

## Mathematical Equations Applicability for Data Interpretation of Pharmaceuticals Nano Sizing by Rapid Expansion of Supercritical Solvent Process

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**Abstract:** A numerical and theoretical method has been applied to approve the empirical data and understand the operational variables influence on the RESS processed Ibuprofen tiny particles characteristics. Through the RESS method, Ibuprofen nano-particles were produced. The pressure of dissolution cell and the temperature of expansion device were considered as the experimental variables and the impressibility of the particle size distribution by the variables was investigated. The compatibility of 3 different 2-dimensional equations with the experimental results was tested and compared. As a result, 2-D Spline equation showed the best accordance with the experimental data. A 2-D Lagrange model was also fitted on the empirical data adequately. However the Spline calculated results showed a more reliability, especially at the high pressure ranges, where the function (mean particles size) is intensively dominated by the supercritical solution characteristics.

**Keywords:** Lagrange, mathematical data correlation, spline, supercritical fluid technology

### INTRODUCTION

Supercritical Fluid Technology (SCFT) presents an innovative and interesting method of nano-particle formation in which most of the negative aspects of conventional methods are eliminated (Fages *et al.*, 2004; Yildiz *et al.*, 2007). The Rapid Expansion of Supercritical Solutions is one of the supercritical fluid processes to produce fine particles, in which a solid compound is dissolved in a supercritical fluid and the solution is suddenly depressurized through a heated and small particles are obtained by rapid nucleation. RESS process consists of 2 parts: extraction and precipitation (Turk and Lietzow, 2004). Indeed, the size and size distribution of the produced particles depends on the chemical structure of the solute and the operational condition such as pre-expansion pressure, nozzle dimensions, fluid flow rate and the expanding jet conditions (Turk and Lietzow, 2008). However some of them are vigorously effective and easily adjustable. In this sense, using a mathematical model to predict the relationship between the variables and the product properties helps to design the process by removing any extra experimental activities (Chiou *et al.*, 2007).

The morphology and size distribution of processed particles are very sensitive to the nozzle temperature and the dissolution cell pressure. However, the residence time is very low in a capillary nozzle; the temperature of the nozzle, because of its effect on supercritical solution density in passing duration, is one

of the most important operational conditions (Corazza *et al.*, 2006). The supercritical solution concentration that is intensively affected by the pressure of the dissolution cell also plays an important role in the particle size distribution. At the nozzle exit a sudden pressure reduction results in solvent power reducing and solute particles appearing. The particle formation driving force is defined as the Super saturation Ratio (S) (Atila and Alya, 2010):

$$S = \frac{y_E(T_E, P_E)}{y^*(T, P)} > 1 \quad (1)$$

In which  $y_E(T_E, P_E)$  and  $y^*(T, P)$  are the pre-expansion and post-expansion solution concentration, respectively. The particle formation rate depends directly on the S factor. The higher the S factor, the higher the precipitation rates. High rate of precipitation leads a large number of nuclei to appear without having enough time to grow up. On the other hand, high concentration of expanding solution as a result of very high pressure of dissolution cell causes aggregation of nuclei because of its high cohesion potential (Huang *et al.*, 2005). Therefore, the choice of the dissolution cell pressure range should be based on the solid component and supercritical fluid characteristics. We endeavored to create several mathematical models based on our experimental results to predict the general trends of particle size changing. In our earlier studies

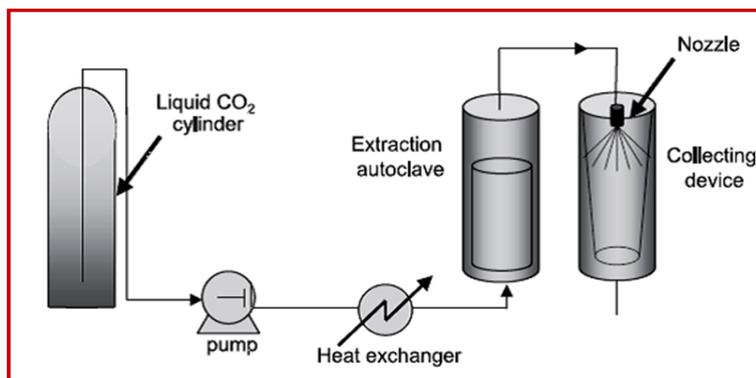


Fig. 1: Schematic diagram of RESS apparatus

the dependence of the mean particle size of RESS processed Ibuprofen powder on pre-expansion pressure (8-12 Mpa) and nozzle temperature (80-100°C) were evaluated experimentally (Zabihi *et al.*, 2011). Comparing the compatibility of the selected equations with the experimental data is another aim of the present work.

