Polmacoxib and its Evaluation Parameters

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Abstract

An important socioeconomic burden that significantly affects daily activities and productivity is osteoarthritis. When treating osteoarthritis, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to improve physical function while reducing stiffness, pain, and inflammation. However, the majority of medical professionals refrain from using NSAIDs for an extended length of time because of the many negative effects. Because they block prostaglandins, which are in charge of shielding the stomach mucosa, nonselective cyclooxygenase (COX) and cyclooxygenase-1 (COX-1) inhibitors have been connected to an increase in gastrointestinal side effects.

Because of their COX-2 inhibitory action in the circulatory system, cyclooxygenase-2 (COX-2) inhibitors are linked to a higher risk of negative cardiovascular effects. As a result, a more recent NSAID with a better safety record is required for osteoarthritis.

Polmacoxib is a novel, first-in-class, oral-active NSAID that inhibits both carbonic anhydrase (CA) and COX-2. It is anticipated that polmacoxib's dual mode of action will reduce harmful cardiovascular effects while optimizing efficacy in inflammatory osteoarthritic joints. Reviewing polmacoxib's pharmacological characteristics, clinical effectiveness, and safety information in relation to osteoarthritis is the goal of this article.

Keywords- NSAIDs, Cyclooxygenase-2, Polmacoxib , osteoarthritis , Inflammation, Pain, and stiffness.

Introduction

Osteoarthritis is the most prevalent chronic rheumatic disease and one of the leading causes of pain globally. It mostly affects the hips or knees and is the fourth most common cause of disability. Osteoarthritis is a global disability. It mostly affects the hips or knees and is the fourth most common cause of disability.[1]About 23.46 million Indians had osteoarthritis in 1990; by 2019, that figure had increased to 62.35 million.[2].

Numerous modifiable and non-modifiable risk factors, such as obesity, inactivity, genetics, bone density, trauma, occupational injury, aging, and female gender, are linked to osteoarthritis.[3]. Age is

an imperative prompting cause for osteoarthritis [1].

In Asia, the part of individuals aged 65 years and over is anticipated to additional than double over the next two periods, rising from 6.8% in 2008 to 16.2% in 2040 [1]. Rural societies with osteoarthritis are the toughest hit due to the routine need to perform heavy physical labor coupled with insufficient admittance and a huge configuration gap with respect to management facilities including joint replacements. On the other hand, obesity is on the rise in developed countries, which is another common factor that favors the development of osteoarthritis [1].Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay and the first line of treatment for most patients who develop disabling pain due to osteoarthritis [4,5].

This review focuses on the recently approved NSAID in India, polmacoxib. Polmacoxib is currently being marketed in South Korea and India [6- 8].

Non-steroidal anti-inflammatory drugs

NSAIDs are a class of drugs that are authorized as anti-inflammatory, antipyretic, and analgesics. Cyclooxygenase (COX) enzyme inhibition is how NSAIDs work therapeutically. COX-1 and COX-2 are the two COX isoenzymes that exist. The body constitutively contains COX-1, which generates prostaglandins that protect the stomach mucosa and activate platelets. Inflammation, fever, and pain are caused by prostaglandins, which are produced by COX-2, which is inducibly expressed in the body during an inflammatory process. The majority of NSAIDs on the market are nonselective COX inhibitors, meaning they block both COX-1 and COX-2. .[4]

Selective COX-2 inhibitors, on the other hand, only inhibit COX-2 and leave COX-1 inhibition intact. This reduces gastrointestinal damage by allowing COX-1 to produce protective prostaglandins and preserves the anti-inflammatory effects by blocking COX-2 in inflammatory tissues. COX-2 inhibitors are preferred over nonselective medications in patients with gastrointestinal comorbidities according to the Osteoarthritis Research Society International (OARSI) guidelines for the nonsurgical treatment of knee, hip, and polyarticular .[4] osteoarthritis.

