Chapter 2

Review of Literature
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Title</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>Review of Literature</td>
<td>9</td>
</tr>
<tr>
<td>2.1</td>
<td>Review on Etoricoxib</td>
<td>11</td>
</tr>
<tr>
<td>2.2</td>
<td>Review on N-Methyl Fluoxetine Oxalate</td>
<td>13</td>
</tr>
<tr>
<td>2.3</td>
<td>Review on Prasugrel Hydrochloride</td>
<td>16</td>
</tr>
<tr>
<td>2.4</td>
<td>Review on Pioglitazone Hydrochloride</td>
<td>19</td>
</tr>
<tr>
<td>--</td>
<td>Bibliography</td>
<td>21</td>
</tr>
</tbody>
</table>
2.1 Review on Etoricoxib

Etoricoxib (Fig.2.1.F1), an active pharmaceutical ingredient discovered by Merck & Co., under the brand name of Arcoxia[1]. It is used in the treatment of osteoarthritis and rheumatoid arthritis. Etoricoxib comes under the class of non-steroidal anti-inflammatory drugs (NSAID). Etoricoxib reduces the second isoform of enzyme [2-16]. COX-2 is vital in the construction of the molecules of the body that are mainly responsible for ache, inflammation, and swelling caused by lots of medical circumstances), by inhibition of cyclooxygenases effectively decreases pain.

There few reports are available for the determination of Etoricoxib in pharmaceutical preparations, biological fluids and combinational drugs [7-16]. Determination of impurities in Etoricoxib was not reported so far and especially literature related to the present impurities determination is not available. The Chemical structures of Etoricoxib, Impurity-A, Impurity-B and Impurity-C were mentioned in Fig 2.1.F1.

**Etoricoxib**

**IUPAC Name:** 5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

**Synonyms:** 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl)pyridine

(or) 2-(6-methyl pyridin-3-yl)-5-Chloro-3-(4-methylsulfonylphenyl)pyridine.

**Molecular Formula** : C$_{18}$H$_{15}$ClN$_2$O$_2$S

**Molecular Weight** : 358.84 g.mol$^{-1}$
Impurity-A:
IUPAC Name: 2-(4-methylsulfonylphenyl) acetic acid
Synonym: [4-(methylsulfonyl)phenyl] acetic acid
Molecular Formula : C_9H_10O_4S
Molecular Weight : 214.24 g mol⁻¹

Impurity-B:
IUPAC Name: methyl 6-methylpyridine-3-carboxylate
Synonym: Nicotinic acid-6-Methyl- methyl ester
Molecular Formula : C_8H_9NO_2
Molecular Weight : 151.16 g mol⁻¹

Impurity-C:
IUPAC Name: 1-(6-methylpyridin-3-yl)-2-(4-methylsulfonylphenyl)ethanone
Synonym: 1-(6-methyl-pyridin-3-yl)-2-(4-Methanesulfonyl-phenyl)-ethanone
Molecular Formula : C_{15}H_{15}NO_3S
Molecular Weight : 289.35 g mol⁻¹

Fig 2.1.F1: Chemical structures of Etoricoxib, Impurity-A, Impurity-B and Impurity-C.
N V S Ramakrishna et al.[7] have reported a Chromatographic techniques in analysis of cyclooxygenase-2 inhibitors in drugs and biological samples, but this method not specific to any impurity determination and not specific to Etoricoxib. HM Patel et al.[8] have reported a HPLC method for the etoricoxib pharmaceutical formulations. NV Dinesh et al.[9] have reported a UPLC method for the Separation of Etoricoxib API and formulation but this article is not specific to impurity determination and technique used is UPLC. U Mandal et al.[10] have reported a HPLC method for the analysis of etoricoxib in human plasma. Z Maitreyi Z et al.[11] have reported a HPLC method for the Determination of etoricoxib formulation.

There are no reports available for the determination of impurities in Etoricoxib drug substance as well as drug products by HPLC. Thus there is need to develop a method for the determination of impurities and degradation products so that it is helpful for the analysis of routine drugs substance samples and stability samples.

2.2 Review on N-Methyl Fluoxetine Oxalate

N-Methyl Fluoxetine Oxalate (NMF) {Fig.2.2.F1, is the precursor [17-19] and a key intermediate in the synthesis of Fluoxetine hydrochloride. The two positional isomers are (ortho-NMF and meta-NMF) generated during the manufacturing of N-Methyl Fluoxetine Oxalate play a vital role in the quality determination of Fluoxetine hydrochloride. It is very important to identify and control these isomeric impurities in N-Methyl Fluoxetine Oxalate. The Chemical structures of N-Methyl Fluoxetine Oxalate, Ortho-NMF and Meta-NMF were mentioned in Fig 2.2.F1.
N-Methyl Fluoxetine Oxalate (NMF/Para-NMF):