## MATERIALS AND METHODS

**Materials:** Ibuprofen (Sina Daru, 99.99% purity) was used as the model component and CO<sub>2</sub> (Roham Gaz, 99.95%) was also used as the solvent. Ethanol (99.8%, Sigma Aldrich) and Acetone (99.9%, Sigma Aldrich) were used in analytical grade form.

**Experimental apparatus:** Ibuprofen nano-particles formation was performed using a conventional RESS apparatus (set up in Research Center of Iran Oil Company), as described at our previous studies (Zabihi *et al.*, 2011, 2010a) Fig. 1.

All the operational variable and their impacts on the particles average size have been already described in our previous publishes (Zabihi *et al.*, 2010a). An enhanced sample of uniform distributed Ibuprofen particles (50 nm) provided during the mentioned experiments while the pre-expansion pressure and nozzle temperature were in turn adjusted on 8.6 Mpa and 82°C. Taking into consider the mean particle size this result is comparable with what are claimed by Pathak and Hirunsit (Hirunsit *et al.*, 2005; Pathak *et al.*, 2006). Even so, there is a significant privilege within the current work, arising from the moderated operational conditions in comparison with the other works. On the other hand, we owe the low size distribution of our products to set the nozzle dimensions and temperature, the expanding solution flow rate and the desirable phase behavior of CO<sub>2</sub>. All the experiments were performed in Iran Oil Company Research Center, on May, 2007 to Sep. 2010. The theoretical studies were carried out on summer, 2011 in Amol Research and Science branch of I.A.U.

**Analysis:** Morphology and the size distribution of particle were determined using SEM (Hitachi, S-570) images and Particle Size Analyzing system (CiLAS, 1068-Liquid).

## Theory and calculation:

**Data fitting and mathematical model development:** Numerical data matching methods have been utilized to develop a satisfactory mathematical model in order to estimate the size distribution of the RESS processed Ibuprofen in different pre-expansion pressures and nozzle temperatures.

Nano-particle production is the major intend of RESS process. Therefore, it is interested to evaluate the operational condition deriving desired powder sample. Empirical results are focused on the individual points. So, getting a desired product is only achievable by experimental trial and error. An accurate data fitting results a mathematical plot that deducing the variable effects on the target function, create the new data points in the range of a discrete set of known data and predict the optimum conditions (Bozorgmanesh *et al.*, 2009).

A two-dimensional equation of state sounds satisfactory to interpret the experimental variable (pre-expansion pressure and nozzle temperature) effects on the particle size distribution, while the other operational conditions are kept constant. We applied different 2-dimensional models and compared their compatibility with the experimental results, their ability to predict the data and their capability to interpolate the RESS processed Ibuprofen particles mean size, such as third, fourth and sixth-order poly-nominal, logarithmic, exponential functions, Lorenz, 2-D Lagrange and 2-D Sp-line equations on our experimental data. As a result, the recent 3 ones were in pretty good conformity with the trend of RESS process results.

**Lorenz model:** The general form of this model is a 2-dimensional non-linear equation See the Eq. (2) (Fowler *et al.*, 1982).

Table 1: Lorenz equation estimated parameters and coefficients

Parameter	Value
$T_0$	$1.32 \times 10^2$ K
$P_0$	87.26 bars
$a$	$4.75 \times 10^3$
$b$	5.378
$c$	5.333

$$D = \frac{a}{\left[1 + \left(\frac{T-T_0}{b}\right)^2 + 1 + \left(\frac{P-P_0}{c}\right)^2\right]} \quad (2)$$

The constants and coefficients were determined by providing a computational MATLAB program. The initial estimations were  $T_{01} = 353$  K and  $P_{01} = 85$  bars. The final values of  $T_0$  and  $P_0$  were calculated after more than 1400 substitutions by the code loop (Table 1).

