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SPECTROPHOTOMETRIC DETERMINATION OF MIRTAZAPINE IN PURE AND TABLET PHARMACEUTICAL PREPARATION

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SUMMARY

Sensitive spectrophotometric method was developed for the determination of mirtazapine from pharmaceutical preparats. The proposed method was based on the formation of a yellow colored ion-pair complex by the reaction of methyl orange with mirtazapine. The ion pair complex was extracted with dichloromethane. Under the optimum condition, the ion pair complex showed an absorption maximum at 427 nm. The linearity range for concentrations of mirtazapine was found to be 2.5-12.5 μg/mL. The proposed method is successfully applied to the determination of mirtazapine tablet formulations.

ÖZET

Mirtazapinin farmasötik preparatlarda tayini için duyarlı spektrofotometrik bir yöntem geliştirilmiştir. Geliştirilen yöntem, mirtazapin ile metil oranj arasında sarı renkli iyon çifti kompleksi oluşturması esasına dayanmaktadır. İyon çifti kompleksi diklormetan ile ekstre edilmiştir. Optimize edilmiş koşullarda iyon çifti kompleksinin maksimum absorbsiyon değeri 427 nm olarak tespit edilmiştir. Mirtazapinin doğrusallık aralığı 2.5-12.5 μg/mL olarak bulunmuştur. Geliştirilen yöntemin tabletlerde mirtazapin miktar tayininde güvenle uygulanabilir.

Key words: Mirtazapine, ion pair complex**,** spectrophotometry, methyl orange

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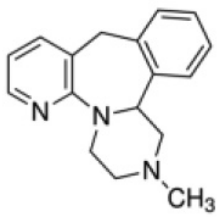
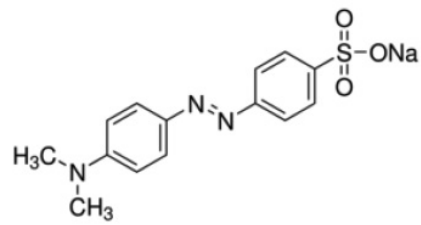
INTRODUCTION

Mirtazapine (MIR) is chemically known as (±)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Fig.1). It is a noradrenergic and specific serotonergic antidepressant (1).

Few analytical methods have been reported for the determination of MIR in pharmaceutical preparats and bulk form, which include spectrophotometry (2), fluorimetry (3), high-performance liquid chromatography (HPLC) with UV detection (3,4), thin layer chromatography (5) and capillary electrophoresis method for determination of MIR from pharmaceutical quality control analysis (6). These methods require multistep reaction procedures and extraction steps for determination of Mirtazapine. Proposed method is based on the formation of ion pair association complex of MIR with methyl orange (MO) in dichloromethane. The developed method is accurate, reproducible, and highly sensitive for determination of MIR.



Mirtazapine



Methyl orange

Fig.1. Chemical structures of mirtazapine and methyl orange

EXPERIMENTAL

Materials

MIR pure samples was obtained from Bilim Pharmaceutical (Istanbul, Turkey). Remeron tablets (30 mg) were purchased from a local pharmacy. The MO was purchased from (Merck, Darmstadt, Germany). All solvents used were of analytical reagent grade (Merck, Darmstadt, Germany). HPLC grade water was used through the analysis (aquaMAX^{TM} ultra, Young Instrument Korea).

Apparatus

UV-160A (Shimadzu, Kyoto, Japan) ultraviolet-visible spectrophotometer was used to obtain spectrum and absorbance measurements.

Preparation of solutions

Stock solution of MIR was prepared in the concentration of 1 mg/mL, in methanol. Standard solutions of MIR of 100 µg/mL was prepared by appropriate dilution of the stock solution with methanol. MO solution was prepared in water with a concentration of 0.08 % (w/v). Phthalate buffer was prepared by dissolving 1.280 g of potassium hydrogen phthalate in 50 mL of water. The pH was adjusted to 3.5 with 0.2 M HCI solution and the volume was completed to 250 mL with water.

Preparation of pharmaceutical preparat solution

Ten tablets containing MIR were weighed and powdered. An accurately weighed portion of the powder equivalent to 100 mg of MIR was transferred into 100 mL volumetric flask and 50 mL methanol was then added. The prepared solution was sonicated for 30 minutes. Then, it was made up to volume with methanol, mixed well and filtered. An aliquot of 10 mL of the filtrate was diluted to 100 mL to prepare of sample tablet solutions (100 µg/mL).

Procedures

1.0 mL of buffer solution of pH 3.5 and 1.0 mL of MO were placed into a series of 12 mL glass stoppered,. An appropriate volume of 100 µg/mL working solution (1250-250 µL) was added and mixed well. The MIR–MO ion pair complex was extracted three times with 3 mL of dichloromethane. After 2 min vortexing the tubes were allowed to separate the two layers. The combined extracts were adjusted to 10 mL with the same solvent. The absorbance of the yellow colored complex was measured at 427 nm, against corresponding reagent blank similarly prepared.

