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ANALYTICAL METHODS USED FOR ESTIMATION OF ELTROMBOPAG OLAMINE – AN OVERVIEW

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Abstract:

Analytical techniques have been developed for the quantitative determination of eltrombopag olamine in bulk and tablet dosage forms. Reverse phase chromatography, liquid chromatography–mass spectrometry, UPLC-MS/MS, HPLC, and RP-UPLC are some of the analytical techniques used for determination of eltrombopag olamine. All the methods produced good results in terms of selectivity and sensitivity. The methods were validated and found to be precise, accurate, and robust. The methods are suitable for pharmaceutical analysis and can be used to study the pharmacokinetics of eltrombopag in humans. The article concluded that the developed methods are useful for the determination of eltrombopag olamine in the pharmaceutical industry for drug development, process validation, and quality control.

Key words: *Eltrombopag olamine, RP-UPLC, validation, chronic immune thrombocytopenia.*

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INTRODUCTION:

Eltrombopag is a member of the biaryl-hydrazone class of compounds. In clinical studies, it has been used as eltrombopag olamine, which is the bis-monoethanolamine salt form of eltrombopag. Eltrombopag displays receptor-specific and species-specific binding.

Eltrombopag was initially approved by the U.S. Food and Drug Administration (FDA) on 20th November 2008, Eltrombopag is used to treat thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura who have not responded adequately to corticosteroids, immunoglobulin therapy or splenectomy. The U.S. Food and Drug Administration (FDA) designated Eltrombopag as a breakthrough therapy in February 2014 for persons with aplastic anemia for whom immuno-suppression has failed. Eltrombopag (Promacta for oral suspension) was given FDA approval on 24th August 2015 to treat idiopathic thrombocytopenia in children aged one and older who have not responded adequately to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag was designated as a standard of therapy for aplastic anemia by the NIH in 2017 [1].

It is marketed under the trade names Promacta and other names. Eltrombopag is marketed by Novartis and offered outside of the US under the trade name Revolade. It is an agonist of the thrombopoietin receptor. It is consumed orally and is now owned by Novartis Pharmaceuticals, originated as an outcome of research collaboration between GlaxoSmithKline and Ligand Pharmaceuticals [2].

Physical characteristics

The orally active ethanol-amine salt of Eltrombopag is a red-brown crystalline solid with a mass of 564.63 and the chemical formula $C_{29}H_{36}N_6O_6$, commonly referred to as the Eltrombopag diethanolamine salt, (Promacta or Revolade) and having solubility physical nature of insoluble in EtOH, insoluble in water and 14.12 mg/ml in DMSO after moderate heat. Its chemically 2-aminoethanol;3-[(5E)-5-[[2-(3,4-dimethyl phenyl)-5-methyl-3-oxo-1H-pyrazol-4-yl] hydrazinylidene]-6-oxo cyclohexa-1,3-dien-1-yl] benzoic acid.

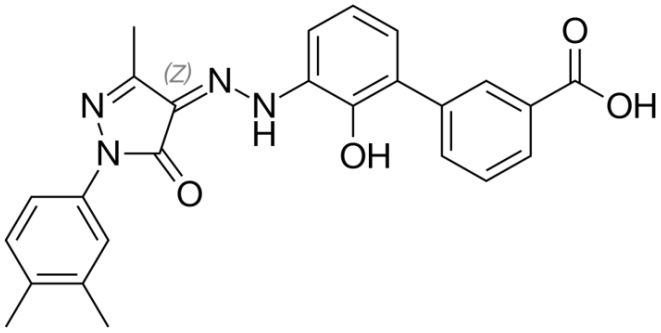

Figure 1: Structure of eltrombopag olamine

Table 1: Physical properties

Molecular formula	$C_{29}H_{36}N_6O_6$
Molecular weight	564.6 g/mol
Appearance	Deep red powder
Solubility	sparingly soluble in water and freely soluble in methanol
Category	Anti-hemorrhagics
Melting point	236 – 238 °C
pKa	3.97

Mechanism of action

This substance is a member of the group of organic substances known as bi-phenyls and derivatives. These are organic substances that have two connected benzene rings that are joined by a C-C bond. Eltrombopag activates by binding with the trans membrane region of the human TPO-receptor and is an orally accessible, small-molecule TPO-receptor agonist. Eltrombopag stimulates the phosphorylation of STAT and JAK. Contrary to recombinant TPO or romiplostim, the medication has no effect on the AKT pathway. It should be noted that other lineages besides platelet count enhanced when administered to patients with aplastic anemia, indicating that either Eltrombopag boosted the effect of TPO *in vivo* or there is an unidentified mechanism of action at play [3].

