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Relation between Metastable Zone Width and Induction Time of Butyl Paraben in Ethanol

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Abstract

Relation between induction time and metastable zone width in cooling crystallization has been developed based on Classical Nucleation Theory and an interpretation equation of this relation has been used to extrapolate metastable zone width from the induction time results in homogenous primary nucleation. The metastable zone width is determined by the interfacial energy and the pre-exponential factor. 440 metastable zone experiments of butyl paraben in ethanol at five different cooling rates have been performed. The experimental metastable zone widths of butyl paraben in ethanol are fairly close to that extrapolated from the induction time results. Positive correlation between cooling rate and experimental metastable zone width is in good agreement with the interpretation equation, by which equation the relations between stirring rate, saturation temperature and volume of solution with estimated metastable zone width have been investigated.

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Key words: metastable zone width, induction time, Classical Nucleation Theory, cooling crystallization, butyl paraben, ethanol, cooling rate, stirring rate, volume of solution, saturation temperature

Introduction

Nucleation is a process of forming new phase and is the widely spread phenomenon in both nature and in industrial. The crystallization is the final step in the manufacture of most active pharmaceutical ingredients and small organic compounds and nucleation has a governing influence on crystallization product. In crystallization experiments by isothermal method and polythermal method,[1] the time period from establishment of the supersaturated state to nucleation is estimated as induction time and nucleation time, respectively. The metastable zone width (MSZW) is determined from nucleation time and cooling rate. The solution is under constant supersaturation and increasing supersaturation in isothermal experiment and polythermal experiment, respectively. Bigger supersaturation results in bigger driving force of the nucleation. Plenty of researches have been reported to investigate the metastable zone in cooling crystallization, for example MSZW of acylanilides in aqueous ethanol,[2] paracetamol in water with an oscillatory baffled crystallizer,[3] paracetamol in ethanol by process analytical technology (PAT) method,[4] benzoic acid in ethanol-water mixtures,[5] and co-crystal of benzoic acid/isonicotinamide.[6] Several approaches to predict MSZW have been developed by Nyvlt,[7] Kubota[8] and Sangwal.[9] Recently MSZW by polythermal method has been investigated by using the probability theory,[10-12] correlating with isothermal method,[9, 12-14] and simulating with software programs.[15] MSZW is influenced by various experimental conditions as cooling rate,[16] saturation temperature,[17, 18] stirring rate[19] and solution volume.[10, 11] Almost all these experiments or theory studies of metastable zone width are based on approach equations,[8] with similar form $J = b_1 \Delta C^{b_2}$ or $J = b_1 \Delta T^{b_2}$, where the nucleation rate, J, is assumed to be linear proportional to b_2 order of supersaturation or supercooling temperature, respectively. These empirical equations of nucleation rate has been utilized[7, 8] to capture fairly good fitting of some experimental MSZW results.[20, 21]

While critical free energy, pre-exponential factor of nucleation and interfacial energy can be determined from induction time experiments, by defining homogenous primary nucleation rate as $J = Aexp\left(-\frac{\Delta G_c}{kT}\right)$, based on the Classical Nucleation Theory which is still the basic theory most widely used in investigations of the nucleation phenomena.[22-25] However, the relation between the Arrhenius-form equation of the nucleation rate employed in the induction time experiments, based on the Classical Nucleation Theory, with the polynomial-form equation of the nucleation rate empirically used in metastable zone experiments is not well estimated, neither is the relation between the isothermal method and the polythermal method. In previous work[26], the induction times of butyl paraben in ethanol have been determined and the solid-liquid interfacial energy, critical free energy and pre-exponential factor in primary homogenous nucleation have been estimated by Classical Nucleation Theory. In this work, metastable stable zone widths of butyl paraben in ethanol at cooling rate of 20.0, 15.0, 12.0, 6.0 and 4.0 K/hour have been determined. The relation between the induction time and the metastable zone width has been developed based on the Classical Nucleation Theory, by which relation the metastable zone width at different cooling rates can be extrapolated from the induction time results. The extrapolated metastable zone widths are compared with the experimental metastable zone widths of butyl paraben in ethanol, as well as of isonicotinamide in ethanol[12] and of paracetamol in ethanol,[27] respectively.

Influences of several thermodynamic and kinetic factors on the metastable zone width have been investigated.

Butyl paraben (butyl 4-hydroxybenzoate), a natural and nonirritating organically derived preservative, is widely used in pharmaceutical products and cosmetics[28] for many years, and is generally considered to be safe[29]. The butyl paraben molecule includes an aromatic ring to which an alcohol group and ester group is attached in the para position, and butyl paraben has a relative low melting point 340.49K[30], a very high solubility in ethanol[31, 32] and only one polymorph[26].

Theory

Induction time

In the Classical Nucleation Theory, the rate of primary homogeneous nucleation, J, is in the form of the Arrhenius reaction rate equation:[28]

$$J = Aexp\left(-\frac{\Delta G_c}{kT}\right) \tag{1}$$

where k is the Boltzmann constant, T is nucleation temperature, A is pre-exponential factor. Free energy of nucleation, dependent on nucleus radius, is calculated by

$$\Delta G = \Delta G_v + \Delta G_s = -\frac{4\pi r^3}{3v_m}\Delta\mu + 4\pi r^2\sigma \tag{2}$$

r is the nucleus radius, v_m is molecular volume of solute, $\Delta\mu$ is driving force of nucleation and σ is the interfacial energy. $4\pi r^2\sigma$ denotes ΔG_s, the excess free energy between surface of the nucleus and bulk of the nucleus, and $-\frac{4\pi r^3}{3v_m}\Delta\mu$ represents ΔG_v, the volume excess energy which is the difference in free energy between a nucleus of infinite size and the solute in solution. As

ΔG_s is positive and ΔG_v is negative, the free energy of nucleation has a maximum value, ΔG_c, at the point $d\Delta G/dr = 0$, when a nucleus forms with critical radius, r_c,

$$r_c = \frac{2v_m\sigma}{\Delta\mu} = \frac{2v_m\sigma}{kTlnS} \tag{3}$$

where S is supersaturation, then combine Equ. (1), (2) and (3),

$$J = Aexp\left(-\frac{16\pi\sigma^3{v_m}^2}{3k^3T^3(lnS)^2}\right) \tag{4}$$

As the induction time, t_{ind}, is inversely proportional to the nucleation rate[29] in a solution with volume of V,

$$lnt_{ind} = -lnJV = -lnAV + \frac{16\pi\sigma^3{v_m}^2}{3k^3T^3(lnS)^2} = -lnAV + \frac{B}{T^3(lnS)^2} \tag{5}$$

Experimental induction time results are usually evaluated by plotting lnt_{ind} versus $T^{-3}(lnS)^{-2}$ for determination of the solid-liquid interfacial free energy, σ, from the slope, B, of the correlated linear line,

$$B = \frac{16\pi\sigma^3{v_m}^2}{3k^3} \tag{6}$$

$$\sigma = \left(\frac{3k^3B}{16\pi{v_m}^2}\right)^{\frac{1}{3}} \tag{7}$$

Knowing the interfacial energy allows for calculation of the critical free energy, ΔG_c, of the nucleation and the radius, r_c, of the critical nucleus.

