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POLMACOXIB: A PROMISING NSAID FOR PAIN AND INFLAMMATION

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ABSTRACT

Polmacoxib is a novel nonsteroidal anti-inflammatory drug (NSAID) that has shown promise in managing pain and inflammation. As an NSAID, it belongs to a class of drugs commonly used to alleviate symptoms associated with various conditions. This review will explore the Discovery, History, Physicochemical properties, Pharmacological profile, efficacy, safety, pharmacokinetics, and patient experience of polmacoxib. 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. It focuses mainly on the Clinical Studies of Polmacoxib along with their applications. It also Provide a brief overview of polmacoxib, including its generic name, indications, and intended use. Polmacoxib has the probable to offer clinicians and patients another positive treatment for different conditions related to pain and inflammation.

KEYWORDS: Polmacoxib, Osteoarthritis, Stability, carbonic anhydrates, NSAID.

INTRODUCTION

Polmacoxib (Acelex) may be a nonsteroidal anti-inflammatory drug (NSAID) utilized to treat osteoarthritis.[1] Polmacoxib is an inhibitor of cyclooxygenase 2 (COX-2) and the carbonic anhydrase subtypes I (CAI) and CAII. It restrains COX-2 within the nonattendance of carbonic anhydrase II). Polmacoxib avoids prostaglandin E2 generation in human colon cancer cells, it hinders polyp arrangement in a transgenic mouse demonstration of intestinal

polyp arrangement and tumor development in human colorectal carcinoma mouse xenograft models when utilized at a measurement of 7 mg/kg.

The hindrance of COX-2 and CAII by polmacoxib has the potential for less genuine systemic antagonistic impacts, counting cardiovascular occasions related to COX-2-specific inhibitors such as celecoxib. Definitions containing polmacoxib have been utilized within the treatment of osteoarthritis. Structure Polmacoxib, developed as CG100649 is additionally a specific cyclooxygenase-2 (COX-2) inhibitor, a sort of non-steroidal anti-inflammatory medicate, and acts as a powerful inhibitor of a few other CA isoforms (CA I and II).

Polmacoxib contains a double mode of activity: hindrance of COX-2 and official to carbonic anhydrase (CA) with tall fondness. A key work of CA is to control the pH level within the body through the intercountry between carbon dioxide and bicarbonate. Where COX-2 and CA coexist, the high-affinity authoritative of polmacoxib CA diminishes the COX-2 inhibitory movement of polmacoxib.

BACKGROUND AND HISTORY

The compound polmacoxib, the dynamic fixing utilized within the pharmaceutical composition of the show innovation, is named 5-(4-(aminosulfonyl) phenyl)-2,2-dimethyl-4-(3-fluorophenyl)-3(2H)-furanone. It could be a specific COX-2 inhibitor and has less gastrointestinal harmfulness than customary NSAIDs. It is known to be compelling in fiery maladies, inflammation-related infections, torment, strong cancer, angiogenesis-related infection, Alzheimer's infection, seizures and shakings, stroke, or epilepsy (Korean Obvious 10-0495389).

Currently, acetaminophen and celecoxib are utilized in combination with tramadol. The advantage of the above-mentioned half-macoxib is that it has the most extreme impact with the least side impacts indeed with a little sum of the dynamic fixing. COX (cyclooxygenase) is the mind of the generation of prostaglandin. Two of its isoforms, COX-1 and COX-2, have been distinguished. COX-2 appeared to be initiated by pro-inflammatory boosts and is a chemical isoform accepted to play a critical part within the amalgamation of prostanoid controllers of pain, irritation, and fever.

The display innovation is coordinated with the utilization of a combination of polmacoxib, which could be a COX-2 inhibitor, and tramadol, which has these activities, for the treatment

of intense and chronic pain. The most thought of the show application is pharmaceutical compositions in which the combination of polmacoxib and tramadol can give extra impacts in tall to direct torment, in specific in torment related to aggravation.

