PREPARATION AND EVALUATION OF IN SITU OPTHALMIC GEL OF AN ANTI INFECTIVE DRUG FOR SUSTAINED OCULAR DELIVERY

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INTRODUCTION

Pharmaceutical Analysis[1, 2] is the branch of chemistry involved in separating, identifying and determining the relative amounts of the components making up a sample of matter. It is mainly involved in the Qualitative identification or detection of compounds and Quantitative chemical analysis of the substances present in bulk and pharmaceutical preparations.

Very often, there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, report of new toxicities, and development of patient resistance and introduction of better drugs by the competitors. Under these conditions, standard and analytical procedures for these drugs may not be available in Pharmacopoeias.

Quality control is a concept, which strives to produce a perfect product by series of measures designed to prevent and eliminate errors at different stage of production. The decision to release or reject a product is based on one or more type of control action. With the growth of pharmaceutical industry during last several years, there has been rapid progress in the field of pharmaceutical analysis involving complex instrumentation. Providing simple analytical procedure for complex formulation is a matter of most importance.

OBJECTIVES

Ranolazine is indicated for the treatment of chronic angina; it may be used in combination with beta blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers. It has been shown to decrease angina episodes in individuals with coronary artery disease on maximal doses of amlodipine. In addition, it has been shown to both decrease angina episodes and increase exercise tolerance in individuals taking concomitant atenolol, amlodipine, or diltiazem.

1) **Development and validation of a New Analytical Method for the Determination of related Components and assay of Ranolazine in bulk Drug and pharmaceutical Dosage Forms by LC**[16]**.**

Madhavi A *et al.*

A novel Liquid Chromatographic method has been developed and validated for the determination of Ranolazine, its potential four impurities in drug substance and drug products. C_{18} stationary phase (150 × 4.6 mm, 3.0 microns particles) has been used with simple mobile phase combination given in gradient mode at a flow rate of 1.0 ml / min. This method was capable to detect all four impurities of Ranolazine at a level below 0.004 % with respect to test concentration of 1.0 mg/ml for a 10 µl injection. The method has shown good, consistent Recoveries for Ranolazine (98.8 – 101.1 %) and for its four impurities (97.2 – 100.3 %).

2) Determination of Ranolazine in Rat Plasma by Liquid Chromatography–electro spray Ionization Mass Spectrometry[17]**.**

Zhong J *et al.*

A rapid and sensitive Liquid Chromatographic–Mass Spectrometric (LC – MS) method, with phenoprolamine hydrochloride as IS, has been developed and validated for determination of Ranolazine in rat plasma. After liquid–liquid extraction the compound was analyzed by HPLC on a C_{18} column, with methanol–10 mM ammonium acetate, 76:24 (v/v), as mobile phase, coupled with electro spray ionization Mass Spectrometry (ESI-MS). The protonated analyte was quantified by selected-ion monitoring (SIM) with a quadrupole mass spectrometer in positive-ion mode. Calibration plots were linear over the concentration range 0.046 – 12 µg / ml.

METHODOLOGY

DETERMINATION OF RANOLAZINE BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC):

A simple, rapid, precise, accurate and specific RP-HPLC method for separation and determination of Ranolazine in pure form and its formulations were developed using UV detector.

After several trials with the different combination and ratio of solvents, the mobile phase 0.05M potassium di Hydrogen ortho phosphate + 0.2% triethylamine Ph-5 adjust with Ortho Phosphoric acid : Acetonitrile (55 : 45, v/v). was selected, since it was found to be ideal to resolve the peaks for the estimation of Ranolazine. Detection wavelength 227 nm was selected by scanning the standard solution of Ranolazine over a wide range of wavelength 200 nm to 400 nm in UV Spectrophotometer.

The described assay was validated in terms of linearity, accuracy, precision, limit of detection and limit of quantification according to the ICH guide lines.

EXPERIMENTAL

Apparatus and Software

The liquid chromatographic system consisted of following components: Thermo scientific HPLC model containing LC-20AT (VP series) pump, variable wavelength programmable UV / VIS detector SPD-20A (VP series) and Rheodyne syringe (705 NR, 50 µl). Chromatographic analysis was performed using Spinchrom software on a Phenomenex-Gemini C-18 column with 150 x 4.6 mm internal diameter and 5 µm particle size.

