Introduction

Ibuprofen is a drug that possesses analgesic (pain-relieving) and antipyretic (fever-reducing) properties. It is particularly known for its use in pain relief from arthritis.

Ibuprofen is also an anti-inflammatory drug and it is classed as a non-steroidal anti-inflammatory drug (NSAID).
**Principle**

Like acetylsalicylic acid (aspirin), another NSAID, and acetaminophen, ibuprofen works by inhibiting the activity of a class of enzymes called cyclooxygenase (COX), which catalyses the synthesis (conversion) of a compound called arachidonic acid into prostaglandins.

Prostaglandins are sometimes called local hormones because they act close to where they are produced rather than all over the body. They have a remarkably wide range of effects, both positive and negative, for example, Prostaglandins are protective against the development of stomach ulcers, but they can also cause inflammation (as well as the pain response).

There is more than one human COX enzymes of them—definitely two, and probably at least three. Ibuprofen and aspirin both inhibit COX-1 and COX-2, but they do it in different ways. Ibuprofen binds non-covalently to a COX enzyme and thus competes with the enzyme's natural substrate. (This is referred to as reversible inhibition.) On the other hand, aspirin forms a covalent bond to a serine residue in the enzyme, and this bond cannot be broken. (This is called irreversible inhibition.)
Figure 0: Prostaglandin synthesis
Lead compound discovery

Ibuprofen was developed and discovered as a drug by the Boots Company.

Boots’ method of making ibuprofen described in their patent starts from the compound 2-methylpropylbenzene (isobutylbenzene).

2-methylpropylbenzene can be made from compounds separated from crude oil and has a similar carbon skeleton to that of ibuprofen.

Ibuprofen was developed and discovered as a drug by the research team at the Boots Company. The leaders of the team were Dr Stewart Adams and his colleagues John Nicholson and Colin Burrows during the 1960s.

Figure 1: Structure of 2-methylpropylbenzene

Figure 2: Stewart Adams, John Nicholson and Colin Burrows, the discoverers of ibuprofen (Courtesy of the International Ibuprofen Foundation)
Timeline:

- 1961: A patent is filed for the compound 2-(4-isobutylphenyl) propanoic acid, later called ibuprofen.
- 1958: After some 600 compounds had been made and screened for activity, a promising compound code named BTS 8402 is given a clinical trial. It is found to be no better than aspirin.
- 1966: Clinical trials of ibuprofen take place at the Northern General Hospital in Edinburgh and show its anti-inflammatory effect in patients.
- 1969: Clinical trials of Ibuprofen are launched in the UK on prescription only.
- 1983: Because of its safety record, ibuprofen is made available without prescription.
- 1964: Ibuprofen is selected for further development.
- 1956: Research started. Only two pain relieving anti-inflammatory drugs, aspirin and phenylbutazone, were available. Originally, the objective of the research was to develop a drug to treat rheumatoid arthritis (inflamed joints) that had fewer side effects than aspirin and had a superior profile both in terms of potency and toxicity to these two drugs. The discovery of ibuprofen achieved both of these objectives.
- 1955: The discovery is made that anti-inflammatory drugs reduce inflammation of the skin caused by ultra-violet light. This gives a simple screening test for new chemical compounds (called new chemical entities or NCEs in the jargon) that the research chemists produced.
Molecular modification

A) The original Boots synthesis of ibuprofen

Step 1

\[
\text{Friedel-Crafts acetylation of 2-methylpropylbenzene}
\]

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \\
\text{O}
\end{array}
\]

AlCl₃

Step 2

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \\
\text{O}
\end{array}
\]

NaOCC₂H₅

Step 3

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \\
\text{O}
\end{array}
\]

H⁺

Step 4

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\]

H₂O

Step 5

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{N}
\end{array}
\]

NH₂OH
Step 5

Then convert to the nitrile

Step 6

Finally, hydrolyze to the desired acid

Ibuprofen

Figure 3: Boots’ synthesis of ibuprofen
B) The ‘green’ synthesis of ibuprofen

The Boots’ synthesis has been replaced by a new, more efficient synthesis shown in Figure 4. It starts with the same compound but has fewer steps - it has been described as the ‘green’ synthesis.

