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Original Research Article

Identification of Etoricoxib Polymorphic Crystalline Form in Pharmaceutical Raw Materials

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Abstract: The determination of the spatial configuration of the compounds structures used in the production of drugs is of utmost importance due to the different physical characteristics that each have in their solid state and therefore the different qualities of each one for its use as pharmaceutical raw material. This study aimed to identify the polymorphic crystalline form of Etoricoxib raw material, a non-steroidal anti-inflammatory drug (NSAIDs) selective inhibitor of cyclooxygenase 2 (COX2) enzyme widely used in the present, which was done through four different instrumental analytical techniques: X-ray diffractometry, differential scanning calorimetry, thermogravimetry and infrared spectroscopy, comparing and studying the results obtained from the analysis with those found in the literature. Using the data obtained with these four techniques it was demonstrated that the study sample exists predominantly in the 1 anhydrous Etoricoxib form.

Keywords: Differential Scanning Calorimetry, Etoricoxib, X-ray scattering pattern, infrared spectroscopy, Pharmaceutical Polymorphism, thermogravimetry.

INTRODUCTION

The issue of pharmaceutical polymorphism increasingly takes on importance, due to the protection that some countries provide to patents of medicines of different polymorphs, the phenomenon of pharmaceutical polymorphism refers to the different phases of the solid state that a pharmaceutical substance undergoes, being these phases different crystalline, amorphous forms, or solvates of the same substance, that make their internal three-dimensional ordering change at molecular or atomic level [1, 2].

The Etoricoxib is a non-steroidal drug of the selective cyclooxygenase-2 (selective COX 2), its IUPAC nomenclature is 5-chloro-6'-methyl-3- [4-(methylsulfonyl) phenyl] -2, 3'-bipyridine, its molecular weight is 358.84 g / mol is a white hygroscopic powder, is excreted by the renal route in 72% and has a biological half-life of 22 hours, has a high bioavailability and its biopharmaceutical classification is II. The drug is used as an analgesic, i.e. it is consumed to relieve acute pain associated with arthritis, osteoarthritis, headaches and other inflammatory processes [3].

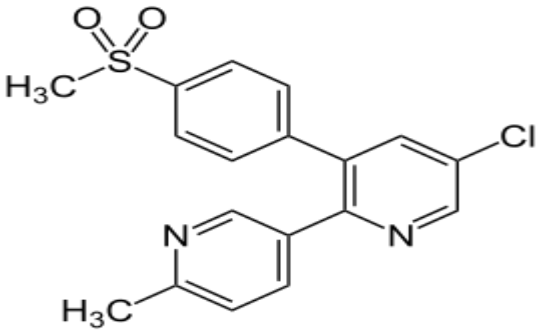

Fig 1: Etoricoxib structure.

The therapeutic application of Etoricoxib as a COX-2 inhibitor is disclosed in the international patent application document WO 96/10012 and WO 96/16934. This compound is disclosed in U.S. patent 5,861,419. A wide variety of crystalline and amorphous forms of Etoricoxib are known, a process for the preparation of this compound is described in patent US6040319, on the other hand, in the international patent application WO 01/992230, five polymorphic forms, an amorphous form and two hydrated forms are described, completing eight different solid forms in the patent publication WO2005085199 which describes eight different new crystalline forms of Etoricoxib, i.e. form IX, X, XI, XII, XIII, XIV, XV and XVI. The application therefore describes eight new forms of Etoricoxib. Finally, in 2015 the Chinese patent application publication CN104418799 further discloses a new crystalline form which adds a total of 17 known solid forms of Etoricoxib [4-11].

In the face of this panorama, it was necessary to identify and to determine the existence of a suitable polymorphic form in the formulation of a medicine. Also to date there are no pharmacopoeial patterns that allow to check the crystalline form of a substance, mainly because of the difficulty of ensuring that there is no phase transition in the pattern affecting its crystalline purity. Given this situation, the aim of this study was to perform analytical techniques, which measured absolute physico-chemical characteristics of Etoricoxib, such as: melting temperature, weight loss with increasing temperature, composition of functional groups, among other characteristics, which together can identify the crystalline type of a substance, and also determine if it could be pure, or mixed with another substance or different crystalline form [4-11].

