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AN OVERVIEW OF POLMACOXIB AND ITS DIFFERENT ANALYTICAL METHOD

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ABSTRACT

Polmacoxib is a novel nonsteroidal anti-inflammatory drug (NSAID). As an NSAID, it belongs to a class of drugs commonly used to alleviate symptoms associated with various conditions. This review will explore the History, Mechanism of action, Pharmacological profile, efficacy, safety, drug interactions, indications. The review article discusses about the Polmacoxib analytical methods done in RP-HPLC, HPTLC and QbD. Polmacoxib has the potential to be utilized as a pain relief drug with diminished gastrointestinal side impacts compared to conventional nonsteroidal anti-inflammatory drugs for Osteoarthritis. Osteoarthritis (OA) is a persistent degenerative and incapacitating condition distinguished by intricate issues affecting the entire synovial joint. NSAIDs and available COX-2 inhibitors that are useful in osteoarthritis show limitations in terms of adverse effects. They all have black box warnings as they are not cardio, renal, and GI safe.

KEYWORDS: Polmacoxib, History, Osteoarthritis, Analytical methods.

INTRODUCTION

Polmacoxib (Fig.1) is 4-[3-(3-fluorophenyl)-4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl]-benzenesulfonamide. Its molecular formula is $C_{18}H_{16}FNO_4S$ and molecular weight is 361.39 gm/mol.[2]

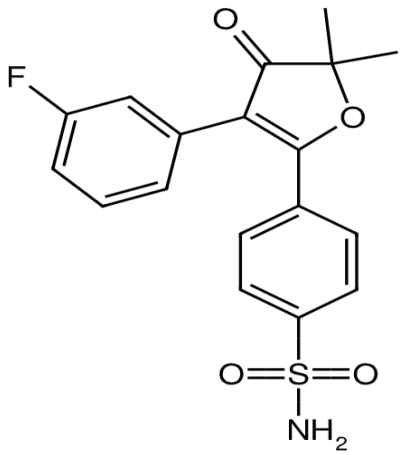

Fig.1. Chemical structure of Polmacoxib.

Polmacoxib is a nonsteroidal anti-inflammatory drug (NSAID) used to treat osteoarthritis. It was developed as CG100649 and approved for use in South Korea in February 2015. It inhibits the enzymes carbonic anhydrase and COX-2. A study in healthy volunteers showed drug effects on urinary prostaglandin metabolites for both Polmacoxib and celecoxib that suggest a similar cardiovascular risk profile.

Polmacoxib has the potential to be utilized as a pain relief drug with diminished gastrointestinal side impacts compared to conventional nonsteroidal anti-inflammatory drugs for Osteoarthritis. Osteoarthritis (OA) is a persistent degenerative and incapacitating condition distinguished by intricate issues affecting the entire synovial joint. NSAIDs and available COX-2 inhibitors that are useful in osteoarthritis show limitations in terms of adverse effects. They all have black box warnings as they are not cardio, renal, and GI safe. Polmacoxib, a novel nonsteroidal anti-inflammatory drug (NSAID), is the first, tissue-selective, once-a-day osteoarthritic drug with a unique mode of action that specifically targets affected joints to relieve pain and restore mobility. Its unique mechanism of action is projected to provide a meaningful enhancement of cardiovascular, renal, and gastrointestinal safety over currently available NSAID options. The pharmacological profile of this drug is characterized by its ability to inhibit COX-2 via the CYP3A4 pathway.

Osteoarthritis (OA) is a chronic disease that involves the breakdown and damage of cartilage. It is highly prevalent in society and leads to a cause of disability. Adults are more susceptible to this disorder as a result of aging and obesity. There is no permanent cure for

osteoarthritis, and the treatments offered primarily focus on pain controlling and improving functionality. It is crucial to employ a multidisciplinary approach customized to the specific needs of patients when treating osteoarthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are primarily used to mitigate painful inflammation and prevent joint damage. However, traditional NSAIDs pose a substantial risk of adverse effects such as gastrointestinal, renal, and cardiovascular, through cyclooxygenase (COX) inhibition. Concerns about health related to traditional NSAIDs and COX-2 inhibitors have resulted in uncertainly regarding the use of COX-2 inhibitors, promoting the development of selective COX-2 drug. Recently, a new COX-2 inhibitor, Polmacoxib (CG100649) has been developed.[4]

PATHOPHYSIOLOGY OF OSTEOARTHRITIS[6]

The pathogenesis of OA (osteoarthritis) has been extensively studied over the past decades. The complex pathological mechanisms underlying the onset and development of OA remain unobserved, even though risk factors have been identified and structural changes in synovial joints are well understood.

