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Organic solvent vapor effects on phase transition of α and β tegafur upon grinding with solvent additives

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ABSTRACT

Solvent effects on α tegafur (5-fluoro-1-(tetrahydro-2-furyl)uracil) phase transition to β tegafur during grinding with solvent additive, as well as phase transition in samples exposed to 95% relative solvent vapor pressure has been studied in this research. Samples containing 0.5% and 0.1% of β tegafur in α and β tegafur mixture, as well as samples of pure α tegafur were ground with different solvent additives, and conversion degrees depending on the solvent were determined using PXRD method. Samples with α and β tegafur weight fraction of 1:1 were exposed to 95% relative solvent vapor pressure, and phase transition rates were determined. Solubility of α tegafur, solvent sorption and desorption behavior on α and β tegafur have been examined.

It was found that the conversion degree of α tegafur to β tegafur mainly depends on solubility of α tegafur in the relevant solvent, and the conversion degree to β tegafur is higher in such solvents, where solubility of α tegafur is higher. The samples ground in a ball mill with solvent additive had a trend of phase transition dynamics from α tegafur to β tegafur similar to the samples exposed to 95% relative solvent vapor pressure.

1. Introduction

Polymorphism is a well-known phenomenon, which is defined as ability of a compound to crystallize into more than one crystalline form that differs with molecule packing arrangements and/or conformations within the crystal lattice (Brittain, 2009; Hilfiker, 2006; Vippagunta et al., 2001). Most of active pharmaceutical ingredients exhibit polymorphism, therefore it is a common Pharmacopoeia requirement that active pharmaceutical ingredients in drugs must exist in one, fixed crystalline form. The thermodynamically stable form is usually chosen for pharmaceutical use, but recently, metastable forms are manufactured more often due to enhanced dissolution or bioavailability profiles and patent concerns (Brittain, 2009).

It is known that grinding can promote phase transition (Boldyrev, 2006; Chieng et al., 2006; Lin et al., 2006; Otsuka and Kaneniwa, 1986) of polymorphs, and solvent additive accelerates the process even more (Shan et al., 2002; Trask et al., 2004, 2005). In our previous experiments (Petkune et al., 2011) we developed a semi-quantitative analytical method for determining trace amounts of the thermodynamically stable polymorphic form in the mixture of thermodynamically stable and metastable polymorphic modifications, where the amount of the thermodynamically stable form was increased by grinding samples with a solvent additive. However, there is a lack of research on how solvents affect phase transition of polymorphs during the grinding.

The purpose of this study was to investigate the effect of solvent additive on phase transition of α and β tegafur and to take a look at possible causes that could affect phase transition during the grinding.

Tegafur (5-fluoro-1-(tetrahydro-2-furyl)-uracil) (see Fig. 1) α and β modifications were selected as a model material in this study.

Tegafur is an antitumor agent widely used in the treatment of various malignancies, particularly gastrointestinal and breast cancers (Uchida et al., 1993). Over years α, β, γ, δ and ε forms of tegafur have been reported in pharmaceutical literature (Actiņš et al., 2006; Needham et al., 2006; Uchida et al., 1993), but only α and β modifications are used for therapeutic purposes.

2. Materials and methods

2.1. Materials

Commercial samples of α and β tegafur were supplied by JSC Grindeks.

Used solvents – methanol, ethanol, *n*-propanol, 2-propanol, *n*-butanol, *n*-pentanol, *n*-heptanol, benzyl alcohol, ethyl acetate, *n*-propyl acetate, *n*-butyl acetate, 1,2-dichloroethane, chloroform,

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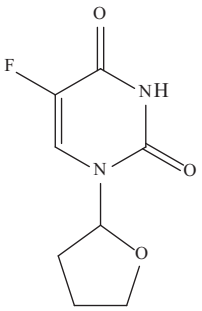

Fig. 1. Tegafur (5-fluoro-1-(tetrahydro-2-furyl)-uracil).

acetone, tetrahydrofuran, acetonitrile and toluene were supplied by Merck and used without any further purification. All of the used reagents had a reported purity >98%.

2.2. Methods

2.2.1. Sample preparation

The entire batches of α and β tegafur used in experiments were ground separately for 3 min to ensure the required sample homogeneity and to avoid preferred crystal orientation effects.

2.2.2. Determination of solvent effect on phase conversion degree during grinding

A sample (10 g) of tegafur α and β form mixture, containing 0.5% weight fraction of β form, was prepared from a 5.0% stock mixture that was diluted to the required concentration. Samples during preparation were homogenized in a Retsch MM300 ball mill (Retsch GmbH, Germany) for 5 min at 20 °C with 15 Hz shaking frequency. The analytical balance (BOECO, Germany) had an accuracy of ±0.0001 g.

The 0.20 g samples of prepared 0.5% mixture were each treated with 0.025 mL of solvent and ground in the ball mill at 10 Hz shaking frequency for 5 min. The solvents used in this experiment were methanol, ethanol, *n*-propanol, *n*-butanol, *n*-pentanol, *n*-heptanol, isopropanol, benzyl alcohol, ethyl acetate, *n*-propyl acetate, *n*-butyl acetate, 1,1-dichloroethane, chloroform, acetone, tetrahydrofuran, acetonitrile and toluene. Prepared samples were dried in opened grinding vessel for 30 min at 20 °C after the grinding. Dried samples were packed into glass holders with a weight capacity of ~150 mg and PXRD patterns were record.

