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Nucleation kinetics of lovastatin in different solvents from metastable zone widths

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HIGHLIGHTS

- Metastable zone width of lovastatin in three solvents was determined.
- Nucleation kinetics of lovastatin in different solvents was estimated.
- Crystal habits of final products were investigated.

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ABSTRACT

Cooling crystallization of lovastatin in methanol, ethanol and acetone was carried out and the metastable zone widths in those solutions were determined experimentally by the polythermal method using a Turbidity Monitoring Technique. Two theoretical approaches, the self-consistent approach and classical 3D nucleation theory approach, were then employed to estimate the nucleation kinetics from the measured metastable zone width. The results suggested that nucleation in ethanol and acetone is instantaneous and follows polynuclear (PN) mechanism, while in methanol the nucleation is progressive with a high nucleation order. Because of the high solubility of lovastatin in these solvents, strong solute–solvent interactions exist, which make the activation energy for crystal formation different from that for self-diffusion.

1. Introduction

Solution crystallization as a unit operation in pharmaceutical industry serves the dual purposes of separation and purification of the active pharmaceutical ingredients (APIs). The primary goal is to produce crystals with high purity. Moreover, other physico-chemical properties such as crystal structure, morphology and size distribution are of equal importance (Myerson, 1993; Doki et al., 2001). To accomplish these goals, one has to gain control over the entire crystallization process.

In solution crystallization, nucleation plays a decisive role in determining the crystal structure and size distribution. Hence, understanding the fundamentals of nucleation is crucial to achieve control over these properties (Erdemir et al., 2009). Nucleation process is known to be affected by many factors such as solvents used for the preparation of supersaturated solution, impurities presented in the solution, crystal seeds added in the system, and cooling and agitation rate applied to the process (Nývlt et al., 1985). Among them, solvent effects are of particular practical importance and can be exploited to control the process of crystallization, and a wide variety of solvents can be employed when dealing with organic compounds. While great efforts have been made to investigate the solvent effects on crystal growth, few papers are found addressing the influence of solvents on nucleation (Mullin, 2001). For the solvent effect on crystal growth, Bennema (1992) suggested that a favorable interaction with solvent could reduce surface tension and transform a smooth interface to a rough one, thus promoting the rate of crystal growth. On the other hand, Lahav and Leiserowitz (2001) indicated that desorption of a preferentially adsorbed solvent molecule may cause additional energy barrier, and the growth rate could consequently be reduced. Solvents will also have influence on the aggregation state (Davey et al., 2013; Vekilov, 2010; Larson and Garside, 1986) and diffusion level of solute molecules (Bennema, 1969; Yürüdü et al., 2011; Perry et al., 2013; Kumar, 2009).

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For solvent effect on nucleation, the classical theory, which assumes that clusters are formed in solution by an addition mechanism, suggests that the change of Gibbs free energy for the formation of new nucleus is strongly dependent on solvent as a result of different liquid–solid interfacial energy. The critical size of nucleus and the nucleation rate will be subsequently changed with solvent (Myerson, 1993). A modern two-step mechanism indicates that the solvent effect can be attributed to the change of conformation and aggregation of solute molecules and the structure of solute clusters in solution (Vekilov, 2010).

Metastable zone width (MZW) measurement has been commonly employed to determine the window for crystallization operation and to probe the nucleation mechanism (Sahin et al., 2007; Titiz-Sargut and Ulrich, 2002; Omar and Ulrich, 2006; Ceyhan and Bulutcu, 2011). The metastable zone width is determined by cooling a saturated solution until nuclei is detected (Nývlt et al., 1985; Mullin, 2001), and is defined as the temperature difference between the saturation temperature and the nucleation temperature. Therefore, MZW is closely related to the nucleation kinetics. Continuous effort has been devoted in determining or predicting the metastable zone width of various compounds during the last four decades, as required for the design, control and optimization of the process of crystallization, and an explanation of the physical basis of MSZW of solute–solvent systems was made clear by Sangwal's group in 2008 (Sangwal, 2009).

