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A novel mathematical method for prediction of rapid expansion of supercritical solution (RESS) processed ibuprofen powder size distribution

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Abstract−A fundamental understanding of the interplay among the variables involved in a rapid expansion of supercritical solution (RESS) process is necessary in order to achieve control of product within the desired specifications. A model is proposed where the experimental data are fitted to a 2-D Sp-line equation that results in a mathematical pattern matching function that can easily be processed analytically to yield a continuous motion estimate. This model presents a novel promising method to interpolate between any two experimental results. Comparison of the mean particles size values which are calculated as a function of nozzle temperature (T_N) and pre-expansion pressure ($P_{pre\text{-}expansion}$) with the experimental data, results in a ±8% accuracy. The optimum operational point that leads to the minimum mean particles diameter (40 nm) is determined through mathematical optimization of this equation and confirmed experimentally. Furthermore, 600 more values of mean particle size are predicted by varying the nozzle temperature and dissolution pressure and the results are presented in the form of a 3-dimesional curve.

Key words: Mean Particles Size, RESS, 2-D Sp-line Equation, Pre-expansion Pressure, Nozzle Temperature, Interpolation

INTRODUCTION

Particle size reduction techniques based on the favorable properties of supercritical solvents have been explored for the last half century [1-3]. Due to the liquid-like density and gas-like transport properties, supercritical fluids are used in various extraction and material modification applications [4-6]. Rapid expansion of supercritical solution (RESS) which can lead to solvent-free, ultrafine and chemically pure powders is a promising process for generation of small and uniform particles. This process offers the advantage of low operational temperature, significant for processing thermally sensitive biological molecules such as many pharmaceuticals [7-11]. In RESS solid processing, the substance of interest is dissolved in a supercritical fluid in the vicinity of the solvent's critical temperature and pressure, where the resulting dilute solution exhibits high compressibility. Therefore, a small change in pressure gives rise to a large change in density and hence solvent power. The expansion of the solution, consequently, results in the precipitation of dissolved solute. Fast expansion leads to high supersaturation and fine powders can be obtained [12-16]. Carbon dioxide as an environmentally benign, inexpensive, non-flammable non-toxic solvent has been widely used in many supercritical particle formation processes. Its low critical pressure and temperature (72 bars, 31.1 °C) makes it a suitable solvent for the processing of thermally labile materials without the risk of degradation [17-19]. Ibuprofen is a chiral, non-steroidal, anti-inflammatory drug which exhibits poor solubility in water.

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Therefore, its bioavailability can be enhanced by reducing the particle size. Experimental and theoretical studies have been carried out previously on the RESS processed Ibuprofen by various groups [20-22]. The aim of most of these studies was the determination of the effect of pre-expansion pressure, spraying distance and nozzle length on the size distribution and morphology of the precipitated powder. In a related method, rapid expansion of supercritical fluid to aqueous solution (RESAS), the supercritical solution is expanded into aqueous solutions instead of expanding into air, in order to study the properties of receiving space on particles growth and agglomeration [23-26]. One-dimensional flow models have been developed on ibuprofen-CO_2 in terms of the degree of supersaturation, nucleation rate, critical nucleus size and critical concentration of nuclei which describe the particle formation through the rapid expansion of supercritical solution [27-29]. However, the effect of important experimental parameters such as nozzle temperature has never been considered in the above-mentioned papers. The goal of most of these studies was to achieve a set of general rules which could control the particle size and distribution by adjusting the operational variables. An understanding of underlying physical phenomena of relationship between the process conditions and the mechanisms of particles formation and growth during RESS process is still at an early stage. We endeavor to create a mathematical equation based on experimental results which can predict the general trends of particle size. In our previous study, the mean particle size of the RESS processed Ibuprofen powder dependence on pre-expansion pressure (8-12 MPa) and nozzle temperature (80-100 °C) was evaluated experimentally [30].

