

# Experimental Validation and Multi-objective optimization of Batch cooling crystallization of sulfanilamide

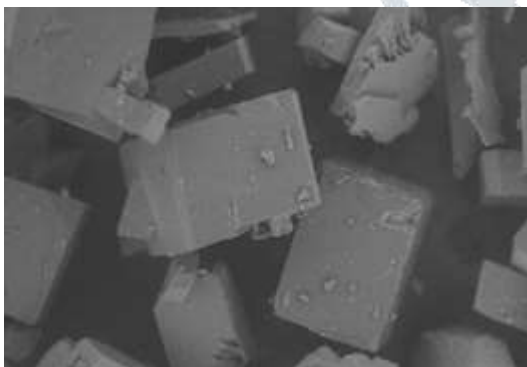
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## Abstract

This research aims to estimate the kinetics of sulfanilamide crystallization from batch crystallizer data obtained from a linear cooling profile and thereby extended to find the optimum cooling profile for the desired combination of conflicting objectives. Real coded genetic algorithm (RCGA) is applied to estimate the rate parameters from the experimental batch cooling crystallization data of liquid phase concentration. The validated model is used to find the different optimal temperature profiles for the combination of conflicting objectives (i.e. maximization of number mean size (NMS) and minimization of coefficient of variance (CV)). This is done by using real coded non-dominated sorting genetic algorithm (NSGA II). In this effort, together with finding the optimum temperature trajectories, the effect of target choice on the final achievable Pareto front is analyzed using the above two conflicting objective functions.



Sulfanilamide

**Key words:** Crystallization, Sulfanilamide, Kinetic model, Multi objective optimization Coefficient of Variance.

## 1. Introduction

Crystallization is an important industrial separation and purification technique because varieties of materials are marketed in the crystalline form. This method is used for obtaining pure chemical

substances in a satisfactory condition for packaging and storing. Batch crystallization is used in the chemical, pharmaceutical and photographic industries as a manufacturing process to prepare a wide variety of crystalline product. In most solutions, the solubility of the compound increases with rising temperature. As saturated solution cool/heat, mixture becomes supersaturated and crystallization starts. The major advantages of cooling crystallization are very high uniformity of crystal size and energy efficiency. Cooling crystallization is attractive when the solubility of the product increases significantly with increasing temperature. As sulfanilamide solubility significantly increases with increasing temperature, cooling crystallization has been chosen in this work [1]. Sulfanilamide is the main raw material and intermediate used for the synthesis of several sulpha drugs. It has applications in Veterinary medicine, as a topical anti-inflammatory drug, and for analysis and detection. It acts as a wide spectrum antibacterial, having antibacterial effects on haemolytic streptococcus, Neisseria meningitides, Staphylococcus aureus and other Gram-positive and negative bacteria [2-5].

The quality of the product is generally analysed by CSD (i.e. crystal size distribution) and it shows strong influence on the crystalline product quality. Obtaining a desired crystal size distribution is essential in commercial crystallization [6]. Batch cooling crystallization is considered as one of the most common mode of operation in industry. Obtaining the optimized cooling profile is very important for the targeted product quality [6]. Significant multi-objective optimization studies have been conducted in past by several researchers in batch cooling crystallization as the real world problems demands more than one desired objectives (i.e. product with maximum mean size and minimum CV (Coefficient of Variation) in less crystallization time [6, 7]). Optimization of the batch cooling crystallizer using different objective functions has been reported to result in significantly different temperature profiles [7]. However, there has been a growing curiosity in the application of many-objective optimisation to different crystallization processes over the last decade. It is necessary to obtain optimal temperature profile for the desired combination of conflicting scenario. As per the knowledge of authors, there is no validated crystallization growth kinetic model and multi-objective optimization study for the product sulfanilamide. In the present effort, from the batch cooling crystallization experiments of sulfanilamide, growth rate kinetics have been developed and is validated with the experimental data of measured concentration of the liquid phase with time, crystal size and coefficient of variation values with the calculated values by model. The developed model is then extended for a multi-objective optimization study to find the optimal cooling profiles for the conflicting objectives (i.e. simultaneous maximization of number mean size and minimization CV).

The novel contributions of the present work can be summarized as follows:

- Batch cooling crystallization of sulphanilamide has been done by considering the linear cooling profile
- A version of growth kinetic model and validation with experimental data has been proposed
- The proposed kinetic model is used in the multi-objective frame work (Deb, 2001) to find the optimal cooling profiles for the desired combination of conflicting objectives.

## 2. Materials & Methods:

### 2.1 Chemicals

Sulphanilamide Extra Pure (99% pure), Methanol (purity 99.6%) were purchased from Molychem and used with no further purification. The cooling method apparatus consist of a cooling bath, crystallizer with aluminium foil, to prevent solvent from evaporating when heated.

