NEW SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF MIRTAZAPINE IN PHARMACEUTICAL FORMULATIONS

FOZIA REHMAN[a], SAIMA GUL[b], SAJJAD HUSSAIN[c], SABIR KHAN[d]

[a]*Interdisciplinary Research Centre in Biomedical Materials(IRCBM) COMSATS Institute of Information Technology, Lahore, Pakistan Tel: +92 (0) 42 111001007 Ext. 828, 829*
[b]*Department of Chemistry University of Swabi for Woman Gulo-Deri, Swabi, KPK,Pakistan.*
[c]*Faculty of Materials & Chemical Engineering GIK Institute of Engineering Sciences & Technology Topi, KPK, Pakistan.*
[d]*UNESP – Universidade Estadual Paulista, Institute of Chemistry, Department of Analytical Chemistry 14801-970, Araraquara – SP, Brazil.*

ABSTRACT

A simple extractive spectrophotometric method has been developed for the quantification of mirtazapine. This method is based on the formation of ion-association complex of mirtazapine drug with bromocresol purple dye. The absorbance of the complex was measured at 400 nm. The method was successfully applied to the determination of mirtazapine in their pharmaceutical formulations. The method shows a linear range from 0.2-10 μg mL^{-1} with a molar absorptivity of 1.53 ‘10 ^{4} L mol^{-1} cm^{-1}. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.096 μg mL^{-1} and 0.32μg mL^{-1} respectively. The developed methodology was successfully applied for the determination of mirtazapine in commercial formulation and the percentage recovery was found 99.91 ± 0.15. The developed methodology promises a feasible, low cost and an efficient method for the routine analysis.

Key words: Spectrophotometric, ion-association, pharmaceutical formulations.

1. INTRODUCTION

Mirtazapineis a tetra cyclic, specific serotonergic, noradrenergic, antipsychotic and antidepressant drug. This drug is recommended for the treatment of psychosis (schizophrenia) and depression disorder, which act by blocking presynaptic alpha-2 adrenergic receptors and inhibit the release of noradrenaline and serotonin and a potent antagonist of 5-HT2, 5HT3 and histamine (H1) receptors. Mirtazapine shows a mild sedating and antipsychotic activity in doses ranges from 15-45 mg, while dose range may be up to 120 mg in severe depression. Mirtazapine is absorbed slowly from the gastrointestinal tract with bioavailability of 50-55 %. [1234]. Mirtazapine has a unique and specific effect on both the noradrenergic and serotonergic neurotransmitter systems in the CNS, being an antagonist of α_2-adrenergic auto receptors and heteroreceptors and an antagonist of postsynaptic serotonin 5-HT_2 and 5-HT_3 receptors. [5]

In individual adverse events, most experiences were mild and transient. Commonly adverse proceedings happening during Mirtazapine treatment were low dose related wakefulness and weight increase, which may be attributed to affinity of the antihistaminic (H1) receptor (2). Some specific considerations were hepatotoxicity, arthralgia, coagulopathy, acute pisa syndrome. Mirtazapine is less likely to cause hypertension [6 7]

Various methods have been reported for the determination of mirtazapine, most of which are High performance liquid chromatography with a variety of detectors and Gas chromatographic methods[8910] . Some other techniques like Spectrophotometric and chemometric, Electrophoresis, voltammetry [1112], [13 14] also have been reported.

Very few spectrophotometric methods are available for the analysis of mirtazapine drug. The aim of this work is to develop a simple, as efficient, cost effective spectrophotometric method for routine analysis of mirtazapine drug. This method describes the application of acidic dyes to the spectrophotometric determinationof mirtazapine in pure and pharmaceutical formulations based on the formation of chloroform soluble ion–pair complex of mirtazapine with bromo cresol purple (BCP) in an acetate buffer of pH 4.

2. EXPERIMENTAL

2.1. Reagents

All reagents and solvents were used of analytical grade, bromo cresol purple, chloroform, acetic acid (**Merck**), sodium acetate (**BDH**) and ethanol (**Merck**) were used in this work. Mirtazapine (Aldrich ≥98%), Commercial formulation containing mirtazapine was obtained locally.

