Ibuprofen

USP, Ph. Eur., JP
1. Medical indication

Ibuprofen is a chiral propionic acid derivative belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs).

Due to its analgesic, antipyretic and anti-inflammatory actions, it is used in the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, mild and moderate pain, dysmenorrhoea, vascular headache and fever.

The application of Ibuprofen as a pain reliever or an antipyretic needs only low dosages (200 – 400 mg). The dose level as an anti-rheumatic for adults is about 1.2 to 3.2 g orally per day in 3 or 4 separate doses.

The common active ingredient dosage in tablets is 200, 400, 600 and 800 mg. In addition, there are slow release tablets with 800 mg. The OTC dosage forms are mainly the 200 and 400 mg forms (except for the United States and some other countries, where the 200 mg form is the only OTC form).

Ibuprofen is often combined with oral decongestants and cough and cold drugs.

Other common dosage forms are capsules, syrups, suspensions, suppositories, and topical dosage forms like creams and gels.

Pharmacology

The mode of action is believed to involve the reversible inhibition of the enzyme cyclooxygenase (COX) which is responsible for the biosynthesis of prostaglandins (PGs) from arachidonic acid in the cellular membrane.

Prostaglandins are distributed in the various tissues and have, among other properties, a powerful effect on the smooth muscles.

In case of an inflammatory stimulus or blood flow disturbances, PGs are synthesized in increased amounts and sensitize the tissues to the action of other agents such as histamine and kinins. As a result, symptoms such as pain and inflammation appear.

Fever occurs by the influence of the PGs on the heat regulation centre in the hypothalamus. There they raise the normal body temperature of 37 °C.

The inhibitory action of NSAIDs on PG synthesis is also the most probable cause of gastrointestinal side effects.

PGs play an important role for physiological functions, like the synthesis of protective alkaline secretion in gastric mucosa cells. The inhibition of the PG synthesis can lead to a reduced protection of the gastric mucosa and may cause sickness, abdominal pain and ulcers.

Among the NSAIDs, Ibuprofen has the best benefit to risk profile and the lowest incidence of serious gastrointestinal adverse effects.

Pharmacokinetics

Ibuprofen is readily absorbed by the gastrointestinal tract. The peak plasma levels are reached within 1 – 2 h. After an oral dose of 200 – 400 mg, 15 – 25 mg/ml appear in the blood serum.

Ibuprofen has an extensive protein binding capacity (99%), and is excreted via the kidneys. The biological half-life is about 2 hours.

After 24 h, 100% of the active substance is excreted in the urine.
2. Chemical information

**Chemical name**  
(2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid

**CAS-No.**  
15687-27-1

**EINECS-No.**  
239-784-6

**Synonymous names**  
(±)-2-[4-(2-methylpropyl)phenyl]propanoic acid  
(±)-Benzeneacetic acid, α-methyl-4-(2-methylpropyl)  
(±)-p-Isobutylhydratropic acid  
(±)-2-p-Isobutylphenylpropionic acid

Ibuprofen is the racemate of (+)-Ibuprofen and (-)-Ibuprofen (optical rotation $[\alpha]_D = 0$)

According to the literature, the pharmacologically active form is (+)-Ibuprofen.

Ibuprofen: a critical bibliographic review, K. D. Rainsford, Taylor & Francis Ltd., London 1999, page 104. Approximately 30 to 70% of the (-)-Ibuprofen is converted to the active form (+)-Ibuprofen in the body.

This process proceeds solely from the (-)- form to the (+)- form.

**Structural formula**

![Structural formula of Ibuprofen](image)

**Empirical formula**  
$C_{13}H_{18}O_2$

**Molecular weight**  
206.28 g/mol
3. Grades
BASF offers 5 pure grades based on different particle size distributions (see particle characterization). Furthermore, a direct compressible grade is offered: Ibuprofen DC 85.