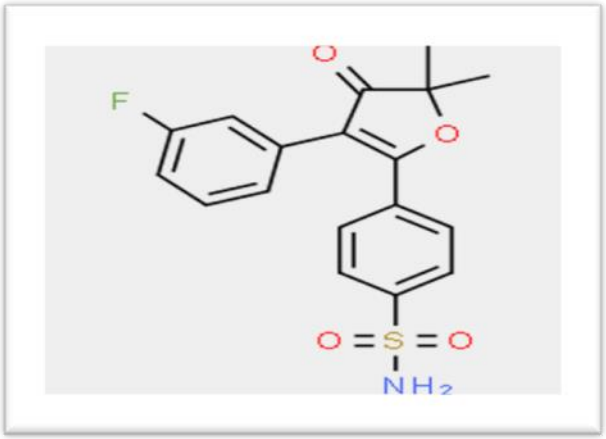


Fig. 1: Structure of Polmacoxib.

PHYSICOCHEMICAL PROPERTIES

Table 1: Physiochemical properties.

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
Purity	≥98%UV/Vis: λmax: 238, 320 nm
Supplied as	A crystalline solid
Storage	-20°C
Stability	≥4 years
Solubility	Polmacoxib is soluble in organic.

Solvents such as ethanol, 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. Polmacoxib is sparingly soluble in aqueous buffers.

PHARMACOKINETICS AND ITS PROPERTIES[2]

Polmacoxib's pharmacokinetic properties contribute to its clinical utilization. It is well-absorbed after verbal organization, with a moderately tall bioavailability. The medicate experiences a hepatic digestion system, essentially through the cytochrome P450 framework, and is killed transcendently using the renal course. Its pharmacokinetic profile bolsters once or twice-daily dosing, giving comfort to patients.

Reason: Polmacoxib, an unused coxib dually repressing cyclooxygenase-2 and carbonic anhydrase I/II, was as of late endorsed for osteoarthritis treatment in South Korea. This thinks about investigating the populace pharmacokinetic and pharmacodynamic characteristics of polmacoxib.

Strategies: Nonlinear mixed-effects modeling was performed utilizing pooled pharmacokinetic information from a Stage I ponder in solid people and pharmacokinetic properties and Western Ontario and McMaster Colleges Osteoarthritis Record (WOMAC) information from a Stage IIb think about in patients with osteoarthritis. Pharmacodynamic models for WOMAC were consecutively fit utilizing person pharmacokinetic parameter gauges.

Discoveries: Polmacoxib concentrations in the entire ety blood were satisfactorily portrayed by the 2-compartmedemonstrationate, with blended zero- and first-order assimilation energy. Press concentration was the critical covariate related to the clearance of polmacoxib. The relationship between the entire blood concentration of polmacoxib and WOMAC was best portrayed by a 2-effect compartment demonstrate that comprised of central and fringe compartments with theatre consistent with 0.408 min-1 for dissemination to the central impact compartment. A diminish in WOMAC was connected to the central impact location compartment concentration through a standard greatest impact model with an impact location concentration required to attain 50% of the most extreme impact of 508 ng/mL.

PHARMACOLOGICAL PROFILE

Polmacoxib shows its helpful impacts by hindering the action of cyclooxygenase (COX) chemicals, particularly COX-2. By specifically focusing on COX-2, polmacoxib viably decreases the generation of prostaglandins capable of torment, irritation, and fever. This focused activity may minimize antagonistic impacts related to conventional NSAIDs, which hinder both COX-1 and COX-2.

EFFICACY

Different clinical trials have illustrated the viability of polmacoxib in overseeing torment and irritation. The medication has been assessed for conditions such as osteoarthritis, rheumatoid joint pain, and postoperative torment, appearing critical advancements in torment scores, joint work, and quality of life. Comparative thinks about have moreover demonstrated comparative

viability to other commonly endorsed NSAIDs, recommending that polmacoxib can be a reasonable treatment choice.

SAFETY PROFILE

Polmacoxib's security profile may be a vital thought in its assessment. Like other NSAIDs, it may cause gastrointestinal antagonistic impacts such as dyspepsia, gastric ulcers, or gastrointestinal death. Be that as it may, the COX-2 hindrance of polmacoxib may diminish the chance of gastrointestinal complications compared to nonselective NSAIDs. Other potential side impacts incorporate cardiovascular occasions, renal impedance, and skin responses. Patients with a history of these conditions or those at higher hazard may require cautious observing.

CLINICAL STUDIES[3]

Table 2: Clinical studies of Polmacoxib.