Metastable zone width extrapolated from induction time

For primary homogenous nucleation of one solute in a solvent, $3k^3B$ in Equ. (6) is constant and only dependent on the solid-liquid interfacial energy, and Equ. (5) can be rewritten to

$$3k^3 \cdot T^3(lnS)^2 \cdot ln(AVt_{ind}) = 16\pi\sigma^3 v_m^2 = N \tag{8}$$

where N is a constant nucleation parameter for one solution with unit of kJ^3.

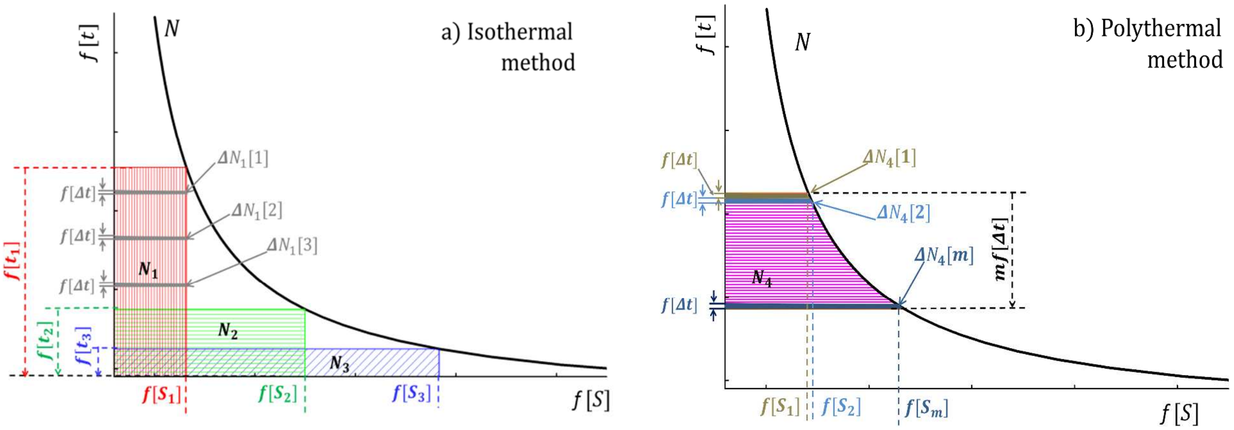

Figure 1 Interpretation of isothermal method and polythermal method in primary homogenous nucleation by Classical Nucleation Theory with Equ. (8).

In a solution $ln(AVt_{ind})$ is inversely proportional to $3k^3T^3(lnS)^2$, where $3k^3T^3(lnS)^2$ is a function of supersaturation S, $f(S)$, and $ln(AVt_{ind})$ can be considered as a function of time t, $f(t)$. Correspondingly, $f(S)$ is inversely proportional to $f(t)$. By isothermal method, Figure 1 a) shows that rectangular area, N_1, determined by $f(S_1) \times f(t_1)$, is equal to the nucleation constant N for one solute in a solvent. In the same system under constant supersaturation S_2 and S_3, the values of $f(S_2) \times f(t_2)$ and $f(S_3) \times f(t_3)$ are both equal to $f(S_1) \times f(t_1)$, i.e. N_1, N_2 and N_3 all equal to N. With decreasing of the supersaturation, i.e. $f(S_3) > f(S_2) > f(S_1)$, induction time increases, i.e. $f(t_3) < f(t_2) < f(t_1)$, shown in Figure 1 a), which also agrees with that the induction time becomes almost infinite at very low supersaturation. By mathematical method of integration, at each $f[\Delta t]$ (represents each very short time period), the system gains $\Delta N_1[1], \Delta N_1[2], \ldots, \Delta N_1[m], \ldots, \Delta N_1[n]$, respectively, which are equal in isothermal method, and when the accumulation value from $\Delta N_1[1]$ to $\Delta N_1[m]$ is equal to N, i.e. the area covered from $\Delta N_1[1]$ to $\Delta N_1[m]$ is up to N, the nucleation happens.

In other words, for each constant supersaturation, S_n, the nucleation would happens at the point when system changes from $f(S_n) \times f(t_n - \Delta t)$ to $f(S_n) \times f(t_n + \Delta t)$, and the parameter N , which equals to $f(S_n) \times f(t_n)$, is constant in one system. Accordingly, for one system N can be defined as the critical potential of the nucleation and $\sum \Delta N_n$ is accumulation of the nucleation potential after solution becomes supersaturated until nucleation at $\sum \Delta N_n \geq N$. In both the isothermal and the polythermal experiment, the accumulation of the nucleation potential continuously approaches to the critical nucleation potential before occurring of the nucleation.

In an isothermal experiment, for example N_1, during each short time period, Δt, the accumulated nucleation potential, ΔN_1, is constant and equal to $\frac{\Delta t}{t_1} N$ under constant supersaturation. When the accumulation of nucleation potential is up to the critical nucleation potential, N, nucleation happens at t_1 (induction time) which can be estimated from $f(t)$, and $f(t)$ can be easily calculated from $f(t_1) = N / f(S_1)$. While in a polythermal experiment shown in Figure 1 b), the temperature decreases and the supersaturation increases (from S_1 as an example) during the cooling process, correspondingly $f(S_n)$ increases with time, i.e. $f(S_1) < f(S_2) < \cdots < f(S_m) < \cdots < f(S_n)$, correspondingly, t_n increases estimated by $f(t_n) = N/f(S_n)$, i,e, $f(t_1) > f(t_2) > \cdots > f(t_m) > \cdots > f(S_n)$. During each short time period, Δt, ($f[\Delta t]$), the accumulated nucleation potential, calculated as $\Delta N_4[n] = \frac{\Delta t}{t_n} N$, increases with time i.e. $\Delta N_4[1] < \Delta N_4[2] < \cdots < \Delta N_4[m]$, and when the accumulation value from $\Delta N_4[1]$ to $\Delta N_4[m]$ is equal to N, i.e. the area covered from $\Delta N_4[1]$ to $\Delta N_4[m]$ is up to N, the nucleation happens.