MATERIALS AND METHODS

The raw material Etoricoxib samples provided by Baselux India Lot No 071200231 were used by a National industry, which were taken randomly and transferred to the test site under controlled conditions of light, humidity and temperature. The conditions and specifications of the equipment used are:

Equipment

- Diffractometer: Bruker model D8

Conditions

- Temperature: room temperature 25 ° C
- Nickel Filter
- Copper anode source Kα (λ 1, 54 A °)
- Polymethacrylate sample holder
- Continuous analysis at 0.1 ° per second in the range of 3 ° to 40 ° 2θ
- Gas detector with photodiodes
- Weight: 8 to 10 mg sample
- Three replicas.

Differential Scanning Calorimetry

- **Equipment**
- DSC Equipment TA Instruments model Q200

Conditions

- Aluminum capsule
- 100% Nitrogen Atmosphere 10 psi
- Flow rate: 40 mL / minute.
- Heating series of 10 ° C / minute
- Temperature range: 25 ° C to 250 ° C
- Sensitivity Instrument and Recorder: Sensitivity 0.1 uW
- Temperature precision: ± 0.05 ° C
- Temperature Accuracy ± 1 ° C
- Calorimetric precision ± .1%
- Calorimetric reproducibility ± .1%
- Weight: 3 to 4 mg sample
- Calibration with Indium and tri distilled water.
- Three replicas

Thermogravimetry

Equipment

- TGA Equipment TA Instruments model Q500

Conditions

- 100% Nitrogen 10 psi Atmosphere
- Volume flow 40 mL / minute
- Heating rate: 10 ° C / minute
- Ambient 25 ° C to 1000 ° C
- Weight 8 to 10 mg sample
- Sensitivity 0.1 ug
- Isothermal temperature accuracy ± 0.1%
- Isothermal temperature precision ± 0.1%
- Precision of mass ± .0%
- Three replicas

Infrared Spectroscopy

Equipment

- Equipment FTIR Thermo Scientific Nicolet 6700 model

Conditions

- Range 600 to 4000 cm^{-1}
- Temperature 25 ° C

- Relative Humidity 30%
- 200 scans per replica

Three replicas

RESULTS

The present study is about the solid nature of Etoricoxib pharmaceutical raw material, by comparing physicochemical parameters reported by scientific literature and/or patents, and those found in the laboratory for the analyzed samples. The results obtained in each of the studies were compared with the state of the art found in the cited bibliography, to find similarities and to conclude on the crystalline or amorphous state of the analyzed sample. There is no pharmacopoeial pattern of comparison of the crystalline form, so the identification process should be related to the comparison of the physicochemical properties described using the techniques specified in the 34 Pharmacopoeia of the United States of America.

X-ray diffraction

Figure 1 shows the results obtained from the analysis of Etoricoxib samples by X-ray diffractometry.

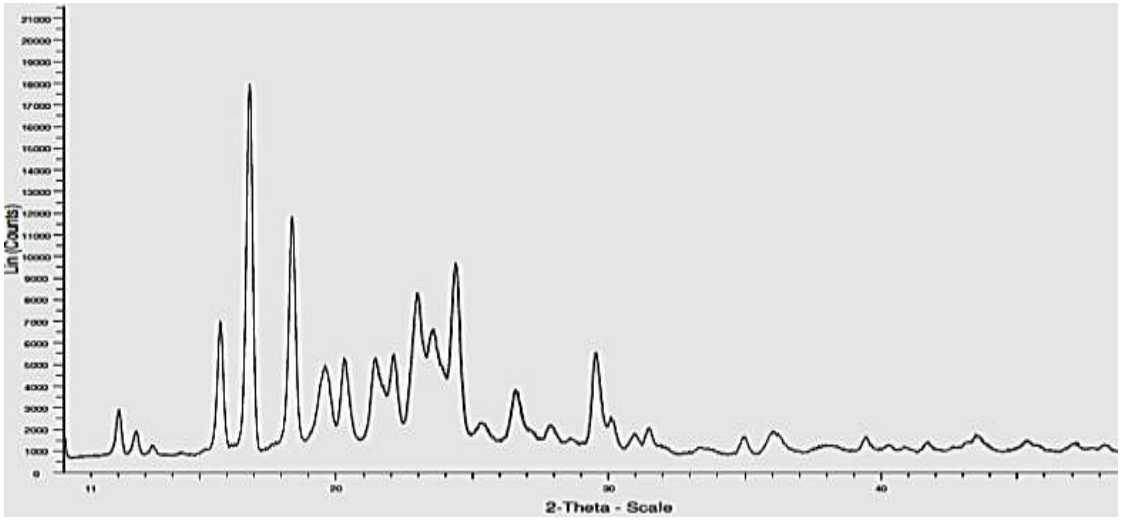

Fig 1: X-ray diffractometry for Etoricoxib, analyzed

Figure 1 shows a classic pattern of a crystalline solid, with a main peak at about 15 2θ, 5 2θ and two other important peaks at 14 2θ and 16 2θ.