Clinical studies	Summary
Phase 1 studies	Measurements subordinate presentation watched. No critical PK differences among diverse ethnic and gender groups No drug intuitive watched. Steady blood pressure kept up all through the whole length of clinical studies Absence of noteworthy side impacts indeed within the supra helpful Mad study Cardiovascular study – Different estimations counting signs ls of CV antagonistic occasions Gastrointestinal safety – Nonappearance of critical Gi unfavorable effect
Phase 2a study	The clinically Significant efficacious dose is 1.2mg per day No dropouts due to lack of efficacy maintenance of stable blood pressure throughout the entire study
Phase 2b study	Uniform dosing on days 1-28 exceptionally high consider medicate compliance rates (81-85% in all bunches) few dropouts (93-95% completion rate among all 3 treatment arms) Polmacoxib 2 mg and 4 mg were non-second rates to celecoxib 200 mg for all adequacy measures Polmacoxib 2 mg dosage created higher viability No dropouts due to the need for viability Polmacoxib 2 mg has a favorable antagonistic impact profile (comparable to celecoxib 200 mg) Polmacoxib 2 mg measurements chosen for stage 3 clinical considers
Phase 3	A double-blind, Randomized, multicenter Active, and placebo-controlled phase 3 study to evaluate the efficacy and safety of polmacoxib in Osteoarthritis patients. Eligibility criteria – subject must have chronic pain for at least 3 months or more than it. **Efficacy assessment** – efficacy assessment is done by evaluating the WOMAC arthritis index questionnaire. A higher WOMAC score represents worse symptom severity **Safety assessment** – it does not show any adverse effect and Physical examination is done for safety assessment purposes For the pharmacokinetics Study –Plasma and whole blood camp were taken after breakfast,

	and administration of the dong was on day 1, for a subject who participated in the main 6-week 6-weekment period. For subject who participated in the 6-week treatment period them safety assessment was conducted at week 3,6,8. For trial extension participants, Safety assessments were conducted at weeks 3,6,12,18, and 24. Polmacoxib showed superior efficacy over celecoxib It also shows quicker onset over celecoxib **Safety assessment results** There was no drug-related adverse effect in either of the polmacoxib or celecoxib treatment groups **Conclusion of this study** A 2 mg dose of polmacoxib was tolerated well and based on results of a 6week treatment period polmacoxib 2 mg demonstrated efficacy and safety like celecoxib 200 mg

MECHANISM OF ACTION[7]

1. NSAIDs inhibit cyclooxygenase (COX) enzymes, which play a role in the regulation of inflammation. COX-1 is to protect the GI mucosa by the synthesis of prostaglandin. while COX 2 is increased by inflammation and is involved in both inflammation and pain pathways. Conventional first-generation NSAIDs are nonselective, inhibiting both COX-1 and COX-2, meaning that GI lesions may accompany their effects to reduce inflammation and pain. Compounds exhibiting greater COX-2 selectivity are thought to reduce damage to the GI tract by the synthesis of protective prostaglandins through COX-1, while simultaneously maintaining anti-inflammatory effects by inhibiting COX-2. This led to the development of COX-2 selective drugs such as celecoxib and rofecoxib, which were reported to reduce GI-related AEs compared with conventional NSAIDs. However, with COX inhibition, some studies have proved an increased risk of adverse cardiovascular (CV) events, including blood pressure elevation and myocardial infarction. The health concerns associated with traditional NSAIDs and COX-2 inhibitors have led to confusion around the use of COX-2 inhibitors12) and provide a strong rationale for the development of safer NSAIDs with fewer AEs on the GI tract and CV system.

