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Itraconazole cocrystallization in fatty acid under high-pressure CO_2

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Abstract (less than 300 words)

Itraconazole, which is an antifungal drug with a low solubility, has been focused on as one of the model molecules in the investigation of processing technologies to improve solubility in human body [1]. Some studies have reported improved solubility of itraconazole by the formation of the cocrystal which is a new crystal structure composed of active pharmaceutical ingredients (APIs) and additives called as coformer (CF) [2, 3]. The cocrystallization processes need multi-steps using organic solvent to dissolve API and coformer. Therefore, in order to solve these disadvantages, we suggest a single step method for the formation of cocrystal with liquefied fatty acids under high pressure CO_2 in terms of their melting point depression by high pressure CO_2. In this study, we investigate the cocrystal composed of itraconazole as API and succinic acid as CF, using liquefied fatty acid under high pressure CO_2.

As the result, the cocrystals of itraconazole can be formed under high pressure CO_2 with linoleic acid, oleic acid and stearic acid used as fatty acid. Itraconazole cocrystals cannot be formed by the cocrystallization with hydrocarbon, ontadecane and 1-octadecene and without the fatty acid .These results show that cocrystal formations is promoted in the media of the fatty acid under high-pressure CO_2. For the purpose of clarifying the role of the fatty acid and the mechanism of the cocrystallization, we also focused on the molecular interaction energies among the fatty acid, itraconazole and succinic acid by thermodynamic relationships and molecular information from quantum chemical calculations. The calculated results give that the molecular interaction of cocrystal compounds with the fatty acid are stronger than those with hydrocarbons. The experimental and calculated results could suggest that the strong molecular interaction with fatty acids achieve the promotion of the itraconazole cocrystallization.

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