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INFLUENCE OF HIGH ENERGY MILLING ON THE KINETICS OF THE POLYMORPHIC TRANSITION FROM THE MONOCLINIC FORM TO THE ORTHORHOMBIC FORM OF (±)5-METHYL-5-(4'-METHYL-PHENYL)HYDANTOIN

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5-methyl-5-(4'-methylphenyl) hydantoin is a chiral compound whose racemic mixture crystallizes as a conglomerate. This molecule has two polymorphs: an orthorhombic form (stable form) and a monoclinic form of monotropic character. These forms share extensive structural analogies (identical 2D periodic fragment) and consistently their lattice energies are quite close. The analyses of the crystal structures lead to propose an irreversible polymorphic transition based on a destructive/reconstructive mechanism.

Under comparable conditions (mass of solid, temperature, etc.) the conversion is completed within 14 days by means of slurring in ethanol (10 days if seeded) whereas 5 h only are necessary by means of mechanical activation under wet conditions and 9 h under dry milling. In the latter conditions the resulting materials appears significantly more defective in comparisons to the other modes of conversion.

Keywords: *high energy milling, polymorphism, transition kinetics*

Introduction

In many areas of material science as well as in pharmaceutical industry, the understanding and control of polymorphism are two essential issues [1, 2]. The access to a pure and stable polymorph can be a difficult task because of the narrow energy gap between the varieties i.e. a very small ΔG separates the free enthalpies of the solid phases. In addition to the weak thermodynamic driving force, a slow kinetics of transition can also result from a large activation energy barrier. In such a case, there are several ways to speed up the conversion towards the stable form by adjusting one or several of the following parameters: temperature, pressure, nature and quantity of solvent and external forces (milling, shearing, irradiation, ultra-sounds, etc…).

The aim of this study is to compare the polymorphic transition kinetics from the monoclinic form to the orthorhombic form of (±) 5-methyl-5-(4'-methylphenyl)hydantoin in four different experimental conditions:

- By using slurring without seed
- By using slurring with seeds of the stable form
- Under wet high energy milling (wHEM hereafter)
- Under dry high energy milling (HEM hereafter)

In addition to the assessment of the durations necessary to ensure a complete conversion to the stable form, the cristallinity of the final solid phases will be also qualitatively compared.

Experimental

Materials and methods

The title compound ((±)17H hereafter, Fig. 1) has been prepared with a good yield (ca. 95%) by using Bucherer Berg synthesis [3]. The crude material has been recrystallized several times in an ethanol-water mixture up to a chemical purity above 99% [4]. The metastable monoclinic polymorph free from the

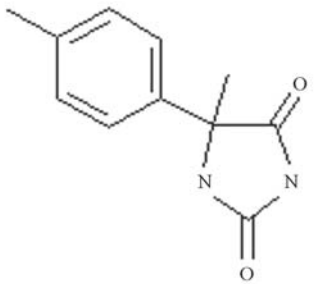

Fig. 1 Developed formula of 17H

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Table 1 Crystallographic data

Form	Space group	Z	a/Å	b/Å	c/Å	β/°	V/Å^3
Orthorhombic	$P2_12_12_1$	4	22.757	6.256	7.344	90	525
Monoclinic	$P2_1$	2	11.732	6.253	7.362	103.79	1046

orthorhombic variety has been obtained by implementing a precipitation e.g. swift addition of cold water (i.e. antisolvent) to an ethanolic solution.

Structures and molecular modeling

Two polymorphic forms have been identified: an orthorhombic form (thermodynamically stable form from room temperature to fusion) and the monoclinic form [5]. These two polymorphs crystallize as conglomerates without any partial solid solution, neither disorder nor solvent molecule. The crystallographic data are summarized in Table 1.

The two forms exhibit a high degree of similarity that results from:

- Almost identical b and c crystallographic parameters (Table 1)
- Very similar molecular conformations
- The presence of superimposable molecular ribbons along b axis, which include the entire hydrogen bond network.
- The molecular slice $(100)_{monoclinic}$ and the slice $(200)_{orthorhombic}$ are identical.