### 2.2 Experimental Procedure:

In this work, batch unseeded cooling crystallization has been done in a batch crystallizer. Sulfanilamide (solute) is dissolved in methanol (Solvent) with 0.160 g/g concentrated clear solution, were taken in 250 ml crystallizer placed with a cooling bath at temperature about 50°C and the mixture was stirred by using mechanical stirrer at 700 rpm. The contents of the crystallizer were taken initially at 50 °C and it is maintained using heating cooling circulator. The experiment has been continued by lowering the temperature of the solution to the linear profile. During the temperature decreasing, at 28.5°C the clear solution becomes unclear which means the nucleation has started at that temperature. About 15 samples were collected intermediately from the bottom of the crystallizer until the solution reaches 9°C temperature. Any crystals formed are collected by filtration and sent for analysis. The samples collected were analyzed using XRD and Optimal Microscopy.

### 2.3 Calculation of Coefficient of Variation (CV)

The parameter chosen for the crystal size characterization is the diameter of the crystal along its major axis as observed by optical microscopy. The experimental results are presented in terms of number average of crystal size and coefficient of variation as obtained from the image analysis. The cooling Profile is 50°C - 9°C and the sieve size of the Crystals (125 – 1000 µm):

$$L = 1/N \sum_{i=1}^n L_i$$

Where L = Number mean size,  $L_i$  = individual crystal size

N = Number of crystals  $\sigma$  = standard deviation

CV = Coefficient of variation

$$L = 1/N \sum_{i=1}^n L_i$$

$$= 1/30*(653.99+692.86+736.02+\dots+686.10)$$

Mean of the sample = 635.35

Standard Deviation is = 94.630

Coefficient of variation (CV) = 94.630/635.35

Coefficient of variation = 0.148

### 3. Model formulation

The population balance equation PBE is a partial differential equation in time (i.e.  $t$ ) and crystal size (i.e.  $L$ ) for a perfectly mixed batch crystallizer of constant volume is shown below in equation 1 [8], in which crystal breakage and agglomeration are presumed to be negligible

$$\frac{\partial n(L,t)}{\partial t} + G \frac{\partial n(L,t)}{\partial L} = 0 \quad (1)$$

Where  $G$  is crystal growth rate, which is size independent and 'n' is the population density. The above population balance equation can be reduced to the following moment balance equations.

$$\frac{d\mu_0}{dt} = B \quad (2)$$

$$\frac{d\mu_i}{dt} = iG\mu_{i-1} \quad (3)$$

Subjected to the boundary conditions  $\mu_i = 0$  at  $t=0$   $i=0,1,2,3,4,5$ .

Where  $n$  depicts the number density of  $L$ -length crystals at time  $t$ . The total nucleation rate  $B$  can be obtained as the sum of number of primary ( $B_p$ ) and secondary ( $B_s$ ) nucleation and are given by the following equations (i.e. eq. 4):

$$\begin{aligned} B_p &= k_p (C - C^*)^p \\ B_s &= k_s (C - C^*)^s \end{aligned} \quad (4)$$

Where  $k_s = k_{s0} \exp(-\Delta E_s / RT)$

Where  $k_p$ ,  $k_s$ ,  $p$  and  $s$  represents the primary nucleation rate constant, secondary nucleation rate constant, frequency factor, activation energy, primary nucleation rate exponent and secondary nucleation rate exponent respectively.  $k_{s0}$  and  $\Delta E_s$  are the frequency factor and activation energy of secondary nucleation rate. The growth kinetics is given by

$$G = k_g (C - C^*)^g \quad (5)$$

Where  $k_g = k_{g0} \exp(-\Delta E_g / RT)$  (6)

The concentration of the solution phase in the crystallizer is represented by a crystallizing solute mass balance:

$$\frac{dC}{dt} = -\rho_c k_v \frac{d\mu_3}{dt} \quad (7)$$

Where  $k_g$  is the growth rate constant,  $k_{g0}$  the frequency factor,  $\Delta E_g$  is the activation energy of the growth rate,  $C$  is the solute concentration in mass of solute per mass of solvent,  $C^*$  is the solubility represented in mass of the solute per mass of solvent,  $k_v$  is the volume shape factor that transforms  $L^3$  into crystal volume and  $\rho_c$  is the density of the crystals. In this analysis, the experimentally measured temperature  $T(t)$  has been used in place of the equation of energy balance. This method has been considered to avoid the mistake in determining the total heat transfer coefficient and also to avoid the calculation of heat of crystallization and its dependency on concentration [9]. Various polynomial cooling profiles used in the literature is given by the following equation (i.e. eq. 8) [8].