Prostaglandin E2 (PGE2) mediated damage in OA One of the initial impacts of proinflammatory cytokines is the activation of phospholipase A2 (PLA2), which cleaves cellular membranes and releases arachidonic acid. During inflammation and catalysing the conversion of arachidonic acid into PGH2, COX-2 is highly up-regulated. PGE2 is a precursor of many eicosanoids, such as prostacyclin and thromboxane, but special attention will be paid to PGE2. This is a major proinflammatory prostaglandin. PGE2 is a major mediator of inflammation, contributing to several pathogenic features of arthritis such as pain, inflammation, and bone loss.

(a) PGE2-mediated pain pathophysiology by reducing the activation threshold of afferent pain nerve endings to pain mediators, PGE2 mediates pain hypersensitization.

(b) PGE2-mediated cartilage degeneration Inflammatory mediators like IL-1β and TNF-α trigger a cascade of events within chondrocytes, notably by stimulating the expression of cyclooxygenase-2 (COX-2), an enzyme crucial in the production of prostanoids. Subsequently, the prostanoids receptor EP4 undergoes upregulation via a COX 2-dependent mechanism. This heightened COX-2 activity leads to increased concentrations of prostaglandin E2 (PGE2), a potent mediator of inflammation. Consequently, the expression of disintegrin and metalloproteinase with thrombospondin repeats (ADAMTS) and matrix.

metalloproteinases (MMPs) are amplified. Moreover, PGE2 exerts detrimental effects on cartilage integrity by reducing proteoglycan production and promoting the release of newly synthesized proteoglycans. Furthermore, IL-1β and TNF-α activate transcription factors NF-κB and JNK, culminating in heightened expression of inducible nitric oxide synthase (iNOS) and subsequent nitric oxide (NO) production. This NO, in turn, plays a multifaceted role in cartilage degradation, inducing chondrocyte apoptosis, inhibiting proteoglycan synthesis, and enhancing MMP activity. Notably, the synergy between NO and PGE2 exacerbates the process of cartilage degradation, further exacerbating the pathophysiological cascade.

(c) PGE2-mediated Synovial inflammation in osteoarthritic synovium, increased levels of IL-1β and TNF-α stimulate the expression of cyclooxygenase (COX)-2 and the ensuing production of prostaglandin E2 (PGE2). PGE2 augments the expression of proteolytic enzymes, including matrix metalloproteinases (MMPs) and urokinase type plasminogen activator (uPA), thereby contributing to the destruction of the articular joint.

(d) PGE2-mediated Subchondral bone resorption in chondrocytes and osteoblasts, IL-1β stimulates the expression of cyclooxygenase (COX)-2, which results in the synthesis of receptor activator of NF-κB ligand (RANKL). Then, RANKL promotes the development of osteoclast precursor cells into quiescent osteoclasts. Moreover, it causes quiescent osteoclasts to express COX-2 and prostaglandin E2 (PGE2), which in return stimulates osteoclasts in an autocrine and paracrine way. In these two ways, number osteoclast increases extensively and that leads to expression of Carbonic anhydrase II. Carbonic anhydrase II, which is extensively expressed on the inner surface of osteoclasts, converts CO_2 and H_2O into bicarbonate and H+. Acidification in the resorption pit is essential to dissolve the inorganic matrix of bone.

HISTORY

Polmacoxib was first approved in South Korea in 2015 for the treatment of colorectal cancer and osteoarthritis. Pre-commercialization will commence immediately and a commercial launch partner for the Korean market will be announced very shortly.[9] It is a first-in-class- NSAID with a dual inhibitory action on COX-2 and carbonic anhydrase (CA) enzyme. Polmacoxib (2 mg) received approval from the Drug Controller General of India on February 14, 2023, for the treatment of idiopathic primary osteoarthritis of the hip and knee.[5]

