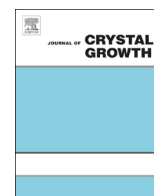




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# Thermodynamic equilibrium, metastable zone widths, and nucleation behavior in the cooling crystallization of gestodene–ethanol systems



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## ABSTRACT

A systematic investigation of nucleation behavior for the batch cooling crystallization of unseeded gestodene–ethanol solutions was carried out. The solubilities of the two polymorphs (forms I and II) of gestodene in ethanol were gravimetrically measured between 268.15 and 333.15 K under atmospheric pressure of 0.10 MPa. In addition, the metastable zone widths (MSZWs) of the gestodene–ethanol solutions were determined by the polythermal method combined with the focused beam reflectance measurement (FBRM<sup>®</sup>) technique. Moreover, polymorphic forms of the grown crystals were identified by X-ray powder diffraction (XRD) and optical microscope. Experimental results indicated that the measured MSZWs were dependent on numerous technological parameters, including cooling rate, saturation temperature, and agitation intensity. With variation of the nucleation temperature and cooling rate, forms I, II, and a mixture of the two forms were crystallized from ethanol solution. The nucleation kinetic parameters were estimated from MSZW data using the self-consistent Nývlt-like approach. Due to the high solubility of form I in ethanol at the corresponding temperature range, the stronger solute–solvent interactions confirmed that the nucleation of form I had a greater activation energy than that of form II.

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## 1. Introduction

Crystallization is a key unit operation in the chemical industry, in particular the pharmaceutical industry, for the production of high quality crystals. The crystallization process involves two main steps, namely nucleation and crystal growth. The driving force of crystallization is supersaturation, which is defined as the difference between the actual and saturated concentrations of the solution. A degree of supersaturation, known as supersolubility, is required for the creation of the new solid interface [1]. The metastable zone, defined as the region between the solubility and supersolubility curves, is considered ideal region for crystal growth [2]. The metastable zone width (MSZW) is conventionally measured using the polythermal method, by cooling of a saturated solution at a constant rate until nucleation occurs. The difference between the nucleation temperature and saturated temperature is known as the supercooling degree. To date, numerous techniques have been employed to detect nucleation, including turbidity [3,4], electrical conductivity

[4,5], ultrasound velocity [3,6,7], focused beam reflectance measurement (FBRM<sup>®</sup>) [8–10], and the heat of crystallization [11].

The Nývlt equation [12,13] is the classical approach for the estimation of nucleation kinetics from MSZWs. It is assumed that the nucleation rate is related to the supersaturation rate at the beginning of the nucleation on a mass basis. Recently, Sangwal proposed a self-consistent Nývlt-like equation [14–16] by defining nucleation rate as a function of  $\ln S_{\max}$  (Eq. (2)).  $S_{\max}$  is defined as the maximum supersaturation ratio. The resulting equation leads to a linear relationship of  $\ln(\Delta T_{\max}/T_0)$  versus  $\ln r$  for the measured maximum supercooling ( $\Delta T_{\max}$ ) of the solute–solvent system saturated at a temperature ( $T_0$ ), followed by cooling at a constant rate ( $r$ ) (Eq. (8)). This plot gives a straight line, with the slope yielding the apparent nucleation order ( $m$ ) and the term  $\ln(f/KT_0)$  being estimated from the intercept. In addition, the activation energy for crystal formation in solution can be estimated by an Arrhenius-type equation, as suggested by Sangwal [16].

Gestodene, i.e., 13-ethyl-17 $\beta$ -hydroxy-18,19-dinor-17 $\alpha$ -pregna-4,15-dien-20-yn-3-one, a potent synthetic progestin, is available for clinical use through combination with low doses of ethinyl estradiol to provide low dose oral contraceptive preparations [17,18]. The molecular structure of gestodene is shown in Fig. 1.

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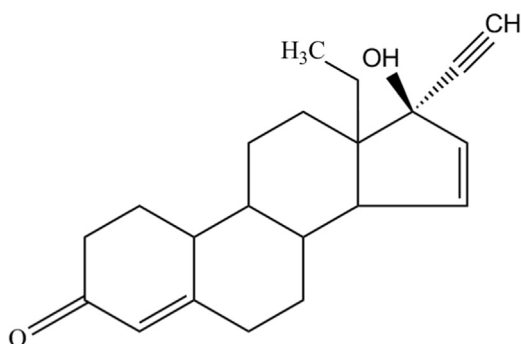


Fig. 1. Molecular structure of gestodene.

A number of studies have reported that gestodene is capable of exhibiting distinct polymorphs [19,20], with accurate crystal structures of the two forms being determined by Geerestein et al. [19] and Eckle et al. [20]. In industry, gestodene is usually refined by crystallization from ethanol. To produce the desired form of this active pharmaceutical ingredient (API) on an industrial scale, control and understanding of the nucleation phenomenon in solution is required to design a robust crystallization process. We herein report a gravimetric method for determining the solubilities of the two gestodene polymorphs in ethanol. An EasyMax reactor system combined with focused beam reflectance measurement (FBRM<sup>®</sup>) was employed to measure the MSZWs of the gestodene–ethanol solutions. Nucleation kinetics were estimated using the self-consistent Nývlt-like approach, and the formation of the two polymorphs in ethanol was discussed.