$$T(t) = T_{\max} + [(T_{\min} - T_{\max})(t/t_f)^a] \quad (8)$$

Where  $a=1$  is for the linear profile. The experimental cooling profile has been compared with the linear and is shown in the Figure 1. In the present work, linear cooling profile has been considered as is matching with the experimental profile. The solubility of sulfanilamide at various temperatures in methanol has been considered from the open literature and was fitted with various thermodynamic models [1]. The temperature dependency of the solubility concentration (mass of solute per mass of solvent) can be represented using a polynomial expression that is suitable to experimental data [1] and is represented by equation 9.

$$C^* = 9 \times 10^{-5} T^2 + 0.0007T + 0.0577 \quad (9)$$

The above mentioned coupled differential algebraic equations are solved by LIMEX DAE solver [10]. The estimation of the appropriate parameters for the representation of experimental data was carried out by the real coded genetic algorithm (RCGA) [11] by integrating with the model. Instead of a single point in classical optimization techniques, RCGA deals with a variety of solutions and these solutions are created randomly within the limits set to optimize the solution parameters. Minimization of the function  $f$  (shown in equation 9) is performed on the sums of squares of deviations between quantities calculated and experimented (i.e. concentrations).

$$f(k_{g0}, \Delta E_g, g, k_p, p, k_{s0}, \Delta E_s, s) = \sum_{i=1}^N \left( \frac{C_i^{\text{exp}} - C_i^{\text{model}}}{C_i^{\text{exp}}} \right)^2 \quad (10)$$

Where  $C_i^{\text{exp}}$ ,  $C_i^{\text{model}}$  and  $N$  are the experimental concentration, model predicted and number of experimental data.

#### 4. Optimization problem formulation

Given the importance of the final crystal size distribution in downstream processes and in product implementations, the targets of the crystallization optimization problems are usually chosen based on specific features relevant to product quality and consumer demands. The prevalent objective functions in crystallization optimization problems are maximizing the mean crystal size, minimizing its variance coefficient (CV) and minimization of batch time [8]. To get a crystal in less batch time, one may get less average crystal mean size and to obtain more average crystal mean size, CV also increase. There is a conflict among the three above objective functions. That means, a positive improvement in one goal causes an unnecessary shift to another target. In the earlier studies, Acevedo et al. [12] did the multi-objective optimization of unseeded cooling batch crystallization of paracetamol by considering the length mean size and target aspect ratio as the objective functions. Nagaveni et al. [8] conducted the multi-objective optimization study by considering the maximization of number mean size and minimization of coefficient of variance by considering the cubic temperature cooling profile. In the present effort, linear cooling temperature profile (i.e. equation 8) has been considered as this profile is fitting with the experimental cooling profile quite well. The above mentioned individual objective functions (i.e. maximization of mean crystal size and minimization of coefficient of variance) have been considered simultaneously with the relevant constraints is represented below (equation 11):

$$\begin{aligned}
 \underset{T(t)}{\text{Max}} NMS &= \frac{\mu_1}{\mu_0} \\
 \underset{T(t)}{\text{Min}} CV &= \sqrt{\left(\frac{\mu_2 \mu_0}{\mu_1^2} - 1\right)} \\
 s / t \\
 T_{\min} &\leq T(t) \leq T_{\max} \\
 \frac{dT}{dt} &\leq 0 \\
 85 \text{ min} &\leq t \leq 115 \text{ min}
 \end{aligned} \tag{11}$$

To find the optimal temperature trajectory  $T(t)$ , the total time interval is divided into  $Q$  of equal length (i.e. total time/ $Q$ ) and the piecewise linear control policy is adopted in each of the time interval  $(t_k, t_{k+1})$  (shown in eq. 12) [7]. Because the initial and final temperatures are set at  $T_{\max} = 50^\circ\text{C}$  and  $T_{\min} = 9^\circ\text{C}$ , the number of variables describing the linear temperature profile for the entire period is  $(Q - 1)$  respectively. Various researchers in the literature [6, 7] carried out this type of discretization. In the present case, the total crystallization period is split into 10 equal sections and each chromosome is represented 9-value vector representing the temperature on each evenly spaced period partition. Now, the total number of chromosomes for the above optimization problem are 10 (including total batch time). Once the optimizer chooses the total batch crystallization time randomly based on the bounds, it will be divided into 10 equal sections. Based on the lower and upper bounds of the temperature provided, the values of the

temperatures are generated randomly, where  $T_{\min}$  and  $T_{\max}$  are the initial and final temperatures. The temperature for cooling crystallization throughout the batch should always be a decrementing function of time. The constraints on inequality ascertain the temperature profile can be implemented. To solve the above mentioned multi-objective optimization problem, real coded non-dominated sorting genetic algorithm (NSGA II) [11] has been utilized. For generating well spread of Pareto optimal (PO) solutions in a single run as opposed to classical optimization techniques, NSGA II was utilized by many authors in literature [13] to solve complicated problems.

$$T(t) = T(k) + \frac{T(k+1) - T(k)}{\text{totaltime}/Q} (t - t_k) \quad (12)$$

## 5. Results and discussion

As can be seen from Fig 1 crystals of sulfanilamide formed were analyzed and confirmed from XRD that original crystals has been grown. From the Fig 2 it can be seen that average crystal size is 600  $\mu\text{m}$ . In Figure 3A some single crystals and in Figure 3B only one single crystal has been shown. Single crystal size is measured as the average of length and width of the single crystal.