DRUG PROFILE

Structure:

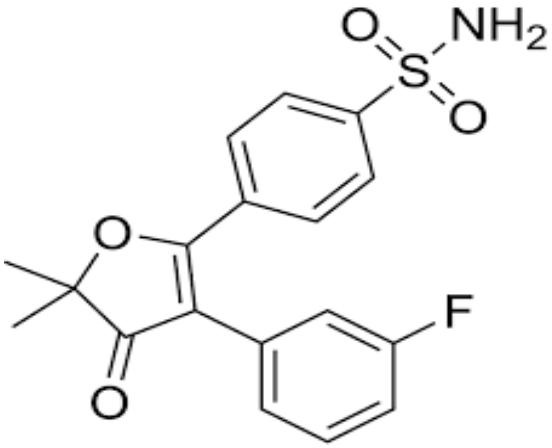

Figure No.:01 Chemical Structure of Polmacoxib

General information

Drug name: Polmacoxib

Molecular formula: C18H16FNO4S.

Molecular weight: 361.4 g/mol

Chemical name: 4-(3-(3-fluorophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-2-yl) benzenesulfonamide.

Therapeutic Category : Treat osteoarthritis

Characters

Description: Off white to yellowish colour powder.

Solubility: Soluble in Acetonitrile & Dimethyl Sulphoxide

Moisture content: NMT 1.0 %

Loss on drying: NMT 1.0%

Residue on ignition: NMT 0.2%

Storage: Store in a tight light resistance & air resistance container at room temperature

CATEGORY: Polmacoxib is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of osteoarthrosis and Degenarative Joint Disease (In this tissue of joint breakdown which causes stiffness , sealing near the joint and pain). Polmacoxib inhibits the enzymes named as carbonic anhydrase and COX-2.

DOSAGE & STRENGTH: Patient is advice to take 2 mg once in a day after a meal. The dose should not exceed 2 mg/day . If exceeds may lead to major side effects i.e. Liver damage

PHARMAKOKINETICS: Erythrocytes are critical for delivering Polmacoxib, in a protected, latent state because they act as drug reservoirs. The concentrations of polmacoxib in whole blood, or erythrocytes, are 85-100 times higher than in plasma without CA. Erythrocytes serve as a tissue-specific transport channel, delivering medicine to inflammatory, CA-deficient tissues at consistent amounts. Because polmacoxib and CA are carried together in erythrocytes, systemic exposure is reduced. As a result, it is anticipated that polmacoxib has the fewest adverse effects on the cardiovascular or gastrointestinal systems and works best in inflammatory osteoarthritic joints. [10,11]
Based on the pharmacokinetic profile, it was discovered that polmacoxib had a longer residence length in inflammatory osteoarthritic joints than blood.
From the perspective of drug tolerability, this suggests that other body areas are not exposed to the medication for prolonged periods of time. The majority of polmacoxib is excreted in the feces, however minute amounts are also removed in the urine.. [10,11]

PHARMACODYNAMICS:
In contrast to other nonsteroidal anti-inflammatory medications, polmacoxib functions by blocking both CA-I/II and COX-2.
The bulk of conventional COX-2 inhibitors do not show much activity toward CA inhibition, but they do have notable COX-2 inhibition in the cardiovascular system, which may result in the development of severe cardiac events. [10,11]
It has been established that the amounts of CA in synovial fluid are negligible. Thus, Polmacoxib eliminates the inflammation and pain of osteoarthritis by totally inhibiting COX-2 in the inflammatory joint tissues .[10,11]

ADVERSE EFFECTS

Polmacoxib may cause side effects such as:

- Flatulence
- Abdominal pain
- Dyspepsia
- Peripheral Edema
- Motion sickness

- Puke
- Hyperacidity
- Pyrosis
- Indigestion
- Stomachache
- Vertigo
- Unsteadiness

THERAPEUTIC USE:

Osteoarthritis in the knee or joint Polmacoxib, the primary component of Polmaflex-2, is a selective COX-2 inhibitor designed to provide accurate pain management. It provides specialist treatment to individuals with a variety of pain problems, including rheumatoid arthritis, osteoarthritis, and postoperative pain management. The selective COX-2 inhibition of polmacoxib provides focused pain relief with potentially fewer gastrointestinal side effects than non-selective NSAIDs.By leveraging the benefits of polmacoxib, polmaflex-2 is widely recognized for its efficacy in managing moderate to severe pain, hence enhancing the quality of life for individuals suffering from chronic pain conditions. [9]

METHOD OF ANALYSIS

Description

Procedure for Sized Granules-

Take 2gm of dried granules in butter paper or petry dish and examine visually.