2.2. Techniques

An S2100 UV-VIS spectrophotometer (**United Products & Instruments** [UNICO®], Dayton,NJ) with 1-cm cell was used having photodiode detector

2.3. Solutions Preparations

a) Bromo cresol purple (0.1% w/v) solution was prepared by dissolving 0.1 g in 2.0 mL ethanol and diluted with distilled water in a 100 mL volumetric flask.

b) Acetate buffer (pH 4) was prepared by mixing acetic acid (0.2*M*) solution and sodium acetate (0.2 *M*) solution.

c) Standard drug solution of 1000 ppm was prepared by dissolving 0.1 g of drug in 5 mL ethanol and diluted it with distilled water in a 100 mL volumetric flask. Through dilution 100 ppm solution and working standards in the range of 0.2 to 10 ppm were prepared from the stock solution.

d) Sample solution was prepared by taking the average weight of three tablets, after dissolving in ethanol; the solution was diluted with distilled water and filtered to remove the suspended particles.

2.4. Recommended procedures

Aliquots of the standard solutions of mirtazapine were transferred into a series of reaction flasks so that the final concentration was in the range of 1–10 μg mL^{-1}, followed by the addition of 1 mL of 0.1% bromocresol purple solution and 1 mL of pH 4 acetate buffer to complete the reaction. These solutions were extracted in 10 mL of chloroform. The absorbance of the resulting yellow ion-pair complex was measured at 400 nm against the corresponding reagent blank solution.

2.5. Determination of Mirtazapine

The average tablet weight was calculated from the content of three tablets. A portion of the powder form of the capsule, equivalent to 15 mg of mirtazapine was accurately weighed. The samples were dissolved in distilled water containing 5 mL ethanol and filtered. The filtrate was diluted further to 100 mL. Appropriate aliquots of the solution obtained were treated according to the recommended procedure.

3. RESULTS AND DISCUSSION

Mirtazapine is a substituted benzamideand preliminary investigations suggested that mirtazapine can form a chloroform soluble ion pair complex with sulphonphthalein dye bromocresol purple[15]. The maximum wave length of this ion-pair complex was observed at 400 nm as can be seen from Figure 1.

1.1. Effect of pH

Bromocresol purple is an acidic dye and the dissociation of acidic dyes at pH 4 is greater due to ionization of sulfonic acid groups [1617]. To achieve maximum complex formation, acetate buffer of pH 4 was selected. To each 5 mL of 100 ppm drug solution 5 mL of BCP of 100 ppm was added. The volume of this acetate buffer was optimized from 0.5 to 2.5 mL and after extraction in 10 mL of chloroform. Maximum absorbance was noticed with 1 mL of acetate buffer solution of pH 4, as shown in Figure 2.

1.2. Effect of dye Concentration

To investigate the effect of bromocresol purple concentration on drug-dye ion pair complex formation, different volumes in the range of 1 to 5 mL of 100 ppm solution were added to the each 5 mL of 100 ppm drug solution. By putting the optimum volume of buffer solution absorbance was measured at

e-mail: sabir@iq.unesp.br, Sabir_chemist@yahoo.com

400 nm. Maximum drug-dye complex formation was achieved with 3 mL taken from 100 ppm solution of BCPas shown in Figure 3.

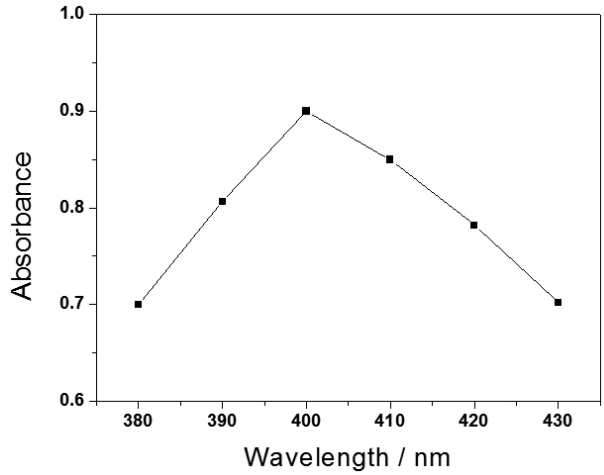

Figure 1. Optimization of wave length for the spectrophotometric determination of mirtazapine.

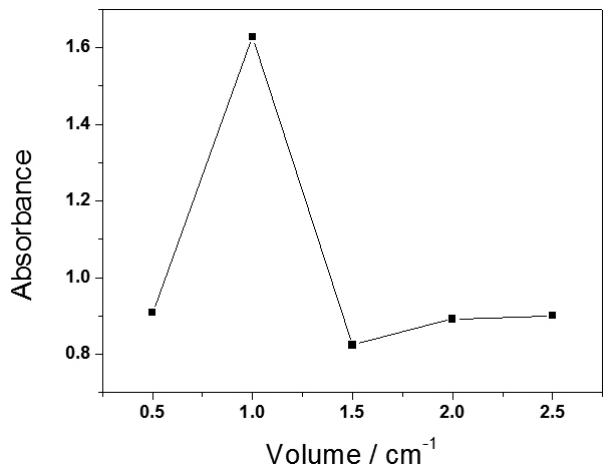

Figure 2. Optimization of buffer volume for the spectrophotometric determination of mirtazapine.