For the batch cooling crystallization of sulfanilamide, the linear cooling profile has been considered and the temperature of the system is decreased in a batch time of 115 minutes from 50<sup>o</sup>C to 9<sup>o</sup>C. The experimental cooling profile with the linear profile is depicted from Figure 4, which is correlated well. The parameter estimation exercise estimates the crystallization kinetic parameters of sulphaniamide by comparing with the experimental data of measured concentration of the liquid phase with time, as explained earlier and is shown in Table 1 for the linear cooling profile. The accuracy of the model can be compared with the optimized parameters, which is shown in Figure 5 (i.e. comparison of model with the experimental data of liquid concentration in the crystallizer). Further, the experimental values of number average crystal size (NMS) and coefficient of variation (CV) at the end of batch crystallization (i.e. 115 min.) is compared with the model, is represented in Table 2, is quite agreed well with the experimental data. From the Figure 5 and Table 2, it can be observed that the experimental data is validating quite well with the model. As per the best knowledge of the authors, the crystal growth kinetic model development and multi-objective optimization to find the optimal cooling profile of sulfanilamide is rare in the literature. Given the importance of the final crystal size distribution in product applications and downstream processes, the objectives of the crystallization optimization problems are normally selected based on the specific features related to the product quality. So, after the model is validated with the experimental data, it has been extended to analyse the optimum process conditions to achieve specific objectives (i.e. simultaneous maximization of NMS and minimization of CV with relevant constraints, which are imposed based on the experimental data, is summarized in equation 11.

Multi-objective optimization (MOO) of crystallization systems is becoming increasingly relevant due to its ability to balance several competing goals together to find optimum operating policies. Unlike the single objective optimization problem, the multi-objective optimization problem solving corresponds to a set of trade-off solutions, each expressing a specific compromise between different goals. Such options are non-nominated are called Pareto optimal options. The picture of such solutions generated in the objective space by the objective components is regarded as the Pareto front (each objective along the trade-off can only be improved if other objective functions are degraded). In this study, the NSGA II parameters considered are as follows: number of generations is 100, population size is 100, crossover probability is 0.9, mutation probability is 0.05, distribution index for the real coded crossover is 0.01 and distribution index for real coded mutation is 0.01. The simulation has been performed for each of the cooling profiles generated randomly by NSGA-II and the objective functions are evaluated using these profiles. In this MOOP problem, the trade-off between the maximization of number mean size (NMS) and minimization of coefficient of variation (CV) has been considered and the resultant Pareto optimal solutions is represented in Figure 6. It has been observed from the figure that NMS is in the range of  $667\mu\text{m}$  to  $835\mu\text{m}$  and CV is in the range of 6.68% to 13%. From these trade-off solutions, three points are considered, which consists of one from the upper end of the Pareto, one from the lower end of the Pareto and a point in the middle region. The optimal temperature profiles for the above three points with time is shown in Figure 7. For different objective functions (i.e. NMS and CV), the temperature profiles are also varying as the time is also considered as decision variable. From the above trade-off solutions, a specific solution can be chosen based on the preferences of the decision-maker and the subsequent patterns among the decision variables can be defined. This kind of optimal trends can be profoundly subsidiary for an operator to run a plant.

## 6. Conclusions

Batch cooling crystallization of sulfanilamide has been experimentally investigated. For a linear cooling profile, the growth parameters and nucleation rates have been estimated by comparing the experimental data of liquid phase concentration with respect to time for sulfanilamide crystallization by utilizing the real coded non-dominated sorting genetic algorithm. The estimated results are in good agreement with the experimental data of liquid phase concentration, number mean size and coefficient of variance of the product. Further, the validated model have been extended to find the optimal cooling profiles for the desired combination of conflicting objectives (i.e. simultaneous maximization of NMS and minimization of CV) with the relevant constraints based on the experimental data. The real coded non-dominated sorting genetic algorithm has been utilized to find the Pareto optimal solutions. From the trade-off solutions, NMS is in the range of  $667\mu\text{m}$  to  $835\mu\text{m}$  and CV is in the range of 6.68% to 13% obtained.