<table>
<thead>
<tr>
<th>PRD-No.</th>
<th>Description</th>
<th>Quantity</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>30076127</td>
<td>Ibuprofen 25 US Quality</td>
<td>50 kg</td>
<td>500 g (sample)</td>
</tr>
<tr>
<td>30076128</td>
<td>Ibuprofen 38 US Quality</td>
<td>50 kg</td>
<td>500 g (sample)</td>
</tr>
<tr>
<td>30076166</td>
<td>Ibuprofen 50 US Quality</td>
<td>50 kg</td>
<td>500 g (sample)</td>
</tr>
<tr>
<td>30487271</td>
<td>Ibuprofen 70 Grade</td>
<td>50 kg</td>
<td>500 g (sample)</td>
</tr>
<tr>
<td>30487274</td>
<td>Ibuprofen 90 Grade</td>
<td>50 kg</td>
<td>500 g (sample)</td>
</tr>
<tr>
<td>30255646</td>
<td>Ibuprofen DC 85</td>
<td>50 kg</td>
<td>2 kg (sample)</td>
</tr>
</tbody>
</table>

Retest period
See separate documentation: "Q&R PI (not for regulatory purposes)" available via BASF's WorldAccount: https://worldaccount.basf.com (registered access).

4. Physical and chemical properties
- Appearance: crystalline powder
- Color: white
- Odor: characteristic
- Melting range: 75 – 78 °C
- Solubility in phosphate buffer pH 7.2 (37 °C): 5.2 mg/ml
- Partition coefficient n-octanol/water: 3.3

The chemical parameters of all pure Ibuprofen grades are identical. The only difference is the particle size distribution (see particle characteristics).

5. Regulatory status
- Ibuprofen grades 25, 38, 50, 70, 90:
  Ibuprofen meets the current USP, Ph. Eur. and JP monographs.
  DMFs and CEPs are available upon request.

- Ibuprofen DC 80:
  The Ibuprofen used to manufacture Ibuprofen DC 85 meets the current USP, Ph. Eur. and JP monographs.
  A Technical Package and a US-DMF are available upon request.

6. Specifications
7. Particle characterization

7.1 Ibuprofen 25

Particle size distribution

An example of particle size distribution is given in the diagram above. The real distribution range is approximately from 5 µm to 150 µm. The mean particle size is about 25 µm.

**Bulk density**

Approximately 0.3 g/ml.

**Tapped density**

Approximately 0.48 g/ml.

**SEM photographs**
7.2 Ibuprofen 38

Particle size distribution

An example of particle size distribution is given in the diagram above. The real distribution range is approximately from 2 µm to 150 µm. The mean particle size is about 38 µm.

Bulk density

Approximately 0.33 g/ml.

Tapped density

Approximately 0.6 g/ml.

SEM photographs
7.3 Ibuprofen 50

Particle size distribution

An example of particle size distribution is given in the diagram above. The real distribution range is approximately from 2 µm to 250 µm. The mean particle size is about 50 µm.

**Bulk density**

Approximately 0.34 g/ml.

**Tapped density**

Approximately 0.6 g/ml.

**SEM photographs**
7.4 Ibuprofen 70

**Particle size distribution**

![Graph showing particle size distribution](image)

**Bulk density**

Approximately 0.38 g/ml.

**Tapped density**

Approximately 0.68 g/ml.

**SEM photographs**

![SEM photograph 1](image)

![SEM photograph 2](image)
**7.5 Ibuprofen 90**

**Particle size distribution**

![Graph showing particle size distribution](image)

**Bulk density**

Approximately 0.48 g/ml.

**Tapped density**

Approximately 0.65 g/ml.

**SEM photographs**

![SEM photograph of Ibuprofen 90 particles](image)
8. General information on the processing of Ibuprofen

Ibuprofen is used mainly in three different dosage forms:

- Oral film-coated tablets showing rapid decomposition and fast release of the active substance. The common strengths are 200, 400, 600 and 800 mg. There are also slow release formulations containing 800 mg of Ibuprofen.
- Oral suspensions which are used mainly for patients who have difficulties in swallowing tablets and for paediatric patients. The doses vary greatly.
- Creams and gels for topical application, generally used for treating rheumatic disorders or sports injuries.