Figure 4: The ‘green’ synthesis of ibuprofen
"Ibuprofen 200mg" means the dose of ibuprofen contained in a normal strength tablet is 200 mg (0.2 g). However, it contains many other components apart from the active ingredient ibuprofen. It should be noted that 200mg is a very small amount and would be difficult to handle and pick up. As a consequence, extra ingredients are included to make it bulky in size so that it is easy to take up. For the whole tablet containing 200mg Ibuprofen, it weighs about 1000 mg.

Ibuprofen tablets consist of a core and a coat. The coat contains sugar for taste and a pigment to give the tablet an acceptable colour.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Active ingredient</td>
<td>Core</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>Disintegrant</td>
<td>Core</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>Lubricant</td>
<td>Core</td>
</tr>
<tr>
<td>Sodium laurylsulfate</td>
<td>Lubricant</td>
<td>Core</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>Buffering agent</td>
<td>Core</td>
</tr>
<tr>
<td>Colloidal anhydrous silica</td>
<td>Anticaking agent</td>
<td>Core</td>
</tr>
<tr>
<td>Carmellose sodium</td>
<td>Coating agent</td>
<td>Coat</td>
</tr>
<tr>
<td>Carnuba wax powder</td>
<td>Coating agent</td>
<td>Coat</td>
</tr>
<tr>
<td>Calcium sulfate dihydrate</td>
<td>Diluent</td>
<td>Coat</td>
</tr>
<tr>
<td>Acacia spray dried</td>
<td>Binding agent</td>
<td>Coat</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Binding agent</td>
<td>Coat</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Pigment</td>
<td>Coat</td>
</tr>
<tr>
<td>Purified water</td>
<td>Diluent</td>
<td>Coat</td>
</tr>
</tbody>
</table>
Safety Test

(I) Pre-clinical testing

Experiment is carried out with cats and rats. It showed that ibuprofen, in doses which gave an anti-inflammatory effect, had no effect on the cardiovascular system. Also, it did not affect the arterial pressure, frequency and strength of cardiac contractions.

It also found that ibuprofen did not adversely affect respiration as the frequency and depth of the respiratory movements remained the same. Examinations of the EEG of cats and rabbits revealed no departures from the normal whatsoever following administration of the drug. Ibuprofen in concentration of $10^{-9}$ g ml$^{-1}$ to $10^{-4}$ g ml$^{-1}$ did not affect the tonus of the smooth muscle of the small intestine in guinea pig intestines or rat uterus. Moreover, it had no effect on the spasmogenic effects of acetylcholine, serotonin and bradykinin.

(II) Human trials

Ibuprofen has undergone extensive clinical trials. Most investigators have found that ibuprofen to possess high therapeutic activity, and it was stressed that it is better tolerated than acetylsalicylic acid, indomethacin and other NAID, even by patients with lesions of the gastrointestinal tract.

The high therapeutic activity of ibuprofen is apparent in the treatment of ankylosing spondylitis and juvenile rheumatoid arthritis, lumbago, and nonspecific hyperpyrexia. Clinical trials on patients with rheumatism, rheumatoid arthritis, osteoarthritis deformans, and systemic scleroderma showed that in most patients receiving ibuprofen in daily doses of 800-1200mg for adults and 200-600 mg for children, there was a clear improvement in the general condition, reduction in joint pain, morning stiffness, swelling of the joints, and symptoms of carditis, and a reduction in the ESR and other laboratory indices characteristic of the rheumatic process.
**Approval for marketing**

Ibuprofen was approved by the FDA in 1974. The pill has been through trials and clinical testing thoroughly. After excessive research the drug was approved for sale in the US and other states and its treatment considered effective. The sole use of this drug is to **relieve pains of bones and muscles** and is also used as a **painkiller for inflammation**.

It is distributed as coated tablets of 200 mg. the recommended initial dose is 600-1200 mg daily. **In acute conditions** and exacerbations of the process, it is desirable to **increase the daily dose to 1600 mg**. Indications for use are rheumatism, rheumatoid arthritis, osteoarthritis, and similar conditions. The drug should be used with **great care in patients suffering from bronchial asthma**.

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