In a polythermal experiment, during each short time period (a step of time), Δt, the accumulated nucleation potential at temperature T and under supersaturation S is estimated as,

$$\Delta N = \frac{\Delta t}{t_n} N = \frac{AV\Delta t}{exp(\frac{N}{3k^3T^3(lnS)^2})} \cdot N \tag{9}$$

where the supersaturation is defined as ratio between actual solute molar activity a and equilibrium solute molar activity a^*, and the supersaturation is usually estimated as ratio between actual solute molar fraction solubility x and equilibrium solute molar activity x^*, assuming ratio between activity coefficients is neglectable,

$$lnS = ln\frac{a}{a^*} \approx ln\frac{x}{x^*} = lnx - lnx^* \tag{10}$$

In this work solubility equation with form of $lnx = A_sT^{-1} + B_s + C_sT$ is used as in previous investigation[30]. If in a polythermal experiment linear cooling rate of z_c is employed, the saturated temperature of the solution is T_0, and the time when solution cools down to temperature T_0, to establish saturation, is recorded as $t = 0$, the supersaturation at time, t, can be calculated as,

$$lnS = A_sT_0{}^{-1} - A_s(T_0 - z_ct)^{-1} + C_sT_0 - C_s(T_0 - z_ct) \tag{11}$$

The temperature and supersaturation are both dependent on the time, with decreasing temperature and increasing supersaturation, combing Equ. (9) and Equ. (11) the accumulated nucleation potential from time, $t = \Delta t$, to time, $t = m\Delta t$, becomes:

$$\sum_{n=1}^{m} \Delta N = \sum_{n=1}^{m} \frac{AV\Delta t}{exp(\frac{N}{3k^3(T_0-z_Cn\Delta t)^3\left[A_ST_0{}^{-1}-A_S(T_0-z_Cn\Delta t)^{-1}+C_ST_0-C_S(T_0-z_Cn\Delta t)\right]^2})} \cdot N \tag{12}$$

where n and m are positive integers. The accumulated nucleation potential increases with time, and at the minimum value of m allowing $\sum_{n=1}^{m} \Delta N$ is equal to or bigger than the critical nucleation potential, N, nucleation happens at $t = m\Delta t$.

Experimental work

Materials

Butyl paraben (BP, CAS reg. no. 94-26-8, mass purity > 99.0%), was purchased from Sigma-Aldrich, and used without further purification and ethanol (E, purity > 99.7%) from Solveco and was used as obtained.

Polythermal experiments

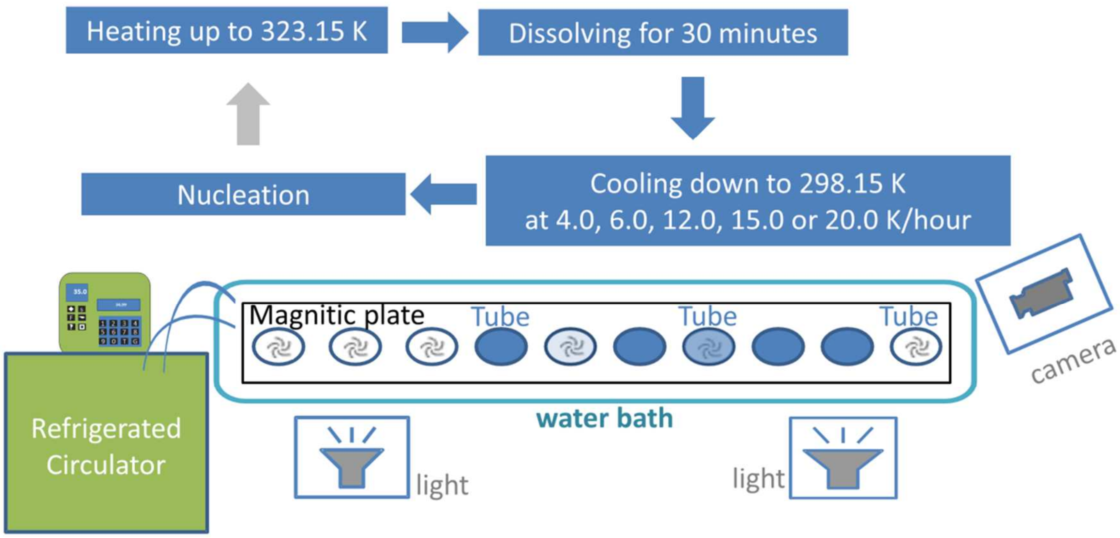

Figure 2 Experimental procedures and multi-vial set-up of metastable zone experiments

100 ml solution of butyl paraben in pure ethanol was prepared in a sealed 300 ml glass bottle, with concentration of 4.688 g butyl paraben per g ethanol. The bottle was then submerged in a water bath kept at a constant temperature of 323.15 K which was about 10 K above the saturation temperature of 313.14 K. The solution was stirred for several hours using a magnetic stir bar during dissolution to make sure all solid material had been dissolved. The solution was transferred into ten 20 ml test tubes (about 5 ml per tube) of size length × diameter: $12\frac{3}{8} \times 1\frac{7}{8}$ cm by pre-heated syringes equipped with 0.2 μm PTFE membrane filters. A PTFE-coated magnetic stir bar of size of $1\frac{3}{8} \times \frac{5}{8}$ was placed in each of the tubes, after which they were sealed by parafilm before capped and then sealed again by parafilm outside the cover to prevent evaporation. Each batch of tubes was first kept in a thermostatic bath at the dissolution temperature, 323.15 K, for 30 min, and then the temperature of the water bath cooled by a Juboo refrigerated circulator, where all the tubes were fixed in a transparent plastic frame (Figure 2). The temperature of the bath was calibrated by a calibration thermometer with a 0.01 K uncertainty before the nucleation experiments were performed. Agitation of 200 rpm was provided by a multi-pole submersible magnetic stirring plate. Nucleation of the initially clear solutions was monitored using a Sony DCR-SR72e digital camcorder mounted on a tripod at a slanting angle as well as white stirrer in each tube and black lines on the magnetic plate were clearly visible before nucleation. Because of the high concentration of butyl paraben, the nucleation and crystallization occurred very rapidly once started. The time from the first appearance of crystals in a tube to the time when the tube was completely turbid (white) was always less than 10 s. The linear temperature profile of the water batch was controlled by a program from 323.15K to 298.15K to assure solution in every tubes nucleate then the water bath was heated to 323.15 K and kept there for 30 min, shown as Figure 2. By visual analysis of the

video recordings, comparing frame by frame (less than 1 second), the time period from the solution cooled down to 313.14 K to the point first observation of decreasing sharpness of the white stirrer and black lines (Figure 2) was identified as the nucleation time. The experiments were repeated 14 times at 20.0 K/hour, 9 times at 15.0 K/ hour, 9 times at 12.0 K/hour, 6 times at 6.0 K/hour and 6 times at 4.0 K/hour for totally 440 nucleation times determined.