Specification –White or off white creamish coloured granular powder.

Procedure for Filled Capsule-

Select Arbitrarily 20 capsules and examine visually in accordance with the requirement set forth in specification.

Specification –Size “4” Hard gelatine capsule with pink cap and transparent body filled with off white to creamish granular powder.

Identification (By HPLC)

Procedure – From the test of Assay .

Specification – The retention time of major peak in the chromatogram of the test solution corresponds to that in the Chromatogram of the standard preparation as obtained in the assay .

Average weight of Filled capsule

Procedure –Weigh 20 intact capsules and weight .

Average weight of Filled capsule =Weight of 20 intact capsule/20.

Specification –135.0±10% (121.50mg to 148.50mg)

Average Net Fill weight

Procedure –Select 20 intact capsules .Weigh each intact capsule individually & Note down weight . Empty & Remove content of each capsules carefully without loosing any part of capsules shell . Care should be taken that after emptying no visible powder sticks to capsule shell . Weigh each empty capsules individually .

Average Net Filled weight = (Weight of 20 intact capsule)-(Weight of 20 empty capsule shells) / 20.

Here , Weight of 20 Intact capsules =Sum of all individual intact capsules weights

Weight of 20 empty capsule shells=Sum of all Empty capsule Shell weights

Specification –95.0±10% (85.50mg to 104.50mg)

Uniformity of Fill weight

Procedure – Select 20 capsules at random from a particular lot or batch. Weigh intact capsules, Open the capsule without losing any part of the shell and remove the contents as completely as possible. Weigh the shell; the Mass (M) of the content is the difference between the weighing of the intact capsule and Emptied capsule shell. Repeat the same procedure for further 19 capsules selected at random, determine the average mass of the capsule by the following formula:

$$\text{Average mass content} = \frac{M1+M2+M3 \ldots+M20}{20}$$

Where, M(X) =Mass of the Individual contents of capsule 1, 2, 3 ……., 20.

20=Total no. of capsules taken.

Calculate the percentage deviation in Capsules as follows:

(-)%Lowest Deviation =(Lowest Individual Mass Content –Average Mass Content)x100
Average mass Content

(+)%Highest Deviation=(Highest Individual Mass Content–Average Mass Content)x100
Average mass Content

Specification –Not more than two of the Individual mass contents deviate from the Average net mass by more than ± 10% and none deviates by more ± 20%.

Locking length

Procedure-Check locking length of each 0f 10 capsules using Vernier Calliper

Specification -14.30mm±0.7mm

Disintegration Time

Procedure –The Apparatus consists of a Basket –rack assembly, a 1 L, Low-form beaker .Take water as medium in beaker. The volume of medium should be such that the wire mesh as its highest point is at least 15 mm below the surface of the liquid, and its lower point is least 25mm above the bottom of the beaker. At no time should the top of basket-rack assembly become submerged. Allow the temperature of water in beaker to reach to 37± 2ºC. After achieving temperature, Place 1 dosage unit of the 6 tubes of the basket. Put disc over each Capsule in each tube. Operate the Disintegration test Apparatus. Observe the Dosage units & Note down time required for Disintegration.

Specification –Not more than 30 Minutes

Dissolution Time

Dissolution Parameters:

Dissolution Medium: pH 7.0 ± 0.05 Phosphate buffer with 1.0% Sodium Lauryl Sulphate

Medium Quantity: 900ml

Apparatus: Paddle with Sinkers

Rotation speed: 75RPM

Time: 45 Minutes

Temperature: 37.0± 0.5ºC

Preparation of Dissolution Medium (pH 7.0 ± 0.05 Phosphate buffer with 1.0% Sodium

Lauryl Sulphate) – Dissolve 68.0gm of Sodium Dihydrogen Orthophosphate

Monohydrate in to 10.0 litre ml purified water , Adjust pH 7.0 ± 0.05 with sodium Hydroxide . Add 100.00gm Sodium Lauryl sulphate and mix well.