Lovastatin (CAS no. 75330-75-5) is one of the member of statins, which is known to exists in open ring hydroxyl acid and also in lactone form. Lovastatin and its analogs inhibit the enzyme 3-hydroxy-3-methyl-glutarylcoenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevolanate, which is an early rate-limiting step in cholesterol biosynthesis in the body. Lovastatin also increases the number of LDL-receptors at the surface of the cell membrane, which removes the LDL cholesterol circulating in the blood, thereby inducing the lowering of blood plasmacholesterol level (Sun et al., 2005).

Table 1
Sample table[a].

Chemical name	Source	Mass purity	Purification method	Analysis method
Lovastatin	Hisun Pharmaceutical	0.998	None	HPLC
Methanol	Shanghai Chemical	0.995	None	HPLC
Ethanol	Shanghai Chemical	0.995	None	HPLC
Acetone	Shanghai Chemical	0.995	None	HPLC

[a] Standard uncertainty for mass fraction u is $u(c) = \pm 0.005$.

In industrial manufacturing, lovastatin is often refined through crystallization from methanol, ethanol and acetone. In this work, the MZW data of lovastatin in methanol, ethanol and acetone at atmospheric pressure, are determined by monitoring the variation of turbidity with time and the kinetics of nucleation is estimated by self-consistent Nývlt-like approach and classical 3D nucleation theory. These results are necessary for the design and optimization of the crystallization process of lovastatin.

2. Theoretical background

2.1. Self-consistent Nývlt-like approach

Nývlt's equation has been frequently employed to estimate the nucleation kinetics because of its analytical simplicity, which can be expressed by (Nývlt et al., 1985)

$$\ln \Delta T_{\max} = \frac{1-m}{m} \ln \left(\frac{dc}{dT}\right)_T - \frac{1}{m} \ln k + \frac{1}{m} \ln b, \tag{1}$$

where $\Delta T_{\max}$ is the maximum temperature difference between saturation temperature, T_0, and nucleation temperature, $T_{\lim}$. c and T denote the mole fraction solubility and temperature, and m, k and b refer to the apparent nucleation order, nucleation constant and cooling rate, respectively. Usually, Eq. (1) gives a good fitting of the measured metastable zone width. However, as the units of the calculated apparent nucleation order and nucleation constant are complicated, their physical meaning still remains obscure. Given this situation, Sangwal recently proposed self-consistent Nývlt-like equation (Sangwal, 2009a, 2009c, 2011). In this approach, the nucleation rate J was redefined as

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

Referring to the regular solution theory, the relationship between supersaturation ratio and the maximum temperature difference can be written as (Sangwal, 2011)

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

where $c_{\lim}$ and c_0 are the solution concentrations corresponding to the nucleation temperature, $T_{\lim}$, and saturation temperature, T_0. $S_{\max}$ refers to the supersaturation ratio when primary nucleation occurs. ΔH_d and R denote the dissolution enthalpy and the universal gas constant.

With

$$\lambda = \frac{\Delta H_d}{RT_0}, \text{ and} \tag{4}$$

$$u = \frac{\Delta T_{\max}}{T_0}, \tag{5}$$

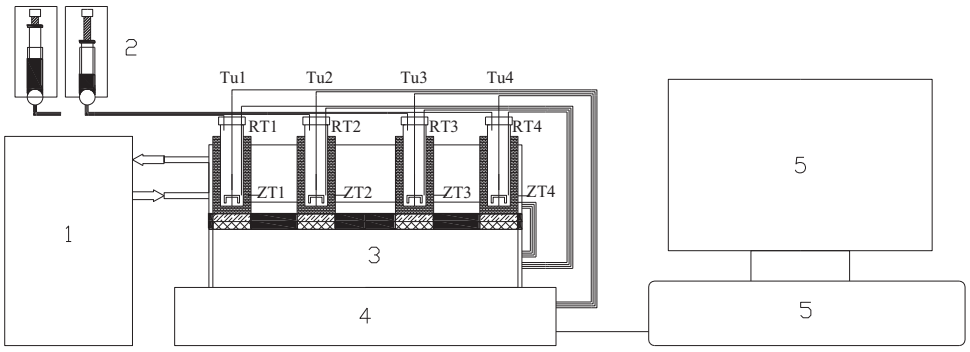

Fig. 1. Schematic diagram of experimental apparatus for measurements of solubility and supersolubility.

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