RESULTS AND DISCUSSION

Mirtazapine has organic amin groups as it contain benzazepine group, therefore, attempts were made to determine MIR in aqueous solution by forming extractable ion pairs between these positively charged amino compounds at the proper acidic pH and negatively charged dye MO. The

theoretical basis of this method is that the dissociation equilibrium of a drug electrolyte dissociating in aqueous medium. The pKa value of MIR was found 7.1 by using potentiometric titration (7). MIR was pozitively charged in acidic media, MO was negatively charged.

The absorption spectrum of MIR-MO ion pair complex under optimum conditions is shown in Figure 2. The maximum absorbance of the complex was observed at 427 nm. The reagent blanks prepared under similar conditions showed no absorption.

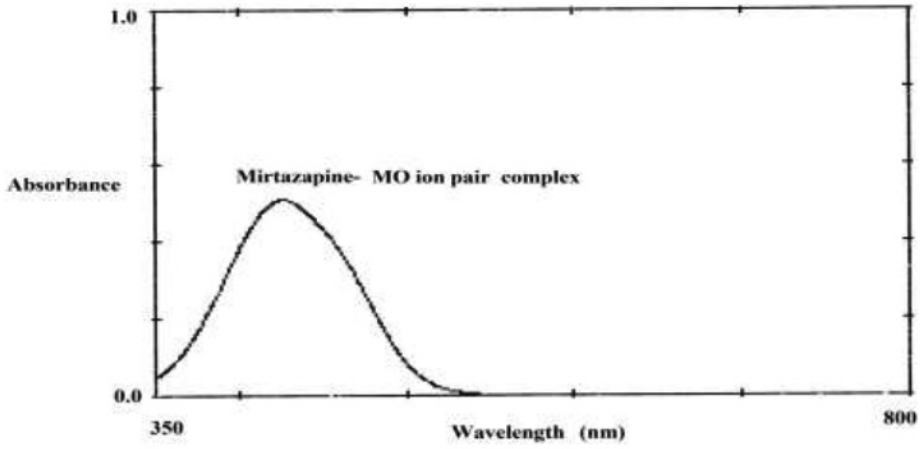


Fig. 2. Absorption spectrum of MIR-MO ion pair complex (10 μg/mL)

The spectrophotometric properties of the colored species formed with MO as well as different parameters affecting the color development were extensively studied. The optimum conditions to improve the sensitivity and accuracy of MIR analysis has been established by studying the reaction as function of the concentration of the reagent, pH, extraction solvent and reaction time. Interferants are mainly basic compounds that contain heteronitrogen atom in their aromatic nuclei. However, such compounds are not present with the examined antidepressant drug formulation and they did not interfere in the proposed method. Mirtazapine is available in the form of tablets (Remeron®) for oral administration, containing 15 or 30 mg of mirtazapine, red and yellow FeO, TiO_2 and other excipients.

The influence of the concentration of MO was studied using different

volumes (0.125-2.0 mL) of 0.08% solution of the reagent. The maximum absorbance was obtained with 1.0 mL of the reagent.

The effect of pH on the drug–reagent complex was investigated over the pH range 2.5–4.5 using phthalate buffers, where the maximum absorbance was obtained at pH 3.5.

In order to select the most appropriate organic solvent the reaction solutions, different solvents were tested: dichloromethane and chloroform. The highest intensity was obtained when dichloromethane was used.

The optimum reaction time was determined by monitoring the color development at ambient temperature (25 ± 1 °C) within 2 min.

The linear relationship was found between the absorbance at λ_{max} and the concentration of the MIR in the range 2.5 -12.5 µg/mL. The representative linear regression equation was: $A = aC + b$, where C is the concentration, A the absorbance, a the slope, and b is the intercept. The regression equation was $A = 0.0778C - 0.1236$ with $r = 0.9993$.

Limit of detection (LOD) and limit of quantification (LOQ) were calculated according to the following equation: LOD =3.3σ/S and LOQ= 10σ/S, where; σ is the standard deviation of the intercept of regression line, S: is the slope of the calibration curve. The LOD and LOQ were found to be 0.67 and 2.01 µg/mL, respectively.

The proposed method was successfully applied to pharmaceutical preparation. The determination of MIR tablets, Remeron (30 mg) were analyzed by the utilizing method. The recoveries were found to be in the range of 100.50-100.59 %.

CONCLUSION

A sensitive, precise and accurate spectrophotometric method for the determination of MIR has been developed in this study. The method is simple, highly sensitive, good selectivity and applicable to routine quality control determination of the tablet formulations of MIR. The methods described here are direct methods for the analysis of mirtazapine without any extraction process to eliminate the excipients, do not use time consuming procedure such as standard addition method and also there is no need any expensive equipment

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