INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Analytical Profiling of Eliglustat for Gaucher Disease: Method Development and Validation

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ARTICLE INFO

Received: 14 May 2024
Accepted: 18 May 2024
Published: 27 May 2024
Keywords:
Eliglustat, Analytical Methods, Gaucher Disease, Pharmaceutical and biological samples.
DOI:
10.5281/zenodo.11348776

ABSTRACT

This review paper comprehensively investigates the analytical profiling of eliglustat, an inhibitor for Gaucher disease. Methodologies employing High-Performance Liquid Chromatography (HPLC), 2D Nuclear Magnetic Resonance (2DNMR), and High-Resolution Mass Spectrometry (HRMS) are explored to elucidate the pharmacodynamic and pharmacokinetic properties of eliglustat. Additionally, it delves into the chemistry, solubility, and mechanism of action of eliglustat. Through a meticulous examination of the available data, this review aims to provide a comprehensive understanding of eliglustat's efficacy and safety profile for the treatment of Gaucher disease. More than 150 papers from eminent institutions doing scientific, technological, and medical research are currently available. The current review effectively outlines the conventional, hyphenated, and distinctive approaches to SFV (structural fingerprinting of variants).

INTRODUCTION

Gaucher disease is the most common sphingolipidosis. First documented by Philippe Gaucher in 1882, this condition initially presented in a patient exhibiting significant splenomegaly without signs of leukemia [1-5]. Gaucher Disease (GD) arises from an insufficiency of the lysosomal enzyme glucocerebrosidase, resulting in the buildup of its substrate, glucosylceramide, within macrophages [6-11]. This metabolic disorder manifests as an inherited error, leading to the accumulation of lipid substrates, particularly glucosylceramide, within the monocyte-macrophage system [12-17]. Its primary effect is the enlargement of various organs spleen and liver, destruction of bone, and abnormalities of the lungs and blood, such as anemia, thrombocytopenia, and leukopenia [18-22]. GD is classified according the

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

presence or absence and severity of neurological involvement, and the age of onset. The most frequent of the three forms of GD is type 1 (GD1) and is characterized by accumulation of undegraded glucosylceramide in lipid engorged macrophages (known as Gaucher cells) in organs, including the spleen, liver and bone marrow, with no overt involvement of the CNS or cognitive regression (i.e. non-neuronopathic) [23-28]. Clinical manifestations within each type of GD are highly heterogeneous. Manifestations in patients with GD1 include visceral symptoms [29-30]. splenomegaly (>90 % of patients), hepatomegaly (>80 % of patients) and, in splenectomized patients, interstitial lung disease and pulmonary hypertension], abnormalities in haematological parameters (anaemia and thrombocytopenia) and skeletal complications (bone pain, bone crises, bony lytic lesions, avascular necrosis of the femoral head, pathological fractures and bony infarctions [31-33]. Treatment options for GD include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Currently, three enzyme replacement therapies (ERTs) are available: imiglucerase, velaglucerase alfa, and taliglucerase atta. Additionally, there are two substrate reduction therapies (SRTs) on the market: miglustat and the latest addition, eliglustat tartrate [33-36].

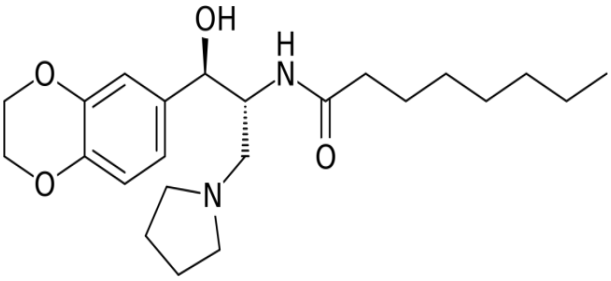
Eliglustat tartrate functions as a potent ceramide analog, exerting selective inhibition on GLC synthase. Concentration-dependent effects of eliglustat include decreased GLC levels and reduction in abnormal macrophage infiltration within tissues. Structurally, eliglustat bears resemblance to D-threo-1-phenyl2-decanoylamino3-morpholino-propanol [36-40]. Metabolism of eliglustat relies heavily on the activity of CYP2D6, with a lesser contribution from CYP3A within the cytochrome P450 pathway. Given its potential for drug interactions, coupled with the variability in CYP2D6 metabolizer status, determining patient eligibility and establishing recommended dosage hinges significantly on these factors received approval in the USA on August 19, 2014 for treatment-naïve and treatment-experienced adult patients with GD1[41-49].