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**Table 1:** Parameters used in the simulation study

Parameter	Value
$k_{g0}$	99651.36 ( $\mu\text{m}/((\text{g}/\text{g})^g \text{ min})$ )
$\Delta E_g/R$	847.005 K
$g$	2.9228
$k_p$	$1 \times 10^{-12}$ ( $\text{no.}/((\text{g}/\text{g})^p \text{ g min})$ )
$p$	5.056
$k_{s0}$	$1.132 \times 10^{13}$ ( $\text{no.}/((\text{g}/\text{g})^s \text{ g min})$ )
$\Delta E_s/R$	18723.47 K
$s$	0.79146

**Table 2:** Experimental vs. model comparison of NMS and CV values

Time (min.)	NMS ( $\mu\text{m}$ )		CV	
	Experimental	Model	experimental	Model
115	635.35	621.75	0.148	0.144

**Captions to Figures:**

Figure 1. XRD pattern of sulfanilamide single crystals

Figure 2. Particle size distribution: Temp-50oC; Stirring speed-700 rpm; Concentration-0.160 g/g; Sieve size-125 $\mu\text{m}$ -1000 $\mu\text{m}$ ;

Figure 3. A. Sulfanilamide crystals B. Single crystal

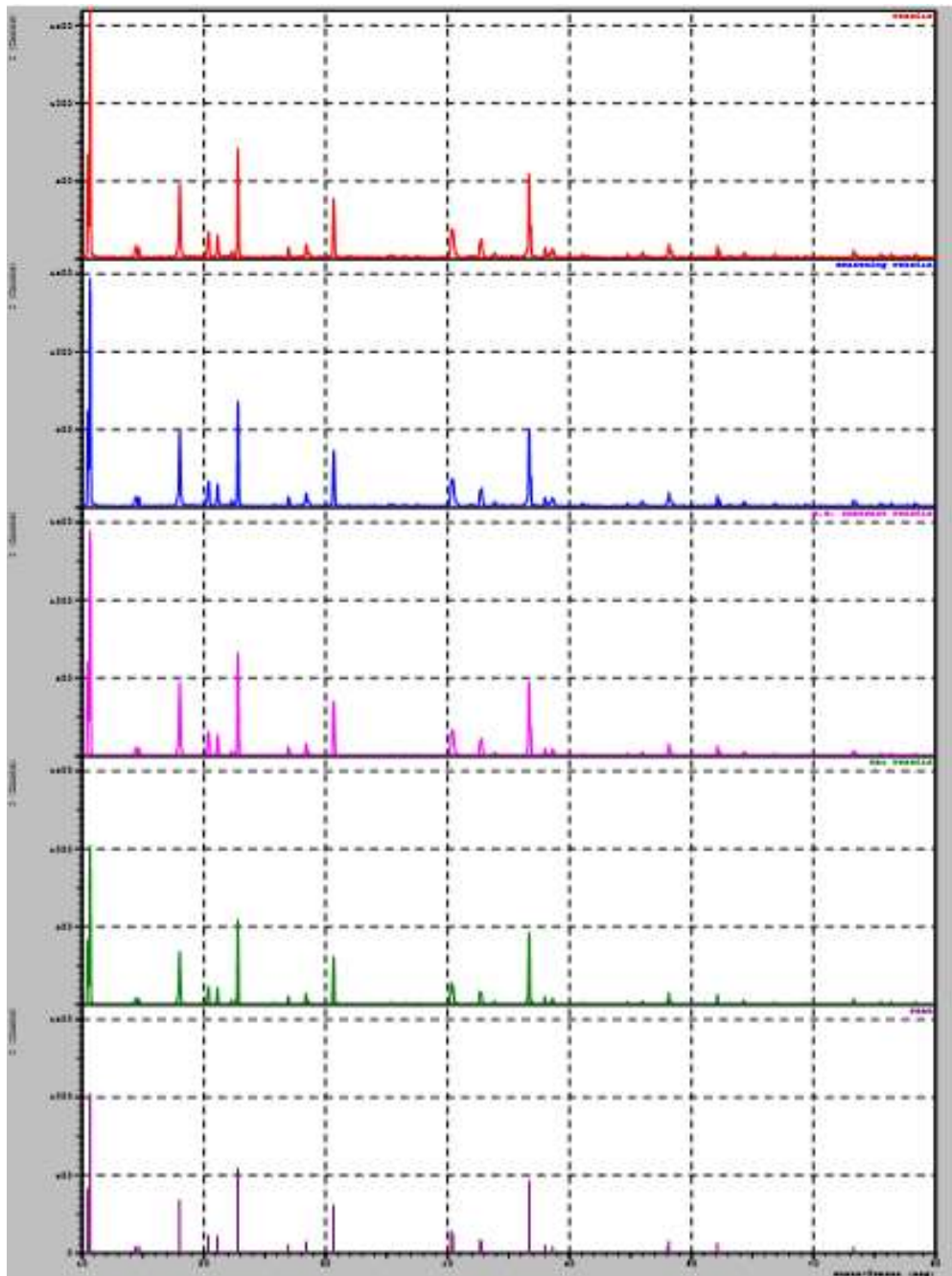
Figure 4. Comparison of cooling profile with the experimental profile

