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Development and applications of spectrophotometric methods for quantitative determination of caroverine in pharmaceutical pure and tablet formulations

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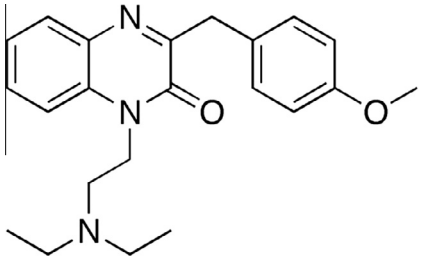
ABSTRACT

This paper describes two simple and novel analytical methods by using spectrophotometric technique for the determination of caroverine a spasmolytic drug in pharmaceutical formulations. The first (A) is a direct method in which analysis of the pure drug was carried out at its λ_{max} 304 nm in ethanol solvent. The method was linear from 0.5 to 18 μg/ml with correlation coefficient of 0.999 and molar absorptivity of 5.55×10^4 L mole^{-1} cm^{-1}. Limit of detection and limit of quantification were 0.44 and 1.47 μg/ml. While the second method (B) is based on the charge transfer reaction between caroverine as n-electron donor and 7,7,8,8-tetracyanoquinodimethane (TCNQ) as pi-acceptor resulting in highly colored stable complex, which showed maximum absorption band at wavelength of 525 nm. The thermodynamic parameters were calculated as association constant K_{CT} of 7.53×10^4 mol^{-1} and Gibbs free energy ΔG° of −6.72 kJ mol^{-1}. Different variables affecting the charge transfer reaction were carefully studied and optimized. At the optimum reaction conditions, Beer's law was obeyed in a concentration range of 1–35 μg ml^{-1} with molar absorptivity of 1.17×10^4 L mole^{-1} cm^{-1} and correlation coefficient of 0.9999. The proposed methods were validated according to ICH guidelines.

1. Introduction

A counterfeit medication or a counterfeit drug is a medication or pharmaceutical product which is produced and sold with the intent to deceptively represent its origin, authenticity or effectiveness. A counterfeit drug may contain inappropriate quantities of active ingredients, or none, may be improperly processed within the body (e.g., absorption by the body), may contain ingredients that are not on the label [1]. The concern about the quality of drugs marketed increases every year not only in commercial terms, but also legal and ethical aspects, since the health of patients depends on the quality and effectiveness of these drugs. For this purpose different regulatory authorities around the world are demanding specific and validated analytical methods for the registration of new drugs to ensure their quality. So there is a great interest in developing rapid and efficient analytical methods that provide precise and accurate parameters for the quantitative analysis of drugs in pharmaceutical raw and dosage forms.

Caroverine 1-(2-diethylaminoethyl)-3-(p-methoxybenzyl)-1,2-dihydro-2-quinoxalin-2-on-hydrochloride is chemically derived from isoquinoline, the basic structure of papaverin. It is clinically available in some countries as a spasmolytic drug based on its unspecific Ca^{2+} channel blocking activity for more than 40 years. Caroverine is a drug used as a spasmolytic and otoneuroprotective (inner ear protective) agent in some countries. It acts as an N-type calcium channel blocker, competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) receptor antagonist, and non-competitive NMDA (N-methyl-D-aspartate receptor) receptor antagonist [2]. It also has potent antioxidant effects [3]. In Pakistan, caroverine is marketed as Sparina tablets 20 mg (Biopharma, Multan, Pakistan) for oral smooth muscle spasms.



Chemical structure of caroverine.

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Detailed survey of literature for caroverine revealed that not a single analytical method is available for the quantitative determination of caroverine in pharmaceutical raw and dosage forms. The assay of caroverine in pure and dosage forms, as far as we know, is not official in any pharmacopoeia, and therefore, requires much more investigation.

The molecular interactions between electron donors and acceptors are generally associated with the formation of intensely colored charge transfer complexes, which absorb radiation in the visible region [4]. A variety of electron donating compounds have been reported to yield charge-transfer complexes with various π-acceptors [5–9].

The objective of this study was to develop a simple and validated spectrophotometric method for routine analysis of caroverine tablets in pharmaceutical laboratories.

2. Experimental

2.1. Apparatus

A Hitachi U 1100, UV/Vis spectrophotometer (Japan) with silica glass cell of 1 cm thickness was used. Officially calibrated Pyrex glass-ware was used throughout this study.