Clinical classification of gaucher disease

	Type 1: Nonneuronopathic (Adult)	**Type 2: Acute Neuronopathic (Infantile)**	**Type 3: Chronic/Subacute Neuronopathic (Juvenile)**
Whom it strikes	Young adults/adults; most common in Ashkenazi Jewish population (1 in 450) 1 in 100 000 general population	Infants rarely, with no ethnicity 1 in 100 000 live births	Children/young adults, with no ethnicity; 1 in 50 000 live births Norrbottnian variant: Sweden; until early adulthood.
Distinguishing symptom	Liver, spleen, and bone; no nervous system problems	Early nervous system problems, brainstem abnormalities	Later onset of nervous system problems: incoordination, mental deterioration, m
Effects of disease	Varies from mild to severe	Death in infancy (age < 2 y)	Slowly progressive; becomes severe later in childhood
Glucocerebrosidase activity	Some activity, but much less than	Very little activity	Little activity

	normal		

Eliglustat tartrate



Chemistry

Cerdelga (eliglustat tartrate), a SRT, is a new molecular entity. It is a member of a novel class of glucosylceramide (GL-1) synthase inhibitors that resembles the ceramide substrate for the enzyme. Eliglustat serves as a potent and specific inhibitor of glucosylceramide synthase Inhibition of glucosylceramide synthase by eliglustat results in a reduction of the accumulation of glucosylceramide, thereby allowing the patient's residual endogenous acid β -glucosidase levels to clear the substrate [49].

Table 1. Physiochemical properties of Eliglustat tartrate

Parameter	Observation
Color	White to off white solid
IUPAC Name	N-((1R,2R)-1-(2,3dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3- (pyrrolidin-1-yl)propan-2-yl)octanamide (2R,3R)-2,3- dihydroxysuccinat.
Molecular formula	$C_{23}H_{36}N_2O_4$+1/2 (C4H6O6)
Molecular weight	404.5 gm/mol
Melting point	87-92°C
Pka	8.79
Refractive Index	1.543
Log p	3.61

The goal of this approach is to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations. Cerdelga is supplied as 84 mg hard capsules and contains standard excipients. 84 mg of eliglustat is equivalent to 100 mg of eliglustat tartrate [50-51].

Solubility

Eliglustat is soluble in organic solvents such as DMSO, and dimethyl formamide. The solubility of eliglistat in these solvent is approximately 20mg/ml[52]. Eliglustat is sparingly soluble in aqueous buffer. For maximum solubility in aqueous buffers, eliglustat should first be dissolved in ethanol and then diluted with the aqueous buffer of choice. Eliglustat has a solubility of approximately 0.03mg/ml in a 1:30 solution of ethanol:PBS ([PH 7.2) using these method . Do not recommend storing the aqueous solution for more than one day. Avoid storing the aqueous solution for more than one day [53].

Mechanism of action

Eliglustat diminishes glucosylceramide production by impeding glucosylceramide synthase, a pivotal enzyme in glycosphingolipid synthesis. By reducing the availability of glucosylceramide within lysosomes, it helps rectify the deficiency of acid β-glucosidase [54].

Pharmacodynamics

Eliglustat is a specific and potent inhibitor of glucosylceramide synthase, with enzyme inhibition leading to a reduction in the accumulation of glucosylceramide [55]. The in vitro half-maximal inhibitory concentration (IC50) of eliglustat in K562 cells is &24 nmol/L, with the drug exhibiting minimal or no activity against several other glycosidases, including a-glucosidase I and II, and lysosomal and non-lysosomal glucosylceramidases [56]. Preclinical studies indicated that eliglustat was effective in the treatment of the visceral pathology of GD . In a murine model of Gaucher Disease (GD), eliglustat exhibited a dose-dependent reduction in glucosylceramide levels and the quantity of Gaucher cells when compared to vehicle treatment in presymptomatic mice. (prior to significant accumulation of the substrate; mice aged 10 weeks) [57]. In older symptomatic mice (aged 7 months) with existing accumulation of glucosylceramide, after 10 weeks of oral eliglustat 150 mg/kg/day, glucosylceramide levels were reduced by 40–60 % in the spleen, lung and liver (p\0.05 vs. age-matched vehicle-treated controls), and there was a significant (p\0.05) reduction in the appearance of new Gaucher cells in the liver [58-60] .

