Systemic Review of Screening the Shapes of Ibuprofen Particles in Different Solvents

Md. Abdur Rashid¹*

¹Department of Pharmaceutics, College of Pharmacy, King Khalid University, Abha, Aseer - 62529, Saudi Arabia.

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i29A31567

Editor(s):
(1) Dr. Aurora Martínez Romero, Juarez University, Mexico.

Reviewers:
(1) Mohammed Gamal, Jouf University, Saudi Arabia.
(2) Tariq Namad, USA.

Complete Peer review History: http://www.sdiarticle4.com/review-history/68076

Received 10 March 2021
Accepted 14 May 2021
Published 17 May 2021

ABSTRACT

Ibuprofen is a very popular analgesic which is mostly available in the market as tablet dosage form. The ibuprofen molecule possesses a chiral center in the propionic acid group. So, there are two enantiomers (R and S), whose chemical properties are similar, but which have optical rotations of opposite sign. The (-) form (l- or laevo-) is the R (-) enantiomer whereas the (+) form (d or dextro-) is referred to as S (+) – ibuprofen. The R (-) isomer is biologically inactive while the S (+) isomer is active. The R (-) form however is slowly converted to the S (+) active form during metabolism in the human body by the presence of the enzyme isomerase (2-arylpropionyl-CoA epimerase). Thus, a large difference in the body potency between the two enantiomers is not found.

During manufacturing of tablet, ibuprofen particle plays a significant role in flowability and compressibility etc. Theoretically particle size and shape have great impact on those sorts of mechanical properties of tablets. The morphology can influence physical properties such as packing density, bulk density, agglomeration, and dissolution behaviour as well as the mechanical strength and wet ability. Furthermore, crystal shapes have also been found to have an effect on the bioavailability of the resulting APIs. Commercial ibuprofen typically has a needle shaped morphology with rough surfaces and show poor flowability, poor compaction behavior and a tendency to stick to the tablet punches. To overcome these problems, a suitable size and shape of ibuprofen crystal is desirable that could be directly compressed with fewer operation steps but still having good product stability and therapeutic efficacy, but it can be changed through

*Corresponding author: E-mail: mdrashid@kku.edu.sa;
recrystallization or other methods such as spray drying, etc. Ibuprofen crystallized from solvents with a high hydrogen bonding ability like methanol will form chunky crystals and low hydrogen bonding solvents like hexane will form needle like crystals. Therefore, it was necessary to review the shapes of ibuprofen particles in different solvents. This review paper has covered a comprehensive studies of ibuprofen particle shapes in different solvents and cosolvents.

**Keywords:** Ibuprofen; recrystallization; solvents; tablets; manufacturing.

### 1. INTRODUCTION

This article reviews the relevant background knowledge of ibuprofen, in particular its crystallization behavior in different industrially used solvents and the mixture of solvents. The prior literature on the properties of ibuprofen, and its crystal growth will be reviewed in this paper. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with chemical name α-methyl-4-(2-methylpropyl) benzenacetic acid. It has the empirical formula C_{13}H_{18}O_2 and a molecular weight of 206.27 g/mol [1]. The word ‘ibuprofen’ is derived from ‘ibu’ (from i-Bu for isobutyl), ‘pro’ (for propyl, the three-carbon unit in the structure and ‘fen’ (for the phenyl ring) [2].

The isomeric form of ibuprofen is shown in Figs. 1 and 2. The ibuprofen molecule possesses a chiral center in the propionic acid group. So, there are two enantiomers (R and S), whose chemical properties are similar, but which have optical rotations of opposite sign. The (-) form (l- or laevo-) is the R (-) enantiomer (Fig. 3). The (+) form (d or dextro-) is referred to as S (+) - ibuprofen (Fig. 4). When equal amounts of the enantiomeric molecules are present together, the material is known as racemic.