2000.07-Founded 2003.09-Publication in nature (article and cover based on platform technology 2006.01-IPO on KOSDAQ. 2006.10-Established US subsidiary, CG pharmaceuticals, lnc. For clinical development. 2012.06-Designated by the Korean government as one of the 'KIPC' certified companies. 2014.07- Designated by the Korean government as one of the 'K-Brainpower' companies. 2015.02-Obtained the NDA approval from MFDS for Acelex® in Korea (Osteo arthritis) 2015.09-Launched of Acelex® in Korea. 2023.02-Polmacoxib approved by the DCGI.[17]

Table 1: Polmacoxib patent.[11]

Patent ID	Date	Patent Title
US2010069483	2010-03-18	Dual inhibition of cyclooxygenase-2 and carbonic anhydrase
US2008306146	2008-12-11	Dosing Regimens for Cox-2 Inhibitor
US2005222251	2005-10-06	Dual inhibition of cyclooxygenase-2 and carbonic anhydrase
US6492416	2002-12-10	4,5-diaryl-3(2H)-furanone derivatives as cyclooxygenase-2 inhibitors
WO0061571	2000-10-19	4,5-diaryl-3(2H)-furanone derivatives as cyclooxygenase-2 inhibitor

CDSCO APPROVAL[14]

Polmacoxib 2mg indicated for treatment of Idiopathic (primary) osteoarthritis of Hip/Knee approved by CDSCO dated 01.05.2023 23 Since cardiovascular (CV) side effects of traditional NSAIDs and COX-2 inhibitors are linked to COX-2 inhibition in the CV system where CA is abundant, this interaction is particularly significant.24 inhibition is believed Functionally, to counteract CA the hypertensive effects that typically follow COX-2 inhibition.25 Polmacoxib was first approved in South Korea in 2015 for the management of colorectal cancer and osteoarthritis. Low-dose Polmacoxib administration has shown minimal impact on overall CA function within the circulatory system. In contrast, inflamed tissues tend to be CA-deficient while exhibiting increased COX-2 expression due to inflammatory processes. Since synovial fluid contains negligible CA, Polmacoxib effectively inhibits COX-2 in inflamed joint tissues, leading to reduced inflammation and pain relief. Erythrocytes play a crucial role in the pharmacokinetics of Polmacoxib by serving as a reservoir, safely transporting the drug in an inactive form to tissues with low CA activity, such as arthritic joints. Polmacoxib achieves 85- to 100-fold higher concentrations in whole blood (i.e., within erythrocytes) compared to plasma, which lacks CA. This mechanism ensures tissue-specific drug delivery, providing sustained therapeutic levels in CA-deficient inflamed tissues. As a result, systemic exposure remains low, as Polmacoxib is carried in a bound state with CA inside erythrocytes. This selective transport mechanism enhances its effectiveness in osteoarthritic joints while minimizing adverse effects on the cardiovascular, renal, and gastrointestinal systems.

PHYSICOCHEMICAL PROPERTIES[12]

Drug profile: Polmacoxib **Formal Name:** 4-[3-(3-fluorophenyl)-4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl]-benzenesulfonamide **Molecular formula:** $C_{18}H_{16}FNO_4S$ **Molecular weight:** 361.4 g/mol **Supplied as**: A crystalline solid **Storage:** -20°C **Stability**: ≥4 years **Solubility:** Polmacoxib is freely soluble in organic Solvents such as ethanol and methanol, soluble in DMSO, and dimethyl formamide (DMF). The solubility of Polmacoxib in ethanol is Approximately 5 mg/ml and approximately 20 mg/ml in DMSO and DMF.[3]

MECHANISM OF ACTION[1]

Polmacoxib, is also a selective cyclooxygenase-2 (COX-2) inhibitor, a type of non-steroidal anti-inflammatory drug, and acts as a potent inhibitor of several carbonic anhydrase isoforms, due to its aryl sulfonamide moiety inhibition of COX-2. Unlike other NSAIDs.

Polmacoxib has a dual mode of action

- Inhibition of COX-2
- Binding to carbonic anhydrase (CA) with high affinity. In instances where both COX-2 and CA (carbonic anhydrase) are concurrently present, the strong affinity of Polmacoxib for CA diminishes its COX-2 inhibitory efficacy. Polmacoxib does not inhibit COX-2 in CA-rich tissues (e.g. CV system), but it fully inhibits COX-2 in CA-deficient tissues (inflamed joints).