**2-D Lagrange model:** A two-dimensional Lagrange modeling includes 2 separated steps. At each step a set of Lagrange polynomials are created that imply the function dependency on one of the variables while the other one is assumed to be constant. At the end, resulted polynomials are combined and form a 2-dimensional Lagrange model where the functional parameters are replaced with the Lagrange polynomials (Jng-Jy and Pei, 1994). In fact, Lagrange model creates an interpolating function that is set on every 2 adjacent empirical data according to the Eq. (3):

$$L = L_i(x)L_j(y) \quad ,0 \leq i \leq n, \quad 0 \leq j \leq m$$

$$L_i(x) = \prod_{s=0, s \neq i}^n \frac{(x-x_s)}{(x_i-x_s)}, \quad L_j(y) = \prod_{s=0, s \neq j}^m \frac{(y-y_s)}{(y_j-y_s)}$$

$$L_{ij}(x_r, y_s) = \begin{cases} 1 & i=r, \quad j=s \\ 0 & i \neq r, \quad j \neq s \end{cases}$$

$$P(x, y) = \sum_{i=0}^n \sum_{j=0}^m f((x_i, y_j))L_{ij}(x, y) \quad (3)$$

$P(x, y)$  is a polynomial that interpolates  $f(x, y)$  in any given pre-expansion pressure and nozzle temperature. Appendix A presents the developed algorithm, applied for Ibuprofen-SC  $CO_2$  system modelling. After simplifying, the functional form of the model is converted to a complicated polynomial.

**2-D Sp-line model:** A 2-D Sp-line ( $S(x, y)$ ) data patch method is also used for the experimental results fitting and prediction. All the modeling steps and details have been entirely discussed on our former works (Zabihi *et al.*, 2010b). The 2-D Sp-line is a continuous depiction of a surface that is adequately utilized for the data interpolation. Each patch within the surface at

index  $(i, j)$  is implied by a polynomial that can be generally expressed using Eq. (4) to (6) (Afsharian and Keihani, 2005; Willian, 2002):

$$S_{ij}(x, y) = \sum ni \sum mj si(x) sj(y), \quad m = 8, n = 8 \quad (4)$$

$$s_j(y) = a_j + b_j(y-y_j) + c_j(y-y_j)^2 + d_j(y-y_j)^3, 0 \leq i \leq n \quad (5)$$

$$s_i(x) = a_i + b_i(x-x_i) + c_i(x-x_i)^2 + d_i(x-x_i)^3, 0 \leq j \leq m \quad (6)$$

where,  $S_i(x)$  and  $S_i(y)$  are the one-dimensional cubic functions that represent, respectively, the nozzle temperature and pre-expansion pressure effects on the particle size distribution. Appendix B shows a schematic of 2-D Sp-line model.

The approach proposed here yields a 15-parameter-polynomial where the term with the highest order (i.e., the coefficient of  $x^3y^3$ ) is forced to be zero (Kharattian and Nikazar, 2006). The Sp-line coefficients ( $k_{ij}$ ,  $a_{ij}$  and  $\beta_{ij}$ ), in the current work, were approximated by solving the equations in MATLAB.

## RESULTS AND DISCUSSION

Table 2 presents both the experimental results and Lorenz model predicted data. Table 2 shows that the Lorenz model has a substantial deviation from the experimental points. To interpret the model behavior, each variable effect on the objective function trend was individually investigated. The Mean particle size versus the pre-expansion pressure was fitted on a 6-order

Table 2: A comparison between the experimental data and the Lorenz model predicted data

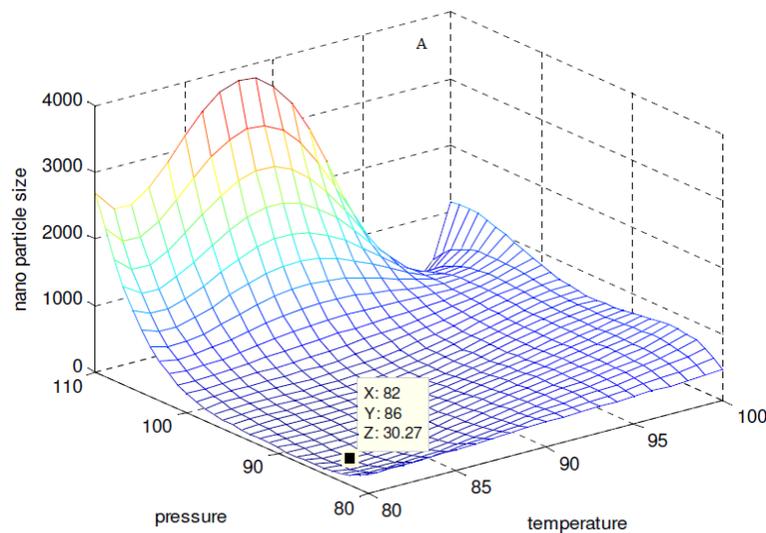
Model calculated	Experimental	P (bar)	T (°C)
116.7874	295	80	80
118.7841	91	85	
118.6818	89	90	
112.4356	287	100	
100.3328	2690	110	
7.7497	325	80	85
161.4147	96	85	
161.2258	93	90	
149.9123	330	100	
129.1419	3200	110	
223.3207	380	80	90
230.7374	315	85	
230.3517	251	90	
207.9315	405	100	
170.0065	3600	110	
335.7180	419	80	95
352.7640	498.5	85	
351.8632	479	90	
302.1056	551	100	
228.1567	1050	110	
542.9954	460	80	100
589.0314	769	85	
586.5242	701	90	
460.1834	812	100	
308.0811	1150	110	