More recent trends in formulation:

- Ibuprofen soft gelatin capsules are available in the market; these are distinguished in particular by the rapid absorption of the active substance and thus a fast drug onset.
- So-called melt extrusion formulations, in which the active substance is molecularly dispersed as a so-called solid solution in the polymer, have been widely tested. These, too, exhibit rapid bioavailability.

8.1 The processing of Ibuprofen to tablets

Ibuprofen is extremely bitter and causes severe tickling in the throat that often gives the impression of being strangled. For this reason, all tablets are coated with a film that prevents the unpleasant taste when being swallowed. Generally, any film or sugar coating is suitable. However, the new BASF excipient Kollicoat® IR offers two advantages over conventionally used polymers:

- Very high concentrations (for example two to three times higher than for HPMC) of the polymer in aqueous solutions are possible. The amount of film coating required is applied to the tablets within a shorter period. The time needed to apply the film coating can be reduced by up to 50%, which translates into clear cost savings.
- Kollicoat IR provides a very flexible coating that can stretch without the film coating splitting. If the formulation causes considerable swelling of the tablet, the flexibility provided by Kollicoat IR would prevent the coating from splitting.

Examples of coating formulations will be given in 9.2.

Ibuprofen has a very low melting range of approximately 75 – 78 °C. Therefore, the tableting tools may become sticky in the production process as a result of the low melting point. This tendency can practically be removed by using Ibuprofen of not more than 70% of the total formulation. An alternative product for direct compression is Ibuprofen DC 85 (BASF), a direct compressible grade with 85% Ibuprofen.

Ibuprofen DC 85 does not show any sticking tendency during compression and is able to be compressed into tablets without any lubricant.

Independent of its origin, Ibuprofen shows incompatibilities with certain excipients used in the production of tablets. The use of PVP and PVP-containing materials must be avoided under all circumstances. At room temperature, Ibuprofen forms with PVP liquid phases (for example in a ratio of 1:1) that no longer exhibit any crystallinity. If PVP is used as a binder in wet granulation or as a dry binder, the tablets show a dramatic reduction in the release of the active substance after 3 months. For example, it has been shown that shortly after it has been produced, an Ibuprofen tablet releases the active substance (according to the USP method) quantitatively within 15 to 20 minutes. After being stored for three months, it releases only 75% after 60 minutes. The physical incompatibility with cross-linked PVP is not so strong, but every customer has to evaluate whether to use crosslinked PVP or not.

Instead of PVP, HPMC 3 cp or HPMC 6 cp can be recommended as a binder, and the cellulose product AcDiSol as a disintegrant.

However, it should be pointed out that Kollicoat IR should be used preferably as the granulating agent or dry binder. Studies at BASF have demonstrated the technological equivalence between HPMC and Kollicoat when used as binders or granulating agents.
There is a further incompatibility between stearic acid or magnesium stearate and ibuprofen. It has been shown by DSC that both the magnesium stearate (used mainly as a lubricant) and the stearic acid considerably lower the melting point of ibuprofen. This may lead to smearing in tableting at high concentrations of the magnesium stearate used. Particularly at high concentrations of ibuprofen, this factor has a negative impact on the tablet formula. If problems are encountered, customers could follow the recommendation below:

- **Switch to Lutrol® F127 and – F 68 micronized (BASF) or other lubricants**
- **Spray the tableting chamber with magnesium stearate during tablet production. Only a few micrograms of this excipient on the surface of the tableting chamber come into contact with the tablet.**

### 8.2 Ibuprofen grades for tableting

The particle sizes of the three grades of BASF’s ibuprofen, namely grades 25, 38 and 50, differ only slightly on account of their history. The figures denote the mean of a distribution curve that is determined by laser diffractometry.

