Drug Development
Ibuprofen
Introduction

- an anti-inflammatory drug
- NSAID
- possesses pain-relieving and fever-reducing properties
- particular use in pain relief from arthritis
Introduction (cont’d)

• 2D Structure of Ibuprofen

• 3D Structure of Ibuprofen
Principle

Arachidonic acid → Prostaglandin

Inhibited by NASIDs
Lead compound discovery

- developed and discovered as a drug by the Boots Company.

- 2-methylpropylbenzene
Timeline

- The discovery was made.
  - anti-inflammatory drugs
  - simple screening test for new chemical compounds

- Research was started.
  - Aspirin and phenylbutazone were available.
  - Objective:
    1. To develop a drug to treat rheumatoid arthritis (inflamed joints)
    2. To have a superior profile both in terms of potency and toxicity to these two drugs.
1958
- compound code named BTS 8402 is given a clinical trial (i.e. a trial on patients).
- no better than aspirin.

1961
- A patent is filed for the compound 2-(4-isobutylphenyl) propanoic acid
- later called ibuprofen.

1964
- further development
Timeline (cont’d)

- **1966**
  - Northern General Hospital in Edinburgh
  - *anti-inflammatory effect* in patients

- **1969**
  - Clinical trials of Ibuprofen are launched in the UK on prescription only.

- **1983**
  - *available* without prescription.
Organic synthesis

- A) The original Boots synthesis of ibuprofen

**Step 1**
Friedel-Crafts acetylation of 2-methylpropylbenzene

**Step 2**
Reaction with ethyl chloroacetate (Darzens reaction) gave the \( \alpha, \beta \)-epoxy ester
Organic synthesis (cont’d)

• A) The original Boots synthesis of ibuprofen

**Step 3**
The $\alpha, \beta$-epoxy ester was **decarboxylated and hydrolyzed** to the aldehyde.

**Step 4**
Reaction with hydroxylamine gave the oxime.
Organic synthesis (cont’d)

- A) The **original** Boots synthesis of ibuprofen

![Chemical structure of ibuprofen](image)

**Step 5**
Then convert to the nitrile
Organic synthesis (cont’d)

• A) The original Boots synthesis of ibuprofen

Step 6
Finally, hydrolyze to the desired acid (Ibuprofen)
B) The advanced ‘green’ synthesis of ibuprofen

Step 1
Friedel-Crafts acetylation of 2-methylpropylbenzene

Step 2
Hydrogenation with Raney nickel to give the alcohol

Step 3
Finally, underwent palladium-catalyzed carbonylation
• the dose of ibuprofen contained in a normal strength tablet is 200 mg (0.2 g)
<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>
(I) Pre-clinical testing

- Experiment is carried out with cats and rats.

Findings

- no effect on the cardiovascular system
- did not affect the arterial pressure, frequency and strength of cardiac contractions
(1) Pre-clinical testing

- Examinations of the EEG of cats and rabbits

Findings

- no departures from the normal whatsoever following administration of the drug
- no effect on the spasmogenic effects of acetylcholine, serotonin and bradykinin
(II) Human trials

- has undergone extensive clinical trials

Findings:

- possess high therapeutic activity
- improvement in the general condition
- reduction in joint pain, morning stiffness, swelling of the joints, etc.
Approval for marketing

• approved by the FDA in 1974
• approved for sale in the US and other states and its treatment considered effective
Approval for marketing (cont’d)

• relieve pains of bones and muscles
• as a painkiller for inflammation
• recommended dose is 600-1200 mg daily

In acute conditions
• increase the daily dose to 1600 mg

**great care in patients suffering from bronchial asthma**