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# Solvent effect on tolbutamide crystallization induced by compressed $CO_2$ as antisolvent

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**Abstract**

The aim of this work is to investigate the crystallization of tolbutamide induced by the addition of compressed carbon dioxide, with a particular focus on the role of the liquor solvent on the product characteristics. Crystals morphology and sizes were documented by microscopy and laser diffraction, respectively; since tolbutamide exists in four polymorph forms, characterizations by powder X-rays diffraction, differential scanning calorimetry and Raman spectroscopy were carried out. When processed from acetone or ethyl acetate, the drug crystallizes as polyedres and in a crystal lattice typical of Form III. If ethanol is added to acetone, Form I appears in the powder and becomes predominant for a content of 29% (in mol) and above; at the same time, mean particles size decreases. However, ethanol improves the solubilization of tolbutamide in the formed $CO_2$–solvent mixture, and is thus not favourable to a good yield of production. Mixtures of acetone with poor solvents such as diethyl ether and water were tested out; both enable the recovery of a mixture of Forms I and III, but with no significant improvement in sizes or yields compared with pure acetone or acetone–ethanol mixtures. Finally, the comparison with crystals obtained by evaporation indicates that the solvent itself was the main cause of the crystal phase observed, rather than the supercritical treatment.


*Keywords:* A1. Crystallization; A1. Polymorphism; A1. Supercritical fluid; A1. Solvent; B1. Tolbutamide

## 1. Introduction

Crystallization is one of the key operations of powder technology in the pharmaceutical industry, since the crystal's habit and size distribution play an important role in the final therapeutic behaviour. The development of effective particle technologies is keeping up with the need for increasingly smaller crystals of increased purity, which allow to reduce the drug dosage whilst keeping the therapeutic benefits and minimizing side effects as well crystallization using supercritical fluids was mostly developed as an alternative approach to conventional liquid crystallization, with the aim of controlling particle sizes and reducing the residual solvent concentration in drugs, in addition to the environmental advantage of reducing liquid waste. Although many fluids could be chosen for crystallization purposes, carbon dioxide ($CO_2$) is by far the most extensively used when processing pharmaceutical compounds, thanks to its mild critical conditions of temperature ($T_c = 31.05\,^{\circ}C$) and pressure ($P_c = 7.28\,MPa$). The non-polar nature of the fluid, which restricts its solvation capability, was turned into an advantage years ago, with the introduction of the compressed anti-solvent concept. In the related techniques, the compound is initially dissolved in an organic solvent and the subsequent addition of $CO_2$ decreases the solvation ability of the original solvent and causes the solute precipitation. Whilst literature is well documented in examples of supercritical anti-solvent applications, it mostly focuses on the effect of operating conditions upon particle morphology and size. Few studies are carried out on polymorphism. Polymorphs are materials

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