polynomial, whereas 3-order polynomial made a reliable agreement with the nozzle temperature vis a vis the mean particles size.

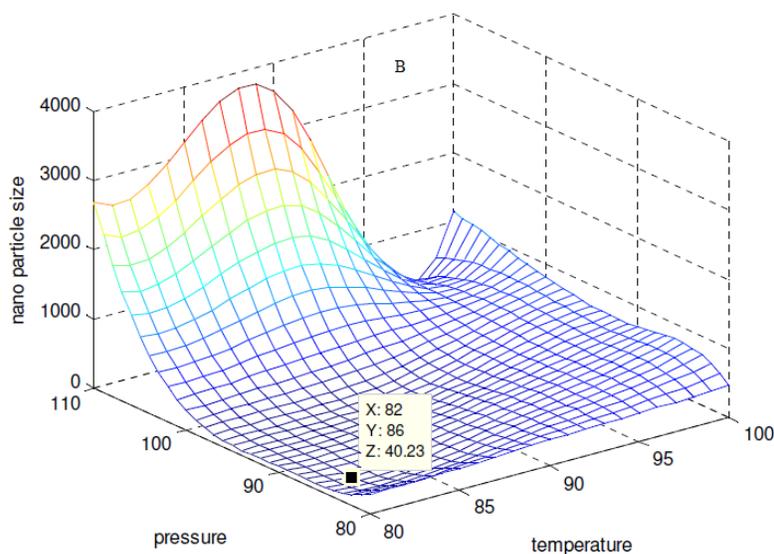
Lorenz equation deficiency in justification of empirical results can be interpreted based on the model limitation. The target function is influenced by the variables with the same order, despite the pre-expansion pressure plays a more significant role than the nozzle temperature. Actually, development of a reliable mathematical model, covering the simultaneous effects of pre-expansion pressure and nozzle temperature on the mean size of RESS processed particles, included a lot of complicated mathematical processes. This claim is reconfirmed by checking out some other

conventional 2-variable equations such as exponential functions and 3, 4 and 5<sup>th</sup> order polynomials on the experimental data.

Interpolating models are trustworthy patterns to clarify the complicated trends of some experimental data, especially where the target function is determined by more than one independent variable. An interpolation model is developed by making the set points on the empirical data. In the 2-variable functions, each one sits as one of the 2 dimensions of a surface. Since the function value at each point is estimated using the one identified at the previous step, the model accuracy depends on the number of intervals and the



(a)



(b)

Fig. 2: Lagrange (a) and sp-line (b) interpolation results

behavior accordance of the variables with the form of equations supporting the model. Lagrange and Sp-line models are, respectively, supported by Eq. (3) and (4) to (6). Figure 2 shows the data interpolating results of Ibuprofen-SC CO<sub>2</sub> system. Particle size distributions for about 600 operational points have been evaluated by both the Lagrange and Sp-line models. The optimum point for both models are 86 bar and 82°C that 30.27 and 40.23 nm were in order calculated by Lagrange and Sp-line.

To prove the accuracy of the models, an experiment was set under the optimum condition. Although the values predicted by the Sp-line and Lagrange models are both in a good agreement with the experimental data, Sp-line equation clearly works more desirable to predict the size of RESS processed particles. We also checked the accuracy of the models at 2 other points (86 °C, 103 bars and 85 °C, 93 bars) to make a better judgment about the models preciseness. Eventually, contents of Fig. 3 confirm the Sp-line model reliability rather than the Lagrange model.