2.2.3. Determination of α tegafur solubility in the solvents used

Approximately 0.2 g of α tegafur was added to ~12 mL of solvent in weighing bottle, and the prepared mixture was held at 30 °C for 48 h in a sealed weighing bottle and stirred occasionally to obtain a saturated tegafur solution. The clear, saturated mixture (4.0 mL, without any precipitate) was transferred to a clean, tared weighing bottle with a pipet that was also held at 30 °C. The weighing bottle with the saturated solution was left to evaporate at 30 °C, and then the weighing bottle with the dry residue was weighed on analytical balance (BOECO, Germany, $d = \pm 0.0001$ g). PXRD pattern was recorded for the dry residue. Solubility of α tegafur was determined in all the previously mentioned solvents.

2.2.4. Determination of solvent vapor effect on phase transition

Two samples (4 g each) of α and β tegafur mixture with weight ratio 1:1 were prepared. Samples were homogenized during the preparation in a ball mill for 5 min at 20 °C with 15 Hz shaking frequency. The prepared homogeneous samples were packed into glass holders and PXRD patterns for initial mixtures and pure α and β forms of tegafur were recorded. The samples were placed in desiccators with 95% relative solvent vapor pressure at 30 ± 0.5 °C, and depending on the transition rate, PXRD data were recorded at fixed moments.

Obtaining 95% relative solvent vapor pressure. To obtain a relative solvent vapor pressure of 95%, methanol, ethanol, *n*-propanol, 2-propanol, *n*-butanol, *n*-pentanol, *n*-heptanol and benzyl alcohol solution in glycerol were prepared, and acetone, acetonitrile, ethyl acetate, *n*-propyl acetate, *n*-butyl acetate, chloroform, tetrahydrofuran, 1,2-dichloroethane and toluene solution in dimethyl sulfoxide were prepared according to the Raoult's law (Eq. (1))

$$X = \frac{p_o - p}{p_o} = \frac{n}{n_o + n} \quad (1)$$

where X is the solvent's mole fraction in solution; p_o is the vapor pressure of pure solvent; p is the solvent's partial vapor pressure over a solution; n represents the investigated solvent molar amount in the solution; n_o is the moles of glycerol or dimethyl sulfoxide in the solution.

Temperature control. Desiccators with the prepared solvent solutions were placed in an air thermostat (Memmert, Universal Oven UFB-500) at 30 ± 0.5 °C 24 h prior to sample insertion.

2.2.5. Solvent sorption studies

Solvent sorption experiments were performed in weighing dishes at 30 °C by using pure α and β tegafur. The 0.20 g samples of pure α and β tegafur were weighed in separate weighing dishes with accuracy ±0.0001 g and placed in desiccators with 95% partial pressure of the relevant solvents (see Section 2.2.4). Depending on the sorption rate, samples were weighed at fixed moments.

2.2.6. Solvent desorption studies

Desorption experiments were performed using completely solvent-saturated samples from the sorption experiment (described in Section 2.2.5). The 30 ± 2 mg of solvent-saturated samples were quickly placed (in less than 20 s) in aluminum sample pan, and desorption experiments were performed using a *TG/DTA6300 EXSTAR6000* instrument with open aluminum sample pans having internal diameter of 5 mm and height of 2.5 mm, under dry nitrogen atmosphere with flow rate of 250 mL/min in isothermal conditions at 30 °C. Desorption rate was highly dependent on mass of the sample; therefore samples with equal mass were used. The highest possible mass (30 ± 2 mg) was placed into each sample pan to minimize the error of sample weighing and to reduce the time of weighing (the sample holder was simply filled up to the edge). Mass changes were recorded every 0.5 s.

2.2.7. Karl Fischer titration

The water amount in solvents was quantified by a volumetric Karl Fischer titrator Metrohm 836 Titrando with one-component system using HYDRANAL – Composite 5 (Fluka, Germany) as titrating solution. The mixture was calibrated against pure water.

The volume of solvents used in Karl Fischer titration was 5.0 and 1.0 mL depending on the expected water content in solvents.

The water content (ω_{H_2O}) of sample was calculated using the following equation:

$$\omega_{H_2O} = \frac{V_{KF} \cdot W_{eq} \cdot 100}{W_{sample}} \quad (2)$$

where V_{KF} is the consumption of titrant (mL), W_{eq} is the titer of titrant (mg H_2O/mL) and W_{sample} is the weight of sample (mg).

2.2.8. PXRD analysis

Samples were analyzed with a Bruker D8 Advance powder X-ray diffractometer (Bruker AXS, Karlsruhe, Germany), equipped with a PSD *LYNXEYE* detector. Measurements were performed with CuK radiation (1.54180 Å) at room temperature. The following conditions were used: step-scan mode with a step size of 0.02°; scan