Polymorphic Transformation of Indomethacin under High Pressures

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ABSTRACT: To study the effect of pressure on polymorphic transformation, intact powder, and ethanol slurry of α, γ, and amorphous forms of indomethacin (IMC) were compressed under high pressures. A quantifying method for the percentages of these three constituents in sample powder was established. Using this method, analysis of compressed samples revealed that α form, which is difficult to prepare in stable form under atmospheric pressure, was easily obtained in stable form from the ethanol slurry of the amorphous IMC, which does not include any specific crystalline forms. In the ethanol slurry of γ form, transformation to α form was observed: a reciprocal phenomenon under atmospheric pressure. These results can be rationally explained as follows: α form is more easily crystallized than γ form in the ethanol solution, the more closely-packed crystal structure of α form is thermodynamically predominant over γ form under high pressure, and pressure-induced amorphization occurs. This study indicates that crystallization experiments from the slurry of amorphous samples under various pressures can be useful in screening polymorphic or other solid states. J Pharm Sci 95:689–700, 2006

Keywords: polymorph; pressure; amorphous; crystallization; X-ray powder diffractometry; crystallinity; indomethacin

INTRODUCTION

It is well known that many organic pharmaceutical compounds can exist in various crystalline forms or solvates.[1] These polymorphs exhibit differing physicochemical properties such as solubility, dissolution rate, stability, and hygroscopicity, and differing pharmaceutical properties such as bioavailability, efficacy, degradation, toxicity, and drug product performance. Therefore, in order to control the quality of drug products in commercial production, most pharmaceutical companies try to explore as many crystal forms as possible by screening polymorphs of the drug substances during the development stage to reduce the risk of unexpected polymorph occurrence after market release, as occurred for the anti HIV drug Ritonavir, for example Reference 2.

Polymorph screening normally includes crystallizing saturated solution using various solvents under atmospheric pressure. Previously, pressure-dependent crystallization had scarcely been investigated as compared to temperature-dependent

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crystallization. However, pressure is essential among the physical variables defining the state of the compound, and, together with temperature, is also a constitutive factor in the construction of phase diagrams. Temperature prescribes the degree of thermal motion of the molecules, while pressure prescribes the mean intermolecular path in a system; thus neither is alone sufficient to describe the state.

A supercritical fluid technology actively studied in recent years is based on how the phase diagram of a compound depends on temperature and pressure. That is, a solvent at higher than critical temperature and higher than critical pressure would obtain physical properties totally different from those at atmospheric pressure, and this phenomenon is utilized in areas such as reaction, separation, purification, material development, and analytical science.[3] For example, crystallization and control of a polymorph using supercritical fluid CO_2 as crystallization solvent has been investigated.[4]

As a fundamental principle, in the crystallization process of compounds, a change in pressure would cause changes not only in the molecular properties of the compound but also in the properties of the crystallization solvent; in other words, this would lead to a change in chemical potential of the whole crystallization system. When crystals exist in saturated solution at equilibrium, the surface energy of the crystal is equal to the chemical potential of the solution. The possibility therefore exists that a potential polymorph may be discovered by varying the chemical potential of the crystallization solution, not only in the supercritical state. Boldyreva et al.[5] reported a new crystal form of an inorganic compound that was found at hydrostatic pressure in the presence of a methanol-ethanol-water mixture used as a pressure-transmitting liquid, but was not found when the solvent was substituted with a polymer oil.

In the previous study[6–13] concerning pressure crystallization, the observation of crystal growth of small-molecule organic crystals such as xylene, etc.,[6,7] the development of pressure crystallization methods,[8–10] and the pressure crystallization of proteins such as lysozyme[11–13] were conducted. The following pressure dependencies have been reported in the literature: the pressure dependency of surface tension and step-free energy in the crystal growth process,[6,14,15] of saturated solubility and nucleation,[12,16–22] in eutectic composition change,[23–25] and in reversible polymorph transition.[26,27] However, no study concerning pressure crystallization using the results of such basic research from a viewpoint of polymorph screening has been reported so far.

In polymorph studies, the effect of pressure has not been completely neglected; drug substances are sometimes investigated under mechanochemical stress such as compaction, to evaluate the impact of tabletting on the crystal form in the formulation process.[28–30] In polymorph screening, however, the pressure applied to the crystallization system in solution or slurry should be positively changed as a factor of the total potential of the system. The pressurization of saturated solutions or slurries of various crystallization solvents would affect the nucleation and the interaction between drug compound and solvent. This effect may lead to new crystal forms that would not be found by conventional cooling crystallization methods under atmospheric pressure, and also may enable achievement of first-time crystallizations that would be difficult to achieve at atmospheric pressure.

This study is an investigation of polymorph transition under high pressure. Indomethacin (IMC) was selected as a model compound. Under atmospheric pressure, the α form of IMC first crystallizes from the supersaturated solution of ethanol, and then undergoes solvent-mediated transformation to the γ crystalline form above room temperature.[31] This is thought to be an example of Ostwald's Rule,[32] namely, for compounds capable of crystallizing in several forms, the least stable form will first be produced by spontaneous crystallization, followed successively by forms of increasing stability.[33]

IMC would be decomposed in supercritical fluid ethanol, since the critical temperature and pressure of ethanol are 240.8°C and 6.148 MPa, respectively, while the melting point and decomposition point of IMC are 162 and 220°C, respectively. In this study, to facilitate evaluation of the effect of pressure, experimental temperature was fixed at room temperature and the pressure was varied. IMC powder or the ethanol slurry of IMC, which has a potential for solvent-mediated transformation, were examined under hydrostatic pressure 400 MPa to determine whether any changes in the solid state or any solvent-mediated changes occur.

In addition to the α and γ crystalline forms, amorphous IMC was also used for this study, prepared by rapid cooling of IMC bulk powder melt in γ form. The use of amorphous solid or

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