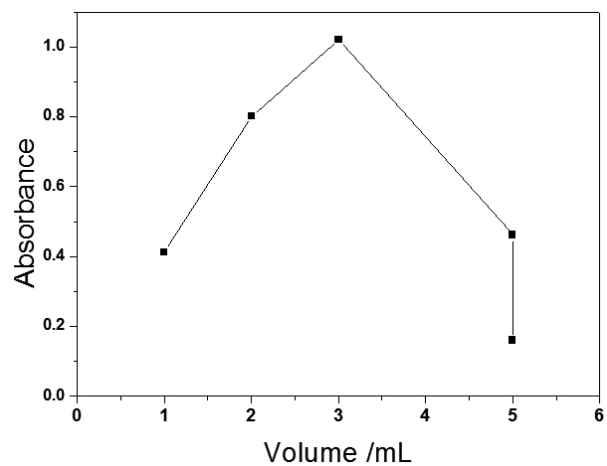

Figure 3. Optimization of BCP dye volume for the spectrophotometric determination of mirtazapine.

1.3. Kinetic study

The ion–pair complex of mirtazapine and BCP dye was formed at room temperature. The ion–pair complex was formedcompletely after extraction, and the stabilizationtimes were more than 2 hr as shown in Figure 4.The stability constant (kf) of the ion–pair complex was calculated from the continuous variation method and was found to be 1.4×10^7.The composition of the ion–pair complex was determined by applying Job's method of continuous variations, and the results corresponded to 1:4 for the Mirtazapine -to-BCP ratio. The schematic representation of ion-pair complex of drug with BCP dye is shown in Figure 5.

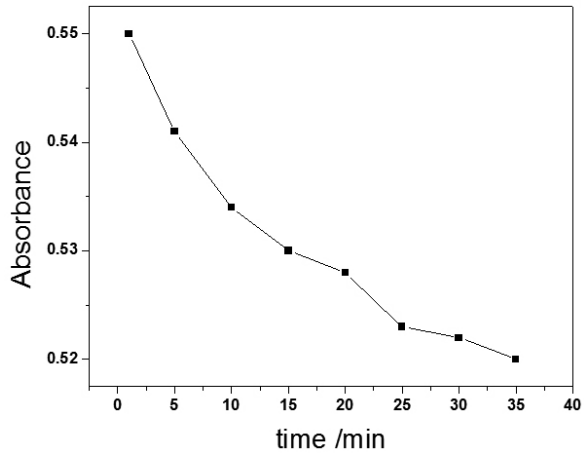

Figure 4. Kinetic study for the stability of ion pair complex of mirtazapine drug with BCP dye.

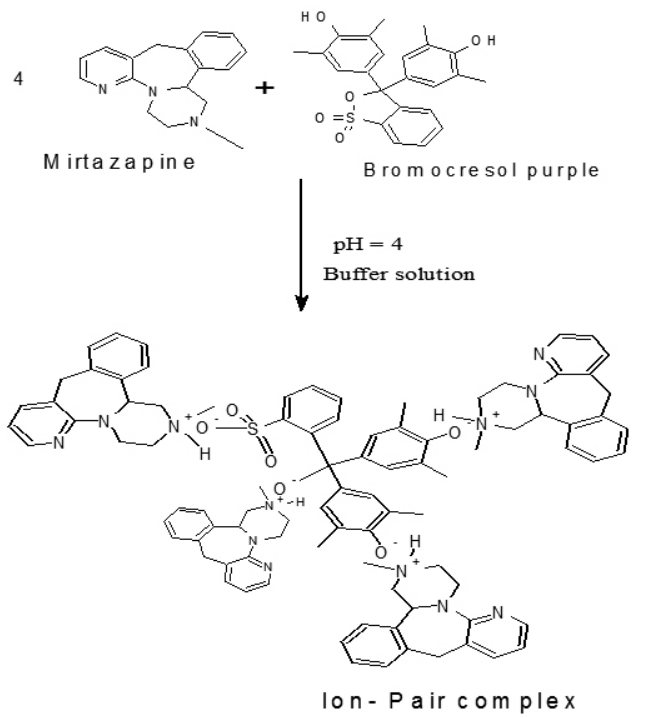

Figure 5. Schematic representation of ion-pair complex formation of mirtazapine drug with bromocresol purple dye.

