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Reversibly changing a painkiller structure: A hot topic for a cold case—Ibuprofen lysine salt

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ABSTRACT

Ibuprofen lysine salt can undergo a fully reversible, thermally induced phase transition into a different enantiotropically related polymorphic form. The structures of both the high and low temperature phases were solved using state-of-the-art X-ray powder diffraction methods, showing many similarities both in the molecular conformation and in the crystal packing. The full structural analysis and comparison of the two crystal structures allowed to understand the mechanism of the phase transition and explain its reversible nature in what appears to be a rare case of isosymmetric temperature-driven phase transformation of an organic solid.

1. Introduction

Polymorphism is a well-known phenomenon in the pharmaceutical industry. Active pharmaceutical ingredients (APIs) frequently exhibit polymorphism, crystallizing in more than one crystal form. As the attention given to solid state issues of new active molecules increases, older, well-known molecules are also investigated in order to solve or prevent problems with production, handling and formulation. Different crystal forms can have very different properties like hygroscopicity, compactability, flowability, solubility and stickiness. These differences can impact many aspects of pharmaceutical production, from the R&D stages all the way to formulation and packaging. Not only is it important to know the characteristics of different crystal forms, it is also crucial to know when one polymorph can interconvert into another. Humidity conditions, temperature, residual solvents, storage conditions can all influence the transition from one crystal form to another. A knowledge of the transition, for example if it is reversible or not, can also help in the understanding of the solid state behavior of API's.

Ibuprofen, or (*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid, is a well-known, over-the-counter analgesic belonging to the class of nonsteroidal anti-inflammatory drugs (NSAID) [1]. Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor, acting on both COX-1 and COX-2 forms. However, most of its effect is achieved through COX-2 inhibition [2]. It is widely used for pain relief, fever and inflammatory diseases. Known from the 1960s, it has been marketed in a great variety of forms and under numerous trade names. Although very effective as an anti-inflammatory drug, ibuprofen in the free acid form has a low solubility which causes a slow onset of therapeutic efficacy. For this reason, different salts having better solubility characteristics have been studied, in particular the lysine [3] and sodium salts [4]. While the crystal structures and solid state characteristics of both ibuprofen free acid [5,6] and ibuprofen sodium salt [7] have been studied, the lysine salt of ibuprofen, shown in the neutral form in Scheme 1, remains relatively absent from solid state literature. This is surprising, considering the widespread use made of ibuprofen lysine salt in solid formulations. The only known characteristic of the lysine salt of ibuprofen is the existence of a reversible polymorphic conversion occurring upon heating [8,13]. Ibuprofen lysine salt therefore exists in two different polymorphic forms, one existing at lower temperatures and one existing at higher temperatures. As many industrial processes, including drying, granulation and melt-extrusion, can involve heating, the detailed knowledge of the behavior of ibuprofen lysine salt at temperatures above ambient conditions can be useful. Moreover, an abrupt and completely reversible transition like the one observed in ibuprofen lysine salt implies a structural correlation between the different crystalline forms involved. The aim of this paper is therefore to report on the behavior upon heating of ibuprofen lysine salt and to provide the structural characterization of ibuprofen lysine salt forms, in

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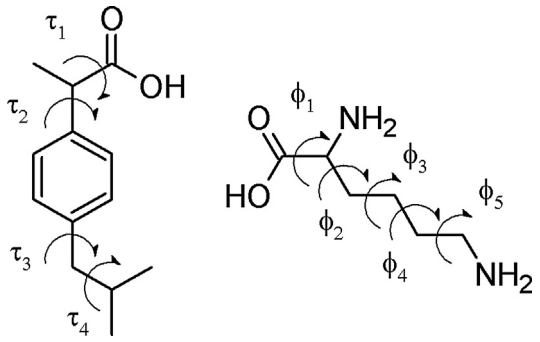

Scheme 1. Molecular constituents of ibuprofen lysine salt (in the neutral from). The dihedral angles shown were used for structure solution for both **IBL-I** and **IBL-II**.

Table 1
Comparative crystal cell data of forms **IBL-I** and **IBL-II**. (E.s.d.'s in parentheses).

	IBL-I	IBL-II
Chemical formula	$C_{19}H_{32}N_2O_4$	$C_{19}H_{32}N_2O_4$
Formula weight [g/mol]	352.47	352.47
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a [Å]	8.4664(6)	8.450 (1)
b [Å]	40.619(3)	42.619(7)
c [Å]	5.7929(4)	5.8226(6)
β [°]	86.326(7)	85.72(1)
V [Å^3], Z	1988.1(3), 4	2091.1(5), 4
V/Z	497	523
T [K]	298	383
λ [Å]	1.5418	1.5418
$\rho_{(calc)}$ [g/cm]	1.178	1.119
μ [mm^{-1}]	0.665	0.632
R_{Bragg}	0.050	0.042

quest of an explanation for the reversibility of the transition. In order to favor the readability of the paper, the crystal form of ibuprofen lysine salt which exists at room temperature will be referred to as ibuprofen lysine salt form I, or **IBL-I** for short, while the high temperature crystal form will be referred to as form II, or **IBL-II**.