A high deviation far from the optimum point is occurred by the experimental and measurement errors rather than the modeling weakness. Experiments have shown that the most uniform and small-particles are made at the optimum point (82°C, 86 bars). While, at the points far from this point the large and wide distributed particles are produced as the result of the nucleation rate reduction. The sample broad distribution makes it probable to mistake in the measurements of the mean particle size by SEM or Particle Size Analyzer (PSA) system. However the Sp-line and Lagrange functional formats are the other reasons causing deviations. Particles size distribution analysis results of the optimum sample and the samples produced at 86°C, 103 bars and 85°C, 93 bars are presented at Fig. 4 (Zabihi *et al.*, 2010b, 2011).

In a mathematical approach an important difference between the applied interpolating functions influences the value of the model. A Lagrange model is supported by long termed polynomials requiring

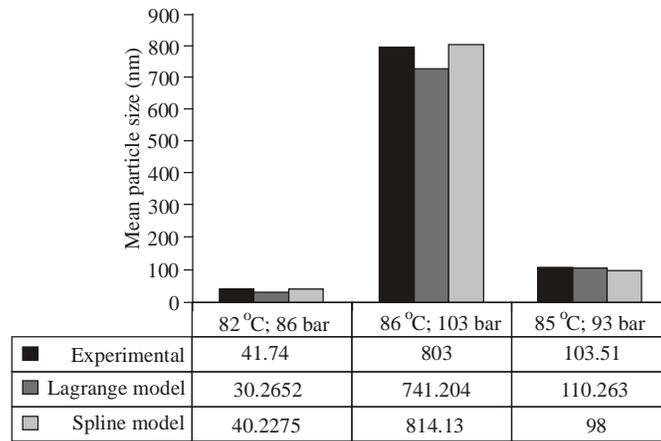
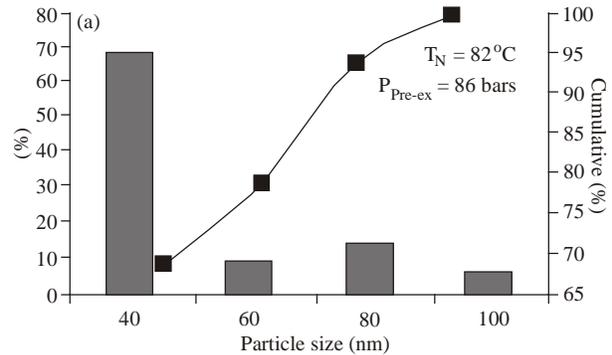
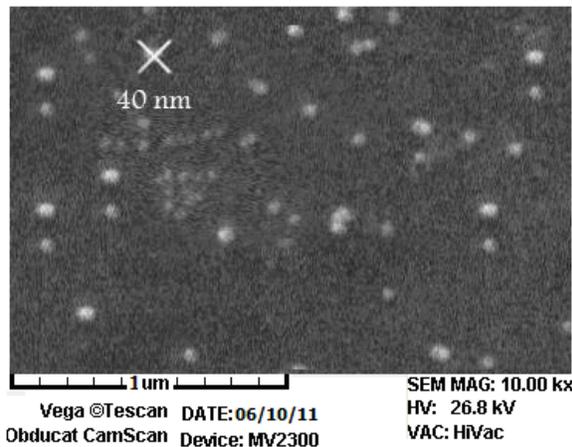
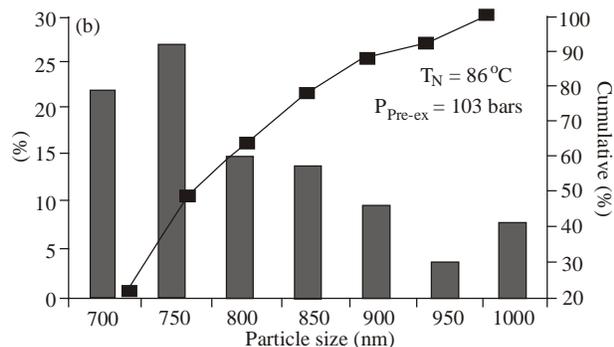
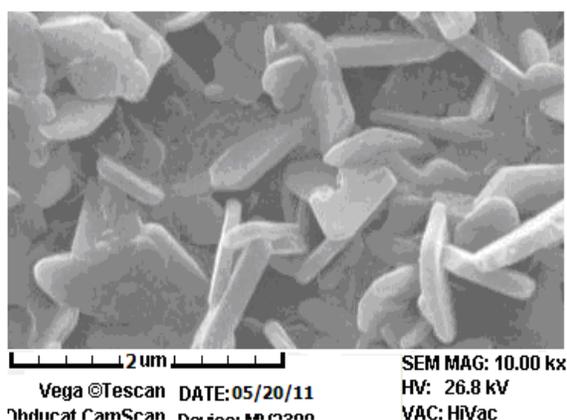