**IUPAC Name:** N, N-dimethyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propan-1-amine; oxalic acid

**Synonym:** N,N-Dimethyl-{3-phenly-3-[4-(trifluoromethyl) phenoxy] propyl}amine oxalate

**Molecular Formula** : \( C_{18}H_{20}F_{3}NO.C_{2}H_{2}O_{4} \)

**Molecular Weight** : 413.38 g.mol\(^{-1}\)

---

Ortho-NMF:

**IUPAC Name:** N, N-dimethyl-3-phenyl-3-[2-(trifluoromethyl) phenoxy] propan-1-amine; oxalic acid

**Synonym:** N,N-Dimethyl-{3-phenly-3-[2-(trifluoromethyl) phenoxy] propyl}amine oxalate

**Molecular Formula** : \( C_{18}H_{20}F_{3}NO.C_{2}H_{2}O_{4} \)

**Molecular Weight** : 413.38 g.mol\(^{-1}\)
Meta-NMF:

**IUPAC Name:** N, N-dimethyl-3-phenyl-3-[3-(trifluoromethyl) phenoxy] propan-1-amine; oxalic acid

**Synonym:** N,N-Dimethyl-3-phenyl-3-[3-(trifluoromethyl) phenoxy] propylamine oxalate

**Molecular Formula:** C\(_{18}\)H\(_{20}\)F\(_{3}\)NO.C\(_{2}\)H\(_{2}\)O\(_{4}\)

**Molecular Weight:** 413.38 g.mol\(^{-1}\)

![Chemical structure of Meta-NMF](image)

**Fig 2.2.F1: Chemical structures of N-Methyl Fluoxetine Oxalate, Ortho-NMF and Meta-NMF**

Some literature reports are available for the determination of fluoxetine using LC, LC/MS, Capillary electrophoresis, HPTLC, spectrophotometry in pharmaceutical preparations [20-30]. Fluoxetine and its simultaneous determination with other substances are also present in the literature [31-41]. So far no literature is available for the determination of impurities in N-Methyl Fluoxetine Oxalate. Literature is available for the determination of its API Fluoxetine hydrochloride.

have reported a method for Identification and Comparison of Impurities in Fluoxetine Hydrochloride Synthesized by Seven Different Routes. However there is no evidence of literature for the determination of isomers in N-Methyl Fluoxetine Oxalate.

2.3 Review on Pioglitazone Hydrochloride

Pioglitazone Hydrochloride [42-48] is an anti-diabetic agent. Various analytical techniques reported [49-67] so far for the determination of this drug substance and pharmaceutical products. The typical structure of Pioglitazone hydrochloride is mentioned in fig.2.3.F1. HPLC method was developed for the quantification of Pioglitazone and the impurities arising during its preparation. Chemical structures of Pioglitazone and its impurities were mentioned in Fig 2.3.F.1

Pioglitazone Hydrochloride:

IUPAC Name: 5-[[4-[2-(5-ethylpyridin-2-yl) ethoxy] phenyl] methyl]-1, 3-thiazolidine-2, 4-dione; hydrochloride

Synonyms: 5-[[4-[2-(5-Ethyl-2-pyridinyl]ethoxy]phenyl)methyl]-2,4-thiazolidinedione hydrochloride
[5-[[4-[2-(5-Ethyl-2-pyridinyl)phenyl]ethoxy]methyl]-2,4-] thiazolidinedione hydrochloride

Molecular Formula : C_{19}H_{21}ClN_{2}O_{3}S

Molecular Weight : 392.90 g.mol^{-1}
Impurity-A:

**IUPAC Name:** 1,3-thiazolidine-2,4-dione

**Synonym:** 2,4-thiazolidinedione

**Molecular Formula:** $\text{C}_3\text{H}_3\text{NO}_2\text{S}$

**Molecular Weight:** $117.13 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-A](image)

Impurity-B:

**IUPAC Name:** 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde

**Synonym:** 4-[2-(5-Ethyl-pyridinyl)-ethoxy]-benzaldehyde

**Molecular Formula:** $\text{C}_{16}\text{H}_{17}\text{NO}_2$

**Molecular Weight:** $255.31 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-B](image)

Impurity-C:

**IUPAC Name:** (5Z)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methylidene]-1,3-thiazolidine-2,4-dione

**Synonym:** 5-\{4-[2-(5-Ethyl-pyridinyl)-ethoxy]-benzylidene\}-thiazolidine-2,4-dione

**Molecular Formula:** $\text{C}_{19}\text{H}_{18}\text{N}_{2}\text{O}_3\text{S}$

**Molecular Weight:** $354.42 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-C](image)

Fig 2.3.F1: Chemical structures of Pioglitazone Hydrochloride and its impurities
Thorough literature review shows absence of any simple and specific stability indicating HPLC method for the determination of selected related substances of Pioglitazone Hydrochloride. Thus there is a need to develop a stability indicating chromatographic method to determine the purity of the drug and estimation of process impurities and degradation products.

