IBUPROFEN AND ITS DIFFERENT ANALYTICAL AND MANUFACTURING METHODS: A REVIEW

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ABSTRACT
Ibuprofen is a nonsteroidal anti-inflammatory drug and many of its similar class includes aspirin, indomethacin (Indocin), naproxen (Aleve), nabumetone (Relafen), and many others. This drug is used in moderate pain, fever, and inflammation, which is promoted by the release in the body of chemicals called prostaglandins. According to the IUPAC, it is (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid. The original synthesis of ibuprofen by the Boots Group started with the compound 2-methylpropyl benzene. Ibuprofen blocks the enzyme that makes prostaglandins (cyclooxygenase), resulting in lower levels of prostaglandins that help in reducing inflammation, pain, and fever. This review is focused on various chemical and functional properties and experimental studies of ibuprofen including various detection methods such as potentiometric, ultraviolet spectrophotometric, gas chromatography, high-performance liquid chromatography (HPLC), and reverse-HPLC which can also be used for the extraction, quantification, and quality analysis.

Keywords: Ibuprofen, Anti-inflammatory, Prostaglandins, Analytical methods.

INTRODUCTION
Ibuprofen is a medication in the nonsteroidal anti-inflammatory drug (NSAID) class which is used for treating pain, fever, etc. [1]. It is used for the treatment of mild-to-moderate pain, inflammation, and fever caused by many and diverse diseases. It is used for treating menstrual cramps (dysmenorrhea), osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis. Besides its upsides, there are some downsides of ibuprofen. It increases the risk of heart, kidney, and liver failure. At low dosage, it does not appear to increase the risk of heart attack; however, at higher dosage, the risk may get an increase. This chemical drug is listed on the World Health Organization’s list of Essential Medicines, the most effective and safe medicines needed in a health system.

Structural formula [2]

Molecular Formula: C13H18O2
Molecular Weight: 206.29 g/mole
IUPAC name: (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid
Density: 1.03 g/ml
Melting Point: 75–78°C
Boiling Point: 157°C
Odor: Characteristic odor
Color: Colorless, crystalline stable solid

Synonyms
1. Alpha-methyl-4-(2-methylpropyl)benzeneacetic acid
2. Aluminum Salt Ibuprofen
3. Brufen
4. Calcium Salt Ibuprofen
5. I.V. Solution, Ibuprofen
6. Ibubrin
7. Ibupron
8. Ibuprofen I.V. Solution
9. Ibuprofen Zinc
10. Ibuprofen, (+)-Isomer
11. Ibuprofen, (R)-Isomer
12. Ibuprofen, (S)-Isomer
13. Ibuprofen, Aluminum Salt
14. Ibuprofen, Calcium Salt
15. Ibuprofen, Copper (2+) Salt
16. Ibuprofen, Magnesium Salt
17. Ibuprofen, Potassium Salt
18. Ibuprofen, Sodium Salt
19. Ibuprofen, Zinc Salt
20. Ibuprofen-Zinc
21. IP 82
22. IP-82
23. IP92
24. Magnesium Salt Ibuprofen
25. Motrin
26. Nuprin
27. Potassium Salt Ibuprofen
28. Rufen
29. Salprofen
30. Salt Ibuprofen, Magnesium
31. Salt Ibuprofen, Sodium
32. Salt Ibuprofen, Zinc
33. Sodium Salt Ibuprofen
34. Trauma Dolgit Gel
35. Trauma-Dolgit Gel
36. TraumaDolgit Gel
37. Zinc Salt Ibuprofen

Solubility
- Readily soluble in most organic solvents [3].
- Very soluble in alcohol [4].
- 21 mg/L (at 25°C) [5].
Ibuprofen has been shown to have analgesic and antipyretic properties. Pharmacologically, it has similarities to other prototypical NSAIDs. Ibuprofen is a propionic acid derivative and has anti-inflammatory, analgesic, and antipyretic effects and also has the cardioprotective effect of aspirin [7].