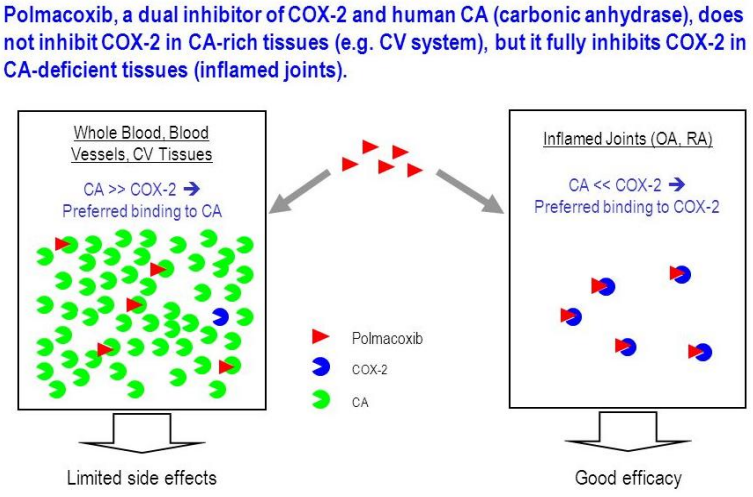

Fig. 2: Mechanism of action of Polmacoxib.

Polmacoxib has unique binding to carbonic anhydrase (CA)[1]

- Polmacoxib showed the strongest inhibitory activity against CA, compared to other coxibs like celecoxib,
- Polmacoxib inhibits CA more effectively than celecoxib and valdecoxib,
- The dual action mechanism of Polmacoxib may minimize the adverse CV effects of COX-2 inhibition,
- While Polmacoxib potentially remains in a mixed state with CA, low-dose administration of Polmacoxib is thought to have a minor influence on total CA function in

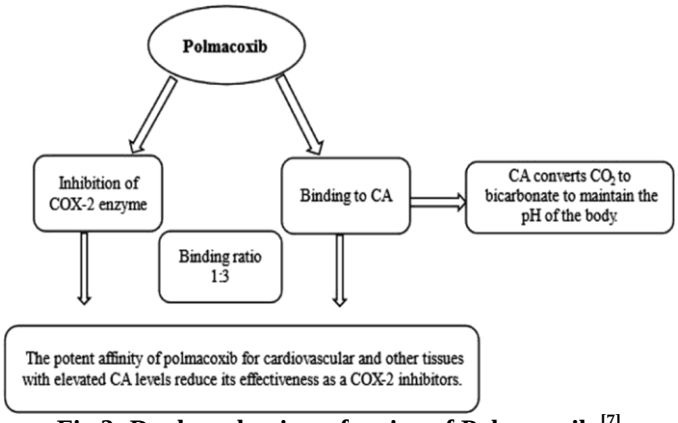

Fig 3: Dual mechanism of action of Polmacoxib.[7]

ADMINISTRATION[13]

Polmacoxib is administered orally. The recommended dose is 2 mg once daily after meals.

USES

1. Osteoarthritis
2. Combination with Tramadol to treat the acute and chronic pain
3. Colorectal cancer- In a premalignant mouse model, Polmacoxib showed growth suppression of colon polyps and a decrease of small intestine polyps in the treatment research.

ADVERSE EFFECT

Polmacoxib is well tolerated with mild side effects such as abdominal pain, enteritis, diarrhoea, dyspepsia, facial oedema, peripheral oedema, headache, urticaria, pruritic, increased blood creatinine, and anasarca.

SAFETY PROFILE[13]

The drug was well tolerated in all dose groups with no clinically significant changes in blood pressure observed. The most frequently reported adverse events were aphthous stomatitis and dyspepsia. Comprehensive safety assessments including physical examinations, clinical laboratory tests, ECG, and vital signs monitoring indicated no serious drug related adverse effects. Polmacoxib has no absolute contraindication, but caution is advised with renal impairment as the drug is eliminated via the kidney. It should be avoided in patients with liver dysfunction and congestive heart failure. The effects of Polmacoxib on pregnancy and breastfeeding are unknown because of the limited data available.