Fusiometry

The results of the fusiometry test for the Etoricoxib raw material described in Table 1 are presented below.

Table 1: Fusiometry results of the Etoricoxib Baselux samples.

Sample number	Melting range °C	Average Melting Point °C
1	135.7-138.0	136.85
2	136.1-137.8	136.95
3	135.8-137.6	136.70
Average	135.9-137.8	136.83
Standard deviation	0.208-0.200	0.126
Relative Standard Deviation	0.153-0.145	0.092%

The three Etoricoxib samples show in the test an average melting point of 136.83 ° C with a standard deviation of ± 0.126 ° C.

Differential Scanning Calorimetry

Figure 2 on the etoricoxib calorimetry assay is presented below.

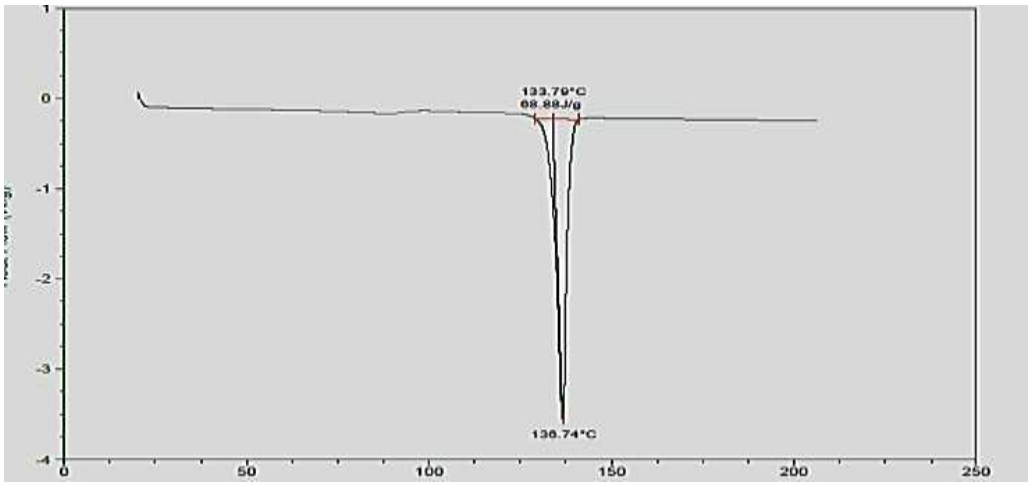

Fig 2: Thermogram of the Etoricoxib raw material Baselux sample

The thermogram shows an endotherm at 136.76 ° C, no secondary peaks or transitions occur before or after the fusion demonstrating the chemical and physical purity of the analyzed sample, no loss of moisture, no decomposition, nor transitions in the solid form are shown.

Thermogravimetry

Figure 3 shows the thermogravimogram of the raw material Etoricoxib sample provided by Baselux.

