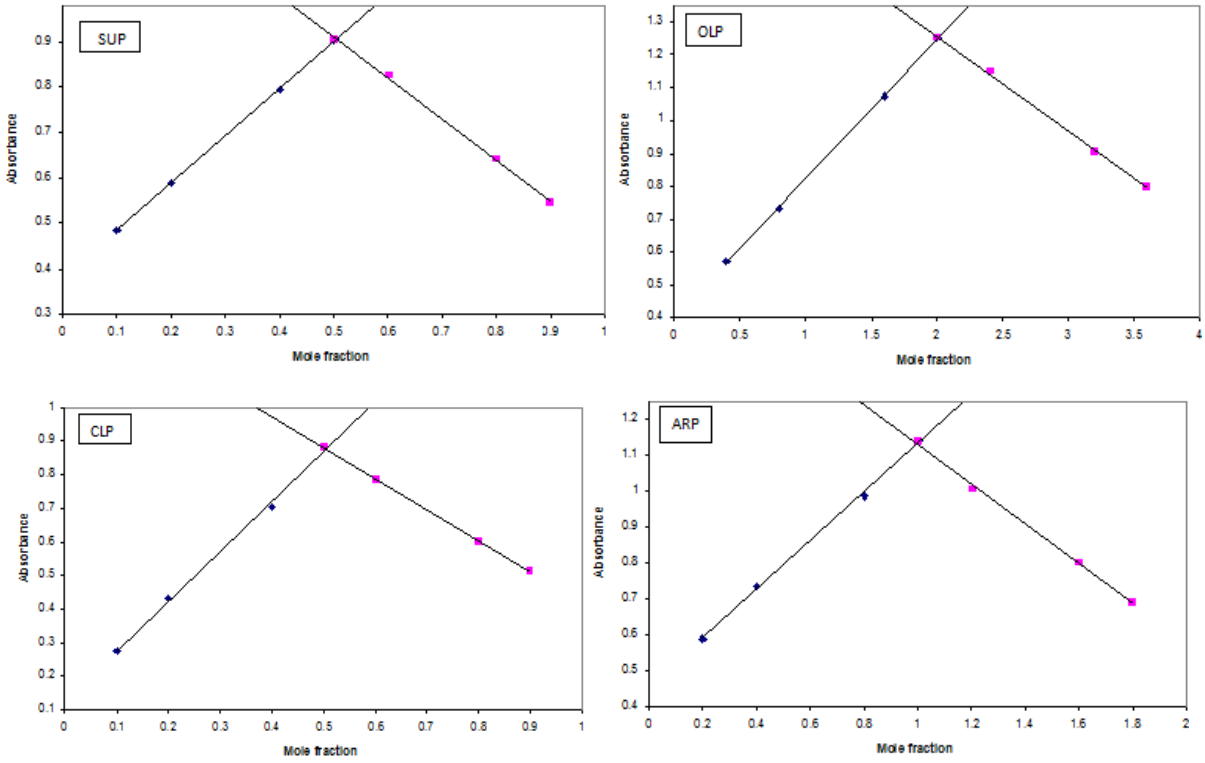

Fig. 5: Job's method of continuous variations of EBT with (a) SUP, (b) OLP, (c) CLP and (d) ARP.

CONCLUSION

The proposed method is rapid, simple, sensitive and accurate which can be used for determination of SUP, OLP, CLP and ARP antipsychotic drugs in dosage forms and in biological fluids. The method presented is based on the formation of dichloromethane extractable ion-pair complex with EBT. The method makes use of a common and simple reagent which an ordinary analytical laboratory can afford. The results showed that the t- and F-values were less than the tabulated value indicating that there is no significant difference between the developed and the reported methods. The main advantage of this method is low cost of reagent and apparatus used and short analysis time.

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