PHARMACODYNAMICS OF POLMACOXIB

Distinct from others NSAIDs, Polmacoxib has a dual mechanism of action that includes inhibition of COX-2 and inhibition of CA-I/II. Most conventional COX-2 inhibitors do not show significant activity towards CA inhibition and demonstrate notable COX-2 inhibition in the cardiovascular system that could result in the development of adverse cardiac events.[5]

The cardiovascular system exhibits the presence of both CA and COX-2 with an abundance of CA in the whole blood, blood vessels, and cardiovascular tissue. Where COX-2 and CA co-exist, Polmacoxib demonstrates a far higher affinity to CA than COX-2, and this, in turn, reduce the COX-2 inhibitory activity in the cardiovascular tissue. The dual-action mechanism of Polmacoxib can, therefore, potentially help minimize the adverse cardiovascular effects of COX-2 inhibition. Additionally, it has been noted that there is a negligible effect on the overall CA functioning of the circulatory system by the low-dose administration of Polmacoxib. Conversely, inflamed tissues are deficient in CA, but express increased COX-2 due to the presence of inflammatory process. Synovial fluid has been found to contain negligible CA. As a result, Polmacoxib fully inhibits COX-2 in the inflamed joint tissue, thus alleviating inflammation and pain associated with osteoarthritis.[5]

Polmacoxib targets inflammation with a 'tissue-specific' approach. It inhibits COX-2 and tightly binds to CA in red blood cells. This dual action aims to maintain high drug levels in inflamed tissues while reducing systemic exposure, potentially influencing its COX-2 inhibitory effectiveness based on CA levels. The cardiovascular system contains both CA and COX-2, with CA being abundant in blood, vessels, and cardiovascular tissues.

Polmacoxib shows a stronger binding to CA than COX-2 when both are present, which reduces COX-2 inhibition in cardiovascular tissues. This dual mechanism may lessen the cardiovascular side effects associated with COX-2 inhibitors. CA catalyses the conversion of carbon dioxide into bicarbonate and hydrogen ions, processes crucial for maintaining acid–base homeostasis in blood cells. By facilitating this reversible reaction, CA plays a vital role in regulating pH balance and bicarbonate production within tissues including synovium tissue. Overexpression of CA isoenzymes, such as CA II and CA IX, has been noted in inflamed synovium, especially in conditions like OA and RA. Elevated CA levels contribute to a more acidic microenvironment, affecting cellular metabolism and contributing to dysfunction in chondrocytes and osteoclasts. This metabolic shift can enhance inflammation within the synovium, as observed in OA and RA. Research has shown that the inhibition of CA may help normalize pH levels in inflamed synovial fluid, thus potentially reducing bone resorption and alleviating symptoms associated with these diseases. Furthermore, CA inhibitors function by inhibiting bicarbonate uptake in the kidneys, which may provide additional benefits in managing these conditions. The dual inhibition of both COX-2 and CA provided by Polmacoxib could represent a promising therapeutic approach.[7]

PHARMACOKINETIC OF POLMACOXIB

Erythrocytes play an important role by acting as a reservoir for Polmacoxib, transporting the drug in a protected, inactive state to tissue with low CA activity, such as arthritic joints. Polmacoxib shows 85-100-fold higher concentration in the whole blood, i.e., erythrocytes, than in plasma where there is no CA. Erythrocytes provide a tissue-specific transport mechanism delivering sustained levels of the drug to CA-deficient inflamed tissues. This, in turn, helps maintain low systemic exposure as Polmacoxib is transported in a combined state with CA within the erythrocytes. Thus, Polmacoxib is believed to offer maximum effectiveness in inflamed osteoarthritic joints while reducing its effects on the cardiorenal system or the gastrointestinal tract.[5,10]

