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ORIGINAL ARTICLE

A new simple and rapid validated RP-HPLC method for determination of ziprasidone in ziprasidone capsules

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Abstract In this work, a new isocratic reverse phase chromatographic method was developed using HPLC for ziprasidone hydrochloride monohydrate (ZHM). The newly developed method is applicable for assay determination of the ZHM in capsule dosage form. The chromatographic separation of ZHM was achieved on a Zorbax SB C-8 (50 × 4.6) mm, 3.5 μm column within a short runtime of 2 min. The method was validated according to the International Conference on Harmonization (ICH) guidelines with respect to specificity, precision, linearity, accuracy, range, stability of analytical solution, robustness and system suitability. The satisfying recoveries (98–100%) and low coefficient of variation confirmed the suitability of the proposed method for the routine analysis of ZHM in pharmaceuticals.

1. Introduction

Ziprasidone hydrochloride monohydrate (ZHM) is an antipsychotic drug that chemically differs from phenothiazine or butyrophenone antipsychotic agents. ZHM is chemically known as 5-[2-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride (Fig. 1) and is used for the treatment of schizophrenia, mania and mixed states associated with bipolar disorder. ZHM has a potent selective antagonist activity for the serotonin type 2 (5-HT2), dopamine type 2 (D2), 1 and 2 adrenergic and H1 histaminergic receptors (Brunton et al., 2006). Comprehensive literature survey reveals that several analytical methods have been reported for the estimation of ZHM, which include reverse phase high performance liquid chromatography (RP-HPLC), high performance thin layer chromatography (HPTLC), UV–visible spectrophotometry and electrophoresis. Among them, most of the analytical methods employed are aimed at quantifying ZHM in biological fluids using UV (Zhang et al., 2007a) and fluorescence (Suckow et al., 2004) detection as well as LCMS/MS (Zhang et al., 2007b) method. Other methods re-

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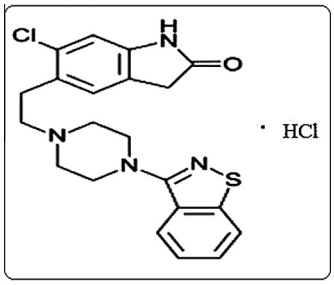

Figure 1 Structure of ZHM.

ported to determine ZHM in bulk and its pharmaceutical dosage forms includes RP-HPLC (Rani and Reddy, 2006; Prasanthi and Rao, 2010; Chudasama et al., 2010; Palvovic et al., 2011), normal and reverse phase HPTLC (Skibiński and Komsta, 2010), capillary zone electrophoresis (Farina et al., 2008), UV-spectrophotometry (Jain et al., 2006; Kumar et al., 2010) and visible-spectrophotometric (Srinubabu et al., 2006; Kishore and Hanumantharao, 2010) methods. All the methods reported in the literatures have longer run time. The utilization of higher sample throughput with more information per sample will decrease the time to market and is an important driving force in today's pharmaceutical industry. The target of this study is to develop a new, simple, rapid, economical, precise and accurate analytical method by RP-HPLC to quantify ZHM in capsule dosage forms together with its validation study. This work describes the validation parameters stated by the International Conference on Harmonization (ICH) guidelines which include specificity, precision, linearity, accuracy, range, stability of analytical solution, robustness and system suitability.

2. Experimental

2.1. Chemicals and reagents

A reference standard of ZHM (Potency: 96.0% w/w on as is basis) and its impurities were synthesized in Jubilant Life Sciences Limited, Nanjangud, India and characterized by using LC–MS, IR and NMR. ZHM capsules were purchased from local pharmacy. The HPLC grade solvents used were of E-Merck (India) Ltd., Mumbai. Potassium dihydrogen orthophosphate, triethylamine, hydrochloric acid, *ortho* phosphoric acid, sodium hydroxide, methanol, acetonitrile, hydrogen peroxide, (Merck, Mumbai, India) were used in the analysis. HPLC grade water was prepared using Millipore purification system.

2.2. Instrumentation

A HPLC instrument (Waters Acquity separations module) consisting of Photodiode Array Detector (ACQ-PDA) equipped with Empower Chromatographic Software at wavelength 229 nm was used for this analysis. The chromatographic separations were performed on a Zorbax SB C-8 (50 × 4.6) mm, 3.5 μm column by keeping it on 40 °C using a flow rate of 0.9 mL min^{-1} with the run time of 2 min. Injection volume was set as 1 μL.

2.3. Mobile phase and diluent

The mobile phase was a mixture of buffer (pH = 3.0) and methanol (45:55 v/v), filtered through 0.2 μm finer porosity nylon membrane filter and degassed prior to use. The buffer (pH = 3.0) was prepared by dissolving about 1.36 g of potassium dihydrogen *ortho* phosphate and 2 mL of triethylamine in 1000 mL of water and adjusting the pH to 3.0 ± 0.05 with *ortho* phosphoric acid. Water and acetonitrile in the ratio of 30:70 was used as diluent.

2.4. Standard preparations

Standard stock solution was prepared by dissolving ZHM standard equivalent to 100 mg of ZHM in 50 mL of diluent. The above stock solution was diluted to get a final standard concentration of 200 μg ml^{-1}.

2.5. Sample solution

The sample solution was prepared by taking the content of five capsules (ZHM capsules, 40 mg cap^{-1} strength) into 250 mL volumetric flask and dissolved in 75 mL of water then sonicated to disintegrate the capsules. Further the solution was diluted with 100 mL of acetonitrile, subsequently sonicated for about 45 min with intermittent shaking. Allowed to cool to room temperature and made up the volume with acetonitrile. A portion of the solution was centrifuged for about 5 min at 4000 rpm, followed that 5 mL of supernatant solution was diluted to 20 mL with diluent. Then the solution was filtered through 0.2 μm nylon membrane filter.

2.6. Validation

The developed method has been validated for the assay of ZHM in capsules, 40 mg cap^{-1}, strength using following parameters (CPMP/ICH/281/95, 1994; CPMP/ICH/381/95, 1996; Sethi, 1996; Gennaro, 2000; Kazakevich and Lobrutto, 2007).

2.6.1. System suitability

200 μg mL^{-1} concentration of ZHM standard was prepared and injected into the chromatography as six replicates. The tailing factor for the ZHM peak from the first injection of the standard preparation should be less than 2.0, and the column efficiency determined from ZHM peak from the first injection of the standard preparation should not be less than 1500 theoretical plates. The relative standard deviation for the mean area calculated for ZHM peak from the six replicate injections of standard preparation should be less than 2.0%.

2.6.2. Specificity

Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities. Specificity consisted of interference and forced degradation studies.

2.6.3. Interference study

Sample and placebo solutions of ZHM capsules were prepared and analyzed to check the peak purity of ZHM peak in sample solution. Further, the sample solution of ZHM capsules was spiked with ZHM hydrochloride related substances (Impurity A, Impurity B, Impurity C, Impurity D and open ring) at about 1% level, in triplicate, to check its interference, if any, with ZHM peak. Peak purity was calculated from the ZHM peak in the spiked sample solution. Specificity of the method