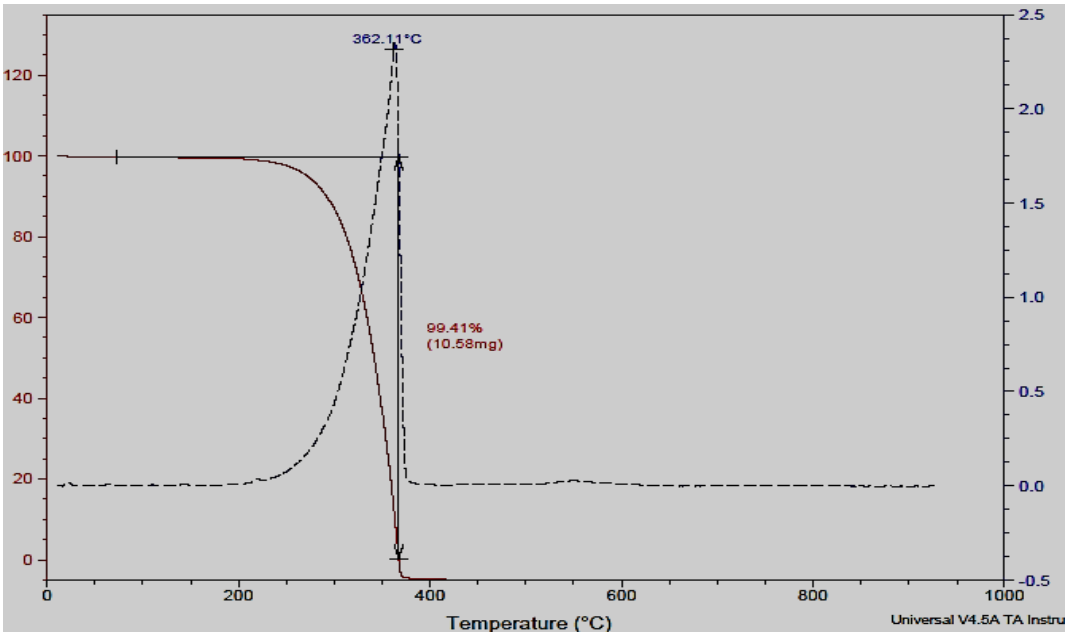

Fig 3: Thermogram of the sample of Etoricoxib Baselux raw material.

Figure 3 shows a weight change at 362 °C that coincides with the decomposition of the sample; there is no loss of surface moisture before that, nor does it appear that there are hydrates associated with the crystal. This fact is very important due to the high hygroscopicity of Etoricoxib, besides that the presence of moisture is related to the crystalline transitions. In addition, the test checks the chemical purity of the sample since there are no pre-decomposition weight losses related to residual solvents or other polluting substances.

