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Review Article

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.

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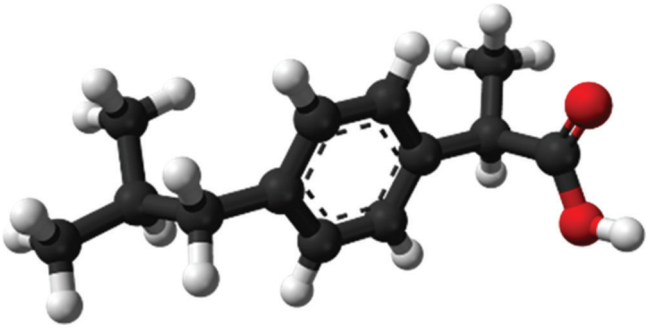
INTRODUCTION

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: $C_{13}H_{18}O_2$
Molecular Weight: 206.29 g/mole
IUPAC name: (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid
Density: 1.03 g/ml g/cm^3
Melting Point: 75–78°C (167–172°F)
Boiling Point: 157°C (315°F)
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. Ibumetin
7. Ibuprofen
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. IP82
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].

Vapor Pressure

- 4.74×10–5 mm Hg @ 25°C [6].

Pharmacology

Ibuprofen has the analgesic and antipyretic properties. Pharmacologically, it has similar action to those of other prototypical NSAIDs. Ibuprofen is a propionic acid derived and NSAID with 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

- Abdominal pain [11].
- Allergic reactions [12].
- Kidney problems [13].
- Hepatic problems.
- Abnormal blood counts.
- Severe skin reactions.
- Feeling sick.
- Loose motions.
- High blood pressure.
- Skin rash.
- Liver problems [14].
- Itching.
- Bleeding from the skin or nose.
- Severe skin allergies [15].
- Heartburn [16].
- Constipation.
- Gas.
- Headache.

Safety methods

- Consult with a doctor before taking ibuprofen.
- Avoid taking an alcohol or salicylates to prevent bleeding.
- Consult your doctor if you develop blurred vision, ringing, or roaring in the ears.
- Consult your doctor if you have systemic lupus erythematosus.
- Inform your doctor if you have bruising or bleeding.
- Take the drug with a meal or snack to prevent upset stomach.
- Keep away from heat, hot surface, sparks, open flames and other ignition sources - no smoking.

Dosage

Ibuprofen can be found in various forms such as tablets and inhalation. The various dosages according to the type of diseases and age of a person can be as follows.

- People of age between 20 to 45 years suffering from fever and minor aches are treated with 200-400 mg for every 4-6 hours.
- A person with arthritis is treated with 300–800 mg 3 or 4 times daily.
- Individuals should not use ibuprofen for more than 10 days for the treatment of pain or more than 3 days for the treatment of a fever unless directed by a physician.
- Children from 6 months to 12 years of age usually are given 5–10 mg/kg of ibuprofen every 6–8 h for the treatment of fever and pain. The maximum dose is 40 mg/kg daily.
- A person suffering from juvenile arthritis is treated with 20-40 mg/kg/day in 3–4 divided doses.

Studies and specifications

Many studies have revealed different cases of the ibuprofen effect on various human cells as well as other living microbes and also other components showing similar activity to ibuprofen. Beauchamp *et al*. found oil from the olive plant showing similar ibuprofen activity due to the presence of oleocanthal [17]. Studies showed that inflammation and plaque pathology is suppressed by ibuprofen in mouse for Alzheimer disease [18]. In 1993, Hasson *et al*. were able to study the ibuprofen effect on the muscle soreness, damage, and performance where they found that prophylactic damage of ibuprofen does not prevent creatine kinase release from the muscle but decrease the soreness of muscle and help in restoring the muscle function for certain period of time [19]. Similarly, in 2002, Trappe *et al*. also studied the effect of two analgesics ibuprofen (IBU: 1,200 mg/day) and acetaminophen (ACET: 4,000 mg/day) on muscle protein and soreness. They found an active influence of ibuprofen in the muscle protein [20]. With the advancement in research, in 2004, Schnitzer *et al*. were able to study and compare lumiracoxib with ibuprofen. They found that lumiracoxib was able to decrease the ulcer complication by two to three folds than the NSAID [21]. Bernard *et al*. studied the effect of ibuprofen on the physiology and survival of patients with Sepsis where they concluded that ibuprofen helps in reducing levels of prostacyclin and thromboxane with a decrease in consumption, tachycardia, fever, oxygen, and lactic acidosis but does not prevent the development of shock or the acute respiratory

