Characteristics, Properties, Analytical and Bio-analytical methods of Enzalutamide: A Review

B. Ramachandra*[1], Ch. Gangu Naidu[2], B. Raju[3]

*[1]Government College for Men, Kadapa-516004, Kadapa Dist, Andhra Pradesh, India.

[2]Division of Chemistry (S&H), Vignan Foundation for Science and Technology Research University, Guntur-522213, AP, India.

[3]Department of Applied Chemistry, College of Applied Science, Kyung Hee University, South Korea-446-701.

*Corresponding Author: Dr. B. Ramachandra, Email: bramachandra84@gmail.com

Phone No: 91-9492753765

Abstract:

EZA (ENZ) is an efficient second-generation androgen receptor inhibitor accustomed treat metastatic castration-resistant prostate cancer (mCRPC). It absolutely was developed by Medivation and Astellas and approved by the FDA in 2012 under the brand name of Xtandi™. EZT has three major anticancer mechanisms, which inhibit the binding of androgens to the ligand-binding domain of androgen receptors (AR); inhibit nuclear translocation of AR; inhibit binding of AR to DNA. It shows the reduced expression of androgen receptor-dependent genes, decreased growth of prostate cancer cells, and induction of cancer cell death and tumour regression. As a result, the survival rate of patients with mCRPC is increased. As EZA holds great importance in anticancer therapy, hence, it's necessary to compile the various analytical and bio-analytical methods to monitoring the bioequivalence, bioavailability and therapeutic monitoring of a drug during patient follow-ups. Thus, this study presents a comprehensive literature review on characteristics, properties, analytical and bio-analytical methods in several matrices which include formulations, biological fluids, and drug delivery systems.

Keywords: Enzalutamide, mCRPC, androgen receptor inhibitor, Analytical methods, Bio-analytical methods

1. Introduction

Prostate cancer is that the second most common cancer in men, with an estimated 31,620 deaths and 174,650 cases in the US during 2019. Nearly 60% of cases are diagnosed in men over the age of 65, the disease seldom occurs before the age of 40.[1] Early in their development, prostate cancers required relatively high levels of male sex hormones i.e., androgens to grow. The testes are the main origin of androgens, and treatments that stop the testes from generating male sex hormones known as Androgen Deprivation Therapy (ADT). Hence, most of the prostate cancers depend on androgen (testosterone–male sex hormone) and the androgen receptors (AR) for their development and survival. The AR regulates the expression of many of genes in response to binding androgen.[2]

There are two important therapeutic approaches employed in ADT: the primary is to decrease the androgen levels by either chemical or surgical castration, and also the second is to inhibit androgen from binding to the androgen receptors by the utilization of a competitive inhibitor called antiandrogen.[3] The first-generation antiandrogens were developed in the early 1990s for prostate cancer like Flutamide, Bicalutamide, Nilutamide, etc, Reduction of circulating levels of androgen (testosterone) by 90% within 24 hrs is accomplished by surgical castration. In chemical castration uses analogs of luteinizing hormone-releasing hormone (LH-RH) to stop prostate cancer. The drugs used as LH-RH agonists are leuprolide acetate and goserelin acetate.[4]

After primary treatment with surgical or chemical castration, most of the patients inevitably reach to a state of the disease named as metastatic castration-resistant prostate cancer (mCRPC) that's associated with tumour development with a median survival of less than 2 years.[5] Antiandrogens and LH-RH agonists are the front line of hormone therapy for advanced prostate cancer, although it's not curative. Recently, new therapy options for

mCRPC with different mechanisms of action are available like targeting androgen receptor signaling viz abiraterone acetate.[6] Besides, second-generation androgen receptor antagonists like, EZA, apalutamide and darolutamide, etc. are developed for mCRPC treatment, which ultimately inhibits tumor growth and proliferation. Also, these drugs increased quality of life and overall survival in mCRPC patients.[7]

Recently, non hormonal therapies were approved for mCRPC include sipuleucel-T (immunotherapy).[8] and radium-223.[9] Unfortunately, these non hormonal therapies only increase survival time by some months with patients succumbing to mCRPC. Hence, the research for new approaches to block the transcriptional activity of the AR is that the main focus of current drug development programs. This highlights the trend to develop drugs with novel mechanisms of action and potentially different mechanisms of resistance compared with antiandrogens.

2. EZA

Enzalutamide (earlier referred to as MDV-3100 & ASP-9785) is an efficient second-generation androgen receptor inhibitor accustomed treat mCRPC. It was developed by Medivation and Astellas and approved by the FDA as a new drug in 2012 under the name of Xtandi™. The formulation of ENZ is available as liquid-filled soft gelatin capsules. Each soft gelatine capsule contains 40 mg of ENZ as a solution in caprylocaproyl polyoxylglycerides. It is administered at a fixed oral dose of 160 mg once daily (OD) regardless of body surface area, age, and clinical condition.[10]

2.1 Physicochemical properties

Enzalutamide is chemically, 4-{3-[4-cyano-3-(trifluromethyl) phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. It is an achiral compound, therefore no stereoisomerism is observed. A single polymorphic form has been observed

which is consistently produced by the manufacturing process. The drug substance melts at 201°C. EZA is a white crystalline non-hygroscopic solid, practically insoluble in water, sparingly soluble in methanol, and soluble in acetonitrile and dimethyl sulfoxide between pH 1 and 11.[11]

2.2. Biological properties

Enzalutamide is a small molecule with no ionizable groups at biologically relevant pH, therefore, EZA solubility isn't affected by pH over the physiological range. EZA exhibits low aqueous solubility (≤2.0 mg/mL at relevant pH range), high permeability across Caco-2 monolayers (mean apparent permeability coefficient ≥31x10-6 cm/sec), and isn't a substrate for P-glycoprotein. Due to its low solubility and high permeability, EZA is a biopharmaceutics classification system (BCS) class 2 drug substance.[12] The EZA and its reactive metabolites i.e., N-desmethyl EZA and carboxylic acid derivatives are highly protein-bound 97-98% and 95%, respectively.[10]

3. Mechanism of action

EZA is among several hormone therapies that are developed to forestall the androgen-fuelled growth of castrate-resistant prostate cancers. EZA has three major anticancer mechanisms, which inhibit binding of androgens to the ligand-binding domain (LBD) of AR; inhibit nuclear translocation of AR; inhibit binding of AR to DNA; inhibit interactions of AR with co-activators and also suppress prostate cancer cell growth by activating the TGF-β pathway.[13-15] It's a competitive inhibitor of dihydrotestosterone, the active metabolite of testosterone.[7] EZA acts to induce apoptosis to decrease tumour volume furthermore the proliferation of cancer cells.[15-16] However, most prostate cancers eventually become castrate resistant that's, they can grow even when androgen levels in the blood are very low. ADT doesn't block the production of the small amount of androgen that's made by the adrenal

glands and by prostate cancer cells themselves, and this low level is sufficient to fuel the growth of castrate-resistant prostate cancers. Overall, compared with other anti-androgen, it shows the reduced expression of androgen receptor dependent genes, decreased growth of prostate cancer cells, and induction of cancer cell death and tumor regression. As a result, the survival rate of patients with mCRPC is increased.[16]

3.1. ADME studies of ENZ

EZA is metabolized by CYP2C8 and CYP3A4. The two basic metabolites found in human plasma were N-desmethyl enzalutamide and a derivative of carboxylic acid. N-desmethyl enzalutamide is an active metabolite formed by means of CYP2C8 metabolism. In contrast, the metabolite of carboxylic acid is inactive. At steady state, N-desmethyl enzalutamide circulates at approximately the same plasma concentration as EZA, while the carboxylic acid metabolite is approximately 25 % lower in vitro assays. In addition, EZA is mainly eliminated by hepatic metabolism, while renal excretion is an insignificant elimination route for EZA and its active metabolite, N-desmethyl enzalutamide.[3,17] But, renal excretion is therefore an important pathway for the metabolite of carboxylic acid. EZA and N-desmethyl enzalutamide have half-lives of 5.8 and 8.6 days when taking a daily oral dose of 160 mg in combination with LH-RH analogs, respectively.[3] Therefore, patients treated with 160 mg once daily reached the steady-state concentrations after approximately one month of dosing. Median steady-state trough plasma concentrations of EZA, N-desmethyl enzalutamide, and enzalutamide carboxylic acid are 11.4 mg/mL, 13.0 mg/mL, and 8.44 mg/mL, respectively. Since, the pharmacokinetics of EZA and the also active metabolite N-desmethyl enzalutamide are rarely affected by hemodialysis, EZA seems to be a viable treatment strategy for patients with end-stage renal disease undergoing hemodialysis.[18]

4. Synthetic Methods:

Many synthesis routes of ENZ have been reported previously.[19-23] Xingling Ma et.al. elucidated structures of the impurities, degradation products and their mechanistic pathways.[24] Zhou et.al. also proposed mechanistic pathway for the formation of EZA impurities and their pathways.[26] **Fig. 1** shows schematic representation of impurities and their path way of formation.

