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RESEARCH PAPER

Solid-Solid Transformation in Racemic Ibuprofen

Emeline Dudognon • Natália T. Correia • Florence Danède • Marc Descamps

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ABSTRACT

Purpose To clarify the polymorphism of racemic Ibuprofen and to determine the kinetic of the phase transformation that follows crystallisation of phase II.

Methods Differential Scanning Calorimetry (DSC), X-ray powder diffraction and Hot Stage Microscopy are complementarily used to perform a kinetic investigation of the particular temperature range where competition between the occurrence of phases I and II is suspected.

Results Experiments performed with the three techniques reveal that at 273 K the crystallisation to phase II is then followed by a solid-solid transition towards phase I. This transformation is exothermic (conversion enthalpy of 8.0 ± 0.5 kJ/mol), which proves that the two phases form a monotropic set. The kinetics of conversion deduced from X-Ray experiments follows a Johnson-Mehl-Avrami equation and the Hot Stage Microscopy allows us to establish that the transformation proceeds by the growth of some nuclei of phase I probably formed at lower temperature.

Conclusions These results allow us to precise the stability pattern of racemic Ibuprofen and to establish the kinetic conditions of appearance and interconversion of the different phases. Therefore such real time resolved investigations would help if applied in the screening of polymorphs when competitive crystallisations occur.

E. Dudognon (✉) · N. T. Correia · F. Danède · M. Descamps
Unité Matériaux Et Transformations, UMR CNRS 8207
Université Lille Nord de France
Bât. P5 B.213
59655 Villeneuve d'Ascq Cedex, France
e-mail: emeline.dudognon@univ-lille1.fr

N. T. Correia
REQUIMTE, Departamento de Química
Faculdade de Ciências e Tecnologia
Universidade Nova de Lisboa
2829-516 Caparica, Portugal

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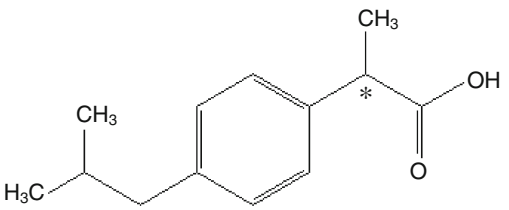
INTRODUCTION

The role of crystalline polymorphism in solid state pharmacy was recognised in the two last decades (1–3). Polymorphism is basically involved in the issues of solubility and physical stability of drugs. Several factors emerge in the course of the investigations referred to above which have a controlling influence on the polymorphs generations and lifetimes: metastable phases and the kinetics of transformations. Their combination in the specific case of racemic Ibuprofen is the subject of this paper.

Ibuprofen, 2(4-isobutylphenyl)propanoic acid is a widely used non-steroidal anti-inflammatory drug having analgesic and antipyretic activities. The molecular structure is as follows:



This molecule contains a chiral carbon so two enantiomeric forms can be found: S(+)-Ibuprofen and R(−)-Ibuprofen, the S(+)-Ibuprofen being the pharmacologically active form. The commercial drug is in fact the racemic compound. It appears at ambient temperature as a white crystalline powder. This crystalline phase I is stable up to the melting point T_{mI} = 349 K (4). Its structure was resolved long time ago (5,6): monoclinic, space group $P2_1/c$, Z=4. Crystallisation of the phase I from the undercooled melt occurs between T_{mI} and T_g, the glass transition temperature