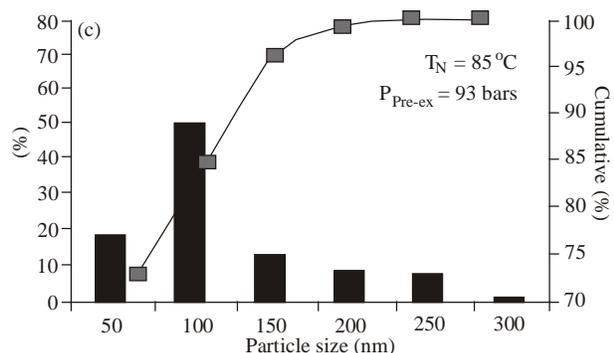
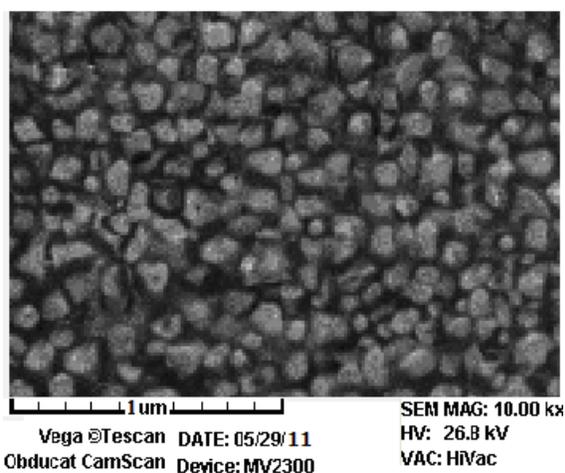
Fig. 3: The experimental and computed results



(a)



(b)



(c)

Fig. 4: Sem images and PSA analysis results of the samples produced at 82°C, 86 bars (A), 86°C, 103 bars (B) and 85°C, 93 bars (C)

a lot of complex computations. The polynomial order of magnitude is only determined after all of the calculations that have to be wholly done again for each added data. On the other hand, the Sp-line has a simpler pattern with the capability of generating much more intervals. Nevertheless, both methods have the same convergence. Meanwhile, the SCF unpredictable behavior and the significant changes in solubility power in the high pressure ranges induce some errors to the model trend. Therefore, both models applicability is more reliable in the low pressure ranges (near critical points) for the supercritical systems.

### CONCLUSION

Nanotechnology application in the various industrial fields is developing considerably. Supercritical fluids technology is a promising way to produce nano materials, due to the enhancement of the

products quality and the controllability of the process. Economical and medical values of the drug make a lot of dilemma in their production. Mathematical methods applied to anticipate the operational condition of nano-particle drug production save not only the amounts of cost and time but also eliminate the production losses.

At the current study, applicability of three various mathematical equations in predicting the particle size distribution of the RESS processed Ibuprofen has been studied. In spite of their simplicity, the polynomials don't show a satisfying fit in RESS experimental results on the basis of data scattered trend. Supercritical fluids density and molecular diffusion are strongly affected by the pressure and the temperature, so that an intensive change of solvent power, super saturation ratio and consequently the particle size distribution is expected by a light condition change. That is why the standard polynomials and logarithmic functions rarely work for interpreting a supercritical system results. While the

interpolating functions such as Sp-line and Lagrange almost create trustable models covering the supercritical systems complicated behavior. Both Sp-line and Lagrange functions showed desirable accordance with the RESS process data. However Sp-line calculated data present better agreement, because the model is supported by a simple and precise calculation process. Equations like Sp-line equation makes us capable of an accurate interpolating among a group of scattered data with an altering and unpredictable functional behavior, as what is expected for a supercritical condition.