Table.1: Impurities and their pathway of formation

5. Analytical Methods

The development of analytical methods for quality control of drugs and pharmaceuticals is a requirement for industries and laboratories. That maintains the product quality and consumer trust. Moreover, analytical methods also play an important role in the pharmaceutical industry, being present from the stages of initial drug synthesis to post-marketing steps. Various analytical methods were reported in the literature not only to detect drugs separately but also in combination with other drugs. The analytical and bio analytical methods used for determination of Enzalutamide are presented in **Table 2.**

A HPLC method was developed for elucidation of structures of EZA impurities. [24] Determination of Related Substances in EZA Bulk Drug by HPLC.[25] Zhou et.al. determined potential impurities formed from the synthetic route and forced degradation studies.[26] HPLC method was developed for quantification of EZA pure drug substance.[27] Zamir et.al.,

developed a validated UV spectroscopic methods for determination of EZA in pure and pharmaceutical dosage form.[28] A stability indicating RP-LC method and UV-Visible spectroscopic method for EZA in bulk and synthetic mixture was reported.[29-30] Quantification of newly discovered anti-cancer drug EZA in bulk and synthetic mixture by stability indicating TLC method. [31]

6. Bio-analytical Methods

Bioanalysis plays a vital role in the ongoing drug development. The literature review showed that the majority of published methods were LC-MS/MS-based bio-analytical methods for quantification of EZA, metabolites and combination drugs. Determination of EZA by LC-MS method in spiked plasma samples [32]. Estimation of EZA and its active metabolite N-desmethyl enzalutamide in biofluids by LC-UV[33], LC-MS [34-37], In addition to EZA, abiraterone and their matabolites were determined in plasma samples by LC-MS-MS.[38] Simultaneous quantitation of abiraterone, EZA, N-desmethyl enzalutamide, and bicalutamide in human plasma by LC-MS/MS.[39], along with other drugs UPLC-MS-MS.[40]

7. Pharmacokinetic Studies

Pharmacokinetic analysis plays a vital role in clinical studies, which in turn related to analytical techniques behaviour. The pharmacokinetic studies of EZA [17-18] in rat plasma using LC-MS-MS [41], along with other second generation non-steroidal antiandrogens and their metabolites by RP-HPLC-UV [42] and LC-MS-MS.[43-44] Simultaneous quantification of EZA, darolutamide and their active metabolites in mice dried blood spots using LC-MS/MS.[44]

Conclusions:

EZA is a second-generation androgen receptor inhibitor used to treat metastatic castration-resistant prostate cancer (mCRPC). Analytical techniques used for pharmaceutical

analyses and therapeutic drug monitoring play an important role in comprehending the aspects regarding bioavailability, bioequivalence, and therapeutic monitoring during patient follow-ups. Thus, this study presents a brief literature review on characteristics, properties, pharmacokinetic studies, analytical and bioanalytical methods developed for the analysis of EZA in different matrices, including formulations, biological fluids, and drug delivery systems.

Conflict of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Acknowledgments

The authors thank to Dr. G. Ravindranath (Principal), Smt B. Rajeswari (In-charge, Department of Chemistry), Government College for Men(A), Kadapa, Andhra Pradesh for constant encouragement and support.

Ch. G Naidu

ORIGINALITY REPORT

50%	41%	36%	17%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.dovepress.com Internet Source	10%
2	link.springer.com Internet Source	6%
3	www.cancer.gov Internet Source	5%
4	www.tandfonline.com Internet Source	4%
5	www.ema.europa.eu Internet Source	3%
6	thieme-connect.de Internet Source	3%
7	M. van Nuland, S. Groenland, A.M. Bergman, J.I. Rotmans, H. Rosing, J.H. Beijnen, A.D.R. Huitema. "Plasma levels of enzalutamide and its main metabolites in a metastatic castration-resistant prostate cancer patient undergoing hemodialysis", Clinical Genitourinary Cancer, 2018	2%

Publication

8	www.tsijournals.com Internet Source	2%
9	journals.sagepub.com Internet Source	2%
10	Mariana Nunes de Menezes, Bianca Aparecida de Marco, Flávia Angélica Masquio Fiorentino, Alexander Zimmermann et al. "Flucloxacillin: A Review of Characteristics, Properties and Analytical Methods", Critical Reviews in Analytical Chemistry, 2018 Publication	2%
11	Alicja Puszkiel, Alain Plé, Olivier Huillard, Gaëlle Noé et al. "A simple HPLC-UV method for quantification of enzalutamide and its active metabolite N-desmethyl enzalutamide in patients with metastatic castration-resistant prostate cancer", Journal of Chromatography B, 2017 Publication	2%
12	Ji-Hye Song, Tae-Heon Kim, Jong-Woo Jung, Nakjeong Kim et al. "Quantitative determination of enzalutamide, an anti-prostate cancer drug, in rat plasma using liquid chromatography-tandem mass spectrometry, and its application to a pharmacokinetic study", Biomedical Chromatography, 2014	2%

	Publication	
13	www.authorstream.com Internet Source	2%
14	Gibbons, Jacqueline A., Michiel de Vries, Walter Krauwinkel, Yoshiaki Ohtsu, Jan Noukens, Jan-Stefan van der Walt, Roelof Mol, Joyce Mordenti, and Taoufik Ouatas. "Pharmacokinetic Drug Interaction Studies with Enzalutamide", Clinical Pharmacokinetics, 2015. Publication	1%
15	Submitted to Kaplan University Student Paper	1%
16	Submitted to Chungnam National University Student Paper	1%
17	Renata Carolina Alves, Richard Perosa Fernandes, Bruno Fonseca-Santos, Francesca Damiani Victorelli, Marlus Chorilli. "A Critical Review of the Properties and Analytical Methods for the Determination of Curcumin in Biological and Pharmaceutical Matrices", Critical Reviews in Analytical Chemistry, 2018 Publication	1%
18	onlinelibrary.wiley.com Internet Source	1%
19	www.futuremedicine.com Internet Source	<1%

20	worldwidescience.org Internet Source	<1%
21	newdrugapprovals.org Internet Source	<1%
22	Submitted to Massachusetts College of Pharmacy & Allied Health Sciences Student Paper	<1%
23	Submitted to Pacific University Student Paper	<1%
24	Guilherme Felipe dos Santos Fernandes, Hérida Regina Nunes Salgado, Jean Leandro dos Santos. "A critical review of HPLC-based analytical methods for quantification of Linezolid", Critical Reviews in Analytical Chemistry, 2019 Publication	<1%
25	Changhua Ji, Mausumee Guha, Xu Zhu, Jessica Whritenour et al. "Enzalutamide and Apalutamide: In Vitro Chemical Reactivity Studies and Activity in a Mouse Drug Allergy Model", Chemical Research in Toxicology, 2019 Publication	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		

Ch. G Naidu

PAPER NAME

Manuscript-EZA revised 13.09.22-R1.doc

AUTHOR

Dr BRC

WORD COUNT

1981 Words

CHARACTER COUNT

12323 Characters

PAGE COUNT

9 Pages

FILE SIZE

82.5KB

SUBMISSION DATE

Jan 5, 2023 10:05 AM GMT+5:30

REPORT DATE

Jan 5, 2023 10:05 AM GMT+5:30

14% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

- 11% Internet database
- Crossref database
- 5% Submitted Works database
- 5% Publications database
- Crossref Posted Content database

Characteristics, Properties, Analytical and Bio-analytical methods of Enzalutamide: A Review

B. Ramachandra[1*], Ch. Gangu Naidu[2], Y. Srinivasa Rao[3], B. Raju[4]

*[1]Government College for Men, Kadapa-516004, Andhra Pradesh, India.

[2]Department of Basic Sciences and Humanities (BS&H), Vignan's Institute of Information Technology (A), Besides VSEZ Vadlapudi Duvvada, Visakhapatnam, Andhra Pradesh-530046, India.

[3]Department of Pharmaceutics, Vignan Institute of Pharmacuetical Technology (VIPT), Besides VSEZ Vadlapudi Duvvada, Visakhapatnam, Andhra Pradesh-530046, India

[4]Department of Applied Chemistry, College of Applied Science, Kyung Hee University, South Korea-446-701.