For tablet production, no matter whether it is carried out via the intermediate stage of moist granulation or compacting or by direct tableting, it is advisable not to recommend the ibuprofen 25 grade. However, the ibuprofen 38 and 50 grades can be recommended more or less equally.

### 8.3 The Processing of Ibuprofen in suspensions

Since suspensions have to be stabilized against sedimentation, fine particles should be used as a rule. This is why it is advisable to recommend the ibuprofen 25 grade. In the case of many formulations, it is also necessary to use micronized ibuprofen. BASF has successfully tested the micronization of ibuprofen with air jet mills by several toll manufacturers (maximum particle size 7 – 8 µm).

As a rule, care should be taken when suspensions are being produced that the pH of the suspension is clearly in the acid range. Then ibuprofen is present in a completely undissolved state and can have the least influence on taste and on the mucous membranes of the mouth and pharynx.

### 8.4 The processing of Ibuprofen in creams and ointments

Ibuprofen is dissolved in the oleaginous phase in the case of creams. Introduction into the aqueous phase is not possible on account of the extremely poor solubility in water. Propylene glycol or low molecular weight polyethylene glycols can be recommended as the oily component.

Since ibuprofen is dissolved in the oleaginous phase, there is no particular preference for an ibuprofen grade.

Ointment formulations are currently not known on the market. However, if one is formulated by a customer, no suspension ointments can be recommended, since ibuprofen causes mechanical itching to the skin. In this case, too, ibuprofen should be dissolved for example in propylene glycol and processed further into an ointment with other fatlike carriers.
9. Formulating examples

9.1 Production of the granules for the 200, 400, 600 and 800 mg forms

The following ingredients are placed in a Diosna mixer (an analogous mixer can also be used) and granulated with water:

- Ibuprofen 50 kg
- Lactose 30 kg
- Corn starch 15 kg
- Kollicoat IR* 6 kg

(* HPMC 6 cp can also be used by analogy)

Amount of water: approximately 20 kg (not contained in the tablet).

Wet sieving (4 mm) and drying in a fluid bed granulator at 60 °C (inlet air) for approximately 30 minutes and sieved dry (1 mm).

The batch is mixed with the following additives to form granules suitable for tableting.

Additives

- Avicel PH 102 6 kg
- AcDiSol 8 kg
- Magnesium stearate 1 kg
- Aerosil 200 0.5 kg

Total 166.5 kg

Table composition

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>200 mg</th>
<th>400 mg</th>
<th>600 mg</th>
<th>800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen*</td>
<td>200 mg</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>60 mg</td>
<td>120 mg</td>
<td>180 mg</td>
<td>240 mg</td>
</tr>
<tr>
<td>Corn starch</td>
<td>30 mg</td>
<td>60 mg</td>
<td>90 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Pharmacoat 606</td>
<td>12 mg</td>
<td>24 mg</td>
<td>36 mg</td>
<td>48 mg</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1 mg</td>
<td>2 mg</td>
<td>3 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>12 mg</td>
<td>24 mg</td>
<td>36 mg</td>
<td>48 mg</td>
</tr>
<tr>
<td>AcDiSol</td>
<td>16 mg</td>
<td>32 mg</td>
<td>48 mg</td>
<td>64 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2 mg</td>
<td>4 mg</td>
<td>6 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Weight/tablet</td>
<td>333 mg</td>
<td>666 mg</td>
<td>999 mg</td>
<td>1332 mg</td>
</tr>
</tbody>
</table>

* In the case of granulation, the three Ibuprofen grades 25, 38 and 50 can be used alternatively without any differences in the quality of the tablets.

Tablets of 600 and 800 mg Ibuprofen are very large and are therefore difficult to swallow. The excipients can be reduced further, but not lower than 30 – 35% of the total tablet weight. In this case, the negative effect of the magnesium stearate can be observed in that the tablets clearly stick to the tools when being pressed.