![Fig. 1. R (-) isomer [2]](image1)

![Fig. 2. S (+) isomer [2]](image2)

The R (-) isomer is biologically inactive while the S (+) isomer is active. The R (-) form however is slowly converted (Fig. 3) to the S (+) active form during metabolism in the human body by the presence of the enzyme isomerase (2-arylpropionyl-CoA epimerase). Thus, a large difference in the body potency between the two enantiomers is not found [2-6].

The conventional industrial synthesis process for ibuprofen was first developed and patented in the 1960s by the Boots Company of England (7]) and this served as the main method of synthesis for many years.

The Boots’ synthesis of ibuprofen is a five-step process (Fig. 4) and results in large quantities of waste chemical by-products that must be disposed of or otherwise managed.

Later, the Hoechst (now Celanese) corporation developed and implemented a new greener industrial synthesis of ibuprofen that has only three steps (Fig. 4) [7,8].
Fig. 4. Ibuprofen synthesis processes by Boots and Hoechst processes [7,8] [44]

In this process, only small amounts of unwanted byproducts are produced. Compared to the Boots' process, the Hoechst process is more eco-friendly and cheaper. Both synthesis processes are shown in Figs. 3-4. Both start with isobutyl phenyl ethanol.

Ibuprofen, which is commercially available as colorless, needle like (acicular) shaped crystals has a melting point in the rage of 75 - 77ºC. It is insoluble in water but soluble in most organic solvents [9,1]. Different references suggest different melting points [10-14] with the average lying in the above range. The density of racemic ibuprofen is 1.110 g/ml [15].

1.1 Crystal Structure of Ibuprofen

Common racemic ibuprofen contains an equal number of molecules of each enantiomer. But it is known the S (+) enantiomer (and possibly the other) has a different size of unit cell (cell dimensions a, b, c) and different space group from the racemic form. The RS (±) racemic and S (+) form of ibuprofen belong to the monoclinic system. Their crystal structural data are reported in Table 1.

Table 1. Crystal structure of racemic and S(+) form of ibuprofen [13,15,43]

| Parameter                | RS (±) ibuprofen | S (+) ibuprofen | R (-) ibuprofen |
|--------------------------|------------------|-----------------|-----------------|
| Formula                  | C₁₃H₁₈O₂         | C₁₃H₁₈O₂        | C₁₃H₁₈O₂        |
| Molecular weight         | 206.3            | 206.3           | 206.3           |
| Crystal system           | Monoclinic       | Monoclinic      | Monoclinic      |
| Space group              | P₂₁             | P₂₁/c           | Not available   |
| a [Å]                    | 12.67            | 12.46           |                 |
| b [Å]                    | 7.88             | 8.03            |                 |
| c [Å]                    | 10.73            | 13.53           |                 |
| α (°)                    | -                | -               |                 |
| β (°)                    | 99.3             | 112.95          |                 |
| No. of molecule in the cell | 4              | 4               |                 |
| Density [g/cm³]          | 1.110            | 1.098           |                 |
1.2 Polymorphism

The investigation of drug polymorphism is an important step in the development of pharmaceutical ingredients. It has considerable influence on the solid-state properties that may modify biopharmaceutical and technological behaviour of the drug [16-18]. Many drugs only receive regulatory approval for a single crystal form or polymorph. For a long time, only one crystal form for ibuprofen was known. It has been reported recently that ibuprofen has a further crystal form [19] but they did not report on the crystal structure. Arlin et al. [20] have identified the structure of form II ibuprofen and contrasted it with that of form I. In this thesis Type I racemic ibuprofen will be used for batch controlled crystallization without further investigation of polymorphism.