*Corresponding Author: Dr B. Ramachandra; bramachandra84@gmail.com ; Phone No: 91-9492753765

Abstract:

EZA (ENZ) is an efficient second-generation androgen receptor inhibitor accustomed treat metastatic maiming safe prostate malignant growth (mCRPC). It totally was created by Medivation and Astellas and permitted by the FDA in 2012 under the brand name of Xtandi™. EZT has three significant anticancer systems, which hinder the limiting of androgens to the ligand-restricting space of androgen receptors (AR); repress atomic movement of AR; restrain restricting of AR to DNA. It shows the diminished articulation of androgen receptor-subordinate qualities, diminished development of prostate disease cells, and acceptance of malignant growth cell passing and cancer retrogression. As a result, the survival rate of patients with mCRPC is increased. As EZA holds great importance in anticancer therapy, hence, it's necessary to compile the various analytical and bio-analytical methods to monitoring the bioequivalence, bioavailability and therapeutic monitoring of a drug during patient follow-ups. Thus, this study presents a comprehensive literature review on characteristics, properties, analytical and bio-analytical methods in several matrices which include formulations, biological fluids, and drug delivery systems.

Keywords: Enzalutamide, mCRPC, androgen receptor inhibitor, Analytical methods, Bio-analytical methods

1. Introduction

Prostate cancer growth is that the second most normal disease in men, with an expected 31,620 passings and 174,650 cases in the US during 2019. Almost 60% of cases are analyzed in men beyond 65 years old, the sickness only occasionally happens before the time of 40. [1] Early in their turn of events, prostate tumors required moderately elevated degrees of male sex chemicals i.e., androgens to develop. The testicles are the primary beginning of androgens, and medicines that prevent the testicles from creating male sex enzymes known as Androgen Deprivation Therapy (ADT). Subsequently, the majority of the prostate cancer growths rely upon androgen (testosterone-male sex chemical) and the androgen receptors (AR) for their turn of gradual enhancement and endurance. The AR directs the declaration of large numbers of qualities in light of restricting androgen.[2]

There are two significant restorative methodologies utilized in ADT: the essential is to diminish the androgen levels by one or the other compound or careful emasculation, and furthermore the second is to hinder androgen from restricting to the androgen receptors by the usage of a serious inhibitor called antiandrogen.[3] The original antiandrogens were created in the mid 1990s for prostate cancer growth like Flutamide, Bicalutamide, Nilutamide, and so on, Reduction of circling levels of androgen (testosterone) by 90% inside 24 hrs is achieved by careful maiming. In synthetic maiming utilizes analogs of luteinizing chemical delivering chemical (LH-RH) to stop prostate malignant growth. The medications utilized as LH-RH agonists are leuprolide acetic acid derivation and goserelin acetic acid derivation.[4]

After essential therapy with careful or castration, the majority of the patients unavoidably reach to a condition of the sickness named as metastatic emasculation safe prostate malignant

growth (mCRPC) that is related with growth improvement with a middle endurance of under 2 years.[5] Antiandrogens and LH-RH agonists are the bleeding edge of chemical treatment for cutting edge cancer disease, in spite of the fact that it's not corrective. As of late, new treatment choices for mCRPC with various instruments of activity are accessible like focusing on androgen receptor flagging viz abiraterone acetate. [6] Besides, second-generation androgen receptor antagonists like, EZA, apalutamide and darolutamide, etc. are developed for mCRPC treatment, which ultimately inhibits tumor growth and proliferation. Also, these drugs increased quality of life and overall survival in mCRPC patients.[7]

As of late, non hormonal treatments were supported for mCRPC incorporate sipuleucel-T (immunotherapy). [8] and radium-223. [9] Unfortunately, these non hormonal treatments just increment endurance time by certain months with patients capitulating to mCRPC. Subsequently, the examination for new ways to deal with block the transcriptional movement of the AR is that the fundamental focal point of current medication improvement programs. This features the pattern to foster medications with novel systems of activity and possibly various instruments of opposition contrasted and antiandrogens.

2. EZA

Enzalutamide (earlier referred to as MDV-3100 & ASP-9785) is an efficient second-generation androgen receptor inhibitor accustomed treat mCRPC. It was created by Medivation and Astellas and endorsed by the FDA as another medication in 2012 under the name of Xtandi™. The definition of ENZ is accessible as fluid filled delicate gelatin containers. Each delicate gelatine case 12 contains 40 mg of ENZ as an answer in caprylocaproyl polyoxylglycerides. It 2 is administered at a fixed oral dose of 160 mg once daily (OD) regardless of body surface area, age, and clinical condition.[10]

2.1 Physicochemical properties

Enzalutamide is chemically, 4-{3-[4-cyano-3-(trifluromethyl) phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. It is an achiral compound, thusly no stereoisomerism is noticed. A solitary polymorphic structure has been seen which is reliably created by the assembling system. The medication substance liquefies at 201°C. EZA is a white translucent non-hygroscopic strong, basically insoluble in water, sparingly dissolvable in methanol, and solvent in acetonitrile and dimethyl sulfoxide amidst pH 1 and 11.[11]

2.2. Biological properties

Enzalutamide is a shrimp particle with no ionizable aggregation at naturally important pH, subsequently, EZA dissolvability isn't impacted by pH over the physiological reach. EZA shows low fluid solvency (≤2.0 mg/mL at important pH range), high penetrability across Caco-2 monolayers (mean evident penetrability coefficient ≥31x10-6 cm/sec), and isn't a substrate for P-glycoprotein. Because of its low dissolvability and high penetrability, EZA is a biopharmaceutics characterization framework (BCS) class 2 medication substance.[12] The EZA and its responsive metabolites i.e., N-desmethyl EZA and carboxylic corrosive subordinates are profoundly protein-bound 97-98% and 95%, individually.[10]

3. Mechanism of action

EZA is among a few chemical treatments that are created to hinder the androgen-fuelled development of mutilate safe prostate malignant growths. EZA has three significant anticancer systems, which repress restricting of androgens to the ligand-restricting space (LBD) of AR; restrain atomic movement of AR; hinder restricting of AR to DNA; restrain cooperations of AR with co-activators and furthermore smother prostate disease cell development by enacting the TGF-β pathway.[13-15] It's a serious inhibitor of dihydrotestosterone, the dynamic metabolite of testosterone.[7] EZA acts to prompt apoptosis

to diminish growth volume moreover the expansion of malignant growth cells.[15-16] However, most prostate tumors at last become mutilate safe that is, they can develop in any event, when androgen levels in the blood are extremely low. ADT doesn't hinder the creation of the modest quantity of androgen that is made by the adrenal organs and by prostate disease cells themselves, and this low level is adequate to fuel the development of mutilate safe prostate tumors. In general, contrasted and other enemy of androgen, it shows the diminished articulation of androgen receptor subordinate qualities, diminished development of prostate disease cells, and enlistment of malignant growth cell demise and cancer relapse. Thus, the endurance pace of patients with mCRPC is expanded.[16]

3.1. ADME studies of ENZ

EZA is utilized by CYP2C8 and CYP3A4. The two fundamental metabolites found in human plasma were N-desmethyl enzalutamide and a subordinate of carboxylic corrosive. N-desmethyl enzalutamide is a functioning metabolite framed through CYP2C8 digestion. Conversely, the metabolite of carboxylic corrosive is latent. At consistent state, N-desmethyl enzalutamide courses at around a similar plasma focus as EZA, while the carboxylic corrosive metabolite is roughly 25 % lower in vitro measures. Moreover, EZA is chiefly disposed of by hepatic digestion, while renal discharge is an irrelevant end course for EZA and its dynamic metabolite, N-desmethyl enzalutamide.[3,17] But, renal discharge is consequently a significant pathway for the metabolite of carboxylic corrosive. EZA and N-desmethyl enzalutamide have half-existences of 5.8 and 8.6 days while taking a day to day oral portion of 160 mg in mix with LH-RH analogs, respectively.[3] Therefore, patients treated with 160 mg once day to day arrived at the consistent state focuses after roughly one month of dosing. Middle consistent state box plasma centralizations of EZA, N-desmethyl enzalutamide, and enzalutamide carboxylic corrosive are 11.4 mg/mL, 13.0 mg/mL, and 8.44

mg/mL, separately. Since, the pharmacokinetics of EZA and the likewise effective metabolite N-desmethyl enzalutamide are seldom impacted by hemodialysis, EZA is by all accounts a reasonable treatment methodology for patients with end-stage renal illness going through hemodialysis.[18]

4. Synthetic Methods:

Many synthesis routes of ENZ have been reported previously.[19-23] Xingling Ma et.al. elucidated structures of the impurities, degradation products and their mechanistic pathways.[24] Zhou et.al. also proposed mechanistic pathway for the formation of EZA impurities and their pathways.[26] **Fig. 1** shows schematic representation of impurities and their path way of formation.

Fig.1 Near Here

Table.1: Impurities and their pathway of formation

Table 1 Near Here

5. Analytical Methods

The improvement of scientific techniques for quality control of medications and drugs is a prerequisite for ventures and research centers. That keeps up with the item quality and shopper trust. Besides, scientific techniques likewise assume a significant part in the drug business, being available from the phases of starting medication union to post-promoting steps. Different logical strategies were accounted for in the writing not exclusively to identify sedates independently yet additionally in mix with different medications. The logical and bio scientific techniques utilized for assurance of Enzalutamide are introduced in Table 2.