Infrared Spectroscopy

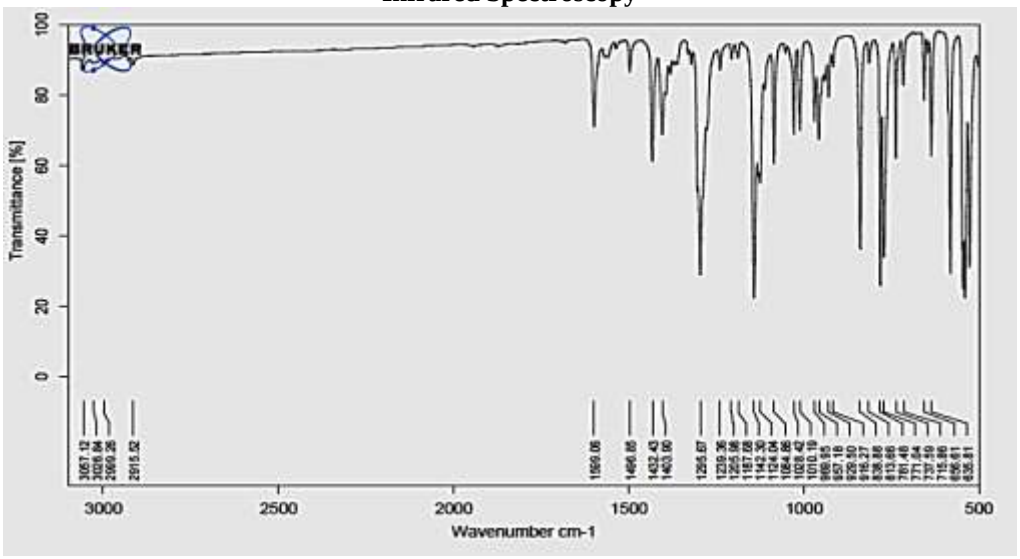

Fig 4: Infrared Absorption Spectrum for Etoricoxib raw material Baselux

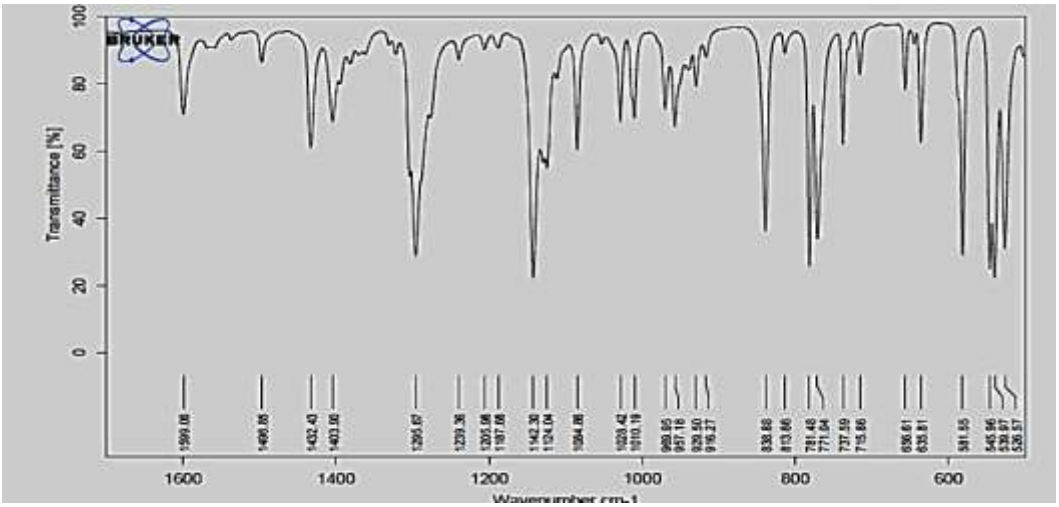

Fig 5: Infrared Absorption Spectrum for Etoricoxib Baselux raw material Digital fingerprint

A number of non-specific peaks were found at approximate wavelengths of 1265, 1142, 1124, 839, 2915, and 3067, in addition they showed specific lines of the Etoricoxib at 1599 this represents the stretches and vibrations of the C=O group. The wave number of 1433, 1295, 1114, 1064 represent stretches and vibrations of the S=O group; while 839, 781, 636 represent stretches and vibrations of the C-Cl group, which help us confirm the identification of the substance, likewise the absence of the watermark, or other solvents with hydroxyl groups, confirms the fact that the sample lacks residual solvents of this type that favor the transitions.

DISCUSSION

The results obtained in each of the tests performed were compared with the art found in the revised bibliography. The physicochemical parameters, melting range, percentage of lost mass, X-ray diffraction pattern and fingerprint pattern of the infrared spectrum were compared with the results of all performed tests. The solid nature of the supplied sample was clearly identified.

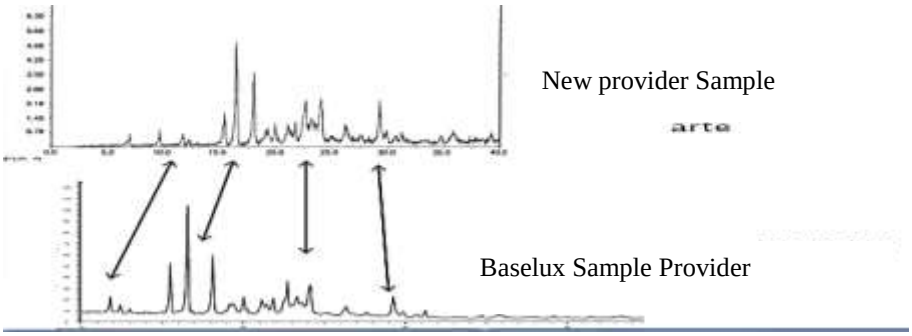

Fig 6: Comparison of the diffractogram of the samples result from the raw material supplier Baselux with the art for form I Etoricoxib shown in the reference [4-11].

A differential comparison is made with other diffractograms found in the literature, and it is found that the sample and the art of the form I structure are those that show greater similarity. Such diffractograms are not included but may be reviewed in the cited literature. The three characteristic peaks between 14 and 16 2θ are shown in both diffractograms, the other triad of characteristic peaks is between 20 and 25 2θ, finally two solitary peaks at 30 2θ approximately and a triad of small peaks between 12 and 14 2θ, confirms the identification of the crystalline form I of Etoricoxib. Below are shown diffractograms of possible polymorphs existing spontaneously and which are compared with the results of the analysis performed.