2. Materials and methods

2.1. Materials

Ibuprofen lysine salt was provided by Dipharma Francis S.r.l. and used without further purification.

2.2. Differential scanning calorimetry (DSC)

Differential Scanning Calorimetric (DSC) measurements were performed on a Mettler-Toledo 822e calorimeter. For initial characterization, the samples (in the 3–6 mg range) were loaded in aluminum pans with pierced lids and heated at 10 °C/min under a flow of nitrogen (80 ml/min) from 30 °C to 300 °C. In order to study more closely the phase transition between forms **IBL-I** and **IBL-II**, the 30–85 °C range was explored at different heating rates (2, 4 and 10 °C/min) and the samples were then cooled at the same rate used for heating. Transition temperatures in the DSC traces were determined using the onset method, i.e. the temperature at which the tangent segment taken in the inflection point of the peak crosses the baseline.

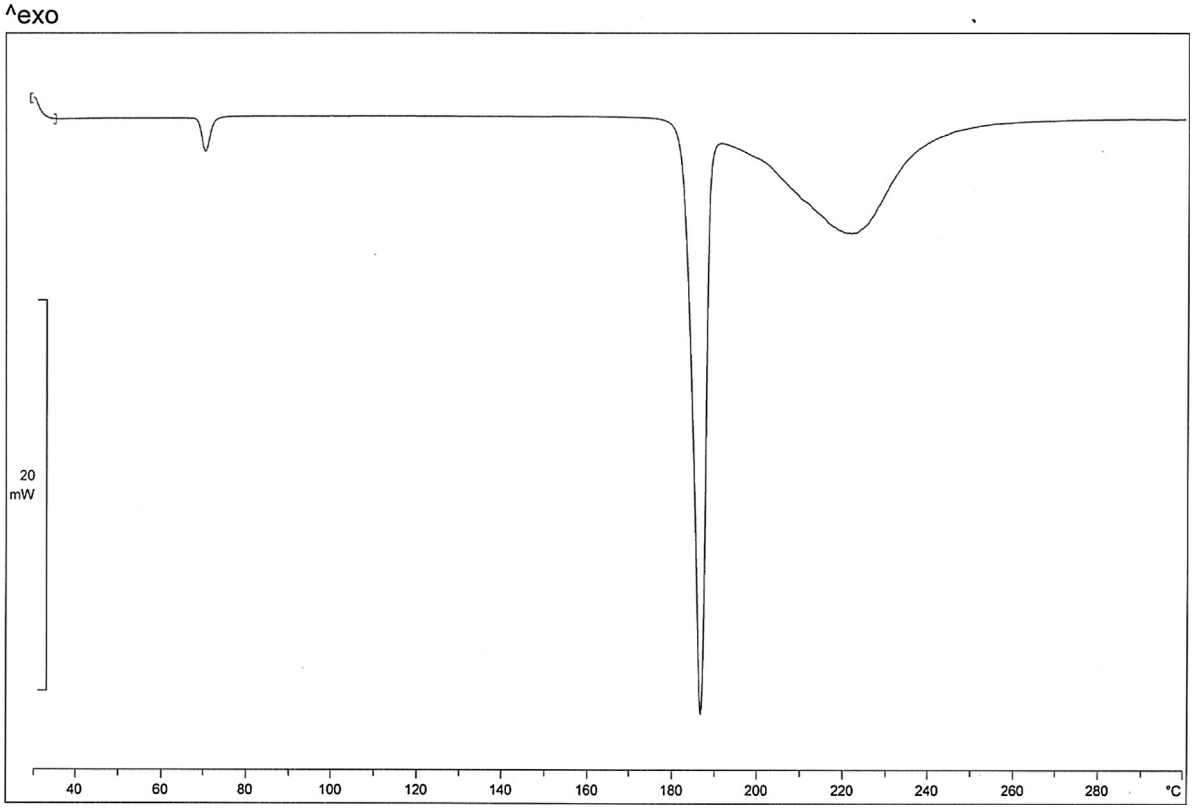

Fig. 1. DSC of ibuprofen lysine salt performed under nitrogen at a scan rate of 10 °C min^{-1}. As discussed in the text, minor, but non-negligible, changes in the onset temperature of the first thermal event, near 70 °C, occur if the heating rate is diminished, toward an ideal infinitely slow process approaching equilibrium conditions. See also Fig. 2.