



“A Comprehensive Review on Selective Dual Inhibitor NSAID - Polmacoxib”

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	<i>Abstract</i>
<p>Article History</p> <p>Received: 20 Nov 2023 Revised: 02 Jan 2024 Accepted: 13 Jan 2024</p>	<p>The review article provides extensive overview on the promising pharmaceutical compound, polmacoxib also known as CG100649, explaining its pharmacological properties, chemical and physical properties, clinical studies and analytical methods. Polmacoxib is a novel nonsteroidal anti-inflammatory drug (NSAID) that has shown significant interest in recent years for its potential therapeutic benefits in Osteoarthritis treatment and distinct analytical characteristics. The chemical and pharmacological section in this review depicts the choice of solvents to be used through its solubility profile and the mechanism of action which focuses on inhibition of both cyclooxygenase-2 (COX-2) and carbon anhydrase inhibition with subsequent modulation of prostaglandin synthesis. The clinical trial of polmacoxib shows especially the phase 3 trial explains majorly about the safety and efficacy of the drug and explains why it is the chosen one among other NSAIDs. Data from randomized controlled trials and observational studies provides understanding of its use in patient population, expressing its potential as an alternate NSAID. Analytical methods for polmacoxib, such as Reverse Phase High Performance Liquid Chromatography (RP-HPLC), Differential Scanning Calorimetry (DSC), and Powder X-Ray Diffraction (PXR) are highlighted in this review. The RP-HPLC is developed for quantification of drug, while DSC and PXR reveals about the solid-state property of CG100649 which will be useful in formulation and stability studies. In conclusion, this review article provides critical information regarding the drug Polmacoxib with its chemical and pharmacological properties, trials conducted as well as analytical procedures performed. It would clearly serve as a valuable resource for analysts, clinicians, researchers and pharmaceutical professionals in understanding its potential and performing further in-process manufacturing and drug product development.</p> <p>Keywords: Osteoarthritis, Polmacoxib, DSC & PXR, RP-HPLC.</p>
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INTRODUCTION:

The most common chronic deteriorating joint disease is Osteoarthritis (OA), which is characterized by breakage in cartilage between the joint bones resulting in bone remodeling, acute joint pain and disability ¹. According to a survey carried out by a study conducted globally in 2019, that the number of cases for Osteoarthritis (OA) was 527.81 million. In this global situation, the highest number of OA were recorded in China about 132.81 million cases, India about 62.36 million cases and then the United States with the record of 51.87 million cases ². The knee and hip OA have a relevant risk of cardiovascular diseases which if severe might lead to death of an individual. According to Norwegian study of 10 years survey followed from 1994 to 2004, obesity was found to be the main and most important risk factor for the OA in both males and females having Body Mass Index (BMI) above 30 ³. Other risk factors for OA would be age, inactivity, family history, previous injury, poor posture, etc.⁴. Since there is not a complete cure for OA, the OA is managed by changing lifestyle habits and by certain medications including Paracetamol, which is a first-line analgesic, various NSAIDS like Celecoxib and Rofecoxib, Glucosamine Sulfate as an oral supplement for management and treatment of Osteoarthritis.

Various NSAIDs inhibiting COX-II like Celecoxib, Rofecoxib and Valdecoxib were in the market to treat pain, OA and Rheumatoid Arthritis (RA) but due to the cardiotoxicity as well as gastrointestinal toxicity few NSAIDs were removed from market ⁵. Patients taking COX-II inhibitors were reported to have a certain increase in cardiovascular diseases including myocardial infarction ⁶. The selective cyclooxygenase 2 (COX-II) inhibitor was developed named Polmacoxib (ACELEX[®]) having relatively low risk of cardiovascular toxicity as well as gastrointestinal toxicity compared to Celecoxib ⁷.

Polmacoxib also known as CG100649 is a 4-{3-(3-fluorophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-2-yl}-benzenesulfonamide. Polmacoxib with brand name Acelex[®] is a non-steroidal anti-inflammatory class of drug (NSAID) which is used to treat OA. It was established by Crystal genomics in Korea and approval of the Korean Ministry of Food and Drug Safety (MFDS) was granted in February 2015 ⁸. C₁₈H₁₆FNO₄S is the molecular formula of polmacoxib with a mass of 361.39 gm/mol ⁹.