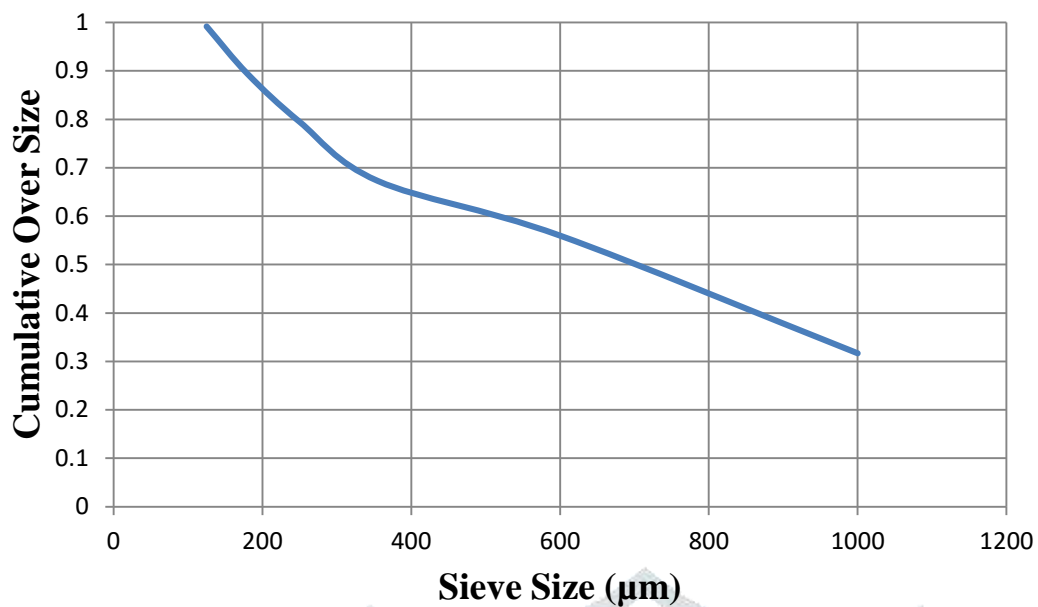
Figure 5. Experimental and model comparison of concentration profile of sulfanilamide in growth solution

Figure 6. Pareto optimal solutions

Figure 7. Optimal temperature cooling profiles (■ upper end point of Pareto front, ● middle point of Pareto front, ▲ lower end point of Pareto front)

Figure 1. XRD pattern of sulfanilamide single crystals





**Figure 2.** Particle size distribution: Temp-50°C; Stirring speed-700 rpm; Concentration-0.160 g/g; Sieve size-125µm-1000µm;