Pharmacokinetics

Eliglustat is moderately bound to plasma proteins (76–83 %) and is mainly distributed in plasma. After intravenous administration, the volume of distribution is 816 L, indicating that the drug is extensively distributed into human tissues [61]. Nonclinical studies demonstrated a wide distribution of the drug into tissues, including bone marrow [61]. Eliglustat is extensively metabolized with a Eliglustat undergoes high clearance, primarily mediated by CYP2D6, with a lesser contribution from CYP3A4. The primary metabolic pathways involve sequential oxidation to several oxidative metabolites, with no active metabolites identified [62]. After a single radiolabelled-eliglustat dose, the majority of the administered dose is excreted in the urine (41.8 %) and faeces (51.4 %), predominantly as metabolites [62]. Following intravenous administration, the total body clearance of eliglustat is 86 L/h. The elimination half-life is &4–7 h in non-PMs and 9 h in PMs, after multiple oral doses of eliglustat 84 mg twice daily [63]. Based on a population pharmacokinetic analysis, gender, age, bodyweight and race had no clinically relevant impact on the pharmacokinetics of eliglustat. he utilization of eliglustat has not undergone investigation in patients with moderate or severe renal impairment [63]. Consequently, its usage is not recommended in such patients within the USA. Conversely, within the EU, no dosage recommendations have been established for the use of eliglustat in individuals with renal impairment [64]. There was also no clinically relevant impact on its pharmacokinetics in patients with mild renal impairment. There are no studies of eliglustat use in patients with hepatic impairment; in these patients, its use is not recommended in the USA and, in the EU, no dosage recommendations can be made [64].

Therapeutic Efficacy of Eliglustat

The efficacy of oral eliglustat in patients (aged C16 or C18 years) with confirmed GD1 was evaluated in the pivotal multinational, phase 3 ENGAGE and ENCORE trials [65]. Results from these trials are supported by evidence from a noncomparative, multinational, phase 2 trial (NCT00358150). with long-term data from the extension phase of this study available up to 4 years [66]. Additional post-hoc analyses, and longer-term data from the ENGAGE and ENCORE trials are available as abstracts. In phase 2 and 3 trials, the dosage of eliglustat was initiated at 50 mg twice daily (single 50 mg dose on day 1) and subsequently individualized to 50 , 100 or 150 mg twice daily ; respective concentrations of the

active drug substance in the 50, 100 and 150 mg dose are 42, 84 and 126 mg [67-68]. In the phase 2 trial, the dosage was adjusted to 50 or 100 mg twice daily at week 2, based on trough plasma concentrations of the drug at day 10 [68-69]. In ENGAGE and ENCORE, dosages were adjusted to 50 or 100 mg at week 4 and, in ENCORE, to 50, 100 or 150 mg at week 8, based on trough plasma concentrations of the study drug at week 2 or week 2 and 6 [70-72].

Majors of safety and adverse reactions of eliglustat

Treatment with Cerdelga appears to have resulted in clinically and statistically significant improvements in major clinical features of Type 1 Gaucher disease in adult patients [73]. The efficacy data from the pivotal Phase 3 ENGAGE trial indicated that spleen volume, liver volume, hemoglobin count and platelet count parameters in treatment naïve type 1 Gaucher disease patients improved following treatment with eliglustat for 9 months. Data from the supportive Phase 3 ENCORE trial demonstrated that patients switched from imiglucerase to eliglustat maintained clinical stability for these parameters up through 52 weeks of treatment [73]. The Applicant's Phase 2 trial also demonstrated improvements in organ volume and hematologic parameters [74]. Eliglustat was shown to inhibit (IC50 = 10 ng/mL) glucosylceramide synthase (GCS) in human K562 cells or human A375 cell-derived microsomes. In animal efficacy studies, eliglustat decreased GL-1 levels in peripheral tissues and plasma of normal rats and dogs following oral administration [75]. In the D409V/null mouse model of GD1, eliglustat decreased the accumulation of GL-1 in tissues. Eliglustat caused an inhibition of hERG channels expressed in HEK-293 cells with an IC50 value of 0.35 µg/mL, indicating a potential to cause QT prolongation. Eliglustat also inhibited sodium and calcium channels with IC50 values of 5.2 and 10.4 µg/mL [76].