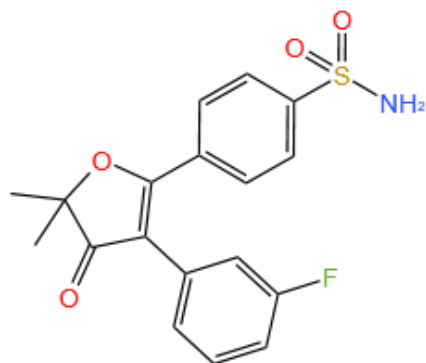


Figure 1: Chemical structure of Polmacoxib (KingDraw)

The chemical structure of Polmacoxib as shown in Fig-1 was drawn using the KingDraw app. NSAIDs are known for their role in suppressing inflammation and pain by inhibiting the Cyclooxygenase (COX) enzymes including both COX-I as well as COX-II inhibitors. There are few studies which showed that the COX-1 inhibiting species cause Gastrointestinal adverse effects and COX-II inhibitors caused certain Cardiovascular disorders as adverse effects in patients ¹⁰. A new NSAID drug was developed recently in the year 2015, Polmacoxib showed dual inhibitory nature – Polmacoxib is COX-II inhibitor as well as Carbonic Anhydrase (CA) inhibitor. In contrast to other NSAIDs, the polmacoxib with its binary mechanism of activity to inhibit cyclo-oxygenase enzymes by binding with the carbonic anhydrase reducing the cardiovascular adverse effects and with lower dosage administration of polmacoxib (2mg) the is reduced adverse effects of GI disorders and have least effect on carbonic anhydrase in the circulatory system ¹¹.

The solubility profile of the CG100649 shows sparing solubility in aqueous phase i.e., water. According to the dissolution studies of polmacoxib, the CG 100649 consists of four different lattice forms in a crystalline solid which shows different solubility in different lattice form in which the most solubility is seen in Dimethyl Sulfoxide (DMSO), ethanol¹². CG100649 is hydrophobic in nature and is also soluble in Dimethyl Formamide (DMF). The polmacoxib in power form is stored at 0°C - 4°C for short time period (for a few days/weeks) and -20°C for about long-term storage period in a monthly or yearly basis^{13,14}. The log P value of 2.6¹⁵. The IC50 value of polmacoxib was found to be 0.21µM. The UV-Vis range for polmacoxib is 318nm, 238nm and 320nm¹⁶. So far there have been very least reports regarding the drug-drug interaction of polmacoxib among which an article published by Expert Opinion on Drug Metabolism and Toxicology stated that polmacoxib with isoform CYP3A affects the metabolism of cytochrome P450. The celecoxib with ketoconazole led to an increase in polmacoxib in plasma concentration by 29%¹⁷.

The correlation of polmacoxib with its various energy bonds have been stated -

Drug	Hydrogen bond	Van-der Waal energy	Electrostatic-energy	Polar-solvation energy	SASA-energy	Binding energy [kJ/mol]
Polmacoxib	3	-227.50	-135.45	166.50	-20.16	-216.61

Table 1: the drug energy bond and values for CG100649¹⁷.