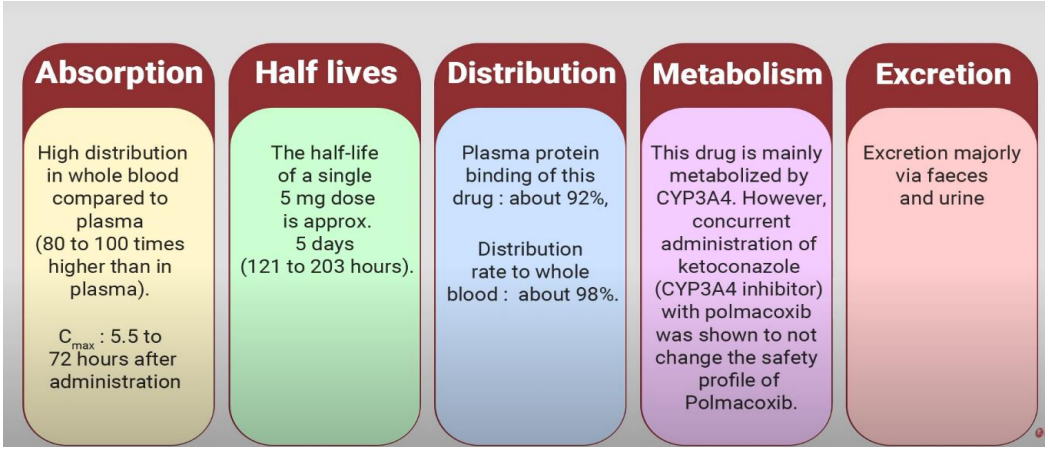

Fig 4: Pharmacokinetics of Polmacoxib.

Based on the pharmacokinetic profile (central elimination rate constant and redistribution rate constant), it was observed that Polmacoxib has a longer residence time in inflamed osteoarthritic joints as compared with blood. From a drug tolerability perspective, this suggest that other body compartment is spared from prolonged exposure to the drug. Polmacoxib is primarily excreted via the fecal route, while small amounts are also excreted via the urinary route. Therefore, a decrease in hepatic catabolism due to any reason may likely affect the clearance of Polmacoxib.[5,10]

The pharmacological properties of Polmacoxib have been summarized in table 2.

Table 2: Summary of features and properties of Polmacoxib 2mg.[5]

Parameter	Features and properties
Class	Non-steroidal ant-inflammatory
Therapeutic use	Osteoarthritis of the hip and knee
Dosage and administration	For oral use, 2mg once daily after a meal. The dose should not exceed 2mg/mg
Pharmacodynamics	Dual mechanism of action: inhibition of COX-2 and inhibition of carbonic anhydrase (CA) with high affinity
Pharmacokinetics	Mean (SD) *T max:* 5.6(1.0) hours; mean (SD) *C max*:3.5 (0.9) ng/ml; mean (SD) *t1/2*:131(19) hours; excretion: primarily via the fecal route.

CLINICAL EFFICACY OF POLMACOXIB[7]

Lee et al. found that Polmacoxib 2 mg was more effective than placebo and maintained noninferiority compared to celecoxib over six weeks in patients with OA. An 18-week extension trial involving a Korean cohort of 362 patients assessed changes in the Western Ontario and McMaster Universities (WOMAC) OA Index, demonstrating a statistically significant difference between the placebo and Polmacoxib 2 mg groups, with a reduction of –12.4 points (P = 0.011). The difference between Polmacoxib and celecoxib was 0.6 (P = 0.425). Significant results were also observed in WOMAC pain, stiffness, and physical function, showing reductions of –2.9 for pain (P = 0.001), –1.4 for stiffness (P = 0.001), and –8.0 for physical function (P = 0.003). Similarly, Schmidt et al. found that an 8 mg loading dose of Polmacoxib followed by 1.2 mg daily for 3 weeks effectively treated OA pain in men, with good tolerability. Polmacoxib was well tolerated and showed a whole blood concentration approximately 50 to 70 times greater than that in plasma among these healthy subjects. It effectively suppressed thromboxane B2 (TXB2) and prostaglandin E2 (PGE2) at all three doses (8-mg loading dose + 2 mg/d, 10-mg loading dose + 4 mg/d, or 12-mg loading dose + 8 mg/d), while only the highest dose reduced the urinary excretion of the prostacyclin Metabolite.

DRUG INTERACTIONS[7]

Co-administration of Polmacoxib with ketoconazole does not adversely affect its safety profile Polmacoxib interacts with various medications, potentially increasing the risk of adverse effects summarized in (Table 3)

Table 3: Interactions of Polmacoxib with other drugs.