Preparation of Buffer –Weigh and transfer about 1.36gm of Potassium Dihydrogen Orthophospahte and 2.0 ml of Triethylamine into a beaker containing 1000ml of Purified water and Sonicate to dissolve. Adjust pH of Solution 3.0 ± 0.05 with Orthophosphoric acid .Filter the solution through 0.45µm membrane filter.

Preparation of Mobile phase –Prepare a degassed mixture of buffer: Acetonitrile in the ratio of 50:50 % v/v.
Diluent: Use mobile phase as Diluent.
Chromatic Condition:

Column: Kromasil 100 C18, 150X4.6mm, 5µ (Part no. M05CLA15, Make: Nouryon) or Equivalent column .

Flow rate: 0.8 ml/min

Injection volume: 50µL

Column temperature: 35 oC

Run time: 12 minutes

Detector: UV Detector

Wavelength: 240mm

Retention time: About 5.8 mins

Preparation of Standard solution:

Weigh accurately about 22.0mg of Polmacoxib working standard into a 100ml volumetric flask, add 70 ml of diluent & sonicate to dissolve the solid completely. Cool at room temperature & dilute to volume with diluent and mix. Transfer 5ml of the above solution into a 50ml flask, dilute up to volume with diluent and mix. Further transfer 2 ml of the above solution into a 20 ml volumetric flask, Dilute up to volume with dissolution medium and mix.

Preparation of test solution: Transfer 900ml of dissolution medium into each of 6 dissolution vessel & set up dissolution parameters and allow the temperature of Dissolution medium to reach to 37.0±0.5oC .Accurately weigh each of 06 capsules & transfer them into dissolution vessels individually and immediately start dissolution apparatus. After end of 45 minutes time, withdraw 20 ml aliquot from each of Dissolution, Filter through 0.45µ Nylon filter and inject.

***Table no.01 - Injection Sequence:**

Sr. no.	Name of Solution	Number of Injections
1.	Blank (Dissolution Medium)	1
2.	Standard Solution	5
3.	Each of six Dissolution test samples	1 for each test sample
4.	Bracketing standard	1

System Suitability Acceptance criteria:

- The RSD % of Polmacoxib Peak area from standard solution should note more than 2.0.
- The Theoretical Plates of Polmacoxib peak from Standard solution should not less than 3000 .
- The tailing factor of Polmacoxib peak from standard solution should not more than 2 .

Calculation:

% Labelled amount of Polmacoxib dissolved == $\frac{AT}{AS} * \frac{\text{WS}}{100} * \frac{5}{50} * \frac{2}{20} * \frac{900}{1} * \frac{P}{100} * \frac{100}{LC}$

Here ,

AT=Area of Polmacoxib in sample solution

AS=Average area of Polmacoxib peak obtained from replicable injections of Standard solutions

WS=Weight of Polmacoxib working standard taken ,in mg

LC=Label claim

P=Potency of Polmacoxib Standards (As is basis)

Specification –Not less than 75% (Q) in 45 minutes .

Related Substance test (By HPLC)

Chromatic Condition:

Column: Inertsil ODS-3V , C18 , 250*4.6mm , 5µ(Cat.No.5020-01802 , Make :GL Sciences) or Equivalent column .

Flow rate: 1.0 ml/min

Injection volume: 10µL

Column temperature: 40ºC

Sample temperature : 10ºC

Run time: 70 minutes

Detector: UV Detector

Wavelength: 240mm

Retention time of main peak: About 21.5 minutes

Buffer Preparation

Dissolve 1.54 gm of Ammonium Acetate into 2000 ml of water . Mix &filter through 0.45µ Nylon membrane filter & Sonicate .