1.3 Crystal Habit and Morphology of Ibuprofen

In pharmaceutical crystallization, control of crystal habit and morphology is very important because this can affect the ease of separation, the washing, drying, packaging, transporting and storage of the crystals. The morphology can influence physical properties such as packing density, bulk density, agglomeration and dissolution behaviour as well as the mechanical strength and wettability [21,22,13]. However, crystal habit can be modified by crystallization. Crystal habit depends on the degree of super saturation reached when crystallization takes place. Super saturation is mainly controlled by the initial solution concentration and the imposed physical conditions such as temperature, pH, impurities and relative humidity as well as crystal properties such as surface area and roughness [23]. The morphology of crystals also affects the ease by which crystals can be compressed into tablets and thus the quality and efficacy of solid dosage form. Crystals of different shapes have different bio-availabilities (rate and amount of drug reaching the system circulation – this is often measured by the dissolution rates of the tablets). Ibuprofen is poorly soluble in aqueous media and therefore the rate of dissolution from the currently available solid dosage forms is limited. This starts to poor bioavailability at high doses after oral administration, thereby increasing the risk of unwanted adverse effects [24]. Furthermore, crystal shapes have also been found to have an effect on the bioavailability of the resulting drug substances [25,26]. The choice of solvent can be the key in the manufacturing of solution grown crystals due to the critical effect it can exert on their morphologically dominant crystal faces of ibuprofen [27]. For these reasons shape must be well controlled for both medicinal and regulatory purposes [28].

Size and shape are the two primary factors in the process efficiency and product quality of pharmaceuticals [29]. Size and shape also appear to have an important role in ibuprofen’s tendency to stick to the faces of the tablet punches and dies during compression and its tendency to laminate during decompression [30] due to its low cohesivity and adhesivity and its low melting point.

The commercially available ibuprofen crystals exhibit needle-like habit with rough surfaces [31-33]. Figs. 5, 6 and 7 show images by different authors of some commercially available ibuprofen crystals.
Therefore, morphological considerations are important during selection of conditions for ibuprofen crystallization. Techniques for producing different habits include rapid cooling, crystallization by different means (e.g., sublimation) or change of crystallization solvent. Large chunky crystals with aspect ratios (ratio between the major dimensions of the crystal) near 1 are often favoured for reasons of efficient downstream processing. The Upjohn Company has patented an improvement to their ibuprofen process; where a range of organic solvents along with water have been used and they have obtained shapes having aspect ratios close to 2 using organic solvents in re-crystallization processes [30].

Due to the expanding world pharmaceutical market and increased competition, the production of pharmaceuticals has been improved considerably, including overcoming bad mechanical properties such as poor compressibility and compactibility during tableting. Many tablets show capping problem [33]. The process efficiency and product quality could be improved by the choice of crystal size and shape, i.e. modifying the crystallization process. Different crystallization processing conditions and solvents may change the crystal size and habit. Crystal habit influences particle orientation, modifying the flowability, packing, compaction and dissolution rate of the drug [22]. The choice of solvent has been shown to be useful in improving particle characteristics such as crystal habit and size distribution [34].

Ibuprofen exhibits quite different morphologies when grown from different solvents. Images of the crystals will now be presented in more detail.

Table 2 summarizes the effect of different solvents on crystal shape from published papers. Shapes have been described as “needle”, “plate”, “chunky” and “agg.” for agglomerated. These words are subject to personal interpretation. Unless the crystals are suspended, it is hard to judge whether they are “plates” or “chunky” as the crystals usually are presented with the large flat face uppermost.