Table 2 Near Here

A HPLC method was developed for elucidation of structures of EZA impurities. [24] Determination of Related Substances in EZA Bulk Drug by HPLC.[25] Zhou et.al. determined potential impurities formed from the synthetic route and forced degradation studies.[26] HPLC strategy was produced for measurement of EZA unadulterated medication substance.[27] Zamir et.al., fostered an approved UV spectroscopic techniques for assurance of EZA in unadulterated and drug dose form.[28] A solidness showing RP-LC strategy and UV-Visible spectroscopic technique for EZA in mass and engineered blend was accounted for the same.[29-30] Quantification of newly discovered anti-cancer drug EZA in bulk and synthetic mixture by stability indicating TLC method. [31]

6. Bio-analytical Methods

Bioanalysis assumes an essential part in the continuous medication improvement. The literature survey showed that most of distributed strategies were LC-MS/MS-based bio-scientific techniques for evaluation of EZA, metabolites and blend drugs. Assurance of EZA by LC-MS strategy in spiked plasma tests [32]. Assessment of EZA and its dynamic metabolite N-desmethyl enzalutamide in biofluids by LC-UV[33], LC-MS [34-37], notwithstanding EZA, abiraterone and their not entirely set in stone in that frame of mind by LC-MS-MS.[38] Concurrent quantitation of abiraterone, EZA, N-desmethyl enzalutamide, and bicalutamide in human plasma by LC-MS/MS.[39], close by various drugs UPLC MS.[40]

7. Pharmacokinetic Studies

Pharmacokinetic analysis plays a vital role in clinical studies, which in turn related to analytical techniques behaviour. The pharmacokinetic studies of EZA [17-18] in rat plasma using LC-MS-MS [41], alongside other second era non-steroidal antiandrogens and their metabolites by RP-HPLC-UV [42] and LC-MS-MS.[43-44] Simultaneous measurement of

EZA, darolutamide and their dynamic metabolites in mice dried blood spots utilizing LC-MS/MS.[45]. Bioavailability of EZA [46] and strategies on HPLC [47] and delicate gel measurements definition technique [48].

Conclusions:

EZA is a second-age androgen receptor inhibitor used to treat metastatic mutilation safe prostate malignant growth (mCRPC). Scientific strategies utilized for drug examinations and remedial medication checking assume a significant part in understanding the viewpoints in regards to bioavailability, bioequivalence, and helpful observing during patient subsequent meet-ups. Consequently, this study presents a concise writing survey on qualities, properties, pharmacokinetic studies, logical and bioanalytical techniques produced for the examination of EZA in various frameworks, including definitions, organic liquids, and medication conveyance systems.

Conflict of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Acknowledgments

The authors thank to Dr. G. Ravindranath (Principal), Smt B. Rajeswari (In-charge, Department of Chemistry), Government College for Men(A), Kadapa, Andhra Pradesh for constant encouragement and support.

References

14% Overall Similarity

Top sources found in the following databases:

- 11% Internet database
- Crossref database
- 5% Submitted Works database
- 5% Publications database
- Crossref Posted Content database

TOP SOURCES

The sources with the highest number of matches within the submission. Overlapping sources will not be displayed.

1	**ncbi.nlm.nih.gov** Internet	3%
2	**repository.ubn.ru.nl** Internet	3%
3	**Nimmu Narendra Varma, Challa Gangu Naidu, Bondigalla Ramachandr...** Crossref	2%
4	**tandfonline.com** Internet	1%
5	**tsijournals.com** Internet	1%
6	**Vels University on 2017-03-23** Submitted works	<1%
7	**mafiadoc.com** Internet	<1%
8	**hrcak.srce.hr** Internet	<1%

9	rsc.org Internet	<1%
10	University of Malaya on 2019-07-12 Submitted works	<1%
11	Pacific University on 2019-08-21 Submitted works	<1%
12	newdrugapprovals.org Internet	<1%

2%	1%	1%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	J. Santhosh Vijitha, S. Hajira, V. Saleem Basha, M. Venkata Ramanaiah, M. Bhushana Reddy, B. Sudhakar Reddy. " Alkali and mixed alkali effect: Spectral investigations on Sm and Dy ions doped zinc tungstate borophosphate glasses ", Ferroelectrics, 2024 Publication	<1%
2	www.coursehero.com Internet Source	<1%
3	J. Santhosh Vijitha, S. Hajira, S. J. Dhoble, G. Venkata Ramana, B. Sudhakar Reddy. " Alkali and mixed alkali effect: spectroscopic properties of Eu and Tb ions doped zinc tungstate boro phosphate glasses ", Ferroelectrics, 2023 Publication	<1%
4	Submitted to Jawaharlal Nehru Technological University Anantapur Student Paper	<1%
5	www.researchgate.net Internet Source	<1%
6	pubs.rsc.org Internet Source	<1%
7	Submitted to Yogi Vemana University, Vemanapuram Student Paper	<1%
8	Submitted to The University of the South Pacific Student Paper	<1%
9	coek.info Internet Source	<1%
10	Raju, K. Vemasevana, C. Nageswara Raju, S. Sailaja, and B. Sudhakar Reddy. "Judd–Ofelt analysis and photoluminescence properties of RE3+ (RE=Er & Nd): Cadmium lithium boro tellurite glasses", Solid State Sciences, 2013. Publication	<1%
11	ir.kluniversity.in Internet Source	<1%
12	uprtou.ac.in Internet Source	<1%

Optical Characterization of Trivalent Europium

by Jillella Santhosh Vijitha

Submission date: 25-May-2024 12:52PM (UTC+0530)
Submission ID: 2387769274
File name: NEW_JSV_THESIS_2.pdf (4.69M)
Word count: 40579
Character count: 216903

Optical Characterization of Trivalent Europium, Terbium, Samarium, Dysprosium, Neodymium and Erbium ions Doped Boro Phospho Zinc Tungstate Alkali and Mixed Alkali oxide Glasses

Thesis submitted to

YOGI VEMANA UNIVERSITY: KADAPA

for the award of the degree of

DOCTOR OF PHILOSOPHY

in

PHYSICS

By

Mrs. Jillella Santhosh Vijitha

Under the Supervision of

Dr.B. SUDHAKAR REDDY
M.Sc., M.Phil., Ph.D.
Department of Physics
Government College for Men (A),
KADAPA-516 004, Andhra Pradesh

YOGI VEMANA UNIVERSITY
VEMANAPURAM
KADAPA-516005
ANDHRA PRADESH

JUNE, 2024

RE-2022-297081-plag-report

ORIGINALITY REPORT

6%	6%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.researchgate.net Internet Source	1%
2	hdl.handle.net Internet Source	1%
3	www.spsl.nsc.ru Internet Source	1%
4	bib.irb.hr Internet Source	1%
5	www.mdpi.com Internet Source	1%
6	G. Moulika, S. Sailaja, J. Santhoshi Vijetha, P. Bayapu Reddy, K. Shanthi Latha, G. Venkata Chalapathi, B. Sudhakar Reddy. " Optical Analysis of RE (RE= Nd or Er): B O -P O -CaF - ZnO – (Li O/Na O/K O) Glasses ", Luminescence, 2022 Publication	<1%
7	mafiadoc.com Internet Source	<1%
8	www.uncfsu.edu Internet Source	<1%

RE-2022-297081 - Turnitin Plagiarism Report

by Shaik Hajira

Submission date: 08-Jun-2024 09:27AM (UTC+0700)
Submission ID: 271717833563
File name: RE-2022-297081.doc (67K)
Word count: 2471
Character count: 14701

PROJECT STATEMENT

1.Project Title:

Spectroscopic investigations on rare-earth ions dopedzinc phospho boro tellurite based optical glasses for energy-saving WLEDs, high-power solid-statelasers and optical fibre applications.

2.Brief Summary of Project Proposal

The proposed work aims to prepare RE^{3+} (RE=Eu, Tb, Sm, Dy, Nd, Er &Yb) ions doped zinc phospho boro tellurite-basedglasses and to observe the energy transfer mechanism between rare earth ions, e.g., from erbium to ytterbium, from terbium to dysprosium etc., which makes zinc phospho boro tellurite-based glasses are most promising glass materials to be used for various novel, laser and optical fibre applications. More specifically, rare earth ions doped into zinc phosphate boro tellurite-based glasses are our unique tools for realizing and utilizing quantum cutting (QC) for white light emitting diodes (WLEDs), lasers, and optical fibres.