Results and discussions

Experimental metastable zone width

Figure 3 shows experimental results including from 60 to 140 nucleation time data with cooling rate from 4.0 K/hour to 20.0 K/hour, respectively. Experiments with cooling rate at 12.0, 15.0 and 20.0 K/hour have similar nucleation times which are much shorter than nucleation times with cooling rate at 6.0 K/hour and the nucleation times with cooling rate at 4.0 K/hour are about 1000s longer on average than the nucleation times with cooling rate at 6.0 K/hour. The shortest, median, average and longest nucleation time increase in the order of decreasing cooling rate that 20.0 K/hour < 15.0 K/hour < 12.0 K/hour < 6.0 K/hour < 4.0 K/hour, respectively. The differences between the smallest nucleation times at every two different cooling rates are fairly similar to the difference between the longest nucleation times, respectively, shown in Figure 3. The ratios between the longest nucleation time with the shortest nucleation time in polythermal method (Figure 3) is about 1.8, 2.3, 3.4, 3.5 and 4.0 with the standard deviation of 479, 484, 424, 321 and 272 seconds at the cooling rate of 4.0, 6.0, 12.0, 15.0 and 20.0 K/hour, respectively. The faster cooling rate tends to narrower distribution, because of faster accumulation of the nucleation potential with quicker increasing of the supersaturation. However, in isothermal method[26] the longest induction time of butyl paraben at each experimental condition in ethanol is six times or more of the shortest induction time, respectively, and the ratio becomes bigger when butyl paraben solution is under lower supersaturation.

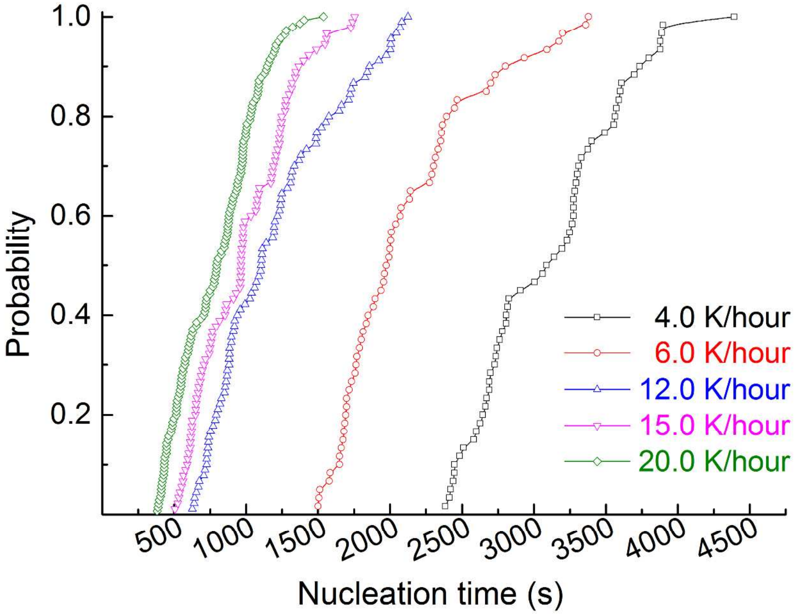

Figure 3 Accumulated distributions of nucleation time of butyl paraben in ethanol at 4.0 K/hour (60 data), 6 K/ hour (60 data), 12.0 K/hour (90 data), 15.0 K/hour (90 data) and 20.0 K/hour (140 data).

The distributions of the metastable zone widths and nucleation times indicate stochastic nature of the nucleation, shown in Figure 4, and the smaller cooling rate was performed in the experiment the narrower distribution of the metastable zone width became. The standard deviation increases with increasing cooling rate shown in Figure 5, however, the distribution of the metastable zone widths at cooling rate of 12.0 K/hour is a little wider than the distribution of metastable zone widths at cooling rate of 15.0 K/hour. Average and largest metastable zone width increase with increasing cooling rate, and correspondingly the maximum driving force during the cooling process (driving force at nucleation) increases with increase of the cooling rate (Table 1).

However, the nucleation time decreases with increase of the cooling rate. The smallest metastable zone width at each cooling rate is similar without an obvious tendency, and the differences between the biggest metastable zone widths at every two different cooling rates are much larger than the difference between the smallest metastable zones widths, respectively, shown in Figure 4. The average metastable zone widths have only about 1.0 K difference between experiments at cooling rate and 4.0 K/hour and 20.0 K/hour, however, the average nucleation time at cooling rate 20.0 K/hour is about 4 times longer than that at cooling rate of 4.0 K/hour, shown in Table 1.

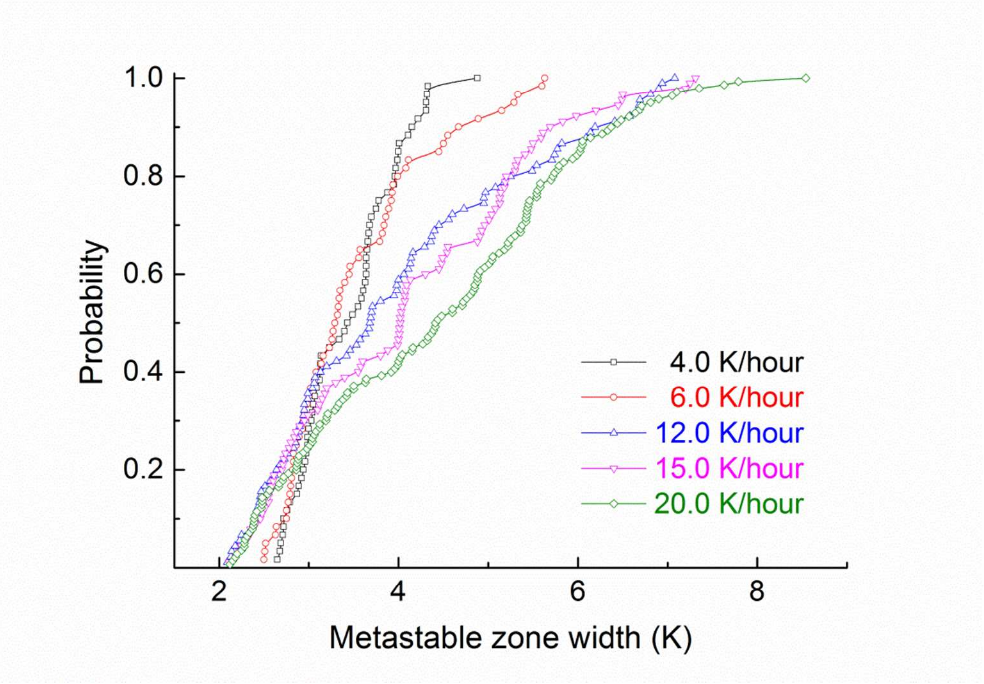

Figure 4 Accumulated distributions of metastable zone widths of butyl paraben in ethanol at 4.0 K/hour (60 data), 6 K/ hour (60 data), 12.0 K/hour (90 dots), 15.0 K/hour (90 data) and 20.0 K/hour (140 data).