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**APPENDIX A**

D = 1/3000 (p-85) (p-90) (p-100) (p-110)\*  
 [295/15000 (T-85) (T-90) (T-95) (T-100) -325/3750 (T-80) (T-90) (T-95) (T-100)  
 + 380/2500 (T-80) (T-85) (T-95) (T-100) -419/3750 (T-80) (T-85) (T-90) (T-100)  
 +460/15000 (T-80) (T-85) (T-90) (T-95)]  
 -1/9375 (p-80) (p-90) (p-100) (p-110)\*  
 [91/15000 (T-85) (T-90) (T-95) (T-100) -96/3750 (T-80) (T-90) (T-95) (T-100)  
 +315/2500 (T-80) (T-85) (T-95) (T-100) -498/3750 (T-80) (T-85) (T-90) (T-100)  
 +769/15000 (T-80) (T-85) (T-90) (T-95)]  
 +1/1000 (P-80) (P-85) (P-100) (P-110)\*  
 [89/15000 (T-85) (T-90) (T-95) (T-100) -93/3750 (T-80) (T-90) (T-95) (T-100)  
 +251/2500(T-80) (T-85) (T-95) (T-100) -479/3750 (T-80) (T-85) (T-90) (T-100)  
 +701/15000 (T-80) (T-85) (T-90) (T-95)]  
 -1/30000 (P-80) (P-85) (P-90) (P-110)\*  
 [287/15000 (T-85) (T-90) (T-95) (T-100) -330/3750 (T-80) (T-90) (T-95) (T-100)  
 +405/2500 (T-80) (T-85) (T-95) (T-100) -551/3750 (T-80) (T-85) (T-90) (T-100)  
 +812/15000 (T-80) (T-85) (T-90) (T-95)]  
 +1/150000 (P-80) (P-85) (P-90) (P-100)\*  
 [2690/15000 (T-85) (T-90) (T-95) (T-100) -3200/3750 (T-80) (T-90) (T-95) (T-100)  
 +3600/2500 (T-80) (T-85) (T-95) (T-100) -1050/3750 (T-80) (T-85) (T-90) (T-100)  
 +1150/15000 (T-80) (T-85) (T-90) (T-95)]

**APPENDIX B**

$f_{ij}(x, y) = 0K_{ij} + 1K_{ij}x + 2K_{ij}y + 3K_{ij}x^2 + 4K_{ij}y^2 + 5K_{ij}xy + 6K_{ij}x^3 + 7K_{ij}y^3 + 8K_{ij}x^2y + 9K_{ij}xy^2 + 10K_{ij}x^3y + 11K_{ij}xy^3 + 12K_{ij}x^2y^2 + 13K_{ij}x^3y^2 + 14K_{ij}x^2y^3$   
 $L1(x) = S_{ij}(x, 0) = 0K_{ij} + 1K_{ij}x + 3K_{ij}x^2 + 6K_{ij}x^3$   
 $L2(y) = S_{ij}(0, y) = 0K_{ij} + 2K_{ij}y + 4K_{ij}y^2 + 7K_{ij}y^3$   
 $L3(x) = 0\alpha_{i+1,j} + 1\alpha_{i+1,j}x + 2\alpha_{i+1,j}x^2 + 3\alpha_{i+1,j}x^3 = S_{ij}(x, 1)$   
 $L4(y) = 0\beta_{i,j+1} + 1\beta_{i,j+1}y + 2\beta_{i,j+1}y^2 + 3\beta_{i,j+1}y^3 = S_{ij}(1, y)$

$4K_{ij} + 9K_{ij} + 12K_{ij} + 13K_{ij} = 2\beta_{ij+1}$   
 $7K_{ij} + 11K_{ij} + 14K_{ij} = 3\beta_{ij+1}$   
 $L5(x) = 0\alpha_{i+0.5,j} + 1\alpha_{i+0.5,j}x + 2\alpha_{i+0.5,j}x^2 + 3\alpha_{i+0.5,j}x^3 = S_{ij}(x, 0.5)$   
 $3K_{ij} + 0.5_8K_{ij} + (0.5)^2_{12}K_{ij} + (0.5)^3_{14}K_{ij} = 2\alpha_{i+0.5,j}$   
 $6K_{ij} + 0.5_{10}K_{ij} + (0.5)^2_{13}K_{ij} = 3\alpha_{i+0.5,j}$   
 $L6(y) = 0\beta_{ij+0.5} + 1\beta_{ij+0.5}y + 2\beta_{ij+0.5}y^2 + 3\beta_{ij+0.5}y^3 = S_{ij}(0.5, y)$   
 $7K_{ij} + 0.5_{11}K_{ij} + (0.5)^2_{14}K_{ij} = 2\beta_{ij+0.5}$

