ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A REVIEW ON ESTIMATION OF CRISABOROLE DRUG BY USING DIFFERENT ANALYTICAL MEHODS

J. N. Suresh Kumar[1], Ramakrishna. M[2], Venkata Lakshmi Roshini. J[3], Jagadeesh. N[4], Sai Tejaswini.T[5]

Narasaraopeta Institute Pharmaceutical Sciences, Yellamanda, Narasaraopeta, Andhra Pradesh

*Corresponding author E-mail: ramakrishna0922@g.mail.com

ARTICLE INFO

Key words:
Crisaborole, UPLC, HPLC, UPLC-MS, RP-HPLC, UPLC-ESI/MS, Analytical method.

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Crisaborole is a non-steroid topical medication which is FDA approved drug. This review article presents the collection and discussion of various validated analytical methods were applied for the drug crisaborole for stability indicating method development and validation, estimation and quantification, to determine genotoxic impurities, stress testing by novel stability indicating and quantification in matrices by using UPLC,HPLC,UPLC-MS,RP-HPLC,UPLC-ESI/MS methods. Crisaborole has a broad-spectrum anti -inflammatory activity by mainly targeting phosphodiesterase 4 (PDE4) enzymes that is a key regulator of cytokine production. Topical application of this drug is useful as it potentiates localization of drug in skin. These methods are all carried out under acid, base, thermal, photolysis, peroxide and neutral conditions.

INTRODUCTION

Crisaborole is a novel oxaborole approved by FDA on December 14, 2016 as Eucrisa. The present invention also provides novel intermediates and process for the preparation of intermediates used in the preparation of Crisaborole. The present invention also provides an improved process for the preparation of Crisaborole and pharmaceutically acceptable salts thereof, that is commercially and industrially scalable.Crisaborole is non- steroidal phosphodiesterase inhibitor and it is the first topical ointment. This ointment is usually prescribed for 28 days in additional it will be used for 48 weeks. It is applied twice in a day.

The chemical structure of crisaborole consist of boron atom which facilitates the skin penetration and binding to the bimetal center of phosphodiesterase 4 enzyme.Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined.EUCRISA may cause side effects including allergic reactions at or near the application site or at a distant site. These can be serious and may include trouble breathing, throat or chest tightness, feeling faint, swelling of the face, eyelids, lips, mouth, tongue or throat, hives, itching, and redness.

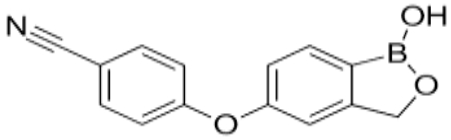
CHEMICAL CHARACTERISTICS:

Crisaborole is a white powder. It is freely soluble in common organic solvents like isopropyl alcohol and propylene glycol. The drug is insoluble in water. The melting range of crisaborole drug is 128.8°c- 134.6°c. The

partition coefficient and dissociation constant of drug are 3.24 and 6.98.

CHEMICAL TAXONOMY:

Crisaborole is chemically known as 4-[(1-hydroxy-1, 3-dihydro-2,1-benzoxaborole-5-yl)oxy]benzonitrile) is a member of the class of benzoxaboroles characterized by the presence of boric acid hemister with a phenolic ether and a nitrile.



Chemical structure of crisaborole

Molecular formula:$C_{14}H_{10}BNO_3$

Molecular weight: 251.05

PHARMACOKINETIC STUDIES:

It has low systemic absorption thus poses less risk of developing systemic side effects. Crisaborole is substantially metabolized into inactive metabolites. Crisaborole is 97% bound to human plasma proteins. The major metabolite 5-(4-cyanophenoxy)-2-hydroxybenzyl alcohol(metabolite-1), is formed via hydrolysis; this metabolite is further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite-2), formed via oxidation , is also called as a major metabolite. Metabolites are majorly excreted through kidney. Toxicity of this drug is hypersensitivity reactions such as contact utricaria may occur.

Drug interactions associated with the crisaborole are with the combination of daprodustat the metabolism of daprodustat can be decreased when combined with crisaborole and with drug erdafitinib the serum concentration of erdafitinib can be increased.

ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY- ELECTRO SPRAYS IONISATION –MASS SPECTROSCOPY:

The validated analytical method was applied for the estimation of Crisaborole in aqueous and human plasma with Crisaborole-D4 as an internal standard by using UPLC-ESI-MS/MS.The chromatographic separation was achieved with 10mM ammonium acetate buffer solution (pH- 4.5): Methanol, (10:90) (% v/v) using the Xterra C18, 100 × 4.6, 5µ. The total analysis time was 2 min, and the flow rate was set to 0.5 ml/min. The mass transitions of Crisaborole and Crisaborole-D4 obtained were m/z 252.1 □ 222.1 and 256.1 □ 222.1. The standard curve shows a correlation coefficient (r2) greater than 0.999 with a range of 75.00-225.00 ng/ml using the linear regression model.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY:

This work describes a simple method for the quantification of the drug in the skin layers at the end of in-vitro permeation experiments. Chromatographic separation was carried out on a reverse-phase C_{18} column using a mixture of trifluoroacetic acid 0.05%-acetonitrile (55:45, v/v) as mobile phase, pumped at 1 ml/min. Column temperature was 35°C and UV detection was performed at 250 nm. The method was linear in the range of concentration from 0.06 to 6µg/ml (R^2 = 1) and was selective, precise and accurate. Depending on the solvent used, the LOQ ranged from 0.014 to 0.030µg/ml and the LOD from 0.005 to 0.010µg/ml. The extraction from all the skin layers was quantitative. The developed method was successfully tested in an in-vitro permeation study, proving to be an effective tool in the development of new formulations containing crisaborole.

REVERSE PHASE- HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

An isocratic reverse phase high performance liquid chromatographic method has been developed for the determination of crisaborole (CRB), a novel non-steroidal topical phosphodiesterase-4-inhibitor. The analyte was separated on an Agilent eclipse XDB-C18 (3.0 × 150 mm, 3.5 µm) analytical column using water: acetonitrile (30: 70 v/v) as the mobile phase at a flow rate of 0.75 ml/min under ambient temperature and PDA detection at 254 nm. Added to this, several validation parameters were exercised on the developed HPLC method as per ICH guidelines. Method variables, viz., mobile phase flow rate (0.75 ± 0.1 ml/min) and percentage of organic modifier in mobile phase (70 ± 5%) were studied by a central composite design for testing the robustness of the proposed method. The method was found to be linear in the concentration range of 2–100 µg/ml (r^2 = 0.999) and precise

(RSD < 2%) satisfying regulatory criteria. The method was found to be robust and ambiguity of worst result for certain responses still are acceptable and likely to occur due to the effect of extreme experimental conditions. Stress testing of CRB was carried out under acid, base, thermal, photolysis, peroxide and neutral conditions. Separation of the forced degradation products from the main analyte was accomplished using a gradient elution of the mobile phase consisting acetonitrile from 0 to 100% in water at a flow rate of 1.2 ml/min.

ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY:

The validated analytical method was applied for the estimation of Crisaborole (CRB) by reverse phase ultra-performance liquid chromatography (RP-UPLC). The drug was subjected to various stress Conditions such as hydrolysis, oxidation, photolytic and thermal degradations to investigate the stability indicating ability of the method. Compound is highly sensitive against hydrolytic stress conditions like basic and oxidative stress conditions. In oxidative condition product completely converted into degradation product with boron ring got opened. Efficient chromatographic separation was achieved by using Acuity; UPLC, CSH; C-18; 100 x 2.1mm; 1.7 µm column with the mobile phase consisting of 0.1% Trifluoroacetic acid in water and 0.1% Trifluoroacetic acid in acetonitrile in a gradient elution mode within a short run time of 6.0 minutes at a flow rate of 0.4 ml/min with column temperature at 25°C. The developed method was validated as per the current ICH quality guidelines with respect to specificity, precision, accuracy, linearity, robustness and solution suitability. The average recovery values of Crisaborole were found to be in the range of 100.05-101.16 %. The developed method was linear with the correlation value of 0.9995 for Crisaborole. The repeatability and intermediate precision expressed by RSD were less than 2.0% for Crisaborole. The test solution was found to be stable in diluent for 72 h when stored at room temperature. The developed UPLC method is superior in technology against conventional HPLC with respect to speed, resolution, solvent consumption and cost of analysis. This method is compatible to LCMS analysis which enables to identify the unknown impurities or the degradants formed in the process.