Pharmacokinetic parameters

A Peak Eltrombopag absorption occurs between two and six hours after oral administration, and at least 52% of drug-related material was ingested orally after a 75 mg dose. The distribution's volume is Eltrombopag concentrations in blood cells range from 50% to 79% of plasma concentrations, according to radio label research. Eltrombopag has a high level of protein binding (>99%). Its metabolism mostly involves cleavage, oxidation, and conjugation with cysteine, glutathione, or glucuronic acid. According to in vitro research, CYP1A2 and CYP2C8 are in charge of the oxidative metabolism of Eltrombopag. The glucuronidation is carried out by UGT1A1 and UGT1A3. Eltrombopag is mostly excreted in the faeces (59%) and is also excreted in small amounts by the kidneys (31%). With a half-life of between 21 and 32 hours in healthy ones and About 26-35 h in patients with idiopathic thrombocytopenia purpura [4].

Uses

Eltrombopag is used to treat chronic immune thrombocytopenia (ITP), an ongoing condition that can result in unusual bruising or bleeding due to an abnormally low number of platelets in the blood, in adults and children 1 year of age and older who have not responded to other treatments or are unable to receive them, such as medication or spleen removal surgery, by increasing the number of platelets (cells that help the blood clot). Eltrombopag is also used to boost platelet counts in hepatitis C patients so they can start and complete therapy with interferon (Peg-interferon, Peg-intron, and other types) and ribavirin (Rebetol), a viral infection that may harm the liver.

Eltrombopag is also used to treat aplastic anemia in adults and children 2 years of age and older. Aplastic anemia is a disorder in which the body does not produce adequate amounts of new blood cells. Adults with aplastic anemia who have not responded to other drugs can also receive it for treatment. Eltrombopag is used to improve platelet counts sufficiently to lower bleeding risks in patients with ITP or aplastic anemia, or to enable interferon and ribavirin treatment in patients with hepatitis C. To bring the quantity of platelets to a regular level, however, it is not employed.

People who have low platelet counts due to illnesses other than ITP, hepatitis C, or aplastic anemia shouldn't be treated with Eltrombopag. Eltrombopag belongs to the group of drugs known as thrombopoietin receptor agonists. It works by increasing the number of platelets made by bone marrow cell [4,5].

Contraindications

Eltrombopag may result in hepatotoxicity, particularly when given to individuals with chronic hepatitis C along with interferon and ribavirin (may raise the risk of hepatic decompensation). Patients with severe hepatic impairment or those who are allergic to the drug or its excipients should not take this medication. AVT recipients with cirrhosis and persistent HCV may experience hepatic decompensation and eventually pass away. The following serious hazards are associated with TCP: thrombotic or thrombi-embolic problems, recurrence of TCP following discontinuation, formation and fibrosis of bone marrow reticulum, hematologic malignancies, hepatic dysfunction and toxicity, and cataract development. People who have low platelet counts due to illnesses other than ITP, hepatitis C, or aplastic anemia shouldn't be treated with Eltrombopag. Eltrombopag belongs to the group of drugs known as thrombopoietin receptor agonists. It works by increasing the number of platelets made by bone marrow cells [6].

Table 2: Drug properties of eltrombopag

Generic drug name	Eltrombopag olamine
Route of administration	Oral
Preparation	12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg
Chemical structure	$C_{25}H_{22}N_4O_4$
Mechanism of action	TPO non-peptide agonist that binds to the trans-membrane and extramembranene domain of TPO receptor. It activates intra-cellular signal transduction pathways, JAK/STAT, and mitogen-activated protein kinase to increase the proliferation and differentiation of HSC.
Bio-availability	~52%
Protein binding	>.99%
Metabolism	Extensive hepatic metabolism via CYP 1A2, 2C* oxidation and UGT 1A1 and 1A3 glucuronidation
Biological half-life	~21–32 h
Time to peak, plasma	2–6 h
Excretion	Feces (~59%) and urine (~31%)
Clinical use	1. Chronic immune thrombocytopenia 2. Chronic hepatitis C-associated thrombocytopenia 3. Refractory severe aplastic anemia
Potential risks	1. Thrombosis 2. Bone marrow fibrosis 3. Clonal evolution 4. Rebound thrombocytopenia 5. Antibody formation 6. Cataract
Common reported side effects (>10%)	1. Reversible hepatic dysfunction 2. Headache 3.Gastrointestinal symptoms (anorexia, vomiting, diarrhea, and abdominal pain) 4. Pyrexia 5. Fatigue 6. Cough 7. Alopecia 8. Arthritis and myalgia