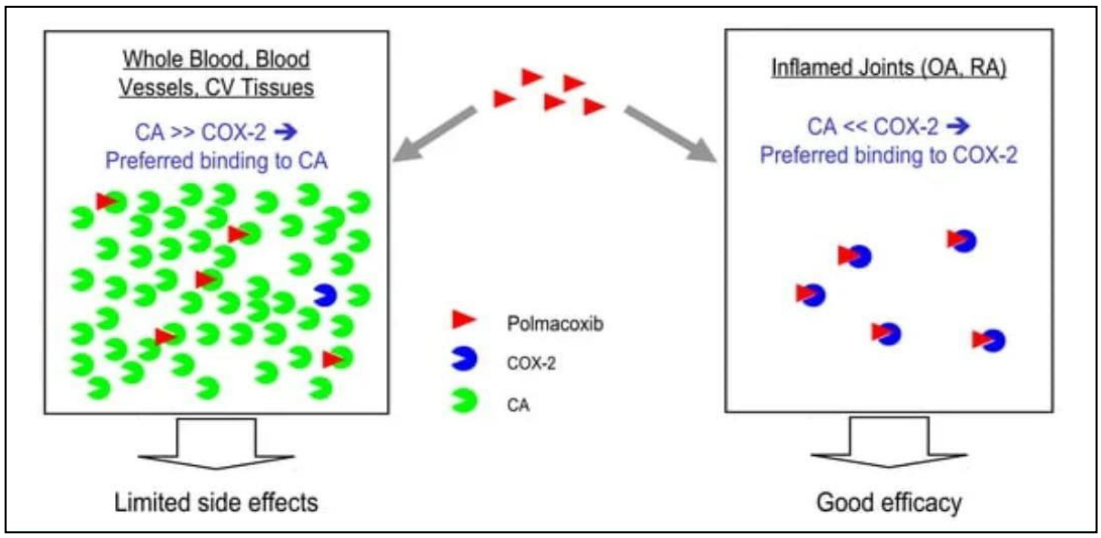


Fig. 2: Mechanism of action of polmacoxib.

2. Tramadol is an analgesic drug that acts by enhancing the activation of opioid receptors and the concentration of monoamine synapses in neurons. The pain-suppressing mechanism in which tramadol suppresses pain by attaching to a μ-receptor which causes pain is like some narcotic analgesics.

METHOD OF SYNTHESIS[9]

Polmacoxib is synthesized by the following method,

The sulfinate compound reacts with hydroxylamine-o-sulfonic acid (HOSA) to form polmacoxib, in this method of preparation reaction solvents are the mixture of organic solvents, and water selected from a group consisting of methanol, ethanol, isopropanol, butanol, dimethyl sulfoxide and mixture.

