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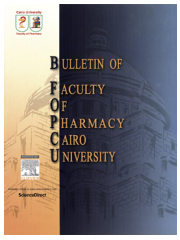

ORIGINAL ARTICLE

Univariate spectrophotometry and multivariate calibration: Stability-indicating analytical tools for the quantification of pimozide in bulk and pharmaceutical dosage form

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Abstract Simple, accurate sensitive and precise spectrophotometric and chemometric stability indicating techniques were adopted for the determination of Pimozide (PIM) in presence of its alkaline and acidic degradation products over a concentration range of 10–100 μg mL^{-1}. The proposed spectrophotometric technique includes first derivative (D^1) spectrophotometric one at 252 nm and 256.6 nm in presence of its acidic and alkaline degradates, respectively, first-derivative of the ratio spectra spectrophotometry (DR^1) at 292.5 nm, the Q-analysis (absorption ratio) method, which involves the formation of absorbance equation at 242.2 nm and 281.7 nm, dual wave length method at 270.1 nm and 284 nm, the H-point standard addition method (HPSAM) and the mean centering of the ratio spectra method. The second technique is chemometric methods which include determination of PIM in presence of both its acidic and alkaline degradates using multivariate calibration methods [the classical least squares (CLS), principle component regression (PCR) and partial least squares (PLS)] using the information contained in the absorption spectra. The proposed methods have been successfully applied to the analysis of PIM in pharmaceutical dosage forms without interference from other dosage form additives and the results were statistically compared with the official method.

1. Introduction

Pimozide; 1-[1-[4, 4-bis (4-fluorophenyl) butyl]-4-piperidinyl]-1, 3-dihydro-2H-benzimidazole-2-one [1] (Fig. 1). PIM is a neuroleptic of the diphenyl butyl piperidine series. It is a potent

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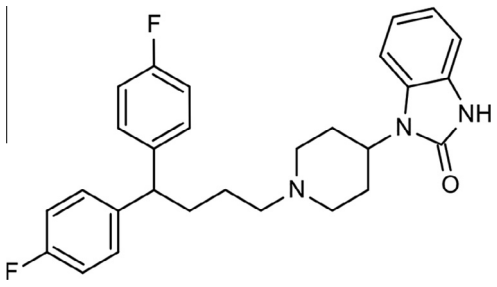

Figure 1 Chemical structure of intact Pimozide.

long-acting anti-psychotic, used mainly to control effectively hallucinations and delusions and to normalize incoherent thought processes and bizarre behavior patterns.[2] PIM appears to undergo significant first pass metabolism. The major route of elimination of its metabolites is via the kidney.[2] PIM is official in British Pharmacopoeia.[3] PIM was determined by several analytical techniques including; spectroscopic methods either colorimetric,[4–6] or fluorimetric[7] methods. PIM can also be determined by electrochemical methods,[8] and HPTLC.[9] High performance liquid chromatographic [HPLC] methods were widely used for analysis of PIM.[10–17]

To the best of our Knowledge, only one stability indicating HPTLC method[9] was reported for pimozide and no other spectrophotometric or chemometric stability indicating techniques was proposed for the determination of PIM in presence of its alkaline and acidic degradation products. So the aim of the present study is to develop and validate simple, accurate and specific stability indicating method for the quantification of pimozide in the presence of its degradation products.

2. Experimental

2.1. Instrumentation

A double beam UV–VIS spectrophotometer (UV-1800, Japan) connected to IBM compatible computer. The bundled software is UV probe software version 2.32 (Shimadzu) and the spectral bandwidth was 0.1 nm. The absorption spectra were carried out using 1 cm quartz cells. The chemometric calculations were performed in Matlab for Windows-version 7 Mathworks Inc. 2004. The PLS procedure was taken from PLS Toolbox 2.0, Eigenvector Research Inc. 2001 created by B.M. Wise, N.B. Gallagher for use with Matlab.

2.2. Materials and reagents

All chemicals were of analytical grade, the solvents were of spectroscopic grade.

PIM was purchased from Sigma Aldrich. Its purity was 100.09% ± 0.14 (n = 5) according to the official non aqueous titration.[3]

Orape forte®4 mg tablets, labeled to contain 4 mg of PIM per tablet were manufactured by Janssen Cilag, Batch No. 12CQ019 and purchased from the Egyptian market.

Sodium hydroxide, hydrochloric acid (Adwic-Cairo, Egypt), and methanol (Analar-Germany) were used.

2.3. Standard solutions of the intact Pimozide

2.3.1. Stock solution

A standard stock solution of PIM was prepared by transferring accurately 100 mg of pure drug into 100-mL volumetric flask, dissolving in 20 mL methanol with the aid of sonication and then the volume was completed to the mark with the same solvent to provide standard stock solution containing 1 mg mL^{-1}.

2.3.2. Working solution

PIM working solution was prepared by transferring 10 mL of the standard stock solution into 100-mL volumetric flask and then the volume was completed to the mark with methanol to obtain standard working solution containing 0.1 mg mL^{-1}.

2.4. Preparation of standard solution of acidic and alkaline degraded PIM

Methanolic PIM solutions containing accurately measured 50 mg were mixed with 25 mL of 2 M HCl and 2 M NaOH, separately then refluxed for 4 h. The solutions were cooled to room temperature, neutralized with 2 M NaOH and 2 M HCl, respectively till pH 7. Then the degradation products were extracted with multiple fractions of methanol (3 × 10 mL), then quantitatively transferred into 50 mL volumetric flasks and the volume was completed with methanol to reach concentration 1.00 mg mL^{-1}. Aliquot portions of these solutions were diluted with methanol to prepare working standard solutions of 0.1 mg mL^{-1}.

Complete acidic and alkaline degradation of the studied drug was confirmed by the TLC method using toluene: acetone: ammonia (5:5:0.1 by volume)[9] where no peaks corresponding to intact drug were detected in case of the degraded samples. The degradates were elucidated by IR spectrometry.

2.5. Procedures

2.5.1. Construction of calibration curves for D^1 spectrophotometric method

Accurately measured volumes of intact PIM working solution (0.1 mg mL^{-1}) were transferred into a series of 10-mL volumetric flasks and diluted to the mark with methanol to obtain concentrations from 10 to100 μg mL^{-1}. The D^1 spectra of each solution were recorded using $\Delta\lambda$ = 8 and scaling factor = 100. For determination of PIM in presence of its acidic and alkaline degradates, calibration curves were obtained by plotting the peak amplitudes of D^1 at 252 nm and 256.6 nm respectively (corresponding to zero-crossing of the degradation product) versus the corresponding drug concentrations, and regression equations were computed.

2.5.2. Construction of calibration curves of (DD^1) spectrophotometric method

Different aliquots of intact PIM working solution (0.1 mg mL^{-1}) were accurately transferred into a series of 10 mL volumetric flasks and diluted to the mark with methanol to obtain concentrations from 10 to100 μg mL^{-1}. The DD^1curves were recorded at $\Delta\lambda$ = 8 and scaling factor = 10.