Table 2. Effect of solvent and additives on ibuprofen crystal shape

| Solvent         | Predicted shape* | Observed shape | References |
|-----------------|------------------|----------------|------------|
| Methanol        | chunky           | chunky         | [30]       |
|                 |                  | plate          | [35]       |
|                 |                  | agg. plate     | [36]       |
|                 |                  | flat plate     | [37]       |
| + 10% water     |                  | chunky         | [30]       |
| Ethanol         | chunky           | chunky         | [13]       |
|                 |                  | plate          | [36]       |
|                 |                  | plate          | [38]       |
| + 5% PEG 8000   |                  | plate          | [33]       |
| + 5% PEG 6000   |                  | plate          | [33]       |
| + 5% PVA22000   |                  | agg. plate     | [33]       |
| Ethyl acetate   | plate            | thin plate     | [13]       |
| Hexane          | needle           | needle         | [37]       |
|                 |                  | needle         | [35]       |
|                 |                  | needle         | [36]       |
| Isopropyl alcohol |              | elongated     | [36]       |
|                 |                  | plate          | [31]       |
| Solvent                        | Predicted shape* | Observed shape | References |
|-------------------------------|------------------|----------------|------------|
| + Polysorbate                 | agg. plate       |                | [39]       |
| + Sucrose monolaurate         |                  | elongated thin plate | [39]       |
| + Hydroxypropyl cellulose     |                  | elongated thin plate | [39]       |
| + Sucrose monolaurate and dextran 200 |                  | hedgehog       | [39]       |
| + Sucrose monolaurate and Hydroxypropyl cellulose |                  | hedgehog       | [39]       |
| Aq. NaOH                      | agg. needle      |                | [35]       |
| Acetonitrile                  | plate            | sph. agg.      | [35]       |
| Dichloromethane               | chunky           |                | [35]       |
| Diethyl ether                 | needle           |                | [35]       |
| Propan-2-ol                   | agg. plate       | [31,35,39]     |            |
|                              | agg. plate       | [36]           |            |
|                              | chunky           | [38]           |            |
|                              | plate            | [38]           |            |
| Acetone                       | plate            | [38]           |            |
| Ethylene glycol               | plate            | [38]           |            |
| Propylene glycol              | plate            | [38]           |            |
| Benzene                       | plate            | [38]           |            |

* [40].

From methanol

The first regular chunky crystal shapes for ibuprofen (Fig. 8, a-b) were achieved by changing the solvent from a linear alkane to aqueous methanol mixtures [30]. Later on plate shaped crystals were also observed (Fig. 9, Fig. 10 (a-b), Fig. 11) when methanol was used as a solvent during recrystallization [37,35].

In addition, aggregated plate like crystals were obtained by a cooling process from methanol [36]. During the cooling process fine ibuprofen powder was added as nuclei (Fig. 12).

![Fig. 8. (a-b) Crystals from methanol (100%) and 10% water + 90% methanol respectively](image)
Fig. 9. Flat plates from methanol [37]

Fig. 10. (a) Ibuprofen crystals (plate shaped) from methanol [35], (b) Morphology (aggregated plate shaped) of ibuprofen crystallized from methanol [36]

Fig. 11. Ibuprofen crystals obtained by solvent evaporation method. Plate shaped crystals from methanol [35]
Furthermore, plate shaped crystals were also observed from methanol (Fig. 11) when ibuprofen was crystallized by the solvent evaporation method [35].

**From ethanol**

A chunky shape of ibuprofen was observed when ibuprofen was grown from ethanol (Fig. 12, a) [13]. Plate like crystals were obtained (Fig. 12, b) by a cooling process from ethanol with the addition of fine ibuprofen powder as nuclei [36]. It has also been reported by Rashid et al. [41].

In addition, the presence of additives also has a marked effect on the crystal habit of ibuprofen when dissolved in ethanol and crystallized out with water [33]. Fig. 13, a and 13,b show ibuprofen recrystallized in the presence of 5% polyethylene glycol (PEG) 8000, 6000 in ethanol resulting in plate-like crystals and agglomerated crystals [33]. Fig. 13,c shows irregular shape ibuprofen crystals with 5% PVA22000 in ethanol.

![Fig. 12. (a) Ibuprofen crystal (chunky shaped) grown from ethanol [13] and (b) plate shaped crystallized from ethanol [36]](image)

![Fig. 13. (a) Ibuprofen grown in presence of 5% PEG 8000 in ethanol, (b) Ibuprofen grown in presence of 5% PEG 6000 in ethanol and (c) Ibuprofen grown in presence of 5% PVA22000 in ethanol [33]](image)
From ethyl acetate

A thin platelet elongated along one axis was achieved (Fig. 14) when crystal grown from non-polar ethyl acetate [13].