Interactions	Characteristics
Safety profile with ketoconazole	When co-administered with ketoconazole, Polmacoxib does not adversely affect its safety profile
Interaction with antidiabetic drugs	Polmacoxib interacts with antidiabetic drugs (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide), potentially decreasing their protein binding
Interaction with antihypertensive medications	Concurrent use with antihypertensive medications (enalapril, fosinopril, lisinopril, and moexipril) could increase the risk of renal failure, hyperkalaemia, and hypertension
Interaction with levamlodipine	Reduces the therapeutic effectiveness of levamlodipine

INDICATIONS[7]

Polmacoxib is a drug currently being investigated for its therapeutic applications in treating (OA). Clinical studies have shown that it holds promise not only for managing both acute and chronic pain associated with OA. But also, for its potential role in treating colorectal cancer. Additionally, Polmacoxib is being explored as a CA inhibitor. Given these diverse potential applications, further trials are necessary to fully understand its efficacy, safety, and the range of conditions it may effectively treat. Although Polmacoxib has been approved for trials in India, the related articles are not publicly accessible. Despite the promising outcomes from early clinical trials, there is currently limited literature on the long-term safety and efficacy of Polmacoxib. Most research has concentrated on specific groups, especially in Asia, which may affect the generalizability of the results. Future studies should focus on larger, multicentre trials involving diverse populations to gain a more thorough understanding of the therapeutic potential of Polmacoxib.

ANALYTICAL METHODS

THERMAL ANALYSIS DSC AND PXRD[15]

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 CG100649.

RP – HPLC

1. 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 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 C_{18} 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, robustness.[2]

2. A Novel, efficient and convenient reversed-phase high-performance liquid chromatography method was developed for Polmacoxib (PCB) drug in the presence of its impurities. Successful separation of Polmacoxib drug from the its impurities was achieved on Zorbax SB-C8 250 x 4.6 mm, 5.0 µm with gradient elution of Acetonitrile: Methanol as a mobile phase. The Ultraviolet detection was monitored at a wavelength of 240 nm at flow rate 1.0 mL/minute. The validation of proposed method was carried for linearity, precision, accuracy, limit of detection, limit of quantification and robustness were determined in accordance with ICH guidelines. The method has good specificity and specified impurities can be effectively separated with good resolution. The proposed method is found to have linearity in the 4-20 µg/mL concentration range of Polmacoxib with correlation coefficients of not less than 0.999. The limit of detection for the drug and impurities are 0.81µg/ml, 0.45µg/ml and 0.65µg/ml and the limit of quantification for the drug and impurities are 2.75µg/ml, 1.50µg/ml and 2.20 µg/ml respectively. The method successfully estimated the drug in formulation tablet in the presence of known impurities. The proposed method can be applied for quality control studies of other drugs with the competence of simplicity, accuracy, robustness, good selectivity, and high sensitivity.[16]

3. An accurate, rapid, economical, precise and robust isocratic RP-HPLC method was developed for determination of Polmacoxib. The chromatographic separation was achieved Agilent Eclipse XBD-C18 (150 mm × 4.6 mm ID x 5 µ particle size) column set at 30 °C temperature. A mixture of Water: Methanol 40:60 %v/v was used as a mobile phase flowing at a rate of 1.0 mL/min. Injection volume was kept at 50 µL. The retention time for Polmacoxib was 4.12 with good repeatability on system suitability analysis. The method was found to be stability-indicating and specific on forced degradation studies. The method was validated as per ICH guidelines. Calibration plots were linear over the concentration range 10–30. Percentage recoveries were found to be close to 100% with low variability. The method may be adopted for routine analysis at industry.[17]

HPTLC[3]

The method was successfully developed by employing TLC aluminium plates pre-coated with silica gel 60 F254 and CAMAG twin through chamber, the study optimized Toluene: Ethyl Acetate: Methanol (8:2:1 v/v/v) as mobile phase for efficient plate development at room temperature (25 ± 2°C). Utilizing CAMAG TLC scanner 4 with vision CATS user software, scanning and densitometric analysis were carried out at 322 nm (λ max), revealing sharp peaks and dense bands with an Rf value of 0.44. The developed method undergoes rigorous validation in adherence to ICH guidelines Q2 (R1), encompassing specificity, linearity, precision, LOD and LOQ, accuracy and robustness. The Linearity studies demonstrated a strong correlation (R^2=0.9919) across the concentration range of 5-30 ng/spot. The precision results met the acceptance criteria, and LOD & LOQ were determined at 700.03 ng/spot and 2100.30 ng/spot, respectively. The recovery studies showed accurate results with RSD of 99.97%. Robustness testing involved deliberate changes confirming the method's suitability for routine analysis. This validated HPTLC method establishes itself as a reliable analytical tool for the routine quantification of Polmacoxib, offering pharmaceutical researchers and technicians a practical and accurate approach. The results of this study contribute significantly to the qualitative and quantitative analysis of Polmacoxib in both bulk and pharmaceutical formulations, providing a robust foundation for quality control processes in the pharmaceutical industry.

