Theophylline Polymorphism Formation Driven by Supercritical CO_2

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In this research, we mainly focus on to obtain the form V of theophylline by using the interaction between supercritical CO_2 and theophylline monohydrate. In past decades, the polymorphism has been a focal topic since polymorphic forms of same active pharmaceutical ingredient (API) can present different physicochemical properties, which influence its processing and product performance.[1] In 2007, Roy and his coworkers reported a new theophylline polymorph, form V, while supercritical CO_2 antisolvent (SAS) process is applied to get the theophylline solid formation.[2] Moreover, by now, this form V is reported as only can be formed by SAS or SAS-like process [3]. But in these process, toxic organic solvents such as tetrahydrofuran, dichloromethane, are applied.

Therefore, in this work, we use the theophylline monohydrate instead of theophylline organic solvent solution to treatment in supercritical CO_2. Because theophylline monohydrate has a sandwich structure with water molecules [4], and this is expected to offer sufficient interaction surface for supercritical CO_2 to induce the formation of form V, while supercritical CO_2 extract water from the monohydrate lattice.

To obtain the form V of theophylline with supercritical CO_2, we put theophylline monohydrate in high-pressure vessel in a temperature-controlled thermostatic oven and pressurize the CO_2 into the cell until determined pressure is reached. Then the pressure and temperature are controlled as a constant for 2 h. Then, the high-pressure cell is depressurized at 0.1 MPa min^{-1}. The solid remained in the vessel is collected and used for further estimation. The pressure is chosen as 10, 15, 20, 25 MPa at 40°C to study the relationship between formation of form V and pressure. Moreover, the temperature is 40 and 60 °C at 20 MPa to study the effect of temperature.

As the X-ray diffraction results showed in Fig. 1., we find out the form V (marked with black square) can be fabricated by our process and the processed powder is a mixture of theophylline Form II, monohydrate, and Form V. In addition, the higher pressure is preferred for the formation of Form V as the intensity of the XRD peak for form V become stronger while higher pressure is applied. And if the temperature reach at 60 °C, only the theophylline form II is remained in processed powder. This may be due to the phase transformation of theophylline Form V to form II, which is then proved by differential scanning calorimeter as a new heat absorb peak around 55 °C for processed powder.

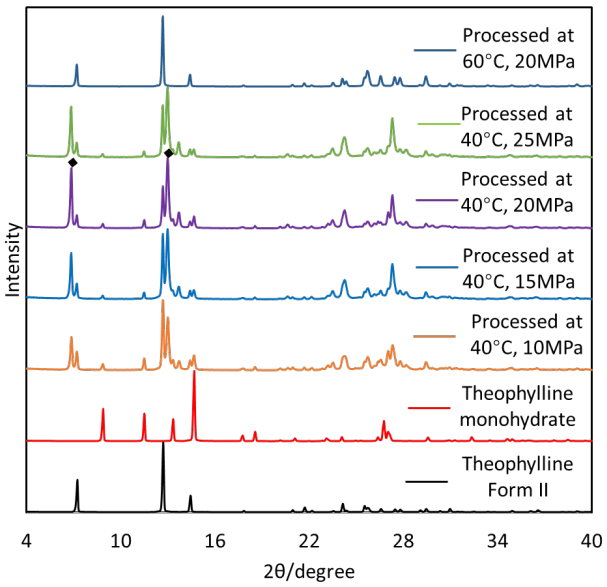

Fig.1 P-XRD of theophylline form II, monohydrate and processed powder under various conditions.

In addition, by scanning electron microscope, we observe the morphology difference of theophylline Form II (smooth strip), monohydrate (big rod) and processed powder (slice, mainly), which also suggest the formation of form V. By Fourier-transformed Infrared spectrum, we confirmed the processed power nearly have the same peaks as the mixture of form II and monohydrate, which indicate the changes in XRD pattern and morphology are because of formation of polymorph instead of chemical change. Moreover, the concentration of theophylline processed powder fabricated at 40°C and 20 MPa is 5.82 mg g^{-1} water at 25 °C in the first 100 min, a little bit improved from theophylline raw (Form II), 5.68 mg g^{-1} water at 25 °C.

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[2] Roy, et al. *International journal of pharmaceutics* 343.1-2 (2007): 79-89.
[3] Rodrigues, et al. *The Journal of Supercritical Fluids* 58.2 (2011): 303-312.
[4] Sun, et al. *Acta Crystallographica Section E: Structure Reports Online 58.4* (2002): o368-o370.