3.Background:

(a)National backdrop

Despite the worldwide demands on the phosphors for display and communication applications, only few groups in India are working on rare-earth-ions-doped glasses in terms of the fundamental and quantum aspects of energy transitions and luminescence phenomena; e.g., C.K. Jayasankar group, Sri Venkateswara University and Dr. S.B. Rai group, Banaras Hindu University, working on Nd^{3+} ions doped phosphate. B. Kanmakar group at CGCRI, Kolkata, K. Marimuthu, Gandhigram Rural Institute and Prof. N. Veeraiah, Acharya Nagarjuna University study the optical properties of various trivalent ions doped glasses.

(b)International backdrop

In the United States of America, the glasses and phosphors made out of rare-earth ions are extremely lacking. Only limited institutions such as Fayetteville State University, University of Arizona, Alabama A&M University, Hampton University and Austin Peay State Universityhave worked on RE-doped glasses. In the present proposal, we propose new combinations of RE^{3+}(RE=Eu, Tb, Sm, Dy, Nd, Er & Yb) ions doped into zinc phospho boro tellurite based optical glasses to optimize the synthesis and emission processes, and provide the visible-to-NIR databases for the development of efficient high-powersolid-state lasers, LEDs, and optical fibers.

4.Introduction

The industrial strength of India in terms of the materials for optoelectronics is the use and reserves of rare-earth-ions-activated glass materials. Rare earth (RE) ions activated glass materials with unusual physical, thermal and optical properties can enhance functionalities of the laser devices, optical fibers and display device performance; e.g.,luminescent materials with cascade emission lines from combination of two rare earth ions can reach the quantum efficiency (QE) higher than 1 and could be useful in the progressive optoelectronics applications.

The selective doping of rare earth ions into zinc phospho boro tellurite-basedglasses allows the energy transfer between rare earth ions, e.g., from erbium to ytterbium, from terbium to dysprosium etc., which makes silicate-based glasses one of most promising glass materials to be used for various optoelectronics applications. More specifically, rare earth ions dopedinto glasses are our unique tools for WLEDs, lasers, and optical fibers.

Quite recently, research and development on *glass technology* have become popular compared to the well-known conventional glasses. Glasses are evaluated to be stronger good quality and to provide on opportunity in accommodating with required amount of rare earth ions as dopants. Especially, glasses containing duel rare earth ions (Er^{3+}&Yb^{3+}) will significantly be rich enough in demonstrating *quantum cutting* phenomenon. Glasses have

paper jsv

ORIGINALITY REPORT

9%	5%	9%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Poh Sum Wong, Ming Hua Wan, Rosli Hussin, Hendrik O. Lintang, Salasiah Endud. "Structural and luminescence studies of europium ions in lithium aluminium borophosphate glasses", Journal of Rare Earths, 2014 Publication	2%
2	C. Madhukar Reddy, B. Sudhakar Reddy, G.R. Dillip, K. Mallikarjuna, B. Deva Prasad Raju. "FT-IR, FT-Raman and fluorescence studies of Tb3+ ions activated lead containing sodium fluoroborate glasses", Journal of Molecular Structure, 2012 Publication	1%
3	C. Nageswara Raju, S. Sailaja, S. Hemasundara Raju, S.J. Dhoble, U. Rambabu, Young-Dahl Jho, B. Sudhakar Reddy. "Emission analysis of CdO–Bi2O3–B2O3 glasses doped with Eu3+ and Tb3+", Ceramics International, 2014 Publication	1%
4	S. Hemasundara Raju, B. Muni Sudhakar, B. Sudhakar Reddy, S. J. Dhoble, K. Thyagarajan, C. Nageswara Raju. " Luminescence properties of barium - gadolinium-titanate ceramics doped with rare-earth ions (Eu and Tb) ", Luminescence, 2014 Publication	1%
5	G. Moulika, S. Sailaja, B. Naveen Kumar Reddy, V.Sahadeva Reddy, S.J. Dhoble, B. Sudhakar Reddy. "Optical properties of Eu 3+ & Tb 3+ ions doped alkali oxide (Li 2 O/ Na 2 O/ K 2 O) modified boro phosphate glasses for red, green lasers and display device applications", Physica B: Condensed Matter, 2017 Publication	1%

Submission date: 10-Mar-2023 02:31AM (UTC-0500)
Submission ID: 2033741709
File name: JSV_BSR__Paper_I_Eu,_Tb_paper_jsv.doc (1.35M)
Word count: 4036
Character count: 21781

Structural, elemental, optical and photoluminescence properties of Eu^{3+} and Tb^{3+} doped zinc tungstate boro phosphate glasses for red and green emitting light applications

J.Santhosh Vijitha[a], S.Hajira[a], S.J.Dhoble[b], B.Deva Prasada Raju[c], U. Ram Babu[d] B. Sudhakar Reddy[e*]
[a]Department of Physics, Government College for Men (A), Kadapa-516004, Andhra Pradesh, India
[b] Department of Physics, R.T.M. Nagpur University, Nagpur-440033, India
[c] Department of Physics, S.V. University, Tirupati-517502, India
[d]Center for Materials for Electronics Technology (C-MET), Department of Information Technology, Government of India, Cherlapally, Hyderabad-5000051, India

Abstract

Doped with trivalent rare-earth ions (Eu3+ and Tb3+), zinc tungstate and borophosphate glasses are reported in this study, along with their structural, elemental, optical, and luminescence properties. Amorphous glass was identified via X-ray diffraction analysis. The elemental evaluation was finished using EDAX. The FTIR spectrum is used to identify ligands. The produced glasses' optical features were studied using optical absorption, FT-Raman spectral analysis, photoluminescence excitation (PLE), and photoluminescence (PL) analysis. Emission spectra of glasses doped with Eu3+ ions reveal the bright red emission at 613 nm (5D0 7F2) with an excitation wavelength of 394 nm. (7F0→ 5L6) Green light is emitted at 545 nm (7F5 7F5) and 379 nm (7F6 5G6) is used for excitation in the emission spectra of glasses doped with Tb3+ ions. By analyzing decay curves, we may estimate how long Eu3+ or Tb3+ ions in BPWLZ glasses will remain stable. The energy level diagram explains the emission procedure that takes place in (Eu3+ and Tb3+) doped zinc tungstate borophosphate glasses.

Keywords: Borophosphate glasses, Alkali oxides, Eu^{3+} ion, Tb^{3+} ion.

*Corresponding author:
Email: drbsreddyphd@gmail.com

16.4%

Paper 5.doc

Not yet Date: 2017-03-01 07:02 UTC

✱ All sources **86** | Internet sources **76** | Organization archive **8**

- [0] www.wjpps.com/download/article/1428323099.pdf
  4.1% 23 matches
- [1] https://www.worldwidejournals.com/intern...5_1425387206__14.pdf
  3.5% 21 matches
- [2] https://ijirset.com/upload/2015/march/5_DEVELOPMENT.pdf
  3.1% 19 matches
- [3] www.mdpi.com/1420-3049/21/4/408/pdf
  2.1% 22 matches
- [4] sphinxsai.com/s_v2_n2/CT_V.2No.2/ChemTech_Vol_2No.2_pdf/CT=10 (822-829).pdf
  2.0% 15 matches
- [5] www.scielo.org.mx/pdf/jmcs/v57n4/v57n4a8.pdf
  2.1% 12 matches
- [6] www.mdpi.com/1420-3049/18/11/14241/pdf
  1.4% 12 matches
- [7] www.mdpi.com/1424-8220/16/10/1585/pdf
  1.4% 14 matches
- [8] www.mdpi.com/1420-3049/21/12/1732/pdf
  1.5% 12 matches
- [9] www.mdpi.com/1420-3049/20/7/12209/pdf
  1.3% 12 matches
- [10] sphinxsai.com/sphinxsaiVol_2No.1/PharmTe...T=64 (411-416).pdf
  2.1% 8 matches
- [11] www.mdpi.com/1420-3049/18/10/12857/pdf
  1.4% 11 matches
- [12] "Paper RG1437-004 (1).pdf" dated 2016-12-03
  0.9% 8 matches
- [13] www.mdpi.com/1420-3049/17/11/12925/pdf
  1.3% 8 matches
- [14] www.mdpi.com/1420-3049/21/3/296/pdf
  1.2% 12 matches
- [15] www.mdpi.com/1420-3049/14/7/2466/pdf
  1.2% 12 matches
- [16] www.mdpi.com/1420-3049/21/5/640/pdf
  1.1% 8 matches
- [17] www.mdpi.com/1420-3049/19/11/18332/pdf
  0.9% 9 matches
- [18] www.mdpi.com/1424-8220/6/10/1245/pdf
  1.1% 7 matches
- [19] www.mdpi.com/1420-3049/17/3/3461/pdf
  1.3% 10 matches
- [20] repositorio.unesp.br/bitstream/handle/11449/7918/WOS000292164200029.pdf?sequence=1
  1.2% 10 matches
- [21] www.imedpub.com/articles/development-and...bulk-dosage-form.pdf
  1.4% 7 matches
- [22] www.mdpi.com/1422-0067/12/12/8740/pdf
  1.0% 7 matches
- [23] www.sciencedirect.com/science/article/pii/S0731708507006978
  1.4% 6 matches
- [24] www.mdpi.com/1420-3049/20/1/1594/pdf
  0.9% 8 matches