QUALITY BY DESIGN (QbD)[4]

Quality by Design (QbD) Approach for the Development and Validation of RP-HPLC Method Enabling Simultaneous Estimation of Polmacoxib and its Process-Related Impurities: Exploring Degradation Pathways and Elucidating Degradant Structures via LC-MS/MS and NMR spectroscopy. A simple, sensitive, and selective method was developed and validated for the determination of POL and its process-related impurities. Chromatographic separation was achieved on Kromasil C18 column 250 mm x 4.6 mm, 5µm using gradient elution with mobile phase containing 10 mM ammonium acetate buffer and acetonitrile in the initial ratio of 90:10 % v/v. The chromatographic condition was optimized such as a flow rate of 1.2 ml/min, UV detection at 232 nm, injection volume of 10 µl, and column temperature of 35° C. The findings were interesting: Resolution for POL and five impurities is more than 1.5 for any pair of analytes. The proposed method was validated per the current ICH Q2 (R1) guidelines, and it is accurate, precise, linear, and sensitive. Specify study proves the method's efficiency in estimating Polmacoxib and their related substances within the same run. Stress conditions were established by exposing the drug to different stress conditions. The forced degradation results demonstrated that the drug was sensitive to alkaline conditions. During the stress study, degrading impurities were identified by the LC-MS technique and characterized by UV, LC ESI QTRAP, 1D-NMR (1H, 13C) and 2D-NMR (1H-1H

COSY, HSQC). A QbD-based design of experimental (DoE) approach was used to establish the robustness of the method.

ANALYTICAL METHODS

Table 4: Analytical methods of Polmacoxib.

STUDY	COLUMN	MOBILE PHASE	FLOW RATE	λ MAX
RP-HPLC	Phenomenex luna C_{18} column (250mm×4.6mm), 5 µm	Water: ACN (1:1)	1.0 ml/min	238 nm
Stability indicating RP-HPLC	Agilent Eclipse XBD-C_{18} (150 mm × 4.6 mm, 5 µm	Water: Methanol 40:60 %v/v	1.0 ml/min	237 nm
Identification of Impurities in Active Pharmaceutical Ingredients of Polmacoxib Using RP-HPLC	Zorbax SB-C_8 250 × 4.6 mm, 5.0 µm	Acetonitrile: Methanol	1.0 ml/min	240 nm
High-Performance Thin Layer Chromatography	TLC aluminium plates pre-coated with silica gel 60 F254 and CAMAG twin through chamber	Toluene: Ethyl Acetate: Methanol (8:2:1 v/v/v)	-	322 nm
QbD Approach for the Development and Validation of RP-HPLC Method	Kromasil C_{18} column 250 mm × 4.6 mm, 5µm	10 mM ammonium acetate buffer: acetonitrile 90:10 % v/v	1.2 ml/min	232 nm

FUTURE DIRECTIONS[14]

Polmacoxib is recognized as the most potent COX-2 inhibitor currently available and effectively targeting the key enzymes involved in OA progression. Additionally, Polmacoxib exhibits potential disease-modifying properties through its dual inhibition of carbonic anhydrase (CA) and prostaglandin E2 (PGE2), which may contribute to altering the disease course. Therefore, the distinctive mechanism of action of Polmacoxib is believed to offer advantages in terms of both effectiveness and reduced systemic side effects compared to traditional NSAIDs. Polmacoxib was first approved in South Korea then in India, however due to some insufficient data it doesn't get the approved in USA. India having large population, more post-marketing surveillance can be done and better outcomes can be obtained from Polmacoxib.

CONCLUSION

Analytical methods are an important aspect for any drug product, API or intermediates. The present review outlines the product details of Polmacoxib and the analytical methods that have been conducted for the method development of Polmacoxib. Literature survey for Polmacoxib shows RP-HPLC, HPTLC and QbD analytical method was processed, and validation was carried out for the Polmacoxib in its pharmaceutical dosage form. In this RP-HPLC methods shows the retention time such as 4.2 and 8.1 minutes, and 10 mM ammonium acetate buffer and acetonitrile were used as a mobile phase in QbD. Toluene: Ethyl Acetate: Methanol were used as a mobile phase in HPTLC method. 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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