CRYSTALOGRAPHIC ANALYSIS OF SOLID IBUPROFEN

Vitória A. M. Silva[1]
Loide O. Sallum[2]
Igor B. Dalarmelino[3]
Antônio S. Aguiar[4]
Hamilton B. Napolitano[5]

Abstract

In this study, we analyzed the supramolecular arrangement of an ibuprofen crystal, a widely used drug with anti-inflammatory and antipyretic properties used in the treatment of acute and chronic pain resulting from inflammatory processes, classified as a non-steroidal anti-inflammatory drug (NSAID). The molecule acts by inhibiting cyclooxygenase activity, reducing prostaglandin synthesis, and through the action of the hypothalamic thermoregulatory center. It is a first-line drug widely used as an antipyretic and pain reliever in patients of all ages, especially in premature infants with patent ductus arteriosus (Yuan et al., 2023). The compression of intermolecular interaction patterns in the supramolecular arrangement of pharmaceutical materials is essential in the context of pharmaceutical materials, as different polymorphic forms can affect physical properties such as solubility, stability, and bioavailability, as well as prevent unwanted transformations during manufacturing.

Keywords: *crystallography; solid state; ibuprofen.*

Introduction

Crystallographic studies seek to obtain the three-dimensional arrangement of crystalline materials, enabling the understanding of supramolecular arrangements, distances, angles, and molecular interactions, which play fundamental roles, in addition to the various types of molecular functionality that are present (Chieng et al., 2010). This is a fundamental step in the production of a drug. Thus, from crystallography studies, we can also obtain what we call polymorphism, known for giving rise to significant changes in the physical and chemical properties of the compound (Chieng et al., 2010). This impacts stability (physical and chemical), bioavailability, and production. In extreme cases, an unwanted polymorph can even be toxic.

These concerns led to increased regulatory requirements by the Food and Drug Administration (FDA) (Chieng et al., 2010). Since then, polymorphism has become an increasingly important research topic in both academia and the pharmaceutical

industry. As a result, the performance of the drug can be significantly altered and/or fail to meet quality specifications (Wang et al., 2021). Ibuprofen was discovered in 1961 by chemist Stewart Adams and began to be marketed in the United Kingdom and the United States as *Brufen, Advil, Motrin*, and *Nurofen.* Over the years, the importance of this drug to the world population has become apparent. It is included in the World Health Organization's List of Essential Medicines, is important in basic healthcare, and can be found as a generic drug (Kleemiss et al., 2020).

Methodology

The Crystallographic Information File (CIF) with the crystallographic information on ibuprofen was collected from the Cambridge Crystallographic Data Centre (CCDC), established in 1965 to record numerical, chemical, and bibliographic data related to published organic and metal-organic crystal structures (Allen et al., 1979). ConQuest will be used to conduct research on Ibuprofen, based on its two-dimensional structure or unit cell, searching the entire CCDC database for the compound to be studied (Spackman & Jayatilaka, 2009). analysis Hirshfeld surface provides a three-dimensional evaluation of the individual characteristics of the molecule and provides information on the topography of its intermolecular interactions, which helps in understanding the packing of the crystal lattice.

The distance function d_{norm} *(*normalized contact distance) is related in terms *of* d_i (the distance between a molecule internal to the surface) and d_e (the distance between a molecule external to the surface) as a function of the Van der Waals radii (r_i^{vdW} ,r_e^{vdW}) represented by Equation 1. (McKinnon et al., 2007).

$$d_{norm} = \frac{d_i - r_i^{vdW}}{r_i^{vdW}} + \frac{d_e - r_e^{vdW}}{r_e^{vdW}} \quad (1)$$

Evaluating existing intermolecular interactions. (McKinnon et al., 2007).