These structures differ by the stacking of the slices: $(100)_{monoclinic}=(200)_{orthorhombic}$. The monoclinic variety is obtained by translation of slice $(100)_{monoclinic}$ along $a_{monoclinic}$ axis. By contrast in the orthorhombic form, a screw axis 2_1 along $a_{orthorhombic}$ ($\approx 2\cdot(\sin\beta)\cdot a_{monoclinic}$) axis generates an antiparallel alternated stacking of (200)orthorhombic slices as schematized in Fig. 2.

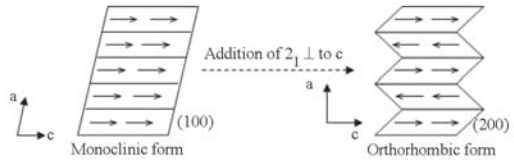

Fig. 2 Schematic representation of 17H monoclinic and orthorhombic forms

After minimization [6], the difference in lattice energy ($E_{orthorhombic}$–$E_{monoclinic}$) between the polymorphs is very small (ca. 0.3 KJ). Therefore, in consistency with their extensive similarities, the two polymorphic forms are almost isoenergetic. Moreover, the mechanism of conversion is necessarily of destruction/reconstruction type. Indeed, no concerted movements can be contemplated that could allows a smooth and continuous transition between the two polymorphs. Consistently, the monoclinic form can be stored for years at room temperature without any sign of 'return' to the thermodynamic stable polymorph.

The ball milling is a way to induce phase transformation [7, 8] or chemical reaction [9]. Under external forces, the crystalline powders are often brought far from their equilibrium. Under HEM, two effects coexist: the local thermal activation and the forced process. The dynamic equilibrium is reached when damage and recovery compensate each other. After a sufficient period of time, the nature of the steady state depends on these dual effects and intrinsic properties of the phase undergoing HEM such as visco-elasticity.

Under HEM, three parameters control the nature and the kinetics associated with the steady state:

- The mean milling temperature (in case of amorphisation ($T_{milling}<T_g$)
- The composition of the system [10], in case of co-milling or addition of solvent.
- The milling intensity. The milling intensity is an extensive variable, which is defined by the following formula:

$$I = \frac{F V_b m_b}{m_p}$$

where I: intensity of milling (m/s^2), F: frequency of the shocks (cps), V_b: impact velocity (m/s), m_b: mass of marble (g), m_p: mass of powder (g).

The milling intensity (I) could be described as the momentum per time unit and per mass unit. Therefore the unit is: m s^{-2}; that is to say an acceleration. In fact, this acceleration is proportional to the damage per shock [11].

Up to now no less than the 5 different behaviours listed below, have been detected when submitting a molecular crystallized compound to high-energy milling:

- No modification! (Except a drop in the crystallinity i.e. the long range order becomes more defective) (cf. saccharine)
- Amorphization (usually, the temperature of milling is below T_g) [12]
- Phase transformation to a new phase that cannot be obtained without using high energy milling [13]
- Phase transformation towards a crystallized solid which is also accessible by other means than high

energy milling. Here two sub-cases can be differentiated:

– The dynamic form (steady state) is one of the thermodynamically metastable forms when no milling energy is applied to the system. So, there is an inversion of 'stability' between two polymorphs (case of (±) modafinil accepted for publication in Cryst. Growth Des., 2007.)

– The nature of the dynamic form and the thermodynamically stable form (when I = 0) are the same (this work).

Some studies have reported that several of these elementary behaviors can happen simultaneously [7].

The planetary mill used in these experiments was the Pulverisette 4 (P4) from Fritsch (Oberstein; Germany). In this series of experiments the vial rotation velocities (ω) equaled the disk rotation speed (–Ω) but they rotated in opposite directions. The couple (Ω,ω) determines the milling mode: predominantly friction mode, i.e. with strong shear forces, Ω and ω have the same sign or predominantly shock mode (also called impact mode) i.e. Ω and ω have opposite signs. Due to the overlapping of milling vials and supporting disc, the material to be ground and the marbles execute movements inside the vials whose effects on the powder depend on the ratio between the rotation velocities of the vials and the disc: On the one hand, the faster the rotation of the vials the more the friction mode is favored. On the other hand, the faster the rotation of the planetary disc the more the impact mode is favored.