From hexane

Needle like crystals were achieved (Fig. 15, Fig. 16 and Fig. 17) when hexane was used as solvent during recrystallization of ibuprofen [35-37]. This is believed to be the solvent mainly used industrially.

From isopropyl alcohol

Elongated crystals were obtained by a cooling process from isopropyl alcohol [36]. During the cooling process fine ibuprofen powder was added as nuclei and elongated crystals were achieved (Fig. 16).

Fig. 14. Plate like crystal from ethyl acetate [13]

Fig. 15. (a) Morphology of ibuprofen crystals (needle like)[35], (b) Morphology of ibuprofen crystals (needle like) [36], (c) morphology of ibuprofen crystals (needle-like) [37]
Rasenack and Müller [39] reported that for the preparation of ibuprofen crystals using a solvent change technique the crystals were plate-shaped. However, with ibuprofen that was crystallized in the presence of additives in isopropyl alcohol different morphologies were seen. Differences observed in crystal morphologies are visible in Fig. 17 (a-e).

Fig. 16. (a) Morphology of ibuprofen crystallized from isopropyl alcohol [36]. (b) Plate shaped crystals obtained from isopropyl alcohol as the solvent [31]

Fig. 17. (a) Different morphologies of ibuprofen crystals. Agglomerated crystals from isopropyl alcohol in the presence of Polysorbate 80, (b) Different morphologies of ibuprofen crystals. Elongated thin plate like with triangular top crystals from isopropyl alcohol in the presence of sucrose monolaurate (c) Different morphologies of ibuprofen crystals. Elongated thin plate with triangular top crystals from isopropyl alcohol in the presence of hydroxypropyl cellulose, (d) Different morphologies of ibuprofen crystals. Hedgehog like crystals from isopropyl alcohol in the presence of sucrose monolaurate and dextran 200 (e) Different morphologies of ibuprofen crystals. Hedgehog like crystals from isopropyl alcohol in the presence of sucrose monolaurate and hydroxypropyl cellulose [39]
From other solvents

Needle-shaped crystals (Fig. 18) were obtained from aqueous NaOH and spherical agglomerates (Fig. 19) from acetonitrile [35]. Furthermore, chunky crystal was observed (Fig. 19, a) from dichloromethane [35] during recrystallization of ibuprofen. Needle shaped crystals resulted from diethyl ether (Fig. 19, b) when ibuprofen was crystallized by the solvent evaporation method [35].

Predicted shapes

Predicted equilibrium shapes of ibuprofen (Fig. 20) were determined using the computer package SHAPE for a wide range of solvents such as hexane, acetonitrile, acetone, ethyl acetate, toluene, methanol, ethanol and propan-2-ol [40]. The predicted progression form a flat plate needle shape to a chunky crystal is well illustrated.

Fig. 18. (a) Needle like crystal prepared from aqueous NaOH, (b) Spherical agglomerate crystal from acetonitrile [35]

Fig. 19. (a) Chunky crystals prepared from dichloromethane, (b) Ibuprofen crystals obtained by solvent evaporation method. Needle like crystals from diethyl ether [35]
Growth kinetics

It has been reported [40] based on the solute-solvent interaction considerations that the growth rates of the various ibuprofen crystal faces grown in ethanol should be all of the same order of magnitude and thus, the ibuprofen crystal should be reasonably isometric as in Fig. 21 and Fig. 22.