**Symbols:**

- a, b, c, d Equations coefficients
- P Pre-expansion Pressure
- P<sub>0</sub> Initial assumption of pre-expansion value for Lorenz model
- S Super saturation factor
- T Nozzle temperature
- T<sub>0</sub> Initial assumption of nozzle temperature value for Lorenz model
- y<sub>E</sub>(T<sub>E</sub>, P<sub>E</sub>) Pre-expansion solution concentration
- y\*(T, P) Post-expansion solution concentration

**REFERENCES**

Afsharian, S. and K. Keihani, 2005. Applied Mathematics in Chemical Engineering. 3rd Edn., Puranpazhuh Publications, Tehran, pp: 3-149.  
 Atila, C. and C. Alya, 2010. Particle size design of digoxin in supercritical fluids. J. Supercrit. Fluids, 51(1): 404-411.  
 Bozorgmanesh, A.R., M. Otadi, A.A. Safe Kordi, F. Zabihi and M.B. Ahmadi, 2009. Lagrange 2-dimensional interpolation method for modeling nanoparticle formation during res process. Int. J. Indust. Math., 1(2): 175-181.  
 Chiou, A.H., M.K. Yeh, C.Y. Chen and D.P. Wang, 2007. Micronization of meloxicam using a supercritical fluids process. J. Supercrit. Fluids, 42(1): 120-128.  
 Corazza, M.L., L. Cardozo Filho and C. Dariva, 2006. Modeling and simulation of rapid expansion of supercritical solutions. Braz. J. Chem. Eng., 23(3): 417-425.  
 Fages, J., H. Lochard, J.J. Letourneau, M. Saucieu and E. Rodier, 2004. Particle generation for pharmaceutical applications using supercritical fluid technology. Powder Technol., 141(3): 219-226.  
 Fowler, A.C., J.D. Gibbon and M.J. Mc-Guinness, 1982. The complex lorenz equations. Physica D., 4(2): 139-163.  
 Hirunsit, P., Z. Huang, T. Srinophakun, M. Charoenchairakool and S. Kawi, 2005. Particle formation of ibuprofen-supercritical CO2 system by rapid expansion. Powder Technol., 145(1): 83-91.  
 Huang, Z., G.B. Sun, Y.C. Chiew and S. Kawi, 2005. Gas anti-solvent precipitation of Ginkgo Ginkgolides with supercritical CO2. Powder Technol., 160(2): 127-135.

- Jng-Jy, S. and S.C. Pei, 1994. Parameter estimation and blind channel identification in impulsive signal environments. *IEEE Trans. Signal Process.*, 42(1): 2884-2897.
- Kharattian, R. and M. Nikazar, 2006. *Applied Mathematics in Chemical Engineering*. 2nd Edn., Amir Kabir University Publications, Tehran.
- Pathak, P., M. Meziani, T. Desai and Y. Sun, 2006. Supercritical fluid processing of nanoscale particles from biodegradable and biocompatible polymers. *supercrit. Fluids*, 51(37): 4320-4324.
- Turk, M. and R. Lietzow, 2004. Stabilized nanoparticles of phytosterol by rapid expansion from supercritical solution into aqueous solution. *APS Pharm. Sci. Tech.*, 5(4): 36-45.
- Turk, M. and R. Lietzow, 2008. Formation and stabilization of submicron particles via rapid expansion processes. *J. Supercrit. Fluids*, 45(3): 346-355.
- Willian, H., 2002. *Numerical Recipes Example Book (C++)*, Book 3. 2nd Edn., Cambridge University Press, Cambridge, ISBN: 0521750342, pp: 318.
- Yildiz, N., T. Sebnem, O. Duker and A. Calimli, 2007. Particle size design of digitoxin in supercritical fluids. *J. Supercrit. Fluids*, 41(31): 440-451.
- Zabihi, F., M. Otadi and M. Mirzajanzade, 2010a. Cortisone acetate nano-particles formation by rapid expansion of a supercritical solution in to a liquid solvent (resolve method): An operational condition optimization study. *Proceeding of ICNB, IEEE, Hong Kong, Sep. 28-30*, pp: 1-6.
- Zabihi, F., A. Vaziri, M.M. Akbarnejad, M. Ardjmand and M. Otady, 2010b. A novel mathematical method for prediction of Rapid Expansion of Supercritical Solution (RESS) processed ibuprofen powder size distribution. *KJChE*, 27(5): 1601-1605.
- Zabihi, F., M.M. Akbarnejad, A. Vaziri, M. Arjomand and A.A. Seyfkordi, 2011. Drug nano-particles formation by supercritical rapid expansion method; operational condition effects investigation. *IJCCE*, 30(1): 7-15.