Methods [7-16]

A sub field of chemistry known as analytical chemistry deals with the qualitative and quantitative identification of the constituent parts of substances, samples, and mixtures. There are two different types of analysis: qualitative analysis and quantitative analysis. The identification of mixture or sample's components or analytes is done by qualitative analysis. Quantitative analysis involves quantifying the components or analytes in a mixture or sample. In addition to other disciplines like biology and zoology, as well as the arts like painting and sculpture, archaeology, space exploration, and clinical diagnostics, analytical data is needed in chemistry. Literature review revealed the various methods available are-

1. LC-MS
2. UHPLC
3. UPLC-MS/MS
4. HPLC
5. RP-UPLC

Table 3: Analytical methods used for estimation of eltrombopag olamine

S. No.	Title	Authors	Solvent used
1	Liquid chromatography–tandem mass spectroscopic assay for Eltrombopag in 50 µL of human plasma: A pharmacokinetic study	Omnia I Ali et. al. (2022)	Acetonitrile and 10mM Ammonium formate (90:10, v/v)
2	Stability Indicating UHPLC Method, Development and Validation for Estimation of Eltrombopag and Related Impurities in Tablet Dosage Form	Tharlapu Satya Sankarsana Jagan Mohan et. al. (2018)	Acetonitrile and 0.1% Glacial acetic acid buffer in the ratio of 60:40
3	Rapid And Sensitive UPLC-MS/MS Validated Method For Eltrombopag Determination in Human Plasma and its Application to Bio-equivalence Study	Rambabu Maddela et. al. (2014)	Formic acid (0.1%) and acetonitrile in a 25:75 (v/v) ratio
4	QBD-driven HPLC method of Eltrombopag olamine: Degradation pathway proposal, structure elucidation, and in-silico toxicity prediction	Balaji Jayagopal et. al. (2021)	Acetonitrile
5	Stability Indicating Analytical Method Development And Validation of Eltrombopag Olamine in Tablet Dosage Form by RP-UPLC	Ajay I Patel et. al. (2020)	Water (adjusted to pH 3 with formic acid) and acetonitrile in the ratio of 30:70
6	Impurity assessment, development and validation of an RP-HPLC method for the determination of eleven potential impurities of eltrombopag precursor	Demirhan T et. al. (2024)	Mobile phase A (0.1% orthophosphoric acid in water) and B (acetonitrile)
7	Development and validation of a UV spectroscopic method to estimate eltrombopag olamine along with bulk and in-house formulation	Aabid M et. al. (2023)	Ethanol
8	Stability-Indicating RP-HPLC Method Development and Validation for Eltrombopag Olamine in the Presence of Impurities and Degradation Products. Robustness by Design of Expert Software	Dandabattina R et. al. (2023)	Buffer and acetonitrile were mixed in the ratio 95:5 v/v. Water, methanol, and acetonitrile were mixed in the ratio 10:15:75 v/v/v
9	Development And Validation of Visible Spectrophotometric Method for Estimation of Eltrombopag Olamine in Bulk and Tablet Dosage Form	Sreelatha G et. al. (2023)	Methanol
10	Dissolution Method Validation with Reverse Phase Chromatographic Method for Determination of Eltrombopag Drug Release in Dissolution Samples of Tablets	Keyur Ahir et. al. (2020)	25% ammonium formate and 75% acetonitrile

CONCLUSION:

This review article's primary goal was to examine the creation and validation of the process used for the drug from the beginning of formulation to the final commercial batch of product. The development and validation of analytical methods are ongoing, interrelated processes that take place throughout the drug development process. The process of validation specifies the performance boundaries for the measurement and confirms that a particular method measures a parameter as intended. The main goals of developing analytical techniques are to identify, purify, and ultimately qualify any required substances, etc. The development of analytical techniques aids in reducing the impact of crucial process parameters on precision and accuracy. In order to ensure that quality work is done in the process that supports the creation of medicines and products, validation is a vital approach in the pharmaceutical industry.

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