![Diagram of ibuprofen crystal faces](image)

**Fig. 21. Predicted morphology of ibuprofen crystal [13]**

![Crystal grown from ethanol and ethyl acetate](image)

**Fig. 22. Crystal grown from ethanol and ethyl acetate [13]. The numbers on the faces are the Miller indices**
Despite this, elongated platelet forms were found for crystals grown from ethyl acetate (stretched out along with b-direction), giving a long \{100\} face. This corresponds to slow growth in both the a- and c-directions of the crystal compared to the b-direction. This may be explained by the interactions, illustrated in Fig. 23 and Fig. 24, between the solvent(s) and the ibuprofen carboxylic group. Since ethyl acetate can form two hydrogen bonds on the surface of faces \{100\} and \{002\} with the COOH functional group against only one for ethanol, the growth rates of the \{100\} and \{002\} crystals faces are expected to be much lower in ethyl acetate when the growth unit is the non-polar unit of the ibuprofen molecule [13,21].

While the \{001\} face (Fig. 24) is dominant in crystal grown from solvents other than the alcohols, the \{100\} face is dominant in ibuprofen grown from ethanol or methanol because the polar solvent will have strong interactions with the non-polar growth unit of ibuprofen resulting in inhibition of growth while the other faces are free to grow, thereby resulting in needle shaped crystals. On the other hand, ibuprofen crystallized from solvents with a high hydrogen bonding ability like methanol will form chunky crystals and low hydrogen bonding solvents like hexane will form needle like crystals [30, 40, 42].

1.4 Effect of Super Saturation and Temperature on Ibuprofen Crystals

Cano et al. [13], studied the growth rates of crystallographic dominant crystal faces of ibuprofen, in low relative supersaturation solutions (\(\sigma\)) of 0.013 in ethanol and ethyl acetate. It has been revealed that the growth rates of the ibuprofen crystal faces are reported in increasing order as \{100\} < \{011\} < \{002\} for ethanol and as \{100\} < \{002\} < \{011\} for the case of ethyl acetate respectively.
In addition, Nguyen et al., (2014) found that mean growth rate of the \{001\} and \{011\} faces increase with increasing relative supersaturation (in the range from 0.55 to 1.3) with R\{011\} being greater than R\{001\}. This is found particularly to be the case for crystals grown in ethyl acetate, acetonitrile and toluene solutions. Plate-like ‘hexagonal’ crystals were obtained from ethanol whilst more elongated forms were found in ethyl acetate, acetonitrile and toluene.

Furthermore Marinova et al., [27] found that fastest solvent exchange rate is for the case of the \{100\} polar surface in both ethanol and ethyl acetate. It also noted that a change in the arrangement of the solvent exchange rates on moving from ethyl acetate to ethanol, with \{002\} being the slowest surface for the latter. It can be said that in some cases the lifetime of the adsorbed state of a solvent molecule is in fact related to the vacation of a kink site by the solvent and has a significant role in the crystal face growth kinetics.

A first order crystal growth model was found for the ibuprofen crystal growth rate measurements in ethanol [41]. The growth of ibuprofen crystal at the same relative supersaturation, was faster at higher temperature and the estimated activation energy \(E_{ac}\) was 13.7 kJ mol\(^{-1}\). Thus, growth appears to be kinetics controlled rather than mass transfer controlled. The shape of the crystals from ethanol were plate like.

2. CONCLUSIONS

Although a large difference, particularly in biological systems in-terms of potency between the two enantiomers is not found. However, the morphology can influence physical and the mechanical properties. Furthermore, crystal shapes have also been found to have an effect on the bioavailability of the resulting APIs. To overcome these problems, a suitable size and shape of ibuprofen crystal is desirable. The solvents (and additives) used by different researchers were reviewed together. It is obvious the solvent choice has a controlling influence on the crystal shape. However, it is also clear crystallization conditions (supersaturation, temperature) have effect on crystal growth. This information will be useful for designing industrial crystallization processes for ibuprofen in different solvents and its mixtures. It could also be used as an example for other API crystallizations.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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http://www.sdiarticle4.com/review-history/68076