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

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

Table 2: Trade name and respective companies of Ibuprofen

Brand Name	Dosage Forms	Company
Motrin	Tablets, Suspension	Sigma-Aldrich
Brufen	Tablets	Wyeth Pharmaceuticals Inc.
Nurofen	Tablets	Reckitt Benckiser Pharmaceuticals
Advil	Tablets	Pfizer
Dolgit	Tablets	Dolorgiet, Budapharma
Lipton	Tablets	Wyeth Pharmaceuticals Inc.
Anflagen	Tablets	Adare pharmaceuticals Inc.
Apsifen	Tablets	TEVA UK Limited
Trendar	Tablets	Zibo Xinhua-Perrigo Pharmaceutical Co., Ltd.
Buburone	Tablets	BCM

Table 3: Chemical and processes for ibuprofen manufacturing

S.No.	Chemicals	Process
1.	Isobutyl benzene+acetyl chloride+triethylaluminum+potassium cyanide.	Friedel-Crafts acylation/cyanohydrin formation/hydrogenation/nitrile hydrolysis [28]
2.	isobutyl benzene+propionyl chloride+methanol.	Friedel-Crafts acylation/ketal formation/alpha bromination/ rearrangement [28]
3.	Isobutyl benzene+acetyl chloride+carbon monoxide.	Friedel-Crafts acylation/carbonyl reduction/carbonylation[28]
4	Isobutyl benzene+acetyl chloride+methyl chloroacetate.	Friedel-Crafts acylation/Darzens reaction/hydrolysis/decarboxylation/ carbonyl oxidation [28]
5	Ethyl 4-isobutyl phenyl acetate and diethyl carbonate with sodium ethoxide gas+methyl iodide and sodium ethoxide.	Methylation, saponification, Decarboxylation [29]

Table 4: Chromatographic and UV spectrophotometric methods for various experiments

S. No.	Title	Method	Mobile phase	Column	Wavelength (nm)
1	Ethambutol hydrogen chloride and ibuprofen determination in tablets [41]	Reversed-phase HPLC	Methanol-H2O (70:30)	Bonda Pak C18 column packed with octadecylsilane bonded to porous silica	254
2	Ibuprofen in acidified plasma extraction application to a C2 extraction cartridge [42]	HPLC	55% acetonitrile/45% 0.02 H phosphate buffer; pH 3.0	Nucleosil C18 column	300
3	NSAIDs in plasma [43]	HPLC	Phosphoric acid 0.03% (pH 2.5) -acetonitriles	Silica column	229-313
4	Chromatographic and electrochemical methods for biological material analyses [44]	Capillary column gas chromatography	500 mg lithium perchlorate trihydrate, 110 ml water, and methanol up to 1 l.	Hypersil APS column	219
5	Detection of ibuprofen in serum [45]	Isocratic liquid chromatography	Water-orthophosphoric acid to pH 3.2: acetonitrile: methanol (52:35:13)	Spherisorb 5µm ODS column	239
6	Screening of plasma samples for the presence of sixteen NSAIDs [46]	Isocratic HPLC	Acetonitrile - 0.3% Acetic Acid - Tetrahydrofuran (36:63.1:0.9, vol/vol)	Octadecyl Reversed-phase column	254 and 370
7	Ibuprofen determination in plasma [47]	HPLC	0.05% Isopropyl alcohol in heptane	Two silica columns	240
8	Ibuprofen determination in serum [48]	HPLC	Methanol-water-glacial acetic acid (pH 3.4) (75:24:1, v/v)	µBondapak C1 column	272
9	Ibuprofen determination in plasma [49]	HPLC	65% Methanol and 35% 0.10 *M* acetate buffer (pH 5.0)	Octadecylsilane column	253
10	Identification of anti-inflammatory drugs from blood. [50]	HPLC	Acetonitrile - acetate buffer (pH 4.2 or 4.8)	Hypersil octadecylsilane analytical column	250

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

replaced by high-performance liquid chromatography (HPLC), gas chromatography (GC) [39], and GC-MS [40], and a recent report describes the use of HPLC Table 4.

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.

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