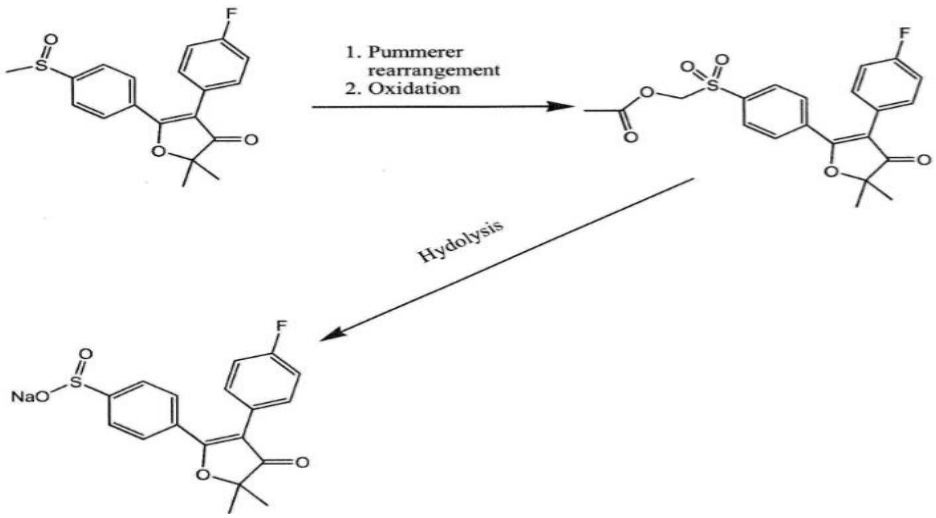


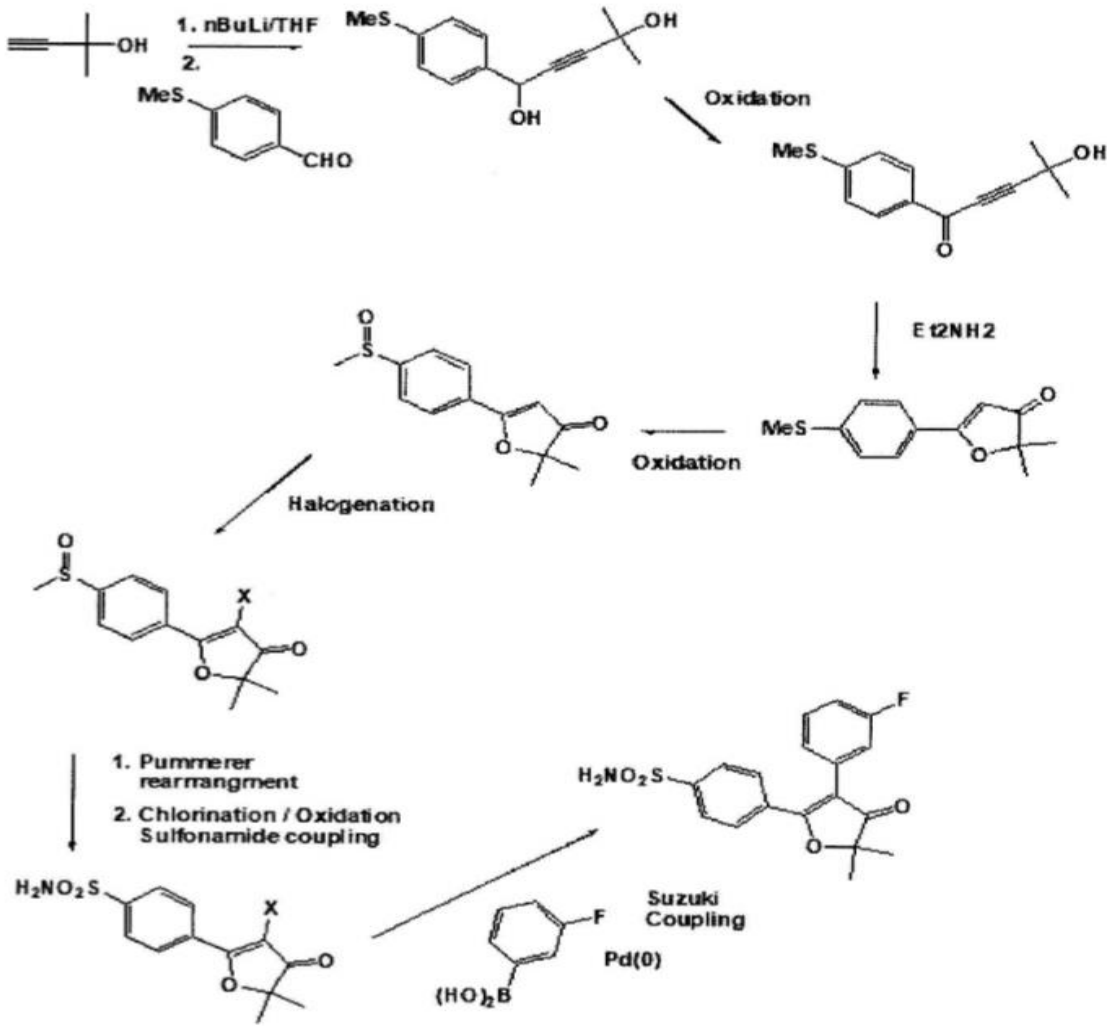
Fig .3.

In the sieve manufacturing method where manufacturing of polmacoxib takes place by using or not generating a chlorine gas. As the present invention, it relates that manufacturing polmacoxib is particularly used as a therapeutic agent for osteoarthritis safely and simply without using chlorine gas.

This drug is approved in Korea, Alex (Alex, crystal genomics, Seoul, Korea) it includes the following manner.

Method [A]

In this Republic of Korea patent registration, no 10-0495389, synthesis of polmacoxib is possible by using a starting material i.e., propargyl alcohol type, and by using iodination, Suzuki coupling, so this is not an economical way further in addition it undergoes a chlorination process using chlorine gas fig. 4.