Ibuprofen having propionic acid derivatives [8] inhibits the activity of cyclooxygenase I and II that decrease the formation of precursors of prostaglandins and thromboxanes. This leads to decreased prostaglandin synthesis, by prostaglandin synthase, the main physiologic effect of the drug. Ibuprofen also causes a decrease in the formation of thromboxane A2 synthesis, by thromboxane synthase, thereby inhibiting platelet aggregation.

The absorption of the drug is rapid and complete when given orally. Ibuprofen is eliminated following biotransformation to glucuronide conjugate metabolites that are excreted in urine, with little of the drug being eliminated unchanged [9]. The excretion of conjugates may be tied to renal function, and the accumulation of conjugates occurs in end-stage renal disease. Hepatic disease and cystic fibrosis can alter the disposition kinetics of the drug. Ibuprofen is not excreted in substantial concentrations in breast milk. Significant drug interactions have been demonstrated for aspirin (acetylsalicylic acid), cholestyramine, and methotrexate.

**Mechanism of action**

Cyclooxygenase (COX), which is required for the synthesis of prostaglandins through the arachidonic acid pathway, converts the arachidonic acid to prostaglandin H2 in the body. Anticoagulant effects are also mediated through inhibition of COX, which converts arachidonic acid into thromboxane A2, a vital component in platelet aggregation that leads to the formation of blood clots. Thus, the excess amount of NSAID may cause the long-term blockage of the COX-1 which is a subtype of COX that may cause gastric toxicity because the maintenance of the gastric mucosa is disturbed.

**Uses**

Ibuprofen is used primarily for:
- Headache.
- Back pain.
- Menstruation pain.
- Pain in teeth.
- Symptoms of cold and influenza.
- Pain in body.
- Analgesic.
- Muscle pain.
- Joint pain.
- Pain in nerves.

**Contraindications**

Hypersensitivity to ibuprofen is a contraindication. In addition, ibuprofen should not be used in the following conditions.
- Active peptic ulcer.
- Aspirin.
- Breastfeeding.
- Gastrointestinal bleeding.
- Hypersensitivity.
- Neonates with congenital heart disease.
- A study of pregnant women suggests that those taking any type or amount of NSAIDs (including ibuprofen, diclofenac, and naproxen) were 2.4 times more likely to miscarry than those not taking the drugs [10].

**SIDE EFFECTS**

distress syndrome [22]. Studies also reveal that ibuprofen possess the antifungal activities [23].

Each drug after a design requires the clinical trial process where several types of animals are used. After successful trials on animals, human trials are performed. Some of the animals trialed during the testing of ibuprofen and their effects toward the given drug are given in Table 1.

**Trade names**
Ibuprofen is available in different trade name by different companies as shown in Table 2.

**METHODS OF MANUFACTURING**
Various methods can be employed to manufacture the ibuprofen and its common constituents Table 3. Industrially, ibuprofen can be produced by biological transformation process, but due to some costlier process, easy methods are being used where chemical synthesis process is the most prominent one.

**ANALYTICAL METHODS**
Several drugs need to be isolated and identified from the impurity source that helps to give in rise to the derivate of several other drugs. These stages were as follows [30-32],

- Sample set selection.
- Chromatographic conditions and phases, typically using solvent strength model.
- Optimization.

Various analytical methods can be used to determine ibuprofen. The methods are as follows:

**Potentiometry**
Potentiometry is a technique based on a measurement of the potential difference between an indicator electrode and a reference electrode in solution, while the current is held at zero [33].

For the potentiometric determination of ibuprofen, sodium hydroxide and triethanolamine can be used as titrants.

The influence of different solvents, such as water, methanol, acetonitrile, dimethyl sulfoxide, and N, N-dimethylformamide, on the conductometric titrations can be investigated.

The same titrants as in the potentiometric titrations can be used.

The methods are accurate, and the results are reproducible in quantities ranging from 1 to 10 mg of ibuprofen in analyzed pharmaceutical dosage forms.