Table 1 Results of the experimental and extrapolated metastable zone widths with respective crystallization parameters

z_c (K/hour)	T_0 (K)	$MSZW_{exp}$ (K)	$MSZW_{Std}$ (K)	t_{MSZW} (s)	$RTlnS_{Max}$ (kJ/mol)	$N^{\frac{1}{3}}$ (kJ)	AV (/s)	$MSZW_{extr}$ (K)
4.0	313.14	3.44	0.532	3098	0.228	1.032	72.90	4.39
6.0		3.52	0.806	2110	0.277			4.68
12.0		3.97	1.415	1192	0.315			5.30
15.0		4.07	1.338	977	0.330			5.55
20.0		4.40	1.509	793	0.351			5.90

z_c: Cooling rate, T_0: Saturation temperature, $MSZW_{exp}$: Average value of experimental metastable zone widths. $MSZW_{Std}$: Standard deviation of experimental metastable zone widths, t_{MSZW}: Average value of nucleation times in metastable zone width experiment, $RTlnS_{Max}$: Driving force at nucleation, N: Critical nucleation potential. A: Pre-exponential factor in the solution with volume of V. $MSZW_{extr}$: Metastable zone width extrapolated from induction time results by Equ. (12).

Extrapolated metastable zone width from induction time

The saturation temperature, T_0, in all experiment was 313.14 K and the time was recorded as starting point when the solution was cooled down to 313.14 K. At constant cooling rate 20.0 K/hour (0.00556 K/sec), the temperature is equal to $313.14 - 0.00556n\Delta t$ K at time $n\Delta t$ with unit of second. If the time step, Δt, is 1 second, combining the solubility equation[30] $lnx = -1430.23T^{-1} + 1.3469 + 0.00826T$, and Equ. (11) changes to

$$T^3(lnS)^2 = (313.14 - 0.00556n)^3\left[-4.567 - \frac{1430.23}{313.14-0.00556n} + 4.593 \times 10^{-5}n\right]^2 \qquad (13)$$

With Equ. (12), the accumulated nucleation potential of every time step (one second) during the cooling process should be calculated as:

$$\sum_{n=1}^{m} \Delta N = \sum_{n=1}^{m} \frac{72.87n}{exp\left(\frac{637058.99}{(313.14-0.00556n)^3\left[-4.567-\frac{1430.23}{313.14-0.00556n}+4.593\times10^{-5}n\right]^2}\right)} \qquad (14)$$

The nucleation occurs at $\sum_{n=1}^{m} \Delta N \geq 1.099\ kJ^3$ with the minimum value of $m = 1062$, then the metastable zone width with unit of K can be estimated by the nucleation time 1062 s and the cooling rate $0.00556\mathrm{K/s}$. The same method is used to extrapolate metastable zone widths at the cooling rates, at 15.0, 12.0, 6.0 and 4.0 K/hour, and the minimum value of m is 1331, 1591, 2808 and 3949 (same value as nucleation time with unit of s), respectively. The extrapolated metastable zone width results are shown in the last column of Table 1 and in Figure 5.

The time step Δt is 1 second in this work for simplifying the equation, which means the temperature step is 0.00556 K for the polythermal experiments at cooling rate of 20.0 K/hour, at cooling rate of 4.0 K/hour the temperature step is only 0.00111K, and the temperature steps at cooling rates 15.0, 12.0 and 6.0 K/hour are in between of 0.00556 K and 0.00111K. Smaller step is employed in estimating MSZW, more accurate the estimated MSZW becomes with Equ. (12). If 0.01 second step is employed to estimate MSZW at cooling rate 20.0 K/hour, the result is only 0.0004 K smaller than the value estimated with 1 second time step. However, bigger time step may induce higher discrepancy.

In Figure 5 shown the extrapolated metastable zone widths from induction time experiments are fairly close to the experimental metastable zone width results, the discrepancies between the experimental results with the extrapolated values are in the range from 0.9 K to 1.5 K. The standard deviation tends to increase from lower cooling rate to higher cooling rate, even though at the higher cooling rate more results were collected than at lower cooling rate. Median values indicate 50% probability for nucleation occurring in both isothermal and polythermal method. Median induction time was investigated since it is independent on several very short or extreme long induction time in isothermal experiments of butyl paraben in ethanol, and the average induction time may have big discrepancy with median value in some experiments[26]. However, in polythermal experiments of butyl paraben in ethanol, the median value of nucleation times and metastable zone widths at each cooling rate are very close to the average value at each cooling rate, respectively.

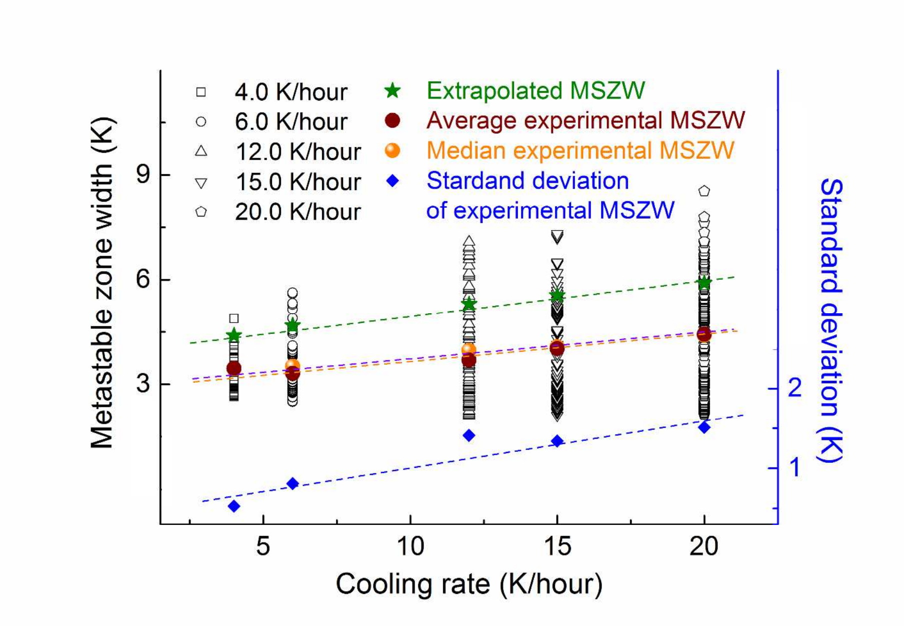

Figure 5 Experimental results of metastable zone width (black open dots) with average values (brown round solid dots), median values (orange round solid dots) and standard deviations (blue square solid dots), and metastable zone widths extrapolated from induction time experiments (green star solid dots) at cooling rate 4.0, 6.0, 12.0, 15.0 and 20.0 K/hour (from left to right), respectively. Dashed lines are guiding lines for linear correlation of respective data.