Method [B]

In Korean patent publication no.10-2015-0060579 synthesis is carried out by chlorination reaction is performed by using a substance which generates chlorine hence there is no significant difference from the method (A)

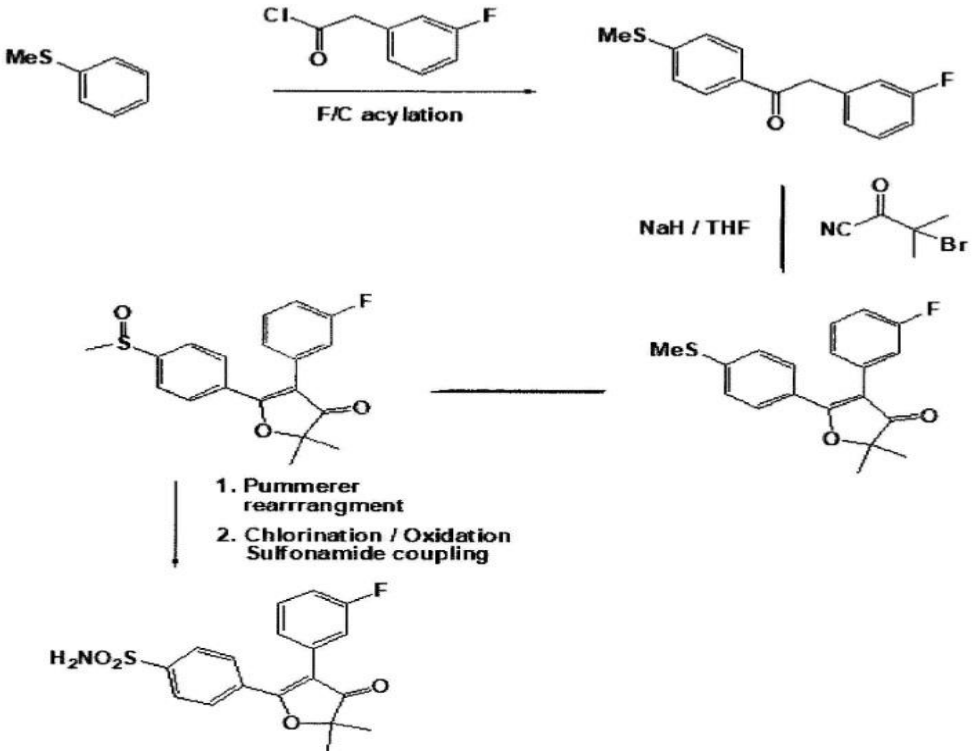


Fig. 5.

As mentioned above chlorine is essential or usually used to manufacture polmacoxib ultimately results in increased cost because equipment like a dedicated reactor is required for the use of chlorine gas, in addition, there is always the risk of gas leakage so due to this manufacturing process quite complicated and productivity is also get reduced hence the main objective of the present invention is the manufacturing of polmacoxib without using chlorine gas.

Method [C]

In this method, the sulfinate compound reacts with hydroxylamine-o-sulfonic acid (HSOA)without generating chlorine gas,

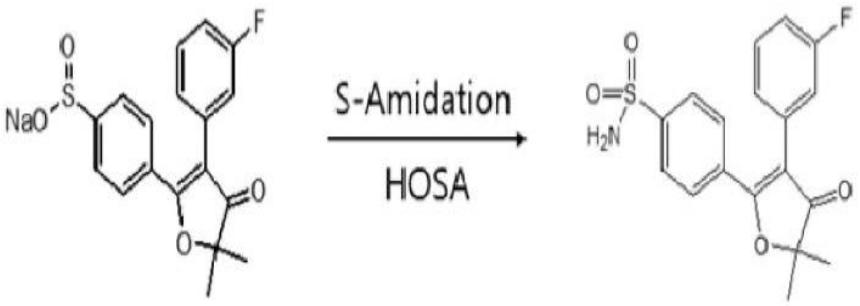


Fig. 6.

APPLICATIONS

1. Osteoarthritis

Osteoarthritis (OA) is a joint inflammatory disease that involves the breakdown and damage of cartilage and surrounding bone tissues and is associated with increased swelling and pain.

There are approximately 54.4 million adults with diagnosed arthritis in the United States, including over half of the population above 50 years old. The most common form of arthritis is OA and about 30% of adults with obesity have doctor-diagnosed arthritis.