[25] innovareacademics.in/journals/index.php/ijpps/article/view/2000
1.4% 6 matches

[26] ijrpc.com/files/13-322.pdf
1.1% 8 matches

[27] www.mdpi.com/1660-4601/13/4/409/pdf
0.7% 7 matches

[28] www.mdpi.com/1420-3049/20/12/19762/pdf
0.7% 7 matches

[29] citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.269.1974
1.2% 5 matches

[30] "بحث موحد ابو الكلام .pdf" dated 2016-11-30
0.8% 5 matches

[31] www.mdpi.com/2077-0472/5/4/1289/pdf
0.5% 6 matches

[32] www.scielo.br/scielo.php?pid=S0100-40422011000300027&script=sci_arttext
0.9% 6 matches

[33] www.mdpi.com/2079-4991/6/11/209/pdf
0.4% 5 matches

[34] www.sciencedirect.com/science/article/pii/S1319016412000060
0.6% 6 matches

[35] connection.ebscohost.com/c/articles/7210...eutical-dosage-forms
0.9% 4 matches

[36] www.mdpi.com/2311-5629/3/1/3/pdf
0.3% 6 matches

[37] www.mdpi.com/1660-3397/9/10/1761/pdf
0.5% 6 matches

[38] www.mdpi.com/1424-8220/13/12/16312/pdf
0.6% 5 matches

[39] https://www.omicsonline.org/lc-ms-as-a-s...2153-2435.S7-006.pdf
0.7% 4 matches

[40] "HEB-MS.docx" dated 2016-12-05
0.0% 4 matches

[41] www.mdpi.com/1420-3049/18/12/14892/pdf
0.1% 4 matches

[42] www.jove.com/visualize/abstract/21783336...degradation-products
0.7% 4 matches

[43] www.mdpi.com/1420-3049/20/12/19806/pdf
0.4% 5 matches
⊞ 1 documents with identical matches

[45] www.mdpi.com/1660-4601/12/9/10783/pdf
0.3% 5 matches

[46] www.mdpi.com/1422-0067/17/7/1091/pdf
0.3% 6 matches

[47] www.mdpi.com/1420-3049/21/10/1275/pdf
0.2% 6 matches

[48] www.mdpi.com/1422-0067/17/12/2027/pdf
0.1% 4 matches

[49] www.nature.com/articles/srep15171
0.4% 4 matches

[50] diposit.ub.edu/dspace/bitstream/2445/50649/1/01.LGC_1de2.pdf
0.6% 4 matches

[51] documents.tips/documents/ce-esi-msms-as-...f-proteinligand.html
0.4% 5 matches

[52] www.mdpi.com/2218-1989/2/3/398/pdf

0.2% 3 matches

[53] www.mdpi.com/2075-4442/2/1/21/pdf
0.2% 4 matches
⊞ 1 documents with identical matches

[55] www.mdpi.com/1420-3049/21/4/369/pdf
0.2% 3 matches
⊞ 1 documents with identical matches

[57] www.mdpi.com/1420-3049/21/9/1108/pdf
0.3% 4 matches
⊞ 2 documents with identical matches

[60] www.mdpi.com/1420-3049/19/12/20139/pdf
0.2% 3 matches

[61] diposit.ub.edu/dspace/bitstream/2445/61124/1/XdBG_PhD_THESIS.pdf
0.2% 3 matches

[62] "Alnahdi 2016 Quadriceps strength asymmetry predicts.pdf" dated 2016-12-25
0.0% 2 matches

[63] www.mdpi.com/1420-3049/21/8/1041/pdf
0.2% 4 matches

[64] www.mdpi.com/2306-5338/3/2/16/pdf
0.2% 4 matches

[65] www.mdpi.com/2304-8158/2/3/295/pdf
0.2% 3 matches

[66] "Nature . Scien. Report.pdf" dated 2016-12-04
0.2% 2 matches

[67] www.alliedacademies.org/articles/simulta...g-tablets-byhplc.pdf
0.5% 4 matches

[68] www.sigmaaldrich.com/catalog/papers/21783336
0.6% 3 matches
⊞ 1 documents with identical matches

[70] www.mdpi.com/1996-1944/9/2/82/pdf
0.1% 3 matches

[71] www.mdpi.com/1422-0067/15/1/850/pdf
0.2% 4 matches

[72] www.mdpi.com/1660-4601/9/7/2412/pdf
0.5% 3 matches

[73] www.mdpi.com/1424-8220/15/12/29822/pdf
0.1% 3 matches

[74] www.mdpi.com/2072-6643/6/1/355/pdf
0.1% 3 matches
⊞ 1 documents with identical matches

[76] www.mdpi.com/1422-0067/14/3/5952/pdf
0.3% 3 matches

[77] www.sciencedirect.com/topics/page/Aceon
0.4% 2 matches

[78] www.mdpi.com/2218-1989/6/2/13/pdf
0.0% 3 matches

[79] "Ferm synthesis.pdf" dated 2016-12-04
0.1% 3 matches

[80] "manuscript.v6- Nahed-Proof reading- no comments.doc" dated 2016-12-01
0.0% 3 matches
⊞ 1 documents with identical matches

[82] www.scielo.org.mx/pdf/jmcs/v54n2/v54n2a6.pdf
0.4% 3 matches

[83] https://www.researchgate.net/publication...eutical_dosage_forms
0.5% 1 matches

[84] www.mdpi.com/1660-4601/6/1/278/pdf

☐	[84]	0.0% 1 matches
☐	[85]	www.mdpi.com/1420-3049/20/11/19657/pdf 0.0% 3 matches
☑	[86]	www.ijabpt.com/pdf/70031-Jignesh[1].pdf 0.4% 2 matches
☑	[87]	www.nexoncn.com/read/eef90e91fe7182a969fbe3be.html 0.2% 3 matches
☑	[88]	https://www.researchgate.net/profile/Sk_...gin=publication_list 0.3% 1 matches
☑	[89]	pubs.rsc.org/en/Content/Database/AWB7334G10062 0.4% 2 matches ⊞ 1 documents with identical matches
☑	[91]	diposit.ub.edu/dspace/bitstream/2445/66853/1/648984.pdf 0.2% 1 matches
☑	[92]	"بحث موحد ابو الكلام 2.pdf" dated 2016-11-30 0.2% 2 matches
☑	[93]	www.scielo.br/pdf/qn/v33n2/26.pdf 0.3% 2 matches
☑	[94]	www.mdpi.com/1999-4923/8/2/13/pdf 0.0% 2 matches ⊞ 5 documents with identical matches

9 pages, 3164 words

PlagLevel: selected / overall

93 matches from 100 sources, of which 92 are online sources.

Settings

Data policy: *Compare with web sources, Check against my documents in the organization repository, Check against organization repository, Check against the Plagiarism Prevention Pool*

Sensitivity: *High*

Bibliography: *Bibliography excluded*

Citation detection: *No detection*

Whitelist: --

applied sciences

MDPI

Article

A stability indicating LC-MS method for determination of Perindopril and its process related impurities

Nadavala Siva Kumar * Mohammad Asif,

Department of Chemical Engineering, King Saud University, P.O. Box 800, Riyadh 11421, Saudi Arabia.

* Correspondence: shivanadavala@gmail.com; snadavala@ksu.edu.sa Tel.: +966-53-722-8108

Academic Editor: name
Received: date; Accepted: date; Published: date

Abstract: Perindopril erbumine is belongs to the member of angiotensin-converting enzyme inhibitors group used in the treatment of heart failure and hypertension. A simple and highly sensitive LC-MS method has been developed for simultaneous determination of three process-related impurities in perindopril (L-norvaline, L-norvaline ethyl ester HCl, and (S)-inodoline-2-carboxylic acid). The samples were separated using the mobile phase: 5mM ammonium formate (A): acetonitrile/methanol (B) on a Symmetry C_{18} column (75 mm x 4.6 mm, 3.5µm) using gradient elution mode at a flow rate of 0.6 mL/min. The developed method was fully validated as per ICH guidelines and can be used for quality testing of perindopril as well as its impurities in pharmaceuticals.

Keywords: Perindopril erbumine, Process related impurities, Hypertension, LC-MS, Stability indicating method.

1. Introduction

Perindopril erbumine (PER) is a tert-butylamine salt of perindopril.[77] Perindopril is a pro-drug and metabolized in vivo by hydrolysis of the ethyl ester group to form perindopril at the biologically active metabolite.[77] PER is an angiotensin-converting-enzyme (ACE) inhibitor being successfully used in treating various cardiovascular diseases such as heart failure, hypertension, high blood pressure and ischemic heart disease [1-3]. However, in some countries in the climatic zones III and IV Perindopril arginine have been using in place of Perindopril erbumine due to its therapeutically equivalent and improved stability [4].