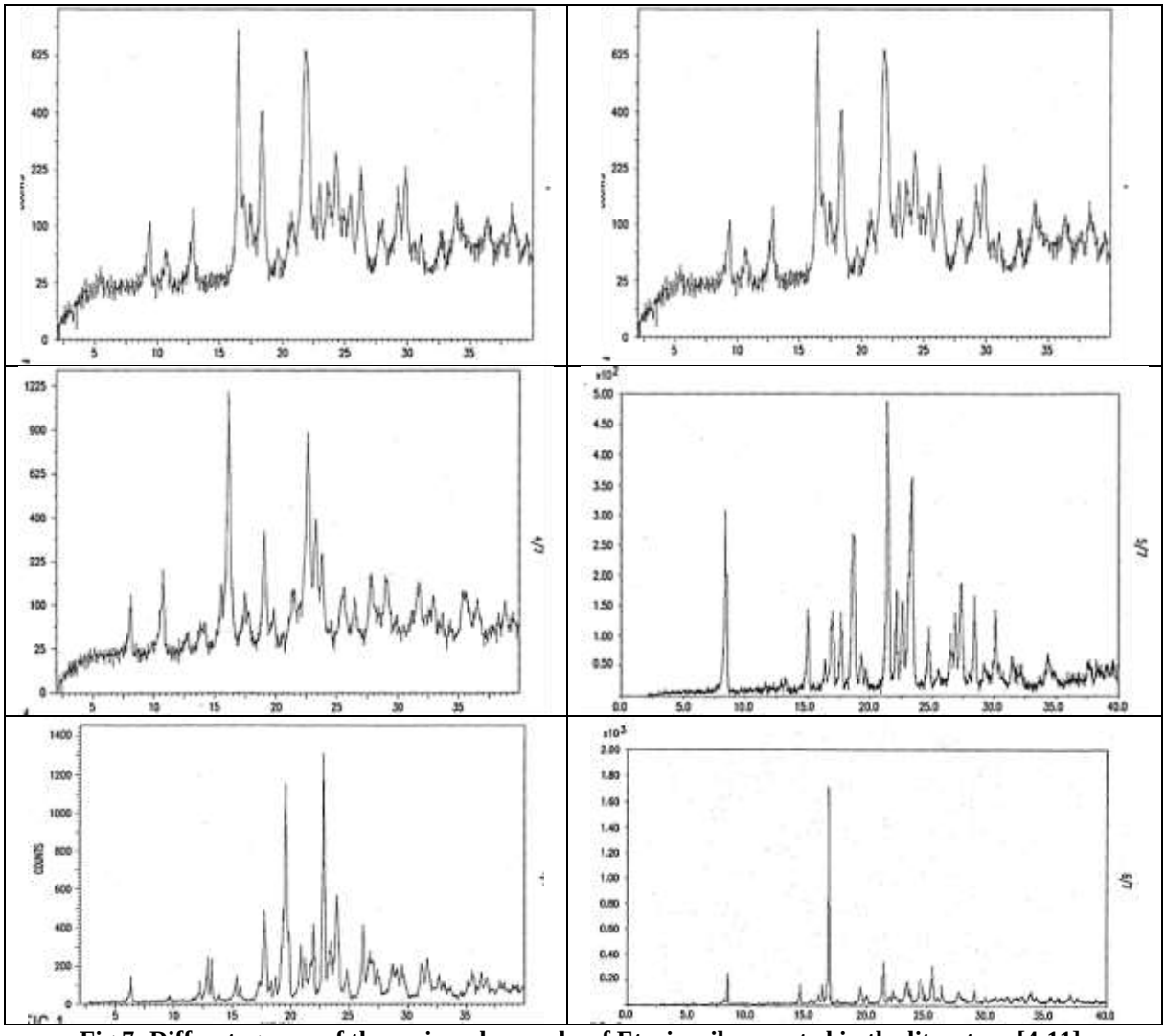

Fig 7: Diffractograms of the main polymorphs of Etoricoxib reported in the literature [4-11].

The differences between the spectra of the main crystalline forms of Etoricoxib are clear, mainly because of the absence of the triad between 14 2θ and 16 2θ, where the central peak is prominent, and these three peaks are the characteristic part of the form 1, which, when combined with the rest of the peaks, identifies the form and demonstrates the well-known existence of transitions according to what is established [12]

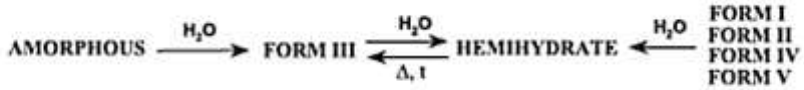

Figure 1. Polymorph relationship of etoricoxib with the hemihydrate form.

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Fig 8: Transitions of Etoricoxib in the presence of water.

The presence of water may generate spontaneous transformation in the different polymorphs previously shown, since there is no water as we can see in Figures 2, 3 and 4 since both the DSC, TGA and Infrared Spectroscopy tests do not show the presence of water in the samples analyzed which prevents polymorphic transformations, and with the results of Figures 5 and 6, the non-existence of polymorphic transitions can be proved, which reinforces the existence of the polymorph form I of Etoricoxib in the sample in a pure state [12, 13]. The average melting point of the Etoricoxib sample is 136.83 °C ± 0.1258 °C, its average melting range is 135.9 °C-137.8 °C, it's been reported in the literature WO01 / 92230 that the onset of the fusion is 135.7 °C ± 0.2 °C which is characteristic of form 1 of Etoricoxib and has a melting point of 137.0 °C ± 0.2 °C.