As there is no cure for OA, treatment plans are based on ways to manage pain and improve function. These plans include exercise and weight control, rest and joint care, surgery, and medication for pain relief Currently, the most widely prescribed medications for OA are nonsteroidal anti-inflammatory drugs (NSAIDs); however, some NSAIDs carry a high risk of adverse events (AEs), including serious gastrointestinal (GI) diseases.

2. Carbonic anhydrase inhibitor[4]

Recently, a new COX-2 inhibitor, polmacoxib (CG100649; Acelex), has been developed. Polmacoxib has a dual mode of action: inhibition of COX-2 and binding to carbonic anhydrase (CA) with high affinity. A key function of CA is to regulate the pH level in the body through the interconversion between carbon dioxide and bicarbonate. If COX-2 and CA coexist, the high-affinity binding of polmacoxib to CA causes reducing the COX-2 inhibitory activity of polmacoxib. Since the CV side effects of traditional NSAIDs and COX-2 inhibitors are associated with COX-2 inhibition in the CV system where CA is abundant, Importantly, low-dose administration of polmacoxib is have a negligible effect on overall CA function in the circulatory system.

3. Combination with Tramadol to treat the acute and chronic pain

A composition consisting of polmacoxib and tramadol is used to treat acute and chronic pain.

In polmacoxib is used as a non-steroidal anti-inflammatory agent and tramadol is used as an opioid-based analgesic agent which shows excellent stability and excellent effect at low content.

Many drugs are useful in the treatment of pain. Among them, opioids are used as an analgesic. Morphine derivatives are therapeutic agents that relieve pain in humans.

One of the widely used morphine derivatives that show good effects on oral administration is tramadol.

side effects of tramadol: constipation, sleeplessness, and anxiety symptoms may occur. In addition, other side effects such as dizziness, drowsiness, nausea, etc. may occur.

4. Colorectal cancer

To Study the prevention and treatment effect of polmacoxib in colorectal cancer

A premalignant mouse model was used to determine the efficacy of polmacoxib in poly reduction and from this study, it was observed that polmacoxib was effective in reducing the polyp number and size in both small and large intestines.

In the treatment study, Polmacoxib demonstrated growth suppression of polyps in the small intestine and reduction of poly growth in the colon.

5. use in Osteoarthritis, Osteoarthritis, Hip, Osteoarthritis, Knee, Localized Primary Osteoarthritis of Hip, and Localized Primary Osteoarthritis of Knee.[5]

DRUG-DRUG INTERACTIONS[6]

When Abciximab or acenocoumarin is used with polmacoxib the risk or severity of bleeding and hemorrhage can be increased Polmacoxib may decrease the antihypertensive activities of acebutolol.

Aceclofenac, acetaminophen, and polmacoxib combination increases the risk or severity of occurrence of adverse effects.

Acemetacin and polmacoxib combination increases the risk or severity of the occurrence of adverse effects.

The protein binding of acetohexamide can be decreased when combined with polmacoxib.

The risk and severity of adverse effects can be increased when polmacoxib is combined with alendronic acid.

Polmacoxib and aliskiren combination leads to an increase in the risk of renal failure and hypertension.

The therapeutic efficacy of ambrisentan can be decreased when it is used with polmacoxib

Increased risk of nephrotoxicity associated with the use of amikacin and polmacoxib combination.

The risk and severity of renal failure, hyperkalemia, and hypertension can be increased when polmacoxib is combined with amiloride Gastrointestinal bleeding can be increased when amoxapine and amitriptylinoxide are combined with polmacoxib . It may decrease the antihypertensive activities of atenolol.

SIDE EFFECTS OF POLMACOXIB

The risk or severity of renal failure, hyperkalemia, and hypertension can be increased when Polmacoxib is combined with Captopril. The risk or severity of adverse effects can be increased when Carprofen is combined with Polmacoxib. It may decrease the antihypertensive activities of Carvedilol.

Stomach upset, heartburn, headache

In rare cases, it may cause more serious side effects such as gastrointestinal bleeding kidney problems, or allergic reactions.

MARKETED FORMULATION

1) Acelex capsule 2 mg.
2) Poliexar capsule 2 mg.