The experimental results of induction time and the metastable zone widths are reported in the systems of isonicotinamide in 1mL ethanol[12] and paracetamol in 200 mL ethanol[27], and Equ. (12) is employed to estimate the metastable zone widths at different cooling rates from induction time data. The extrapolated and experimental metastable zone widths are compared in Figure 6. In isonicotinamide-ethanol solution at cooling rate 24.0 K/hour and 30.0 K /hour, the extrapolated metastable zone width from induction time is 12.59 K and 12.06 K, which is in good agreement with the extrapolated values 12.6 K and 11.9 K respectively. In paracetamol-ethanol solution the extrapolated and the experimental metastable zone widths are 17.05 K and 17.50 K at cooling rate of 42.0 K/hour respectively, and are 15.41 K and 14.96 K at cooling rate of 30 K/hour, respectively, which show good consistence between the extrapolated values and the experimental results. However, in both systems, at cooling rates of 6.0 K/hour and 60.0 K/hour, the variations between extrapolated and experimental values are a little larger than variations at the cooling rate between 24.0 to 42.0 K/hour. The extrapolated values from induction time experiments are a little higher than the experimental results when the cooling rate is below 30.0 K/hour in both of these two systems, which discrepancies are consistent with that in system of butyl paraben in ethanol at cooling rates from 4.0 – 20.0 K/hour.

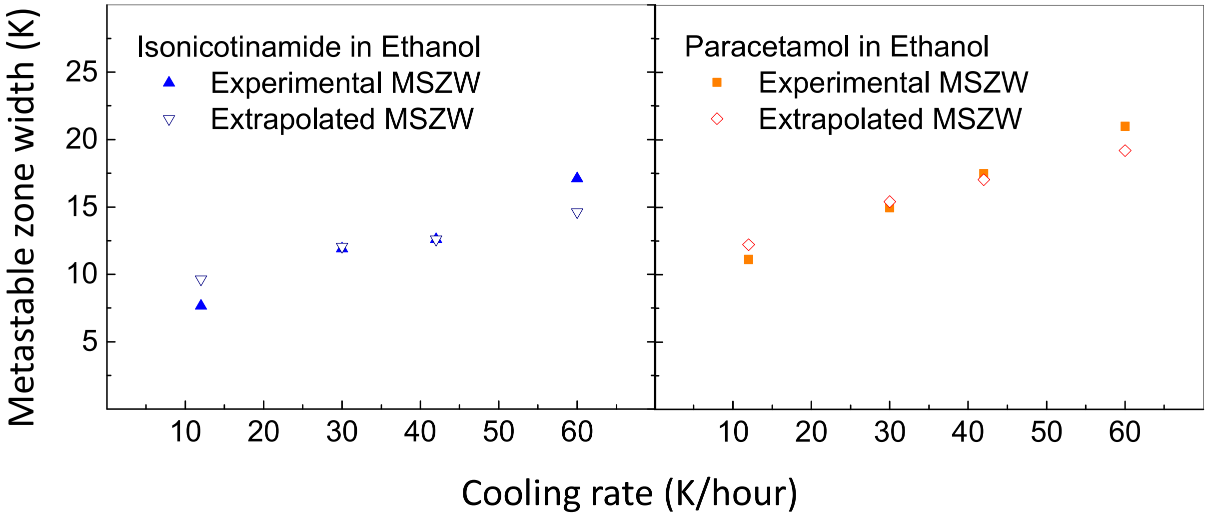

Figure 6 Experimental[12, 27] metastable zone widths and extrapolated values with Equ. (12) of isonicotinamide in ethanol (left) and paracetamol in ethanol (right).

Influence of the experimental conditions on metastable zone width

The metastable zone widths of butyl paraben in ethanol are narrow, in range of 3.44 K - 4.40 K at cooing rates, 4.0 K/hour to 20.0 K/hour while the extrapolated metastable zone widths from induction time experiments are from 3.86 K to 5.89 K by Equ. (14) or Equ. (12). The narrow metastable zone widths of butyl paraben in ethanol result from low value of the critical nucleation potential N about 1.099 kJ^3 and $N^{\frac{1}{3}}$ about 1.032 kJ calculated by Equ. (6) which is determined by the low solid-liquid interfacial energy of butyl paraben in ethanol[26, 31] about 1.13 mJ/m^2. The interfacial energy of isonicotinamide[12] and paracetamol[27] are estimated to be both higher than butyl paraben in ethanol, and accordingly the critical nucleation potential in these two systems are higher than butyl paraben-ethanol system and the experimental metastable zone widths of isonicotinamide[12] and paracetamol[27] are larger than butyl paraben in ethanol at cooling rate of 6.0 K/hour.

The metastable zone width of organic compound in solvents is not only dependent on the thermodynamics but also dependent on kinetic parameters during the nucleation process, like cooling rate, volume of the solution and stirring rate. Based on the Equ. (12), the dependency of metastable zone width on the experimental conditions can be estimated and investigated, and the influences of cooling rate, saturation temperature, volume of solution and stirring rate on the metastable zone width are shown in Figure 7, and these estimated correlations are in agreement with experimental results of butyl paraben-ethanol system or tendencies in other systems.