Variations between the lactose and corn starch fractions are also possible with the above formulations.
9.2 Coating formulations for Ibuprofen tablets

Kollicoat IR – red

<table>
<thead>
<tr>
<th>Composition</th>
<th>Fraction with reference to the atomised suspension [%]</th>
<th>Fraction with reference to the dry film [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollicoat IR</td>
<td>16.0</td>
<td>64</td>
</tr>
<tr>
<td>Pigments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaolin</td>
<td>6.0</td>
<td>24</td>
</tr>
<tr>
<td>Sicovit® Red 30</td>
<td>3.0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>25.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Production of the spray suspension

Kollicoat IR, kaolin and Sicovit red are weighed and stirred into the water with a paddle agitator.

Care must be taken to prevent too much air from being introduced into the suspension. After the polymer fraction has dissolved, the agitator is switched off. After ten minutes the majority of the air bubbles have disappeared from the spray suspension. Then the suspension is homogenized with a high-shearing mixer, in this case an Ultra-Turrax. The Ultra-Turrax must be placed deep in the vessel in order to prevent air from being introduced.

The coating suspension can now be sprayed, although the contents of the vessel have to be stirred gently in order to prevent sedimentation.

Spraying conditions

Batch with 5 kg of tablet cores in the Accela Cota 24"

<table>
<thead>
<tr>
<th>Type of nozzle</th>
<th>Schlick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nozzles</td>
<td>1</td>
</tr>
<tr>
<td>Diameter of nozzles</td>
<td>1 mm</td>
</tr>
<tr>
<td>Spraying (atomizing) pressure</td>
<td>1.5 – 2 bar</td>
</tr>
<tr>
<td>Pattern air</td>
<td>1 bar</td>
</tr>
<tr>
<td>Temperature of inlet air</td>
<td>60 °C</td>
</tr>
<tr>
<td>Temperature of outlet air</td>
<td>38 – 41 °C</td>
</tr>
<tr>
<td>Volume of air</td>
<td>360 m³/h</td>
</tr>
<tr>
<td>Spraying rate of spray suspension</td>
<td>20 – 23 g/min.</td>
</tr>
<tr>
<td>Drum revolutions</td>
<td>15 rpm</td>
</tr>
<tr>
<td>Amount of coating</td>
<td>3 mg/cm² (polymer)</td>
</tr>
</tbody>
</table>

Gloss coating

If a higher gloss is required, a top coating with a 5% solution of PEG 6000 and water is recommended.

Rate of spraying: 15 – 18 g/min.

Drum revolutions: 21 rpm

Amount of coating: 0.3 mg/cm²
9.3 Recommendation for direct compression

Today the manufacturing of Ibuprofen tablets is often done by direct compression. By this way the expensive and time consuming wet granulation method can be avoided. But in general, Ibuprofen has the disadvantage of sticking on the tablet tools, so that the process must be often interrupted.

Therefore, direct compression formulations with a high content of Ibuprofen per tablet are often avoided. Mostly tablets with an Ibuprofen content of maximum 60% are compressed.

BASF offers a formulated Ibuprofen product ideal for direct compression: Ibuprofen DC 85. For direct compression of Ibuprofen (especially tablets with higher concentrations) please see TI “Ibuprofen DC 85”.

Formulation with Ibuprofen 90

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>75</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>20</td>
</tr>
<tr>
<td>Ac-Di-Sol</td>
<td>3</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
</tbody>
</table>

Tablets of 200, 400, 600 and 800 mg have been successfully tested by compressing under production conditions over several hours at an external toll manufacturer.

The resulting hardness of tablets is between 80 and 120 N. Please use high compression forces over 14 – 16 kN.

The disintegration time of the tablets is about 2 – 3 minutes. After 10 minutes more than 80% of the labelled drug is dissolved under USP conditions.

Note

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