**Figure 3.** A. Sulfanilamide crystals

B. Single crystal

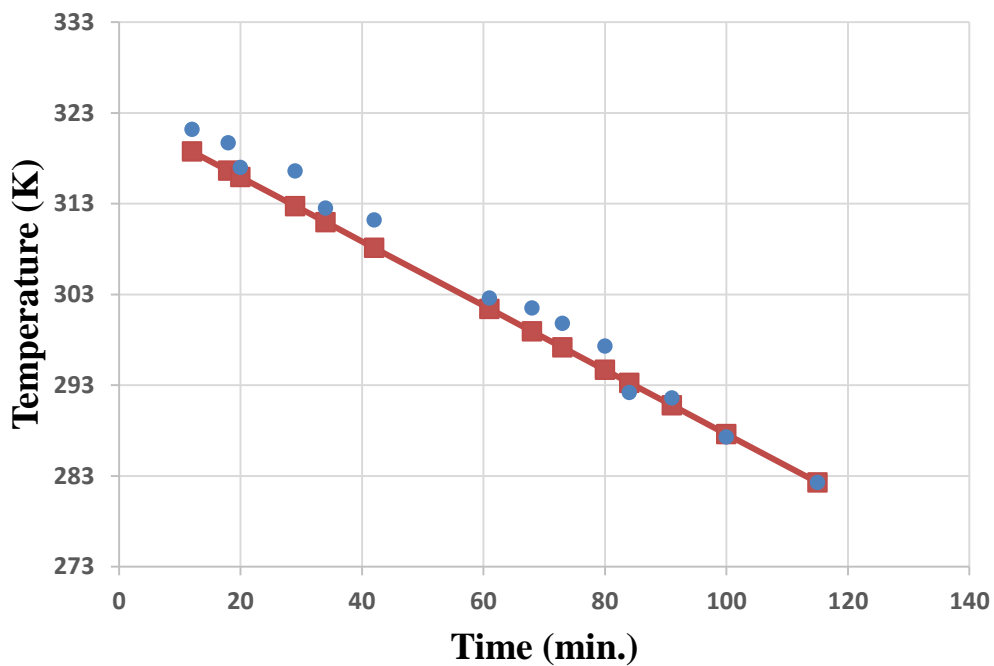


Figure 4. Comparison of cooling profile with the experimental profile

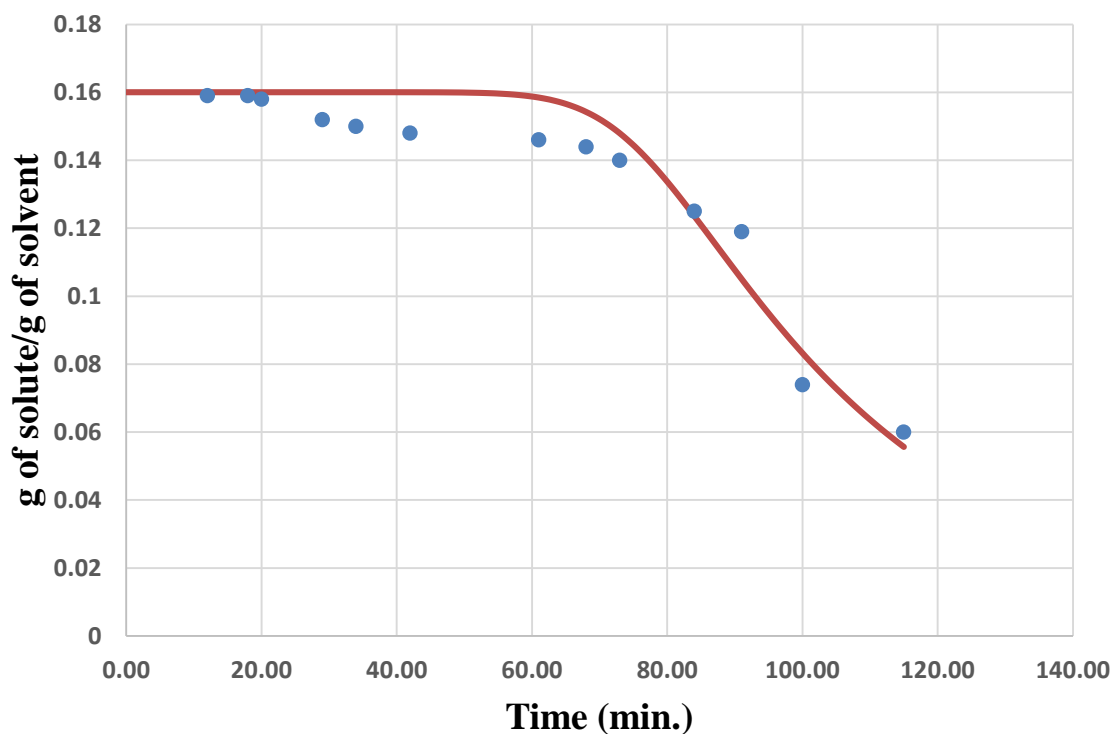


Figure 5. Experimental and model comparison of concentration profile of sulfanilamide in growth solution