2.2. Reagents and standards

Caroverine pure sample and Sparina tablets were supplied by Bio Fine Pharmaceuticals (Pvt.) Ltd. Multan, Pakistan as gift samples. All reagents and solvents used were of Analytical Reagent Grade. While 7,7,8,8-tetracyanoquinodimethane (TCNQ) (Fluka, Switzerland) 1.0 mg ml^{-1} solution was prepared in acetonitrile (Merck, Germany). The standard drug solution of 1 mg ml^{-1} was prepared by dissolving 100 mg of pure drug sample in 100 ml DMSO (Sigma–Aldrich, Germany) solvent. 0.001 M solution of caroverine and TCNQ was prepared by dissolving 0.402 mg of pure drug in 100 ml DMSO and 0.204 mg TCNQ in acetonitrile solvent respectively.

2.3. Recommended procedures

2.3.1. Method A

Different aliquots of standard solution of caroverine (0.5–18 μg ml^{-1}) were prepared in DMSO. Absorbance of these solutions was noted at 304 nm against a reagent blank.

2.3.2. Method B

A suitable amount of the drug solution, containing 1–35 μg ml^{-1} caroverine was pipetted into a series of 10 ml volumetric flask. Then 1 ml of TCNQ solution was added to each flask. The solution was kept in thermostat at 40 °C of water bath for 5 min. After cooling at room temperature the volume was made up to mark with DMSO and the absorbance of the colored complex was measured at 525 nm against a reagent blank.

2.4. Analysis of pharmaceutical formulations

2.4.1. Method A

20 tablets were weighed accurately then were pulverized carefully with mortar and pistol. An amount of the powdered equivalent to 100 mg of the pure drug was weighed accurately and transferred into a 100 ml calibrated flask. Dissolve the contents in 50 ml DMSO solvent by sonicated then made the volume up to the mark with same solvent. Filter the solution through Whatman filter paper 42. Then take 10 ml from this filtrate and dilute up to 100 ml with DMSO and take the absorbance of this 10 μg ml^{-1} solution at 260 nm against reagent blank.

2.4.2. Method B

20 tablets were weighed accurately then were pulverized carefully with mortar and pistol. An amount of the powdered equivalent to 100 mg of the pure drug was weighed accurately and transferred into a 100 ml calibrated flask, dissolved in DMSO, swirled and sonicated for 3 min, the solution was diluted to volume with ethanol. Then take 1 ml from this solution in 100 ml volumetric flask and treat as described in recommended procedure (method A). After filtration from Whatman filter paper 42 take absorbance at 525 nm against reagent blank.

2.5. Molar ratio of reactants in complex

The Job's method of continuous variation was employed [10]. An equal molarity solution of the caroverine and TCNQ were prepared. A series of 10 ml portions of the master solutions of the drug with TCNQ reagent were made up comprising different complementary proportions (0:10, 1:9,...,9:1, 10:0) in 10 ml volumetric flasks. The reaction was allowed to proceed as the described in proposed method. The absorbance of the solutions was measured at 525 nm against the reagent blank.

3. Results and discussion

The method A is based on the simple scanning of caroverine in DMSO solvent and its determination in the presence of various excipients. While the method B is based on the charge-transfer (CT) reaction. The CT reaction has been widely studied recently. Many drugs are easy to be determined by spectrophotometry based on color CT complexes formed with electron acceptors. The charge-transfer (CT) reactions have been widely studied recently. Many drugs are easy to be determined by spectrophotometry based on color charge-transfer (CT) complexes formed with electron acceptors [11–14]. The charge-transfer (CT) complexes are formed between electron donors, having sufficiently low ionization potential, and acceptors, having sufficiently high electron affinity.

3.1. Absorption spectra

For method A 10 μg/ml solution of caroverine in DMSO was scanned from 200 to 400 nm against a reagent blank and maximum absorbance was determined at 304 nm as shown in Fig. 1(a). While in method B caroverine reacts with TCNQ solution in DMSO medium and produce the highly colored complex that show maximum absorption at 525 nm as shown in Fig. 1(b).

3.2. Reaction mechanism

TCNQ has been used for quantitative determination of pharmaceutical drugs in dosage forms by charge-transfer complex formation. Interaction with TCNQ in acetonitrile solution was found to yield a deep color causing characteristic longer wavelength absorption band. The predominant chromogen with TCNQ is blue colored radical anion, which probably resulted through the dissociation of an original donor–acceptor complex with the drug. This complex is formed by the lone pair of electron donated by the caroverine base as n donor and the charge transfer reagent as an electron acceptor, where a partial ionic bond (D^+ A^+) is assumed to be formed.

$$\underset{\text{Donor Acceptor}}{D + A} \rightarrow \underset{\text{Donor-acceptor complex}}{[D \rightarrow A]} \rightarrow \underset{\text{Radical anion}}{D^+ + A^+}$$