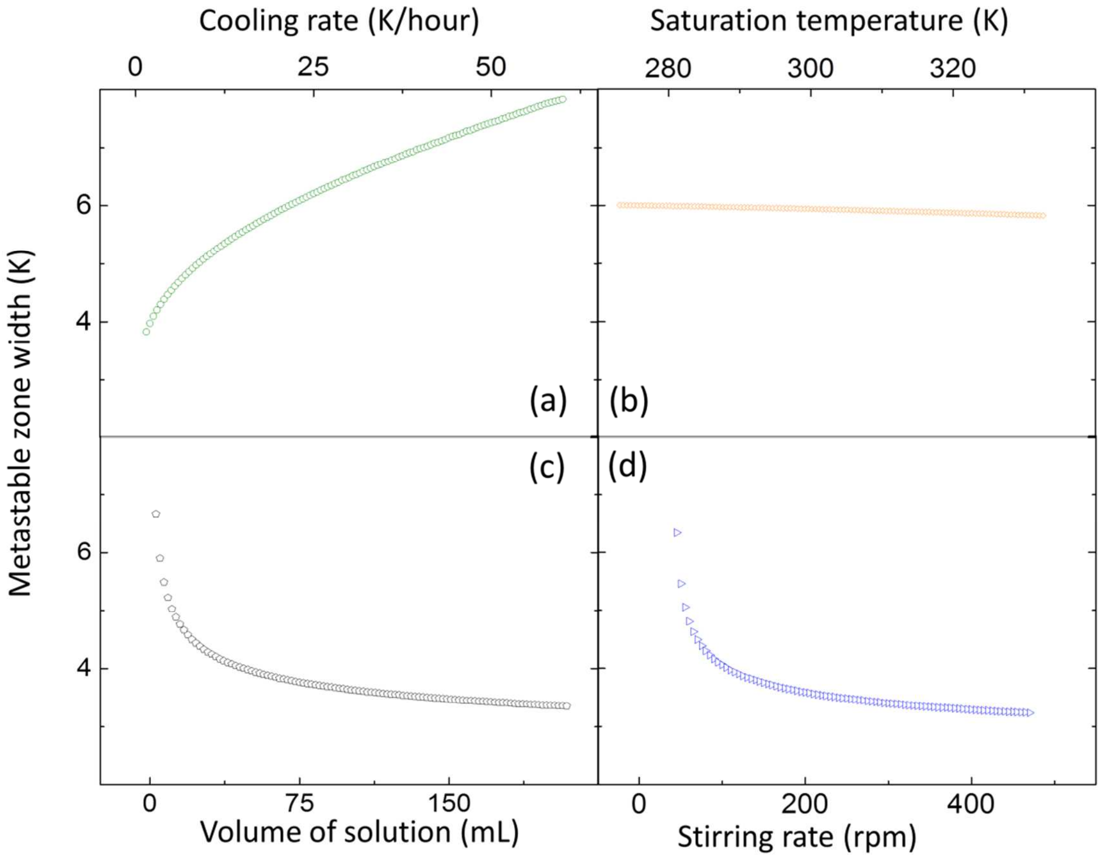

Figure 7 Influence of cooling rate (a), saturation temperature (b), volume of solution (c) and stirring rate (d) on metastable zone widths estimated by Equ. (12).

Based on Equ. (12), the metastable zone widths of butyl paraben-ethanol solution with constant solution volume extrapolated with the same saturation temperature at the same cooling rate (first row of Table 2) are positive proportional to the cooling rate, shown as Figure 7 (a), which is not only in good agreement with the experimental MSZW results of butyl paraben in ethanol but also in consistence with the tendency of other systems, like triethanolamine hydrochloride in aqueous solvents.[16] In Figure 7 (b) shown the estimated metastable zone width of butyl paraben in ethanol decreases with increasing saturation temperature (other constant factors for estimating MSZW shown in second row of Table 2). However, the estimated metastable zone width decreases only less than 0.2 K when saturated temperature increases from 278.15K to 328.15K, indicating a weak dependency of MSZW on saturation temperature. It is reported metastable zone decrease with increasing saturation temperature in several metastable zone experiments, e.g. *n*-dodecanol-*n*-decanol system[32] and pentaerythritol–water system[18], and the metastable zone widths of salicylamide in methanol, acetonitrile, acetic acid, acetone and ethyl acetate[33] is only slightly influenced by saturation temperature. The influence of the solution volume on the metastable zone widths is shown as Figure 7 (c), and the tendency from estimated metastable zone widths of butyl paraben in ethanol (factors shown in third row of Table 2) is in good agreement with the literature that the average values of metastable zone width and induction time both decrease with an increase of the sample volume.[10, 11]

Table 2 Influence of crystallization parameters (with variable parameters of italic numbers) on metastable zone width extrapolated from Equ. (12).

Factors	V (mL)	STIR (rpm)	T_0 (K)	z_c (K/hour)	Correlation	Shown in
z_c	5	200	313.14	*1-60*	Positive	Figure 7 (a)
T_0	5	200	*278.15 - 328.15*	20	Negative	Figure 7 (b)
V	*2-200*	200	313.14	20	Negative	Figure 7 (c)
$STIR$*	150	*45-450*	313.14	20	Negative	Figure 7 (d)

z_c: Cooling rate, T_0: Saturation temperature, V: Solution volume, $STIR$: Stirring rate. * In Taylor-Couette system[34].

In Taylor-Couette system of butyl paraben in ethanol, the nucleation experimental work under stirring rates from 100 to 400 rpm show that the induction time in isothermal method decreases with increasing stirring rate, and indicate a linear correlation between the pre-exponential factor and the stirring rate,[34]

$$A = 12.86\ \times stirring\ rate - 511.5 \qquad (15)$$

Combining Equ. (12) with the pre-exponential factor[34] (as well as stirring rates from 45 rpm to 100 rpm) extrapolated from Equ. (15), the influence of the stirring rate on metastable zone width of butyl paraben in ethanol (other factors are constant shown in the last row of Table 2) is estimated and shown in Figure 7 (d). The metastable zone width decreases with increasing stirring rate resulting from the increasing pre-exponential factor, and this tendency is also reported in aqueous solution of L-glutamic acid.[19]

In butyl paraben-ethanol solution, at higher cooling rate, with bigger volume of solution or at higher stirring rate, the metastable zone widths tend to be linear correlated with these factors estimated by Equ. (12), respectively, when other factors are constant, shown in Figure 7. The influences of one or more factors in some solution systems on the experimental metastable zone widths are consistent with this kind of ‘linear’ correlation. However, we could expect that in solution systems the cooling rate, volume of the solution or stirring rate is not monotonously linear correlated to the metastable zone width, neither of the ln values, respectively, and at the lower cooling rate, with smaller volume of solution or at lower stirring rate the metastable zone width could be more sensitive to each of these factors, respectively.

If the heterogeneous nucleation happens in the system, in Equ. (4), (8) and (12), a heterogeneous interfacial energy, (solid-solid interfacial energy), instead of the homogenous interfacial energy (solid-liquid interfacial energy) should be employed. The heterogeneous interfacial energy is smaller than homogenous interfacial energy. Because of the lower interfacial energy in heterogeneous nucleation, the critical nucleation potential N is smaller than in homogenous nucleation as expected, indicating shorter induction time or nucleation time in isothermal experiment or polythermal experiment, respectively. It is reported[29] the heterogeneous nucleation occurs under low supersaturation, indicated by a smaller slope in Equ. (5) than in homogenous nucleation. When the interfacial energy of butyl paraben in ethanol was determined from the in the isothermal experiments[26], and no heterogeneous nucleation under very low supersaturation 1.09 was captured. The maximum supersaturation (supersaturation at nucleation) in polythermal experiment in this work is from 1.11 to 1.15 at cooling rate from 4.0 K/hour to 20.0 K/hour, and correspondingly only homogenous primary nucleation should occur in MSZW experiments.