Literature survey revealed that several methods for quantification of PER and its process-related impurities. Medenica et al.[21] developed an isocratic HPLC method for estimation of PER and its impurities [5]. A micro-emulsion LC method for quantification of PER and its impurities was reported, but it was not completely validated [6]. Zaazaa et al. reported TLC-densitometric and HPLC methods for the impurity testing of amlodipine and perindopril in pharmaceutical formulation [7]. The British Pharmacopeia (BP) monograph proposes a long run time (65 min) gradient RPLC method using perchloric acid as mobile phase additive (pH: 2.5). The method is not only time consuming but also produces inadequate peak shapes [8]. Micro-calorimetry and HPLC methods for quantification perindopril erbumine in aqueous solutions was reported [9].[10] Simultaneous estimation of perindopril and indapamide in presence of impurities and degradation products was reported [10, 11]. Prameela Rani et al.[48] developed an HPLC method for PER and the results were statistically compared by applying Student's t-test and F-test [12]. A stability-indicating RPLC method for perindopril erbumine was reported [13, 14]. Darshana et al.[29] developed absorbance correction spectrophotometric and simultaneous equation spectrophotometric methods for the simultaneous determination of perindopril and indapamide in pharmaceutical formulation [15]. Nevin et al.[29] published a paper on first-derivative spectrophotometric method with zero crossing technique and ratio derivative spectrophotometric technique for perindopril and indapamide in pharmaceutical dosage forms [16]. Abdalla et al. developed a RPLC method for separation of perindopril with indapamide and captopril with indapamide in pharmaceutical formulations [17]. Vijayalakshmi et al. reported a first-order derivative spectrophotometric method for estimation of PER and losartan in formulations [18]. A kinetic study on the isomerization of perindopril by HPLC was reported [19]. Juddy et al.[83] reported simultaneous estimation of perindopril erbumine and indapamide by RP-HPLC in pharmaceutical dosage [20]. RPLC method for quantification of losartan potassium and perindopril erbumine in formulations was reported [21].

Many authors studied for determination of some process-related impurities by excluding few low UV absorbance synthetic route intermediates. To quantify such low absorbance impurities, highly sensitive mass detector is essential rather than classical detection methods like UV and RI.[35] The aim of the present study was development of a simple stability-indicating LC-MS method for quantification of three process-related impurities in Perindopril bulk drug substances, which were not studied earlier.

2. Experimental

2.1. Chemicals and reagents

Perindopril erbumine, L-norvaline, L-norvaline ethyl ester HCl and (S)-inodoline-2-carboxylic acid were procured from Sigma-Aldrich Ltd (St. Louis, USA) (Fig. 1).[0] Methanol and acetonitrile (HPLC grade) were purchased from J.T Baker (Phillipsburg, USA).[20][2] GR grade ammonium formate, ammonium acetate, and potassium dihydrogen phosphate were procured from Merck (Mumbai, India).[0] Water was prepared from Milli Q water purification system purchased from Millipore (Bangalore, India).

2.2. Instrumentation

The Liquid Chromatography experiments were performed on a Shimadzu HT containing with binary pump (LC-20 AD), a DGU-20A5 degasser unit, and an auto sampler (SIL-HTC) (Shimadzu Corporation, Kyoto, Japan).[0]

Quantification was achieved by mass spectrometry using an AB Sciex (Model: API-4000) mass spectrometer (Foster City, CA, USA) equipped with a Turboionspray™ interface at 400ºC.[72] The mass spectrometer was operated in the positive detection mode.[0] The ion spray voltage was set at 5000 V.[0] The source parameters viz., the nebulizer gas, 14 psi; curtain gas, 30 psi; auxiliary gas, 35 psi; and collision gas, 10 psi were applied.[46][8] The compound parameters such as declustering potential, 60 V; entrance potential, 10 V; collision energy, 25 V; and collision cell exit potential, 15 V were used.[0] Detection of components were carried out in the multiple-reaction monitoring mode (MRM).[46] Quadrupoles Q1 and Q3 were set to unit resolution.[50] The analytical data acquisition and processing were performed using Analyst software™ (version 1.5.1).

2.3. Sample Preparation

The stock solutions of perindopril (1 mg/mL) and 3 process-related impurities (0.1 mg/mL) were prepared by dissolving in Acetonitrile: Water (70:30 v/v).[16] The stock solutions were stored at 5ºC and found to be stable for 30 days.[34] The stock solutions were further diluted with the mobile phase containing Acetonitrile: 5 mM ammonium formate (30:70 v/v) for working standard

solutions. Before analysis, all the prepared standard samples were filtered through a 0.45µm nylon membrane and degassed ultrasonically for 5 min.

3. Results and discussion

3.1. Optimization of chromatographic conditions

Preliminary experiments for method development were tried on Symmetry C_{18} column (75 mm x 4.6 mm, 3.5 µm) using water and methanol as the mobile phase. All impurities having ionizable groups such as amines and carboxylic acids groups may undergo ionization during the interaction with the mobile phase and stationary phase. Hence, to change the selectivity, the effect of buffers such as potassium dihydrogen phosphate, ammonium acetate, and ammonium formate on separation was tested. In the isocratic mode, unfortunately, Imp-II was co-eluted with Imp-III due to their similar polarities.

Further, gradient elution mode was selected to not only enhance resolution and peak shape, but also reduce the retention time of late eluting peaks. It was found that gradient elution mode gave better separation than isocratic elution mode. Finally, ammonium formate (A) was chosen as a buffer because its volatile nature and suits for LC-MS analysis. To reduce the gradient drift, a mixture of Acetonitrile and Methanol (B) was selected as organic phase. A gradient program was framed in such a way that 15% B was applied from 0 to 3 min for the separation of Imp-I and PER. Then, a fast gradient (15-50% B) from 3 to 7 min was necessary for the separation of polar substances II and III. Then, isocratic condition (75% B) was maintained from 7-9 min to stabilize the column. Then sharp decrease of gradient was found to be optimal. As a last step of the gradient program, 4 min re-equilibration with the initial mobile phase (15% B) was necessary for repeatability of retention times. In addition, to reducing the runtime column compartment temperature was maintained at 40 ºC without disturbing the resolution between critical pairs such as Imp-II and Imp- III. The optimized LC conditions were extended to LC–MS studies. LC-MS spectra of Perindopril and its process-related impurities are shown in Fig. 2.

3.2. LC-MS conditions

The separation of perindopril and its process related impurities were carried out on a Symmetry C_{18} column (75 mm x 4.6 mm, 3.5 µm) with mobile phase containing 5 mM ammonium formate buffer (A) with acetonitrile: methanol (95:5 v/v) (B) under gradient elution mode. The flow rate was maintained at 0.6 mL/min. The optimized gradient program was as follows: 0.01 min-15% B, 3.0 min-50% B, 7.0 min - 75% B, 9.0 min-75% B, 9.5 min-15% B, 12.0 min-15.0% B-re-equilibration The column compartment temperature was maintained at 40 ºC. The injection volume was 10 µL. Detection of components were carried out in multiple-reaction monitoring mode (MRM) by

monitoring the transition pairs of m/z 118.1 and 88.1 for L-norvaline, m/z 146.1 and 118.1 for L-norvaline ethyl ester HCl, and m/z 163.1 and 120.1 for (S)-inodoline-2-carboxylic acid, respectively (Fig. 1).

4.0. Method validation

The quantitative aspects of the method were validated according to ICH Q2 (R1) guidelines [22].

4.1. Specificity

The specificity of the method was determined by spiking perindopril to its three impurities and calculated the resolution factors. The resolution factors for perindopril and its related impurities were greater than 2.0. There was no obvious interference from other components. Hence, the developed LC-MS method was found to be specific.

4.2. System suitability

The system suitability was conducted for PER and 3 process-related impurities at 25 µg/mL and their %RSD values were evaluated by making five replicate injections. The %RSDs were 1.9, 1.8, 1.9, and 2.5 for L-norvaline, PER, L-norvaline ethyl ester HCl, and (S)-Inodoline-2-carboxylic acid, respectively. The system was deemed to be suitable for analysis as the resolution factor was greater than 2.0, and tailing factor for all analytes were ≤ 1.20. System suitability results are given in Table 1.

4.3. Sensitivity

The sensitivity of the method was assessed in terms of limit of detection (LOD) and limit of quantification (LOQ). The LOD and LOQ values for the impurities were estimated based on signal-to-noise ratios of 3:1 and 10:1, respectively. The LOD and LOQ values for perindopril and related impurities were obtained in the range of 0.6-1.5 µg/mL and 1.8-4.5 µg/mL, respectively. It indicated sensitivity of the method is high. The LOD and LOQ results are given in Table 3. LOQ spectra of perindopril process-related impurities are shown in Fig. 3.