## 2. Theory

The Nývlt approach [12,13] can be expressed according to Eq. (1):

$$\ln \Delta T_{\max} = \frac{1-m}{m} \ln \left( \frac{dc}{dT} \right) - \frac{1}{m} \ln k + \frac{1}{m} \ln r \quad (1)$$

where  $\Delta T_{\max}$  is the difference between the saturation temperature ( $T_0$ ) and nucleation temperature ( $T_{\text{lim}}$ ),  $c$  is the mole fraction solubility,  $T$  is the temperature, and  $m$ ,  $k$ , and  $r$  denote the apparent nucleation order, nucleation constant, and cooling rate, respectively. Usually, Nývlt's equation gives a good fit to the experimental MSZW. However, the physical nature of the apparent nucleation order and nucleation constant remains unclear. Thus, Sangwal recently proposed a self-consistent Nývlt-like equation [14–16], where the nucleation rate ( $J$ ) could be described by the power-law expression as a function of supersaturation ratio ( $S_{\max}$ ), as shown in Eq. (2):

$$J = K(\ln S_{\max})^m \quad (2)$$

Based on the theory of regular solutions for the temperature dependence of solubility, the relationship between relative supersaturation ( $S_{\max}$ ) and the maximum metastable zone width ( $\Delta T_{\max}$ ) can be expressed according to Eq. (3):

$$\ln S_{\max} = \ln \left( \frac{c_0}{c_{\text{lim}}} \right) = \left( \frac{\Delta H_d}{RT_0} - \frac{\Delta T_{\max}}{T_{\text{lim}}} \right) \quad (3)$$

where  $c_0$  and  $c_{\text{lim}}$  are the concentrations of the saturated solution temperature and nucleation temperature, respectively. In addition,  $\Delta H_d$  and  $R$  represent the change of dissolution enthalpy and universal gas constant ( $8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ ), respectively.

Furthermore, Eq. (2) can also be expressed as shown in Eq. (4):

$$J = K \left( \frac{\lambda u}{1-u} \right)^m \quad (4)$$

using Eqs. (5) and (6) below:

$$\lambda = \frac{\Delta H_d}{RT_0} \quad (5)$$

$$u = \frac{\Delta T_{\max}}{T_0} \quad (6)$$

The nucleation rate ( $J$ ) is related to the rate of supersaturation generation ( $\Delta c/c_0$ ) according to Eq. (7):

$$J = f \frac{\Delta c}{c_{\text{lim}} \Delta t} = f \frac{\Delta c}{c_{\text{lim}}} \frac{\Delta T}{\Delta t} = f \left( \frac{\lambda}{1-u} \right) \left( \frac{r}{T_0} \right) \quad (7)$$

where  $f$  is the proportionality constant. The combination of Eqs. (4) and (7) gives Eq. (8):

$$\ln u = \varphi + \beta \ln r \quad (8)$$

where

$$\varphi = \frac{1-m}{m} \ln \left( \frac{\lambda}{1-u} \right) + \frac{1}{m} \ln \left( \frac{f}{KT_0} \right) \quad (9)$$

$$\beta = \frac{1}{m} \quad (10)$$

where  $\lambda$  can be derived from the solubility data of the compound of interest. Therefore, the nucleation order ( $m$ ) and the term  $\ln(f/KT_0)$  can be estimated from the slope and intercept of the resulting plot of  $\ln u$  versus  $\ln r$ .

## 3. Materials and methods

### 3.1. Materials and sample preparation

Ethanol (analytical grade) was purchased from Bolt Chemical Trade Co., Ltd. (Tianjin, China) and employed without further purification. Gestodene (mass fraction purity  $\geq 99.5\%$ ) was provided by the China Resources Zizhu Pharmaceutical Co. Ltd (Beijing, China), and was recrystallized under the following conditions to obtain pure crystals. Pure crystals of form I were obtained using 2-propanol, while pure crystals of form II were obtained from crystallization in ethanol. Solutions of the gestodene were prepared, filtered, and allowed to crystallize at  $35^\circ \text{C}$  and  $10^\circ \text{C}$  for forms I and II, respectively.

### 3.2. Analytical and observation methods

#### 3.2.1. X-ray powder diffraction (XRD)

XRD was conducted on a XD-3 automatic diffractometer (Puxi, China) using a  $\text{CuK}\alpha$  tube powered at 40 kV and 40 mA. The data were collected at the room temperature of  $25 \pm 2^\circ \text{C}$  from  $5^\circ$  to  $75^\circ$  ( $2\theta$ ), in steps of  $0.02^\circ$  with a scan speed of  $2^\circ \text{ min}^{-1}$ . An aluminum sample holder was used, and approximately 200 mg of sample was loaded, taking care not to introduce a preferential orientation of crystals.

#### 3.2.2. Optical microscope

The crystal habits of the polymorphs of gestodene obtained in the ethanol by cooling crystallization have been characterized using an optical microscope GMR-213 system (Guangmi Instrument Co., Ltd., Shanghai, China).

#### 3.2.3. Focused beam reflectance measurement (FBRM<sup>®</sup>)

A focused beam reflectance measurement (FBRM<sup>®</sup>) probe (D600L-C22-K, Mettler Toledo, Switzerland) was used to provide in situ detection of nucleation. The FBRM<sup>®</sup> probe was equipped with iC FBRM<sup>®</sup> software for recording and analyzing the experimental data. For all measurements, a 10 s frequency was employed

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