Nuclear resonance analysis (NMR) available for eliglustat

Nuclear magnetic resonance (NMR) is getting used for the quantitation and characterization of pharmaceuticals within the academic and pharmaceutical industries [77]. NMR analysis of API and isolated impurities of EGT were recorded on Agilent MR400 MHz NMR instrument equipped with 5 mm ONE NMR probe with Z-gradient shim system which has the sensitivities of 480:1 & 225:1 for 1 H and 13C nuclei respectively [77]. All the NMR analysis has been performed at 298K probe temperature with fine automatic tuning and matching for the frequency of respective nuclei [78]. Tetra methyl silane (TMS) was used as reference standard and its singlet peak was referenced at 0.0 ppm in 1 HNMR and 39.5 ppm for DMSO-D6 septet in 13C NMR [78]. Key parameter used for NMR analysis 1. One Dimensional Analysis - 1 H NMR data acquired and processed with following parameters like spectral width (SW) =17.95 ppm, relaxation delay time (D1) =1sec, number of scans (NT) =16, number of data points (NP) =64k, 90° pulse width (PW90) =7.4 µsec, acquisition time (AT) =4.0 sec, operating spectrometer frequency (SF) =399.63 MHz and line broadening (LB) =0.5Hz. 13C NMR data acquired and processed with following parameters like spectra width (SW) =248.8 ppm, relaxation delay (D1) =3sec, number of scans (NT) =4000, data points (NP) =64k, 90° Pulse width (PW90) =7.6 µsec, acquisition time (AT) =1.31 sec line broadening (LB) =2.0Hz spectrometer frequency (SF) =100.48 MHz parameters [79-80]. 1.One dimensional (1D) analysis-. 13C NMR data acquired and processed with following parameters like spectra width (SW) =248.8 ppm, relaxation delay (D1) =3sec, number of scans (NT) =4000, data points (NP) =64k, 90° Pulse width (PW90) =7.6 µsec, acquisition time (AT) =1.31 sec line

broadening (LB) =2.0Hz spectrometer frequency (SF) =100.48 MHz parameters [81].

2.Two-Dimensional Analysis - Homonuclear 1 H-1 H g DQCOSY experiment has been performed to know the proton-proton correlations [82].

High resolution mass spectrometry (HRMS) for eliglustat

Isolated impurities were analyzed on Thermo scientific Q-exactive orbi-trap HRMS instrument with ESI ion source. [83] The front-end inlet used was UHPLC Dionex Ultimate 3000 instrument which comprises of binary pump, column manager and PDA detector [84-85]. The mass parameters were optimized as follows, Capillary voltage: 3500 V; Sample cone voltage: 30 V; Extraction cone voltage: 5 V; Source temperature: 140°C; Desolvation temperature: 300°C; Cone gas: 50 L/hr.; Desolvation gas: 650 L/hr. MS/MS analysis was performed to identify the fragmentation patterns [86-87].

HPLC for Eliglustat

The HPLC system (LC Waters, Milford, MA, USA) consisted of quaternary gradient system, in-line degasser (Waters, model AF), Ultraviolet detector (Water, 2487 model) [88-90]. Isocratic elution of the mobile phase methanol and Acetonitrile in the ratio of 75:25 v/v with the flowrate of 1.0 ml/min. Separation was performed on a Waters C18 (250 x 4.6 mm I.d, 5 µ particle size) analytical column and a pre- column to protect the analytical column from strongly bonded material. Integration of the detector output was performed using the Lc-Solution software to determine the peak area. Before usage, the mobile phase's contents were sonicated to remove any gas and filtered using a 0.45 m membrane filter. As diluents, mobile phase was used [91-93].