Mobile Phase A

Use buffer as Mobile Phase A

Mobile Phase B

Acetonitrile

Diluent :Mix Acetonitrile :Water (500:500)

***Table no.:02 Gradient programme for Related Substance test**

Time (minutes)	Mobile Phase A (%)	Mobile Phase B (%)
0.01	70	30
50.0	25	75
60.0	25	75
62.0	70	30
70.0	70	30

Preparation of Standard solution:

Weigh accurately about 50mg of Polmacoxib working standard into a 50ml volumetric flask, add 30 ml of diluent & sonicate to dissolve the solid completely. Cool at room temperature & dilute to volume with diluent and mix .Transfer 5ml of the above solution into a 100ml flask, dilute up to volume with diluent and mix. Further transfer 5 ml of the above solution into a 50 ml volumetric flask, Dilute up to volume with dissolution medium and mix.

Preparation of Sample solution:

Weigh 30 capsules .Empty capsules & mix capsules contents properly. Weigh empty capsules shells. Accurately weigh and transfer about 2375mg capsules content powder (Equivalent to about 50mg of Polmacoxib) into a 50 ml volumetric flask. Add 30ml Diluent and Sonicate for 35 minutes with Intermitted shaking. Cool to room temperature and Dilute up to the mark with diluent .Mix & filter through 0.45µm pvdf filter after discarding first few ml of Filtrate.

Preparation of Placebo solution:

Accurately weigh and transfer about 2325mg Placebo powder into a 50 ml volumetric flask . Add 30ml Diluent and Sonicate for 35 minutes with Intermitted shaking . Cool to room temperature and Dilute up to the mark with diluent .Mix & filter through 0.45µm pvdf filter after discarding first few ml of Filtrate

Injection Sequence:

***Table no.:03 Injection Sequence for Related Substance test**

Sr. no.	Name of Solution	Number of Injections
1.	Blank	1
2.	Placebo Solution	1
3.	Standard Solution	6
4.	Each of Sample samples	1
5.	Bracketing standard solution	1

System Suitability Acceptance criteria:

In Standard solution

- The % RSD for the Polmacoxib Peak area obtained from six Replicate injections of standard solution should note more than 5.0.
- The Theoretical Plates for the Polmacoxib peak should not less than 3000 .
- The tailing factor for the Polmacoxib peak should not more than 2 .

Specification –Not more than 1.5%.

Residual Solvent test

***Table no.:04 Detail of Reagents for Residual Solvent test**

Name od Reagent	Make
N.N Dimethyl Formamide (GC-HS Grade)	Fisher Scientific
Acetone (HPLC Grade)	Fisher Scientific

***Table no.:05 Chromatographic Parameters for Residual Solvent test**

Column	Capillary GC Column DB-624 .30mx0.53mm , 3 µ
Oven Temperature Programming	
Initial temperature	40 ^{O}C
Initial time	8.0 minutes
Rate of Increase	25^{O}C /minute
Final temperature	240 ^{O}C
Final time	1.0 minutes
Injection Port temperature	200^{O}C
Detector temperature	250^{O}C
Column Head pressure	2.3 psi (if necessary , Adjust the column head pressure to attain the retention time of analyte .

Split Ratio	5:1
Carrier gas	Nitrogen
Head Space Parameters	
Equilibration time	30 minutes
GC Cycle time	35 minutes
Zone Temp-Vial	$85^{O}C$
Zone Temp-TR Line	$110^{O}C$
Zone Temp-LOOP	$100^{O}C$
Pressurization Time	1.0 minutes
LOOP Equilibration time	0.05 minutes
Injection time	1.0 minutes
Loop fill time	0.1 minutes

Standard Solution

Weigh & Transfer accurately about 500mg of Acetone into a 100ml volumetric flask containing about 10 ml of diluent make up the volume to mark with Diluent and Mix. Dilute 10.0 ml of this solution to a 100.0ml with diluent and mix (500ppm) .

Transfer 5ml of the above solution into a 20 ml Head space vial and quickly seal the vial.