**Chromatographic and ultraviolet (UV) spectrophotometric methods**
In early ages, most of the analytical methods were done using thin-layer spectrophotometric, differential pulse polygraph, colorimetric [34], gas-liquid chromatography [35-38], paper chromatography, or direct liquid introduction mass spectrometry (MS). However, due to greater facilitate sample preparation, those early methods have largely been

### Table 1: Experimental studies of ibuprofen

<table>
<thead>
<tr>
<th>Organism</th>
<th>Route</th>
<th>Reported dose</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holstein’s calves</td>
<td>Intraperitoneal</td>
<td>10 mg/kg</td>
<td>Ibuprofen decreased PGE2, modulated the immune response, lung histopathology was not affected, and viral shedding was increased [24]</td>
</tr>
<tr>
<td>Rat</td>
<td>Intravenous</td>
<td>20 mg/kg body wt./day</td>
<td>Rats injected with ibuprofen significantly worsened compared to non-treated injured animals [25]</td>
</tr>
<tr>
<td>Sprague-Dawley rats</td>
<td>Oral</td>
<td>15 mg/kg</td>
<td>Fracture histology and serum osteocalcin levels were no different in treated animals than control animals [26]</td>
</tr>
<tr>
<td>Infants</td>
<td>Oral</td>
<td>2.2 mg/kg/day</td>
<td>Prophylactic ibuprofen reduces the need for surgical ligation of patent ductus arteriosus but does not reduce mortality or morbidity [27]</td>
</tr>
</tbody>
</table>

### Table 2: Trade name and respective companies of Ibuprofen

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dosage Forms</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motrin</td>
<td>Tablets, Suspension</td>
<td>Sigma-Aldrich</td>
</tr>
<tr>
<td>Brufen</td>
<td>Tablets</td>
<td>Wyeth Pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Nurofen</td>
<td>Tablets</td>
<td>Reckitt Benckiser Pharmaceuticals</td>
</tr>
<tr>
<td>Advil</td>
<td>Tablets</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Dolgit</td>
<td>Tablets</td>
<td>Dolorget, Budapharma</td>
</tr>
<tr>
<td>Lipton</td>
<td>Tablets</td>
<td>Wyeth Pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Anflagen</td>
<td>Tablets</td>
<td>Adare pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Apsifen</td>
<td>Tablets</td>
<td>TEVA UK Limited</td>
</tr>
<tr>
<td>Trendar</td>
<td>Tablets</td>
<td>Zibo Xinhua-Perrigo Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>Buburone</td>
<td>Tablets</td>
<td>BCM</td>
</tr>
</tbody>
</table>

### Table 3: Chemical and processes for ibuprofen manufacturing

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Chemicals</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Isobutyl benzene+acetyl chloride+triethylaluminum+potassium cyanide.</td>
<td>Friedel-Crafts acylation/cyanhydrin formation/hydrogenation/nitrile hydrolysis [28]</td>
</tr>
<tr>
<td>2.</td>
<td>isobutyl benzene+propionyl chloride+ethanol.</td>
<td>Friedel-Crafts acylation/ketal formation/alpha bromination/rearrangement [28]</td>
</tr>
<tr>
<td>3.</td>
<td>Isobutyl benzene+acetyl chloride+carbon monoxide.</td>
<td>Friedel-Crafts acylation/carbonyl reduction/carbonylation [28]</td>
</tr>
<tr>
<td>4.</td>
<td>Isobutyl benzene+acetyl chloride+methyl chloroacetate.</td>
<td>Friedel-Crafts acylation/Darzens reaction/hydrolysis/decarboxylation/carbonyl oxidation [28]</td>
</tr>
<tr>
<td>5.</td>
<td>Ethyl 4-isobutyl phenyl acetate and diethyl carbonate with sodium ethoxide gas+methyl iodide and sodium ethoxide.</td>
<td>Methylation, saponification, Decarboxylation [29]</td>
</tr>
</tbody>
</table>
Table 4: Chromatographic and UV spectrophotometric methods for various experiments