4.4. Precision

Precision of the method was tested at three 3 concentration levels by making six replicates. The analysis was performed three times on the same day and also on three consecutive days, respectively. The %RSD values for intra-day and inter-day analysis were found to be within the accepted limits (Table 2). These results revealed that the analytical method is precise.

4.5. Linearity

The linearity of the method was examined at 6 different concentrations of PER and related impurities from their consequent LOQ 40%, 60%, 80%, 100%, and 150% concentration level. LOQ

values for L-norvaline, L-norvaline ethyl ester HCl, and (S)-inodoline-2-carboxylic acid, were 4.5 (µg/mL), 1.8 (µg/mL), and 3.0 (µg/mL), respectively. The calibration curve was drawn by plotting peak areas versus respective analyte concentrations. The straight line and correlation coefficient values were regressed using a linear equation model. The correlation coefficients (r^2) of perindopril and its 3 impurities were greater than 0.9990 (Table 3). Linearity was estimated for perindopril in the concentration range 10–200 µg/mL (r^2 = 0.9998). The method exhibited good linearity over the given concentration range for each analyte (Table 3).

4.6. Accuracy

Accuracy of the method was examined by recoveries of all the impurities at four different concentration levels such as LOQ, 50%, 100%, and 150% with six replicates (n = 6). PER (specified limit of 200 µg/mL) was spiked to each impurity at LOQ, 12.5, 25, and 37.5 µg/mL. The percentage of recoveries and %RSDs of process-related impurities were found to be in the range of 97.5-100.7% and 0.2-1.6%, respectively. It demonstrated that the accuracy of the method was high (Table 4).

4.7. Robustness

The robustness of the method was examined by making small but deliberate variations in the chromatographic method conditions. The effect flow was altered by 0.1 unit (-10% to +10%), column oven temperature altered by 2 °C units (-2 °C to +2 °C) and % of organic modifier also altered by 0.2 units (-0.2 to +0.2 units) from the optimal values. Under the robustness study, the resolution between the closely eluting impurities namely impurity-II and impurity-III was 2.0. It indicated that the developed method was highly robust and is unaffected by small changes in experimental conditions.

4.8. Solution stability

The solution stability of PER and all related impurities were placed at room temperature and we assessed the recoveries at their LOQ value at time intervals of 0, 12, and 24 hrs. The recoveries were in the range of 97.31-98.46%, 99.10-101.78%, and 99.47-100.78% for L-norvaline, L-norvaline ethyl ester HCl, and (S)-Inodoline-2- carboxylic acid, respectively. It indicated that the working standards were stable up to 24 hrs.

5. Conclusions

A simple and highly sensitive LC-MS method has been developed and validated for simultaneous determination of three process-related impurities in perindopril. The components were separated on a Symmetry C_{18} column in gradient elution mode. The developed method was fully validated according to ICH guidelines. This stability-indicating LC-MS method can be used for quality control of PER and its related impurities in bulk drug substances and formulations.

195 Acknowledgements: M. Asif appreciates the support of the Deanship of Scientific Research at the
196 King Saud University for the Prolific Research Group PRG-1437-31.

197 Conflicts of Interest: The authors declare no conflict of interest.

198 References

199 1. Werner, C.; Poss, J.; Bohm, M. Optimal antagonism of the renin–angiotensin–aldosterone
200 system: do we need dual or triple therapy. Drugs, 2010, 70, 1215–1230.
201 2. Werner, C.; Baumhakel, M.; Teo, K.K.; Schmieder, R.; Mann, J.; Unger, T.; Yusuf , S.; Bohm, M.;
202 RAS blockade with ARB and ACE inhibitors: current perspective on rationale and patient
203 selection. Clin. Res. Cardiol. 2008, 97, 418–431.
204 3. Anderson, P.J.; Critchley, J.A.; Tomlinson, B.; Resplandy, G. Comparison of the
205 pharmacokinetics and pharmacodynamics of oral doses of perindopril in normotensive Chinese
206 and Caucasian volunteers. Br. J. Clin. Pharmacol. 1995, 39, 361–368.
207 4. Telejko, E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. Curr.
208 Med. Res. Opin. 2007, 23, 953–960.
209 5. Medenica, M.; Ivanovic, D.; Maskovic, M.; Jancic, B.; Malenovic, A. Evaluation of impurities
210 level of perindopril tert-butylamine in tablets. J. Pharm. Biomed. Anal. 2007, 44, 1087–1094.
211 6. Maskovic, M.; Dotsikas, Y.; Malenovic, A.; Jancic-Stojanovic, B.; Ivanovic, D.; Medenica, M.
212 Validation of an oil-in-water microemulsion liquid chromatography method for analysis of
213 perindopril tertbutylamine and its impurities. J. AOAC. Int. 2011, 94, 723–734.
214 7. Zaazaa, H.E.; Abbas, S.S.; Essam, H.A.M.; El-Bardicy, M.G. Validated chromatographic
215 methods for determination of perindopril and amlodipine in pharmaceutical formulation in the
216 presence of their degradation products. J. Chromatogr. Sci. 2013, 51, 533–543.
217 8. British Pharmacopoeia Commission. Perindopril erbumine tablets monograph, British
218 Pharmacopoeia. The Stationery Office, London, UK, 2014, p. 938.
219 9. Simoncic, Z.; Roskar, R.; Gartner, A.; Kogej, K.; Kmetec, V. The use of micro calorimetry and
220 HPLC for the determination of degradation kinetics and thermodynamic parameters of
221 perindopril erbumine in aqueous solutions. Inter. J. Pharm. 2008, 356, 200–205.
222 10. Jogia, H.; Khandelwal, U.; Gandhi, T.; Singh, S.; Modi, D. Development and validation of a
223 stability-indicating assay method for simultaneous determination of perindopril and
224 indapamide in combined dosage form by reversed-phase high-performance liquid
225 chromatography. J. AOAC. Int. 2010, 93, 108–115.

11. Gumusta, M.; Ozkan, S.A. A validated stability-indicating RP-LC method for the simultaneous determination of amlodipine and perindopril in tablet dosage form and their stress degradation behavior under ICH-recommended stress conditions. J. AOAC. Int. 2013, 96, 751–757.
12. Prameela Rani, A.; Bala Sekaran, C.A. validated RP-HPLC method for the determination of perindopril erbumine in pharmaceutical formulations. Inter. J. Pharm. Tech. Res. 2009, 1, 575-578.
13. Dugga, H.H.T.; Peraman, R.; Nayakanti, D. Stability-indicating RP-HPLC method for the quantitative analysis of perindopril erbumine in tablet dosage form. J. Chromatogr. Sci. 2014, 52, 315–320.
14. Paczkowska, M.; Zalewski, P.; Garbacki, P.; Talaczynska, A.; Krause, A.; Cielencka-Piontek, J. The development and validation of a stability indicating UHPLC DAD method for determination of perindopril arginine in bulk substance and pharmaceutical dosage form. Chromatographia. 2014, 77, 1497–1501.
15. Darshana, K.M.; Chhagan, N.P. Development and validation of spectrophotometric method for simultaneous estimation of perindopril and indapamide in combined dosage form by absorbance correction method. Inter. J. Pharm. Tech. Res. 2010, 2, 411-416.
16. Nevin, E.R.K. Comparison of spectrophotometric and an LC method for the determination perindopril and indapamide in pharmaceutical formulations. J. Pharma. Biomed. Anal. 2001, 26, 43-52.
17. Abdalla, A.E.; Samia, M.M.; Mohamed, S.E. Development and validation of LC- method for simultaneous determination of two binary mixtures containing perindopril and indapamide. Chromatographia. 2008, 67, 837-840.
18. Vijayalakshmi, R.; Archana, S.; Dhanaraju, M. Simultaneous estimation of perindopril and losartan in solid dosage forms by UV spectrophotometry. Asian. J. Res. Chem. 2010, 3, 571-574.
19. Bouabdallah, S.; Trabelsi, H.; Bendhia, M.T.; Ben Hamida, N. Kinetic study on the isomerization of perindopril by HPLC. Chromatographia, 2012, 75, 1247–1255.
20. Juddy, J.; Blessen, P.; Sundarapandian, M. Method development and validation for simultaneous estimation of perindopril erbumine and indapamide by RP-HPLC in pharmaceutical dosage forms. Inter. J. Pharm. Tech. Res. 2011, 3, 288-293.
21. Patel, A.; Chaudhary, G.; Rajgor, N.B.; Rathi, S. RP-HPLC method for the determination of losartan potassium and perindopril erbumine in combined tablet dosage form. Int. J Pharm. Tech. Bio. Res. 2010, 1, 18-24.
22. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH), Q2(R1): validation of analytical procedures: text and methodology, Geneva, Switzerland, 1994.