During the isothermal experiments, the supersaturation increases rapidly to be constant, during which period the accumulated nucleation potential is usually neglected resulting from the short time period to reach constant temperature, however, the uncertainty during the initial periods of the induction time experiment also need be investigated in the future. In addition, in industrial not always the linear cooling rates are used. By applying the new interpretation of the metastable zone width, it is possible to extrapolate and analyse the metastable zone width with complex cooling temperature profiles.

Conclusions

More than 400 metastable zone width experiments of butyl paraben in ethanol have been investigated at cooling rate 4.0 K/hour to 20.0 K/hour, the probability distributions of the metastable zone widths show the stochastic nature of the nucleation. The distributions of the nucleation time in polythermal experiments are relative much narrower than the distributions of the induction time in isothermal experiments. The relation between metastable zone width and induction time has been developed by Classical Nucleation Theory, by which relation the metastable zone width values extrapolated from induction time fairly agree with the experimental metastable zone width results in the system of butyl paraben in ethanol. The relation reveals that the metastable zone width is determined by the solid-liquid interfacial energy of the solute in the solvent, and indicates the metastable zone width nonlinearly increases with increasing cooling rate, with decreasing stirring rate or with decreasing solution volume and metastable stable zone width slightly decreases with increasing saturation temperature, which are all consistent with the experimental results of butyl paraben-ethanol system or tendencies in other systems in literatures.

Notations

A	Pre-exponential factor	$[\mathrm{m^{-3}\bullet s^{-1}}]$
A_s, B_s, C_s	Constant in solubility equation	
B	Slope in determination of interfacial energy	$[\mathrm{K^{3}}]$
b_1	Constant in empirical nucleation rate equation	$[\mathrm{m^{-3}\bullet s^{-1}}]$
b_2	Constant in empirical nucleation rate equation	
$f(S), f(S_n)$	Function of supersaturation	$[\mathrm{J^{3}}]$
$f(t), f(t_n)$	Function of time, function of estimated induction time	
J	Nucleation rate	$[\mathrm{m^{-3}\bullet s^{-1}}]$
k	Boltzmann constant, 1.38×10^{-23}	$[\mathrm{J\bullet K^{-1}}]$
m	Integer number parameter in accumulation equation	
N_n	Nucleation potential, area	
$MSZW_{exp}$	Experimental metastable zone width in	$[\mathrm{K}]$
$MSZW_{extr}$	Extrapolated metastable zone width from induction time experiments	$[\mathrm{K}]$
$MSZW_{Std}$	Standard deviation of experimental metastable zone widths	$[\mathrm{K}]$
n	Integer number variable from 1 to ∞	
N	Critical nucleation potential	$[\mathrm{kJ^{3}}]$
r_c	Critical nuclei radius	$[\mathrm{nm}]$
r	Nuclei radius	$[\mathrm{nm}]$
S, S_n	Supersaturation	
$STIR$	Stirring rate	$[\mathrm{rpm}]$
t_{ind}	Induction time of nucleation	$[\mathrm{s}]$
t_{MSZW}	Nucleation time in MSZW experiment	$[\mathrm{s}]$
t_n	Induction time, estimated induction time	$[\mathrm{s}]$
T	Temperature	$[\mathrm{K}]$
T_0	Saturated temperature	$[\mathrm{K}]$
v_m	Molecular volume of solute	$[\mathrm{m^{3}}]$
V	Solution volume	$[\mathrm{m^{3}}]$
x	Actual solute molar fraction solubility	$[\mathrm{mol\bullet mol^{-1}\ total}]$
x^*	Equilibrium solute molar fraction solubility	$[\mathrm{mol\bullet mol^{-1}\ total}]$
z_c	Linear cooling rate	$[\mathrm{K\bullet s^{-1}}]$
a	Actual solute molar activity	
a^*	Equilibrium solute molar activity	

σ	Solid-liquid interfacial energy in homogenous nucleation	［$mJ•m^{-2}$］
ΔG_c	Critical free energy of nucleus	［$kJ•mol^{-1}$］
ΔG_s	Excess free energy	［$kJ•mol^{-1}$］
ΔG_v	Volume excess energy	［$kJ•mol^{-1}$］
$\Delta N, \Delta N_n[n]$	Nucleation potential accumulated during Δt	［kJ^3］
Δt	Time step, short time period	［s］
ΔT	Supercooling temperature	［K］
$\Delta\mu$	Driving force of nucleation	［$kJ•mol^{-1}$］

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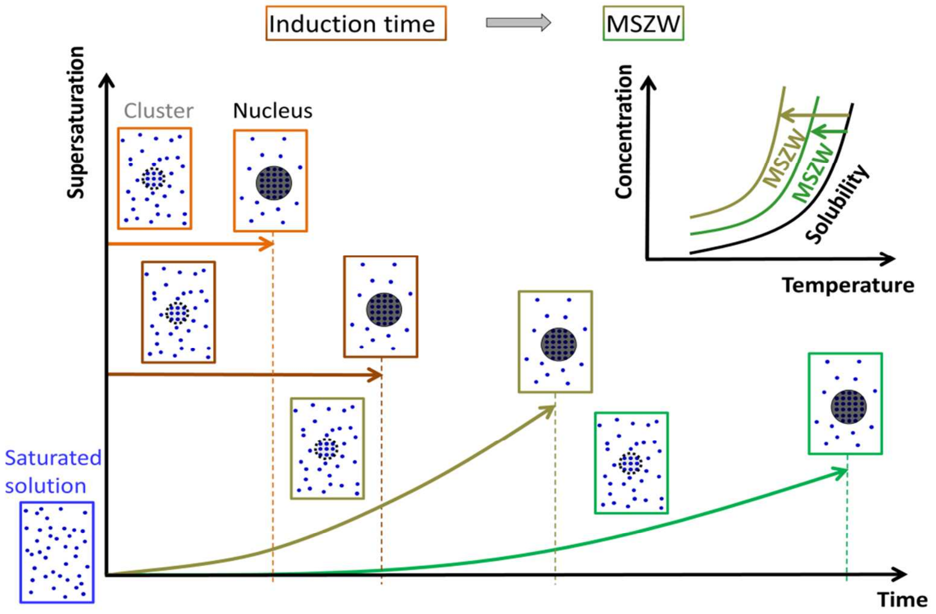
Relation between Metastable Zone Width and Induction Time of Butyl Paraben in Ethanol



- 440 metastable zone widths (MSZW) of butyl paraben in ethanol at cooling rate from 20.0 K/hour to 4.0K K/hour
- Relation between MSZW and induction time developed from Classical Nucleation Theory
- MSZW estimated from induction times in isothermal experiments ~ MSZW from polythermal experiment
- MSZW determined by interfacial energy and pre-exponential factor
- The relation indicates nonlinear correlation: MSZW↑ with cooling rate ↑, stirring rate ↓ or volume of solution ↓