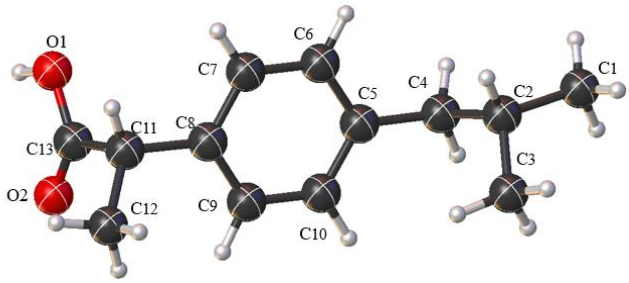
Partial results

Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID) whose chemical structure includes a benzene ring linked to two carboxylic acid functional groups and an isobutyl chain, as shown in Figure This structure gives ibuprofen two

chiral forms, which influence the rotation of the molecule in space. Among chiral drugs, anti-inflammatory drugs derived from propionic acid are particularly noteworthy, with ibuprofen being one of the most representative examples. The (S)-(+) enantiomer of Ibuprofen shows greater affinity for plasma proteins, resulting in superior pharmacological efficacy. However, the enzyme 2-arylpropionyl-CoA epimerase can convert the less active enantiomer (R)-(-) enantiomer into the more active (S)-(+) enantiomer, which justifies the commercialization of ibuprofen in racemic form due to the high cost associated with the synthesis of pure enantiomers (Yuan et al., 2023).

The name "Ibuprofen" is derived from the initials of isobutylpropanoic acid phenolic. Crystallographic studies using data from the Cambridge Crystallographic Data Centre (CCDC) have revealed that Ibuprofen crystallizes in a monoclinic system with space group $P2_1/c$. Analyses performed using Olex2 software (Platon data) indicated that the molecule has both nonpolar and polar characteristics, with electronegativity influenced by the oxygen atom. These factors are decisive for the pharmacokinetic and pharmacological properties of the molecule in the body, influencing critical aspects such as the solubility and bioavailability of the drug.

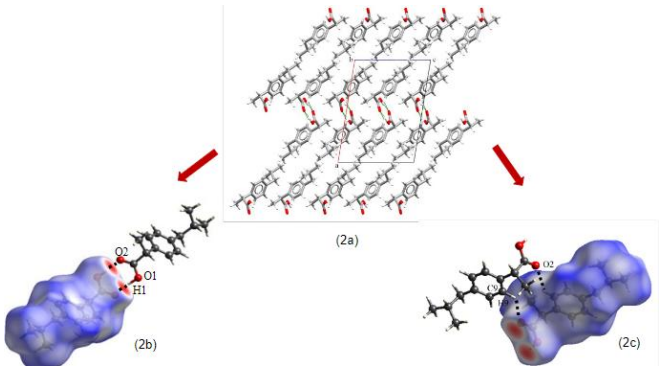
Figure 1. ORTEP representation of the molecular structure of Ibuprofen.



Packing is related to intermolecular interactions, such as the intermolecular interaction $O_1{-}H_1{\cdots}O_2$, which forms a dimer around the inversion center along the *b* axis , and can be described asR_2^2 (8), thus determining a classic type interaction. Another intermolecular interaction $C_{(9)}{-}H_{(9)\ (\cdots)\ }O_{(2)}$ appears as a dimer around the inversion center along the b axis and can be described asR_2^2 (12), thus determining a non-classical interaction, both of which are described in Figures 2b and 2c. The crystalline packing shown in Figure 2a is responsible for the formation of the polar sheets that are involved in intermolecular interactions and the apolar layers. Thed_{norm} surface (Figures 2b and 2c), in which the analysis is useful in identifying the most dominant

intermolecular interactions between neighboring packings, appear as two identical red dots.

Figure 2. Crystal packing (2a) and intermolecular interactions (2b and 2c).



Conclusion

In conclusion, the study of the correlation between the structure and activity of ibuprofen is essential to describe its physicochemical properties. The supramolecular arrangement in the crystal occurs through apolar and polar layers of the drug, facilitated by the formation of dimers. These arrangements, in turn, determine crucial aspects for the quality control of the drug. Currently, the study of ibuprofen polymorphism and theoretical calculations of the molecule and its polymorphs are underway.

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