NOVEL MARKETED FORMULATION[15]

POLMACOXIB-CONTAINING INJECTION COMPOSITION

This injection has excellent stability. The present invention relates to a polmacoxib-containing injection solution which contains polmacoxib, which is a poorly water-soluble nonsteroidal anti-inflammatory drug exhibiting an excellent effect even at a low dose, is solubilized and stabilized in an aqueous solution. the invention, the utilization of a stabilizer that is both available for injection agents allows the acquirement of a polmacoxib-containing injection composition excellent in stability without any deposition phenomenon.

CONCLUSION

Polmacoxib, a specific COX-2 inhibitor, illustrates promising adequacy in overseeing torment and aggravation. Its pharmacological profile and pharmacokinetic properties bolster

its utilization as a reasonable NSAID choice. Whereas assist investigation is required to evaluate long-term security and quiet encounters, early proof recommends a favorable adjustment between adequacy and security. Polmacoxib has the potential to offer clinicians and patients a successful treatment alternative for different conditions related to pain and inflammation.

REFERENCES

1. Song, I.-G.; Jung, K. U.; Kim, H. O.; Kim, H.; Chun, H.-K. An Unusual Case of Colon Perforation With Multiple Transmural Ulcers After Use of Polmacoxib and Everolimus in a Metastatic Breast Cancer Patient. *Ann Coloproctol*, 2021; *37*(2): 120–124. https://doi.org/10.3393/ac.2019.08.17.
2. Cho, Y.-S.; Bae, K.-S.; Choi, S. C.; Cho, J. M.; Lim, H.-S. Population Pharmacokinetic and Pharmacodynamic Analysis of Polmacoxib in Healthy Volunteers and Patients With Osteoarthritis. *Clinical Therapeutics*, 2022; *44*(1): 67-80.e1. https://doi.org/10.1016/j.clinthera.2021.11.008.
3. Lee, M.; Yoo, J.; Kim, J. G.; Kyung, H.-S.; Bin, S.-I.; Kang, S.-B.; Choi, C. H.; Moon, Y.-W.; Kim, Y.-M.; Han, S. B.; In, Y.; Choi, C. H.; Kim, J.; Lee, B. K.; Cho, S. A Randomized, Multicenter, Phase III Trial to Evaluate the Efficacy and Safety of Polmacoxib Compared with Celecoxib and Placebo for Patients with Osteoarthritis. *Clin Orthop Surg*, 2017; *9*(4): 439. https://doi.org/10.4055/cios.2017.9.4.439.
4. Kim, H. T.; Cha, H.; Hwang, K. Y. Structural Insight into the Inhibition of Carbonic Anhydrase by the COX-2-Selective Inhibitor Polmacoxib (CG100649). *Biochemical and Biophysical Research Communications*, 2016; *478*(1): 1–6. https://doi.org/10.1016/j.bbrc.2016.07.114.
5. Lee, M.; Yoo, J.; Kim, J. G.; Kyung, H.-S.; Bin, S.-I.; Kang, S.-B.; Choi, C. H.; Moon, Y.-W.; Kim, Y.-M.; Han, S. B.; In, Y.; Choi, C. H.; Kim, J.; Lee, B. K.; Cho, S. A Randomized, Multicenter, Phase III Trial to Evaluate the Efficacy and Safety of Polmacoxib Compared with Celecoxib and Placebo for Patients with Osteoarthritis. *cios*, 2017; *9*(4): 439–457. https://doi.org/10.4055/cios.2017.9.4.439.
6. Drug. Com https://www.drugbank.com/academic_research.
7. https://cdn.caymanchem.com/cdn/insert/17509.pdf.
8. http://www.jddtonline.info/index.php/jddt/article/view/4984.
9. method of synthesis https://patents.google.com/patent/KR20200091980A/en.
10. https://patents.google.com/patent/KR20190107987A/en.

11. https://newdrugapprovals.org/tag/polmacoxib/.
12. https://www.glpbio.com/polmacoxib.html.
13. https://golden.com/wiki/US_Patent_11602517_Pharmaceutical_composition%2C_comprising_polmacoxib_and_pregabalin%2C_for_treatment_of_pain-X9JZ8YY/structured_data.
14. https://newdrugapprovals.org/2016/04/22/polmacoxib-cg-100649/.
15. https://patents.google.com/patent/RU2769555C2/en.