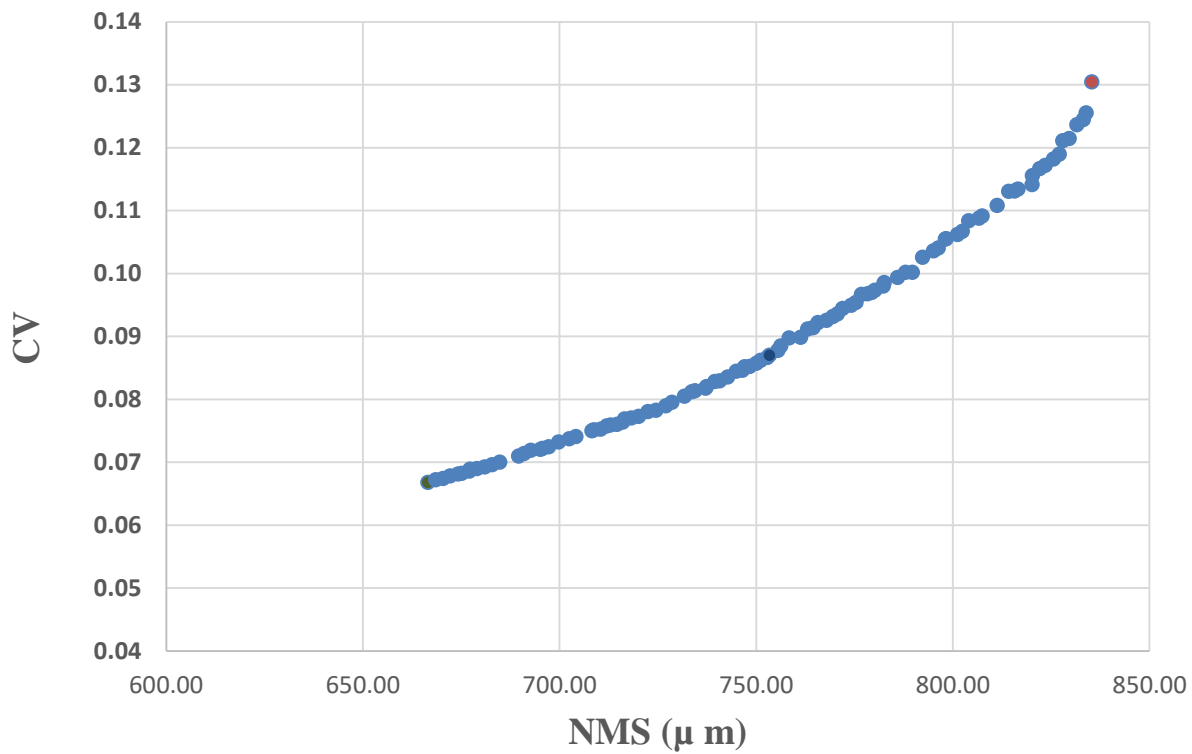


Figure 6. Pareto optimal solutions

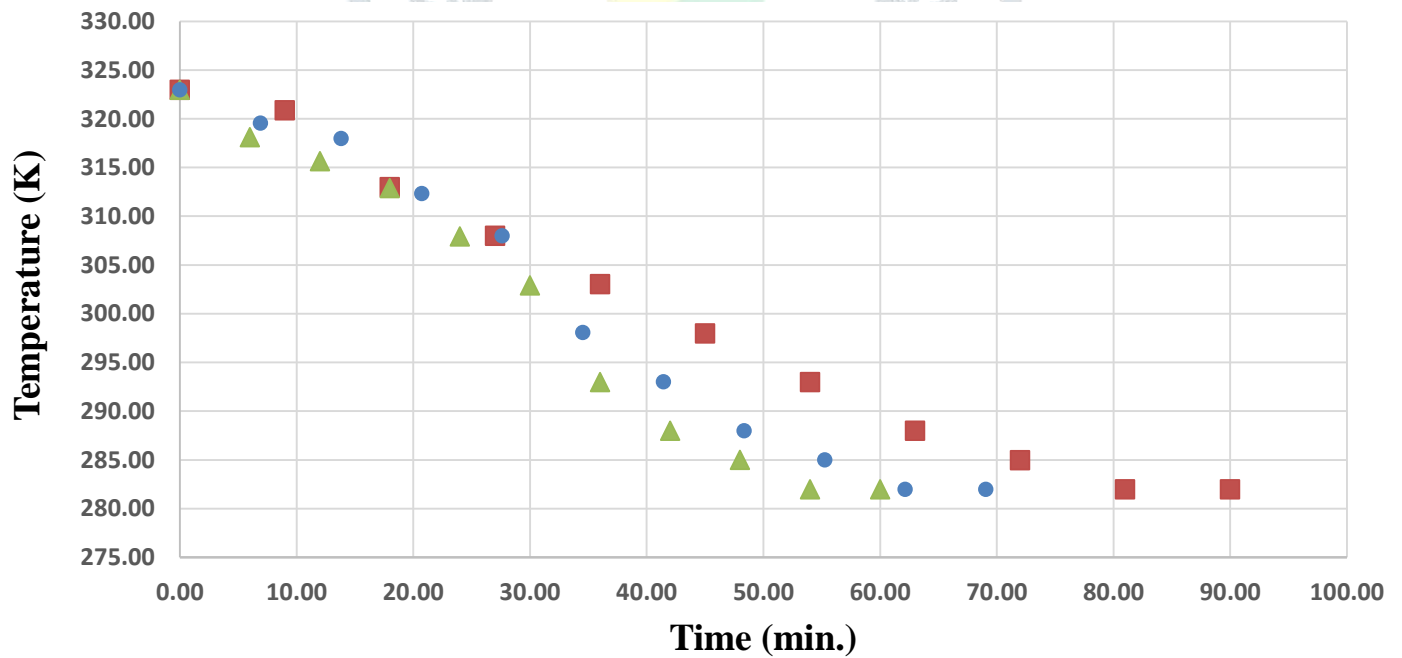


Figure 7. Optimal temperature cooling profiles (■ upper end point of Pareto front, ● middle point of Pareto front, ▲ lower end point of Pareto front)