WZ Zhong et al.[50] have reported a method for the Determination of Pioglitazone in dog serum by HPLC. K Yamashita et al.[51] have reported a HPLC method for the determination of Pioglitazone and its metabolite. E Souri et al.[54] have reported a method for the Development and validation of a simple and rapid HPLC method for determination of pioglitazone. N. Rashmithaa et al.[55] have reported a method for the determination of impurities in Pioglitazone hydrochloride but the selected impurities are not covered. S Sayed et al. [56] have reported RP-HPLC method determination of Pioglitazone hydrochloride in formulation. Smita Sharma et al.[57] have reported a method for the Study of stressed degradation behavior of Pioglitazone Hydrochloride but this is an assay method. DB Wanjari et al.[58] have reported a method for the Determination of Pioglitazone Tablets. T.Thilak kumar et al.[59] has reported a method for the pioglitazone hydrochloride. Singh Surendra Rao et al.[60] have reported a method for separation of pioglitazone degradant in drug product. K Ramulu et al.[61] have reported a method for the Identification of degradation products in pioglitazone hydrochloride. T Radhakrishna et al.[62] have reported a method for the Determination of pioglitazone hydrochloride in formulations. A Jedlieka et al.[63] have reported a method for the Reversed-phase HPLC methods for purity test and assay of pioglitazone hydrochloride in tablets

However, there are no reports available for the determination of the selected impurities in Pioglitazone Hydrochloride drug substance as well as drug product.
Thus there is need to develop a simple, specific and sensitive method for the
determination of impurities and degradation products in Pioglitazone Hydrochloride
so that it is helpful for the analysis of routine drugs substance samples and stability
samples.

2.4 Review on Prasugrel Hydrochloride

Prasugrel Hydrochloride [68-74] is a novel platelet inhibitor. Different
analytical techniques reported [74-86] so far for the determination of Prasugrel
hydrochloride drug substance and drug product. The typical structure of Prasugrel
hydrochloride and its impurities were mentioned in fig.2.4.F1.

Prasugrel Hydrochloride:

IUPAC Name : 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-
tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride

Synonyms: 2-[2-(Acetyloxy)-6,7-dihydrothieno[3,2-c]pyridin-yl]-1-cyclopropyl-2-
(2-fluorophenyl)ethanone hydrochloride (PSG)

Molecular Formula : C₂₀H₂₀FNO₅S.ClH

Molecular Weight : 409.90 g.mol⁻¹

![Prasugrel Hydrochloride Structure](image)
Impurity-A:

**IUPAC Name:** 1-cyclopropyl-2-(2-fluorophenyl)ethanone  
**Synonym:** 1-cyclopropyl-2-(2-fluoro-phenyl)-ethanone  
**Molecular Formula:** $C_{11}H_{11}FO$  
**Molecular Weight:** $178.20 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-A](attachment:image.png)

Impurity-B:

**IUPAC Name:** 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone  
**Synonym:** 2-Bromo-1-cyclopropyl-2-(2-fluoro-phenyl)-ethanone  
**Molecular Formula:** $C_{11}H_{10}BrFO$  
**Molecular Weight:** $257.10 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-B](attachment:image.png)

Impurity-C

**IUPAC Name:** 5, 6, 7a-tetrahydro-4H-thieno [3, 2-c] pyridin-2-one; hydrochloride  
**Synonym:** 5,6,7a-Tetrahydrothieno[3,2-c]pyridine-one hydrochloride  
**Molecular Formula:** $C_7H_{10}ClNOS$  
**Molecular Weight:** $191.68 \text{ g.mol}^{-1}$

![Chemical structure of Impurity-C](attachment:image.png)

Fig 2.4.F1: Chemical structures of Prasugrel Hydrochloride, Impurity-A, Impurity-B and Impurity-C
Some literatures are available for the determination of Prasugrel using LC, LC/MS, Capillary electrophoresis, HPTLC, spectrophotometry in pharmaceutical preparations. Prasugrel and its simultaneous determination with other substances are also present in the literature.

Till date no method is available for the determination of the impurities in Prasugrel Hydrochloride and the present study describes a novel method for the determination of impurities in Prasugrel Hydrochloride.

Prabahar A.Elphine et al.[77] have reported a HPLC potency assay of Prasugrel tablets. Ishaq B Mohammed et al.[81] have reported HPLC method for the determination of prasugrel in bulk and its pharmaceutical formulation using the RP-HPLC method. ER Wickremsinhe et al.[82] have reported chiral HPLC method. AE Prabahar et al.[84] have reported a Method for the HPLC potency assay of prasugrel tablets.

There are no reports available for the determination of impurities in Prasugrel Hydrochloride drug substance as well as drug product. Thus there is need to develop a method for the determination of impurities and degradation products so that it is helpful for the analysis of routine drugs substance samples and stability samples.

**BIBLIOGRAPHY:**


69. http://dmd.aspetjournals.org/content/35/7/1096.full