Results and discussion

Conversion of the monoclinic form to the orthorhombic form via slurring in ethanol

A suspension composed of 4 g (±) 17H monoclinic form and ethanol (24 g) has been prepared at 20°C. The solubility of two polymorphic forms in ethanol at 20°C are reported in Table 2.

The monitoring of the conversion kinetics was carried out by sampling the suspension and analyzing the solid by means of X-ray powder diffraction. Without seeding, 14±0.5 days were necessary to obtain a complete conversion. The same experiment, except that seeding by few milligrams of the orthorhombic variety was implemented, led to the complete conversion within 10±0.5 days.

Table 2 Solubility of 17H in ethanol at 20°C

	(±)17h monoclinic form	(±)17h orthorhombic form
Solubility	8.92%	8.89%

By using a solvent that offers a reasonable solubility (ethanol in this study), the transition kinetic is driven by a dissolution/recrystallization mechanism. The presence of a common 2D periodic fragment between the orthorhombic form and the monoclinic form could have led to a spontaneous heteronucleation of the stable form onto the metastable form. The significant influence of seeding on the conversion kinetics shows that, if it exists, this mechanism has a minor impact on the global kinetics. The small difference between the solubilities, corresponding to a small ΔG, could explain this slow kinetic of transition, which is limited by a poor crystal growth rate [14].

Conversion of the monoclinic form to the orthorhombic form via HEM and wHEM

In order to determine the kinetics of transformation driven by mechanical stress, 2.5 g of monoclinic form of (±)17H with five marbles of 10 mm in diameter (in tungsten carbide) were loaded in each vial ($Volume_{vial}$=80 mL; milling couple (Ω,ω)=(400, –400) rpm). After a series of trial and error experiments it appeared that 9 h (±0.5 h) were sufficient to ensure the complete conversion towards the orthorhombic form. Therefore, under these milling conditions, the thermodynamic stable form and the dynamic form are identical. Nevertheless, the crystallinity of this steady state was poor (bottom spectrum in Fig. 3). This drop in crystallinity is due to the introduction of a large number of defects in the structure (dislocations, twinning…) concomitant to the diminution of the mean particle size. The absences of modification in the nature of the steady state and the constant crystallinity even after extended period of milling up to 40 h suggest that the T_g of this compound is below room temperature.

In order to improve the crystallinity of this steady state, wHEM has been carried out on 2.5 g of monoclinic form mixed with 30 mg of ethanol (i.e. 1.2% of ethanol; purity 99%) with five marbles (in tungsten carbide) of 10 mm in diameter in each vial (milling couple (Ω,ω)=(400, –400) rpm). After 6 h (±0.5 h), the pure orthorhombic form was obtained with a good crystallinity (second spectrum from the bottom in

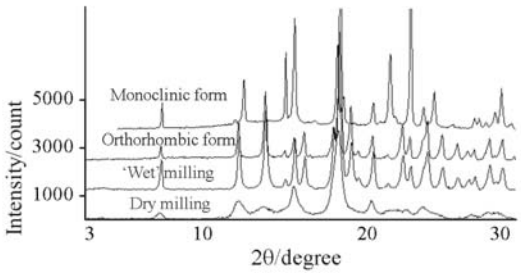

Fig. 3 XRPD pattern of different milling

Fig. 3). This result clearly shows that a very small amount of solvent (ethanol) has a decisive impact on the reconstructive step.

Conclusions

High energy milling applied to the title compound appears to be an efficient technique to ensure a swift conversion from the monoclinic metastable form to the stable orthorhombic polymorph. This latter phase is therefore both the thermodynamic stable form and the steady state under a constant flux of high-powered mechanical energy.

At room temperature and without solvent the conversation rate is accelerated from years to 9 h. Nevertheless, the solid phase obtained under HEM is highly defective. By slurring, 14 days (10 days with seeding) were necessary to convert the monoclinic form into the orthorhombic form, in ethanol at ambient temperature. Under 'wet' HEM, the conversion duration was reduced to 5 h without impairing the crystallinity of the solute. The solvent (ethanol), even in minor quantity, acts as a very efficient catalyst during the reconstructive step of the dynamic equilibrium.

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