RESULTS

REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD (RP-HPLC METHOD)

In RP-HPLC method, HPLC conditions were optimized to obtain, an adequate separation of eluted compounds. Initially, various mobile phase compositions were tried to elute title ingredient. Mobile phase and flow rate selection was based on peak parameters (height, capacity, theoretical plates, tailing or symmetry factor), run time, resolution. The system with mobile phase combination containing 0.05M potassium di Hydrogen ortho phosphate + 0.2% triethylamine P^H-5 adjust with Ortho Phosphoric acid : Acetonitrile with flow rate 1 ml / min was Used. The optimum wavelength for detection was 227 nm at which better detector response for the drug was obtained.

DISCUSSION

The objectives of the proposed work was to develop some new and sensitive analytical methods for the determination of Ranolazine and to validate the methods according to USP and ICH guidelines and applying the same for its estimation in pharmaceutical formulations.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

In HPLC method, HPLC conditions were optimized to obtain, an adequate separation of eluted compounds. The objective of this study was to develop a rapid and sensitive RP-HPLC method for the analysis of Ranolazine in bulk drug and pharmaceutical dosage form by using the most commonly employed RP C-18 column with UV-detection.

Initially, various mobile phase compositions were tried to elute the drug. Mobile phase ratio and flow rate were selected based on peak parameters (height, capacity, theoretical plates, tailing or symmetry factor), run time and resolution. The system with0.05M potassium di Hydrogen ortho phosphate + 0.2% triethylamine Ph-5 adjust with Ortho Phosphoric acid : Acetonitrile, (55 : 45) v/v and 1 ml / min flow rate was selected.

The optimum wavelength for UV detection was 227 nm at which better detector response for the drug was obtained. The retention time for Ranolazine was found to be 3.41 min. The calibration was linear in concentration range of 20-120 mcg / ml, with regression 0.999, intercept 10.67 and slope 61.28 for Ranolazine and the calibration curve are

CONCLUSION

Development of methods to achieve the final goal of ensuring the quantity of drug substances and drug products is not a trivial undertaking. The capabilities of the four

methods were complementary to each other. Hence they can be regarded as simple, specific and sensitive methods for the estimation of Ranolazine in Bulk drug and Pharmaceutical dosage forms.

A very few analytical methods appeared in the literature for the determination of Ranolazine includes UV spectroscopic, LC, HPLC, LC-MS and High Performance Thin Layer Chromatography modified methods has been reported for the quantification of Ranolazine. In view of the above fact, some simple analytical methods were planned to develop with sensitivity, accuracy, precision and economical.

In the present investigation, simple, sensitive, precise and accurate RP - HPLC method was developed for the quantitative estimation of Ranolazine in its Bulk drug and Pharmaceutical dosage forms.

SUMMARY

Several drugs are available in the form of pharmaceutical formulations to control diseases. Methods of assay for controlling the concentration of these chemicals in the medicine and in the living body are necessary. Pharmaceutical analysis occupies a pivotal role in statutory certification of drugs and their formulations either by the industry or by the regulatory authorities. The complexity of problems encountered in pharmaceutical analysis coupled with importance of achieving the selectivity, speed, cost, simplicity, precision and accuracy results in new methods of analysis being quickly adopted by the pharmaceutical industry. The ever increasing use of pharmacodynamic and chemotherapeutic agents in pharmaceutical preparations makes their determination a matter of foremost importance. In some cases, no precise analytical methods are reported

and quite often the reported methods need improvement or changes keeping in view of the advances.

Among several instrumental techniques (HPLC, GLC, Fluorimetry, IR, UV, Vis, NMR, and Mass spectrometry) available for the assay of drugs. HPLC is a versatile tool for the qualitative and quantitative analysis of drugs and pharmaceuticals, chemical and biological materials and has become indispensable in pharmacokinetics studies. HPLC technique has been regarded as the best among various instrumental ones in spite of its heavy cost and maintenance problems. Due to the importance of analysis, present analytical methods have been developed for some of the widely used Anti-hypertensive drugs such as Ranolazine. Hence both RP-HPLC and spectrophotometric methods were planned to develop.

There is a wide scope for the development of new analytical methods for the assay of the above drug. UV Spectrophotometry, RP-HPLC techniques have been used as tools in the present work. The above tools have been used for the development of new analytical methods for the assay of the above mentioned drug. The contents of the thesis have been divided into nine chapters.

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