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Title</th>
<th>Method</th>
<th>Mobile phase</th>
<th>Column</th>
<th>Wavelength (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethambutol hydrogen chloride and ibuprofen determination in tablets</td>
<td>Reversed-phase HPLC</td>
<td>Methanol-H2O (70:30)</td>
<td>Bonda Pak C18 column packed with octadecylsilane bonded to porous silica</td>
<td>254</td>
</tr>
<tr>
<td>2</td>
<td>Ibuprofen in acidified plasma extraction application to a C2 extraction cartridge</td>
<td>HPLC</td>
<td>55% acetonitrile/45% 0.02 H phosphate buffer; pH 3.0</td>
<td>Nucleosil C18 column</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>NSAIDs in plasma</td>
<td>HPLC</td>
<td>Phosphoric acid 0.03% (pH 2.5) - acetonitriles 500 mg lithium perchlorate tridecyl, 110 ml water, and methanol up to 1 l</td>
<td>Silica column</td>
<td>290-313</td>
</tr>
<tr>
<td>4</td>
<td>Chromatographic and electrochemical methods for biological material analyses</td>
<td>Capillary column gas chromatography</td>
<td>Water-orthophosphoric acid to pH 3.2: acetonitrile: methanol (52:35:13)</td>
<td>Hypersil APS column</td>
<td>210</td>
</tr>
<tr>
<td>5</td>
<td>Detection of ibuprofen in serum</td>
<td>Isocratic liquid chromatography</td>
<td>Acetonitrile - 0.3% Acetic Acid - Tetrahydrofuran (36:63:1:0.9, vol/vol)</td>
<td>Spherisorb 5μm ODS column</td>
<td>239</td>
</tr>
<tr>
<td>6</td>
<td>Screening of plasma samples for the presence of sixteen NSAIDs</td>
<td>Isocratic HPLC</td>
<td>0.05% Isopropyl alcohol in heptane</td>
<td>Reversed-phase column Two silica columns μBondapak C1</td>
<td>254 and 370</td>
</tr>
<tr>
<td>7</td>
<td>Ibuprofen determination in plasma</td>
<td>HPLC</td>
<td>Methanol-water-glacial acetic acid (pH 3.4) (75:24:1, v/v)</td>
<td>Octadeyl Octadeylsilane column</td>
<td>272</td>
</tr>
<tr>
<td>8</td>
<td>Ibuprofen determination in serum</td>
<td>HPLC</td>
<td>65% Methanol and 35% 0.10 M acetic buffer (pH 5.0)</td>
<td>Octadeylsilane column</td>
<td>253</td>
</tr>
<tr>
<td>9</td>
<td>Ibuprofen determination in plasma</td>
<td>HPLC</td>
<td>Acetonitrile - acetic acid (pH 4.2 or 4.8)</td>
<td>Hypersil octadeylsilane analytical column</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>Identification of anti-inflammatory drugs from blood</td>
<td>HPLC</td>
<td>Reversed-phase HPLC</td>
<td>Spherisorb 5μm ODS column</td>
<td>239</td>
</tr>
</tbody>
</table>

HPLC: High-performance liquid chromatography, NSAIDs: Nonsteroidal anti-inflammatory drugs, UV: Ultraviolet

CONCLUSION

The study revealed that ibuprofen is a popular drug popular for its medicinal features in the pharmaceutical sector that can be used for the treatment of pain, fever, and inflammation. Although there are a lot of advantages, one should use the right amount of drug with consultation by doctor. Ibuprofen has been discussed in all its aspects in this review. HPLC-UV methods were found to be the most widely used. Furthermore, the analytical mentioned are time-saving simple and do not require elaborate treatments associated with chromatographic methods. With any no doubt, future will be gifted by newer types of ibuprofen formulation techniques.

CONFLICTS OF INTEREST

The author declares that no conflict of interest occurred during the work.

REFERENCES