1.4. Analytical performance

The absorbance-concentration curves were found to be linear in the lower concentration range of 0.2–1.0 µg mLand in the higher concentrationrange of 2.0–10.0 µg mL^{-1} as shown in Figure 6a and 6b. The statistical parameters calculated from the calibrationgraphs are shown in *Table 1*. The linearity of the calibration graphs was proven by the high value of correlation coefficient (R^2). The molar absorptivity of the resulting colored ion–paircomplex was calculated and found to be **1.53 ´10 ^{4} L mol^{-1} cm^{-1}.** The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.096 µg mL^{-1} and 0.32µg mL^{-1} respectively.The validity of the proposed method was tested to

determine Mirtazapine in pharmaceuticalformulation(see *Table 2*). For further confirmation, the standard addition techniquewas applied to test the reliability and recoveryof the proposed method in which knownconcentrations of mirtazapine were added to thepreviously analyzed portion of pharmaceuticalpreparation. The results are given in *Table 2*.The percent recovery was found 99.91 ± 0.15% for commercial formulation MIRTAZAP-ZAFA.

Table 1. Spectral Characteristics for Spectrophotometric determination of mirtazapine.

Characteristics	Value
Wave length, λ (nm)	400
Linear range (ppm)	0.2-10
Slope	0.06
Correlation coefficient (r)	0.99
standard deviation (SD)	$5.3´10^{-4}$
Limit of detection (μg mL^{-1})	0.096± 0.01
Limit of quantification (ppm)	0.32 ±0.03
Molar Absorptivity (L/mol/cm)	$1.53´10^{4}$

Table 2. Recovery and determination of mirtazapine in pharmaceutical sample.

Sample	% Recovery	Calculated amount (mg)	Labeled amount(mg)
MIRTAZEP	99.91±% 0.015	15.97.2±0.12	15

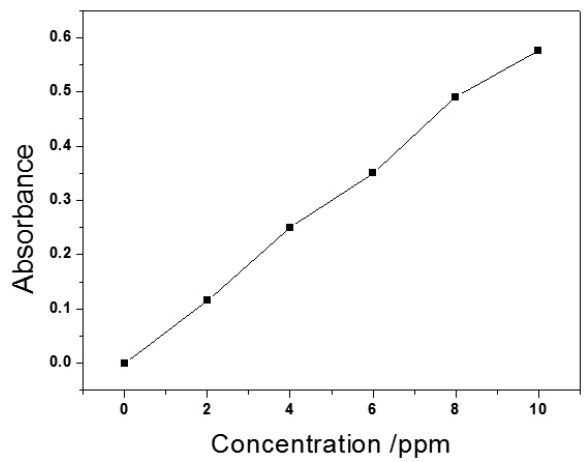

Figure 6a. Relationship between absorbance and mirtazapine concentration on ion–pair complex at higher concentration (2.0–10.0 ppm

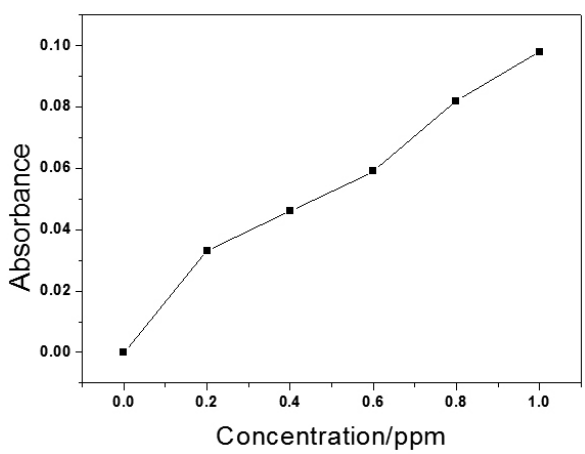

Figure 6b. Relationship between absorbance and mirtazapine concentration on ion–pair complex at low concentration (0.2–1.0 ppm).

The ion–pair complex with theanionic dye requires the presence of a basic functionalgroup,therefore no possible interference islikely to occur from coformulated drugs lacking abasic center. Common excipients such as talcumpowder, starch, gelatin, and lactose did not interferewith the analysis of mirtazapine.As can be seen the above results, the proposed method is sensitive, and can beeasily applied for routine analysis of mirtazapine in raw from and also in pure and inpharmaceutical preparations.

CONCLUSION

A simple extractive spectrophotometric method was developed for the determination of mirtazapine in pure and pharmaceutical formulations. The developed method is based on the formation of an extractive ion–pair complex with acid dyes and offers the advantages of simplicity, precision, sensitivity, and the use of inexpensive equipment.

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