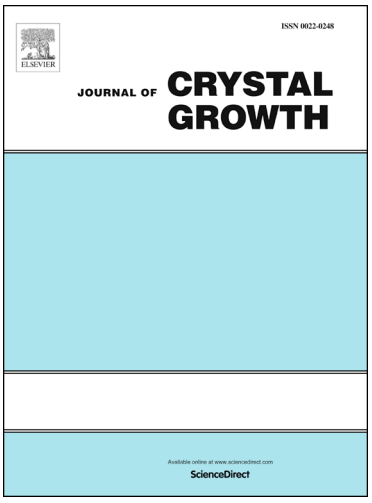

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A New Polymorph of Fenofibrate Prepared by Polymer- mediated Crystallization

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Abstract:

The polymer-mediated crystallization is an effective means to control the drug crystal. This project was focusing on a new form of Fenofibrate (Form IV) obtained by polymer-mediated crystallization. Medical polymer materials such as Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxyl Methyl Cellulose (CMC-Na) and Polyvinylpyrrolidone (PVP) were tested in this study. The powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA) and Fourier Transform Infrared Spectroscopy (FTIR) were used to differentiate the new form and other known forms. Material studio was applied to solve structures of Form IV. These polymorphic forms present different physicochemical properties. The crystallization conditions of Form IV were also detected. The study disclosed the Form IV has a low melting point of 65 °C and it is more stable compared with other metastable forms. This new form was proved to be more soluble in 0.5% tween-80 solution, which suggested it has highly potential to generate medicinal crystal.

Key words: Fenofibrate; Crystallization; Polymorph; Polymer material; Physicochemical properties.

1. Introduction

Polymorphic forms of one drug substance could have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure and density. In the 60's of 20 century, the second form of Aspirin (Form II) was first predicted [1], after the bioexperiment, it was found that blood concentration of Form II was 70% higher than Form I [2]. But this Form II was not admitted soon. This issue appeared to be resolved in 2005, when the predicted second polymorph was obtained [3]. The polymorphic forms can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability [4]. Lots of methods have been used to enhance the bioavailability, such as amorphous drug or a metastable form [5], [6].

Fenofibrate is a hypolipidemic drug with low water solubility [7] and poor bioavailability [8], with a relatively low melting point of 79–82°C, which was first commercialized in France in the 1970s. In order to improve the water solubility of Fenofibrate, pharmaceutical companies have used lots of methods. The most commonly method to improve the bioavailability of Fenofibrate was micronization, such as milling [9], [10], [11], spray-drying [12], [13], using co-crystal [14],[15], using supercritical carbon dioxide[16], [17], [18]. The use of an amorphous drug or a metastable form with higher solubility would improve the bioavailability of Fenofibrate [17]. The crystallization behavior of amorphous Fenofibrate is still unknown. So the metastable form of Fenofibrate will become the investigative breakthrough. Fig. 1 is structural formula of Fenofibrate.