**Determination of nucleation kinetics from metastable zone width and induction time data for sonocrystallization of pyrazinamide.**

Abhishek Maharana1, Debasis Sarkar2

*1,2 Dept of Chemical Engg, IIT Kharagpur, West Bengal, India*

*\*Corresponding author: abhi.mrana@gmail.com*

**Highlights**

* Nucleation kinetics is estimated from MSZW and induction time data.
* Sangwal’s nucleation theory is used for estimating nucleation parameters.
* Induction time showed a sharp decrease with increase in ultrasound amplitude.

**1. Introduction**

Crystallization is an important separation and purification technique in many chemical and pharmaceutical industries. Most industries use simple batch crystallization for generating crystals of definite crystal size distribution (CSD) and purity. However, it is very difficult to control primary nucleation to obtain crystals of definite properties because it occurs in a thermodynamically unstable region [1]. Primary nucleation requires very high levels of supersaturation which brings difficulty in controlling the crystallization process. To overcome this situation sonocrystallization can be used. Cavitation induced during ultrasound can create high supersaturation even at a lower superstation ratio which can induce nucleation to achieve target CSD and create nuclei of desired polymorph [2]. MSZW denotes region between solubility curve and onset of nucleation. Information about MSZW helps in avoiding excessive nucleation, ensures required CSD and also helps in determining nucleation kinetics. Induction time is the measure of ability of a supersaturated solution to remain in state of metastability. It has been related to size of nuclei and thus it is important for evaluation of nucleation kinetics.

Pyrazinamide is an important API drug for treatment of *Mycobacterium tuberculosis.* The effect of continuous sonication with different amplitude on nucleation kinetics for cooling crystallization of pyrazinamide from its solution in acetone is studied. Nucleation parameters are calculated from metastable zone width (MSZW) and induction time experimental data. To the best our knowledge, a study on effect of continuous sonication on nucleation kinetics of pyrazinamide has not been reported in open literature.

**2. Methods**

Solubility of pyrazinamide in acetone is computed gravimetrically in the temperature range of 283.15 K to 323.15 K. A 500 ml jacketed crystallizer with a temperature controller having a precision of ±0.05 K is used. Probe sonicator is installed to introduce ultrasound of different amplitude. The ultrasound probe is dipped 1 cm from the solution surface. The onset of nucleation is observed by visual inspection. Polythermal method is used to determine MSZW and isothermal method is used to determine induction time. Next classical nucleation theory is used to estimate the nucleation rate:



**3. Results and discussion**

Figure 1 represents MSZW in presence and absence of ultrasound. It is evident from the figure that in presence of ultrasound, the MSZW decreases significantly. The Sangwal’s classical three dimensional nucleation theory approach is used for estimation of nucleation parameters as follows:



The value of ΔHg/R can be obtained from the plot of [mole](https://www.sciencedirect.com/topics/physics-and-astronomy/moles) fraction of solubility versus 1/T0. The value of f is inverse of molecular volume of pyrazinamide. The parameters A and B is estimated from the plot of (T0/ΔTmax)2 versus lnR. Figure 2 represents effect of supersaturation on induction time. The decrease in induction time with increase in ultrasound amplitude is shown in Figure 3.

 

**Figure 1.** MSZW experiments in presence and absence of ultrasound.

 

**Figure 2.** Plot of induction time vs. supersaturation **Figure 3.** Induction time at different ultrasound amplitude

**4. Conclusions**

The metastable zone width was measured for different cooling rates and different ultrasound amplitudes. It was observed that the MSZW increases with increase in cooling rate and decreases with increase in ultrasound amplitudes. The nucleation parameters (A and B) were calculated from Sangwal’s classical three dimensional approach. Induction time decreases with increase in supersaturation ratio. It also showed a sharp decrease with increase in ultrasound amplitude at constant supersaturation.

**References**

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