When performing a statistical analysis with a 95% confidence and two-tailed t student test, the following formula is used to calculate the value of the calculated t: 1.6641 for the lower average range where the fusion process begins.

$135.9\text{-}135.7/\ (0.208166/\sqrt{3}) = t_{cal} = 1.6641$

The following hypotheses were considered:

Ho = theoretical pf = practical pf
Ha = theoretical pf ≠ practical pf

Criterion:
Ho is accepted if tcal <ttab
Ho is rejected if tcal> ttab

The result for n-2 degrees of freedom at 95% for t in the table is: 25.45, so the value obtained is accepted Ho and it is shown for the value where the fusion initiates that there is no statistically significant difference with the start of the melting point shown by the art, similarly a calculated t value of 1.4145 for the melting point shows that there is no statistically significant difference with the melting point of the polymorphic form I of Etoricoxib with that reported in the literature [4-13]. On the other hand, there is a statistically significant difference between the melting point found and the melting point of the polymorphic form II of Etoricoxib, which is 131.5 °C ± 0.2 °C since its calculated t is 44.3484, which rejects the null hypothesis, this demonstrates the significant difference of the raw material samples of Etoricoxib with the polymorphic form II of Etoricoxib with a melting point at 131.5 °C, which again proves the existence of Etoricoxib form 1 only, since there are no indications of the coexistence of other crystalline forms.

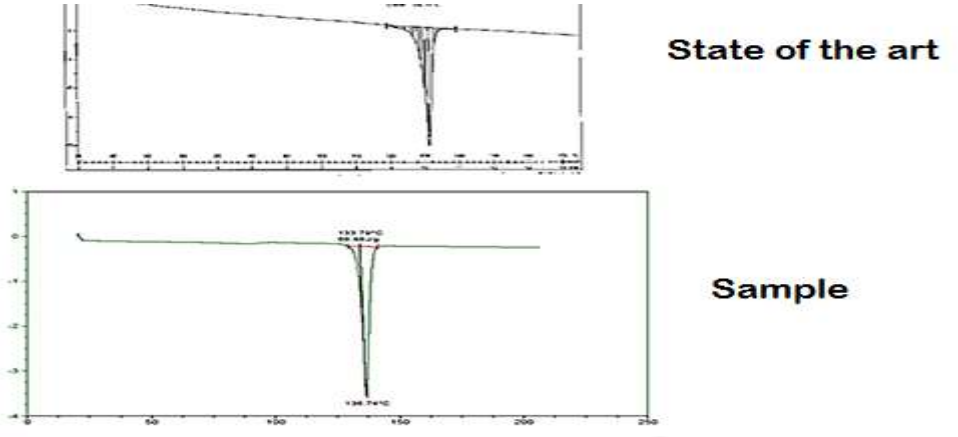

Fig 9: Comparison of DSC result of the Etoricoxib sample with Etoricoxib crystal form I [12, 13].

DSC analysis verifies that the Etoricoxib fusion point of the sample is 136.74 °C, which is characteristic of form I Etoricoxib. The purity of the calorimetric peak, Figure 9, demonstrates the purity of crystalline form I, since there are no posterior or inferior secondary peaks.