In the pharmacokinetic studies, the relationship of dosage with its exposure for CG100649 was estimated in plasma and whole blood, the volume distribution (V/F) are 559 for 6.7% RSE L/70kg, 7.6 for 2.4% RSE L/70kg in plasma and whole blood respectively¹⁸. A phase 3 clinical trial was carried out for the safety and efficacy of CG100649 by the Korean Orthopedic Association on 441 OA patients in comparison with Celecoxib and placebo treatment over 6 weeks. This trial confirmed facts like – firstly, polmacoxib 2mg once daily has superior analgesic property than the placebo treatment and is same as that of celecoxib 200mg dosage once daily. Secondly, polmacoxib 2mg showed higher PGA (prostaglandin A) than celecoxib 200mg suggesting polmacoxib 2mg to provide rapid onset of action and relief from OA than celecoxib. Thirdly, polmacoxib 2mg was considered “acceptable” for the safety profile and over a trial period of 6 months, polmacoxib was noticed to be well-tolerated and showed higher efficacy than placebo and was same as celecoxib in this profile. Lastly, the trial was concluded with the statement that polmacoxib 2mg showed possibility for a pain relief treatment usage with lessened gastrointestinal adverse effects in comparison to the other NSAID class of drugs^{19,20}. Patent information of polmacoxib drug describes the preparation of polmacoxib using solvents like dimethyl sulfoxide and methanol along with purified water and hydroxylamine-O-sulfonic acid. It also demonstrated the High-Performance Liquid Chromatography analysis of injectable solution containing polmacoxib for gaining knowledge about content uniformity of polmacoxib as well as testing stability of polmacoxib comprising injection^{21,22}.

Thermal analysis DSC and PXRD -

Differential Scanning Calorimetry (DSC) is a thermic analytical technique to measure the heat difference by increasing temperature of sample and reference standard of a product. X-Ray diffraction is a scattering technique which is used to determine the crystal structure. During the literature survey, a research article was found about the DSC and X-Ray diffraction technique for understanding the crystal structure and polymorph forms of CG100649 in solid state. In this article, for DSC analysis 3 milligrams of sample was used between 30°C - 200°C temperature with 10°C heat rate per minute. In an atmosphere of highly refined nitrogen gas at 30ml (about 1.01 oz)/min flow rate. In the article the DSC curves showed single melting endothermic peak at various temperatures for each of the 4 polymorph forms of polmacoxib crystalline solid. The X-Ray diffraction method was also mentioned in detail in this article and the results were noted. Both the Differential Scanning Calorimetry and Powder X-Ray Diffraction techniques were conducted in order to monitor the transformation that each polymorph form of polmacoxib (form 1 to form 4) develops from one form to another. Both DSC and PXRD method confirmed the availability of all 4 forms of polymorph in solid state of CG100649²³.

RP - HPLC -

Reverse phase - High Performance Liquid Chromatography (RP-HPLC) is an analytical technique used for quantitative and qualitative analysis of any compound coupled with UV, PDA or fluorescence detector. According to the literature survey, only one analytical development has been conducted and validation of

polmacoxib in dosage form carried out by RP-HPLC method. There are no other analytical methods developed and validated so far for CG100649. A simple, accurately performed, very sensitive Reverse phase - High Performance Liquid Chromatography has been developed and validated by Chaudhary A. et al. for quantitative estimation of polmacoxib using PDA detector. Separation was achieved within 8.12 minutes using Phenomenex luna C18 column. The mobile phase consisting of Acetonitrile: water in 1:1 proportion was used. The flow rate was measured at 1.0 ml (about 0.03 oz)/ min and detected by PDA detector at 238nm wavelength. This RP-HPLC method was optimized, and analytical validation was conducted in accordance with the International Conference on Harmonization (ICH) Q2 guidelines including – accuracy, precision, specificity, system suitability, linearity and range, LOD and LOQ, robustness²⁵.

CONCLUSION:

Analytical methods are an important aspect for any drug product, API or intermediates. This helps in estimation, quantification and qualification of products and improves their safety, efficacy, stability, and shelf-life. The present review outlines the product details of Polmacoxib (Acelex®) and the analytical methods that have been conducted for the method development of Polmacoxib. Literature survey for polmacoxib shows only a single RP-HPLC analytical method was processed, and validation was carried out for the CG100649 in its pharmaceutical dosage form. This reveals that there is an immense need for method development using other analytical techniques and validation of that method for more information regarding the drug – Polmacoxib and also it would help in better development, optimization, validation and better selection of method during other multiple component studies. The review would also help analysts for selection of components, solvents and combinations for instruments and methods to be developed in the analytical laboratory. The analytical methods are also important and useful for the in-process evaluations during drug manufacturing.

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