ULTRAPERFORMANCE LIQUID CHROMATOGRAPHY-MASS SPECTROSCOPY

Atopic dermatitis (AD) is an allergic skin disease that can be inherited. Crisaborole is a specific drug developed to deal with this disease. The compounds of 4-(4- Bromo-3-formyl-phenoxy)-benzonitrile4-(4-(4-bromo-3-formylphenoxy)-3-formylphenoxy) benzonitrile are the representative impurities in the synthesis of Crisaborole active pharmaceutical in gradient (API). Owing to the genotoxic impurities that could lead to cancer and gene mutations, it is necessary to develop a simple, efficient, sensitive, and accurate method to detect these impurities. In this study, the 4-(4-Bromo-3-formyl-phenoxy)-benzonitrile and 4-(4-(4-bromo-3-formylphenoxy)-3-formylphenoxy) benzo- nitrile present in Crisaborole API were detected using UPLC-MS/MS. The separation was made on a ZORBAX Eclipse XDB-Phenyl column (4.6 mm ×75mm, 3.5µm) with the mobile phase of acetonitrile solution containing 0.1% trifluoroacetic acid (A) and water containing 0.1% formic acid (B) in gradient elution mode. Quantification was performed using positive ion electrospray ionization (ESI), and the contents of two compounds were determined using the multiple reaction monitoring (MRM) modes. The quantitative analytical method was fully validated with respect to linearity (r > 0.9998), sensitivity, precision, accuracy (the average recovery of two impurities was 84.1% to 90.7%), and robustness. Three batches of samples were detected by UPLC-MS/MS, indicating that the proposed approach was applicable for the quality evaluation of Crisaborole.

REPORTED ANALYTICAL METHODS:

S.NO	Method	Description	Reference
1.	UPLC-ESI/MS	Stationary phase: Xterra C_{18} (100x4.6) Mobile phase: 10Mm ammonium acetate buffer solution:methanol(%v/v) (10:90) Run time: 4min Flow rate: 0.51ml/min Column Temperature: 40^{o}c Injection rate : 150.0ng/ml % recovery: 101.43% LOD : 4.30ng/ml LOQ :14.32ng/ml	1
2.	HPLC	Stationary phase: reverse phase C_{18} column Mobile phase: Triflouroacetic acid: acetonitrile(%v/v) Flow rate: 1ml/min Column temperature: 35^{o}c Wavelength: 250nm LOD: 0.005- 0.010 µg/ml LOQ: 0.014- 0.030µg/ml	2
3.	RP-HPLC	Stationary phase: Agilent eclipse XDB-C_{18} (3.0X 150mm) Mobile phase: water: acetonitrile(30:70%v/v) Flow rate: 0.75ml/min Wavelength: 254nm LOD: 0.185µg/ml LOQ: 0.56µg/ml	3
4	UPLC	Stationary phase: Acuity UPLC,CSH-C_{18}(100X2.1mm) Mobile phase: 0.1%Triflouroacetic acid in water 0.1% Triflouroacetic acid in acetonitrile Flow rate: 0.4ml/min Column temperature: 25^{o}c LOD: 0.006µg/ml LOQ: 0.01µg/ml	4
5.	UPLC/MS	Stationary phase: ZORBAX Eclipse XDB-Phenyl column(4.6nmx75mm) Mobile phase: acetonitrile solution contain 0.1%triflouroacetic acid+ water containing 0.1% formic acid	5

CONCLUSION:

The above study presents analytical methods for estimation of crisaborole in bulk materials and pharmaceutical dosage forms. Literature survey suggested that various UPLC-ESI/MS, HPLC, RP-HPLC, UPLC methods were developed and reported for crisaborole drug in bulk and its formulations. Hence these all methods are used to estimate and validate by Simple, economic, precise, accurate and reproducible ways. This review suggested that Liquid chromatographic methods are widely used for the estimation of drug crisaborole in bulk and its formulation. This review will help in future to develop the novel analytical methods for estimation of crisaborole in bulk and its formulations.

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