Table 2 System Suitability Parameter

Sr.no	Parameter	Result (Eliglustat)
1.	Retention time	4.114 min
2.	Tailing	1.41
3.	Theoretical plates (n)	3967.73
4.	Resolution factor	-------
5.	Similarity factor	1.05

The mobile phase's flow rate was calibrated to 1.0 ml/min, resulting in a column back pressure of 2500–2800 PS. The column temperature was kept at 25°C and the run time was set to 8 minutes. The injection volume was 20 l, and the column was pre-equilibrated with the mobile phase for 30 to 40 minutes before the analyte was injected. At 282 nm, the eluents were discovered [94-96]. Standard stock solution A: -10mg of Eliglustat tartrate drug sample was weighed accurately and transferred to 10mL volumetric flask and diluted up to the mark with methanol (1000µg/ml) [97-99]. Standard working solution: - From stock A 8ml was pipette out and was diluted up to 10ml with methanol in 10ml volumetric flask (80µg/ml) [100-105]. Number of mobile phase and their different proportions were tried and finally was selected as Methanol and Acetonotrile in the ratio of 75:25 v/v appropriate mobile phase which gave good resolution and acceptable system suitability parameters [106-110].The limit of detection (LOD) and limit of quantitation (LOQ) of Eliglustat was determined by calculating the signal-to- noise(S/N) ratio of 3:1 and 10:1, respectively according to International Conference on Harmonization guidelines [111-135]. The HPLC method developed for the analysis of eliglustat in their pharmaceutical preparations is

simple, rapid and economic with less run time. The method has been validated, and it has been demonstrated that it is robust with modest fluctuations in chromatographic parameters as well as dependable, linear, accurate, and exact. Therefore, it can be applied for both routine analytical and quality control assay and it could be a very powerful tool to investigate stability of Eliglustat [136-161].

Table 3 System Suitability Parameter

Sr. no	Parameter	Description /value
1.	Stationary phase	Inertsil C_{18} column 5µm
2.	Mobile phase	Methanol: Acetonitrile (75.25v/v)
3.	Flow rate	1.0ml/min
4.	Detection wavelength	282 nm
5.	Detector	Ultraviolet detector
6.	Injection	Manual
7.	Retention time	Eliglustat 4.00 min
8.	Injection volume	20µm
9.	Column temperature	Ambient (25^0 c)
10.	Run time	8 mins
11.	Diluent	Mobile phase

CONCLUSION

The conclusion of the review paper on eliglustat as an inhibitor for Gaucher disease underscores its significant therapeutic potential. Through a comprehensive analysis of various analytical techniques, including HPLC, 2DNMR, and HRMS, this review provides valuable insights into the pharmacodynamic and pharmacokinetic properties of eliglustat. The collective evidence highlights eliglustat's ability to effectively inhibit glucosylceramide synthase, leading to a reduction in glucosylceramide levels, thereby addressing the underlying pathophysiology of Gaucher disease. Moreover, the review delves into the chemistry, solubility, and mechanism of action of eliglustat, elucidating its structural features, formulation considerations, and molecular interactions with the target enzyme. By synthesizing these findings, the review reaffirms eliglustat's role as a promising therapeutic agent for Gaucher disease management. The review emphasizes the importance of continued research and clinical development to further elucidate eliglustat's efficacy, safety profile, and long-term effects in Gaucher disease patients. Furthermore, it highlights the need for future studies to explore novel formulations, dosing regimens, and combination therapies to optimize eliglustat's therapeutic benefits and address potential limitations.

ACKNOWLEDGEMENT

We are grateful to Principal Dr. M. J. Umekar, Principal, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Dist- Nagpur (MS.) 441001 for making availability of necessary library facilities.

CONFLICT OF INTEREST

- There are no conflicts of interest
- Ethics approval and consent to participate
- No animal or human was used during this experimental study.

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HOW TO CITE: Abhishek Lawsare, Vaishnavi Umretkar, Shyam Rangari, Milind Umekar, Radheshyam Lohiya, Analytical Profiling of Eliglustat for Gaucher Disease: Method Development and Validation, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 1492-1510. https://doi.org/10.5281/zenodo.11348776