Sample Preparation

Take 20 capsules .Completely transfer whole content of each capsules on butter paper and mix properly .Weigh and Transfer accurately amount 500mg of sample into a 20 ml head –space vial .Add 5.0ml of diluent and quickly seal the vial .

System Suitability Parameters

Chromatograph the standard solution and record peak responses as directed under procedure .

The RSD for six replicate injections is not more than 15.0%

Procedure :Inject Separately diluent , Standard preparation and Sample Preparation into the Chromatograph , Record the Chromatograms and measures the peak responses .

***Table no.:06 Injection Sequence for Residual Solvent test:**

Sr. no.	**Name of Solution**	**Number of Injections**
1.	Diiluent	1
2.	Standard Preparation	6
3.	Sample Preparation	1
4.	Bracketing standard	1

Specification –Not more than 5000ppm.

Assay (By HPLC)

Preparation of Buffer – Weigh and transfer about 1.36gm of Potassium Dihydrogen Orthophospahte and 2.0 ml of Triethylamine into a beaker containing 1000ml of Purified water and Sonicate to dissolve . Adjust pH of Solution 3.0 ± 0.05 with Orthophosphoric acid .Filter the solution through 0.45µm membrane filter .

Preparation of Mobile phase – Prepare a degassed mixture of buffer: Acetonitrile in the ratio of 50:50 % v/v

Diluent: Use mobile phase as Diluent.

Chromatic Condition:

Column: Kromasil 100 C18 , 150X4.6mm , 5µ (Part no. M05CLA15 ,Make :Nouryon) or Equivalent column .

Flow rate: 0.8 ml/min

Injection volume: 10µL

Column temperature: 35 oC

Run time: 12 minutes

Detector: UV Detector

Wavelength: 240mm

Retention time: About 5.8 minutes.

Preparation of Standard solution: Accurately Weigh & transfer about 40.0mg of Polmacoxib working standard into a 100ml volumetric flask, add 70 ml of diluent & sonicate to dissolve. Dilute to volume with diluent and mix .Transfer 5ml of the above solution into a 50ml flask, dilute up to volume with diluent and mix.

Preparation of Sample solution: Weigh 50 capsules .Empty the capsules & weigh empty capsules shells. Mix the capsules contents properly. Accurately weigh and transfer about 1900mg capsules powder (Equivalent to about 40mg of Polmacoxib) into a 100 ml volumetric flask . Add about 70ml of Diluent and Sonicate for 20 minutes with Intermittent shaking.

Dilute to volume with diluent & Mix .filter through 0.45µm pvdf filter.

Transfer 5ml of the above solution into a 50ml volumetric flask .Dilute to volume with diluent and mix.

Equilibrate the column with mobile phase for not less than 30 minutes at a flow rate of

0.8ml/minutes .Inject the solution as per below sequences .

***Table no.:07 Injection Sequence for Assay test:**

Sr. no.	Name of Solution	Number of Injections
1.	Blank	1
2.	Standard Solution	5
3.	Sample Solution -I	1
4.	Sample Solution -II	1
5.	Bracketing standard solution	1

System Suitability Acceptance criteria:

In Standard solution

- The % RSD for the Polmacoxib Peak obtained from Replicate injections of standard solution should note more than 2.0.
- The Theoretical Plates of Polmacoxib peak from Standard solution should not less than 2000 .
- The tailing factor for Polmacoxib peak from Standard solution should not more than 2.0 .

Specification –Not less than 90% to Not more than 110.0%.

Conclusion

Polmacoxib is a pristine, first-of-its-kind, oral NSAID that hinders both the CA enzyme and COX-2. As a selective COX-2 inhibitor, it reduces the abdominal adverse effects that old-style nonselective NSAIDs usually cause. Clinical research data signpost that polmacoxib propositions statistically and analgesic and well-designed recompenses that are clinically significant. In order to treat osteoarthritis, polmacoxib may substantiate to be a useful, long-lasting, and well-tolerated medication. Moreover, its separate, tissue-specific transport appliance may lessen the negative cardiovascular effects of COX-2 inhibition. More extensive randomized clinical trials are necessary to examine the long-term safety and effectiveness of polmacoxib.

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