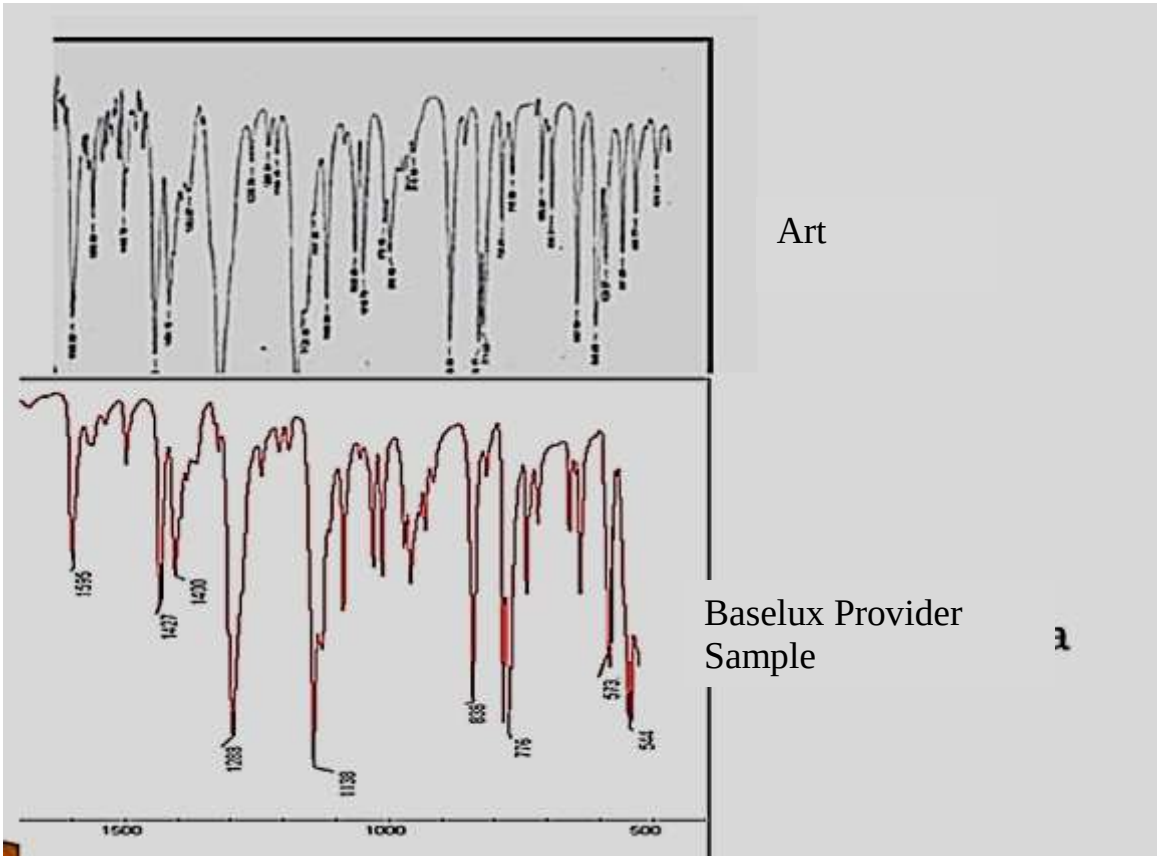

Fig 10: Comparison of fingerprint infrared spectrum of the Baselux supplier sample with art [14].

The FTIR spectra of pure Etoricoxib showed non-specific peaks at approximate wavelengths of 1265, 1142, 1124, 839, 2915, and 3067 cm $^{-1}$, and showed specific lines of Etoricoxib at 1599 cm $^{-1}$, representing stretches and vibrations of the C=O group. The wave number of 1433, 1295.1124, 1064 cm $^{-1}$ represent stretches and vibrations of the group S=O; while 839, 781, 636 cm $^{-1}$ represent stretches and vibrations of the C-Cl group, which help us confirm the identification of the substance, also the absence of the watermark, or other solvents with hydroxyl groups, confirms the fact that the sample lacks residual solvents of this type that favor the transitions. This corroborates the identification of the substance in its 1 anhydrous polymorphic form, without evidence of the existence of other polymorphic derivative forms [4-14].

CONCLUSIONS

The X-ray diffraction characterization shows the existence of crystalline form I of Etoricoxib and does not show peaks related to other known forms. The differential scanning calorimetry assay demonstrates the existence of an endotherm at 136.74 °C which represents the melting point of crystalline form I of Etoricoxib. The thermogravimetric test does not show loss of mass before 300 °C which indicates the absence of solvents in the sample of raw material. The infrared characteristic bands demonstrate the presence of Etoricoxib, both in the raw material sample and in the final dosage form, in both spectra there are no peaks related to water or other solvents, confirming that the sample both in the Pharmaceutical form and in the tablet are anhydrous.

Fusiometry validates the existence of crystalline form I of Etoricoxib reinforcing the data obtained by X-ray diffraction, infrared and differential scanning calorimetry. The analyzed sample of raw material was identified as crystalline Etoricoxib anhydroform Form I without the presence of traces of other polymorphic forms. It was also demonstrated the absence of water or volatile solvents in the sample which improves the stability profile of the substance since it avoids spontaneous transitions in another form of polymorphs. With the analysis of DSC and Infrared Spectroscopy the presence of Etoricoxib hemihydrate

and amorphous forms were ruled out. Because of the purity of the signals obtained and the comparison of the tests, traces of other related substances or degradation products that affect the study are not identified.

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