Experiments were designed based on middle operational condi-

tions that make the process more feasible and attractive from the practical and economical aspects. A two-dimensional Sp-line model was fitted on the experimental data (27 points) that implies the mean particle size of the RESS processed powder, as a function of pre-expansion pressure and nozzle temperature, in order to predict the processed particles mean diameter made in an extended range of pre-expansion pressure and nozzle temperature sets. Values of the optimum variables were also calculated for our mathematical equation by a computational optimization method and confirmed experimentally. Scanning electron microscopy (SEM) and particle size analyses were applied to determine the obtained powder in optimum conditions (nozzle temperature 82 °C and pre-expansion pressure 8.6 MPa), and a good agreement (within ±8%) was achieved between calculated and experimental results. Furthermore, the values of mean particle size were interpolated for 600 experimental points by using the fitted equation. One of these calculated points was randomly selected to run experimentally in order to re-confirm the model accuracy.

EXPERIMENTAL METHODS

1. Materials

Ibuprofen (Sina Daru, 99.99% purity) was used as model compound and CO_2 (Roham Gaz, 99.95%) was also used as solvent. Ethanol (99.8%, Sigma Aldrich) and Acetone (99.9%, Sigma Aldrich) are used in analytical grade form.

2. Equipment

The experimental apparatus is shown in Fig. 1. SC solvent (CO_2) flows to a liquefier (cooling system, F38-Me, Julabo) from the reservoir by an HPLC pump that is set at the flow rate required for the desired pressure. It then passes through a pre-heater to the solute loaded columns, in a temperature controlled oven.

A glass wool plug is packed at the end of each column to prevent the powder entrainment. The solute saturates the supercritical solvent, which is then throttled across a pressure reducing valve and an expansion nozzle within an expansion chamber where the solute fine particles participate. The expansion device is a stainless-steel capillary tube (5 mm Length and 0.05 mm I.D.) wrapped with temperature adjustable heating elements. All connections and tubes are stainless steel and wrapped by wire heaters equipped with temperature controllers to keep temperatures constant. The pressure values in the extraction columns are also measured by pressure gauges (Ashcroft, f5503).

Flow rate is constant and the same in all runs. Nozzle tip is kept at the distance of 0.5 cm, relative to a collection surface. In each run, sample collection starts after 4 min to ensure condition consistency.

3. Analysis

Morphology and size of particles were determined by SEM (Hitachi, S-570), and size distribution curves were achieved by Particle Size Analyzer system (Horiba, LA-950-V2).

RESULTS AND DISCUSSION

As described in the previous work, during the experimental runs, we gained 27 mean particle sizes in 27 different operational points. Five different supercritical pre-expansion pressures (8, 9, 10, 11 & 12 MPa) and in each pressure, five different nozzle temperatures (80, 85, 90, 95 & 100 °C) were set as experimental variables. With the exception of the above-mentioned variables, all other parameters were kept constant during all runs. Experimental conditions were selected based on Ibuprofen physical properties and CO_2 phase behavior and critical point [31-34]. In the series of experiments conducted at 12 MPa, the resulting particles were too aggregated.

So their morphology, size and distribution were not determined exactly. All other products were analyzed by SEM and particle size analyzer systems and their mean particle size and particle size distribution were calculated by Eq. (1) [34,35].

$$D.a. = \frac{\sum nd}{\sum n} \quad (1)$$

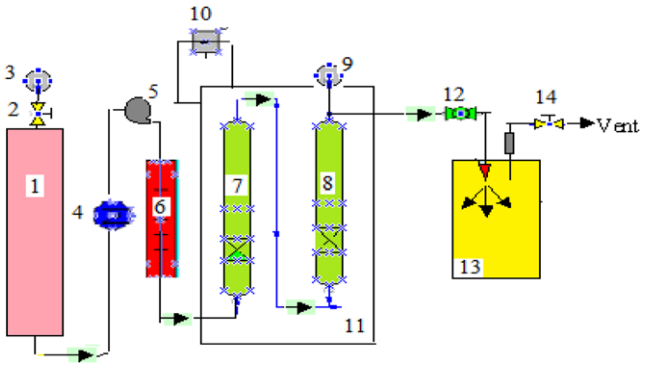

Fig. 1. Shematic diagram of RESS apparatus.

1. CO_2 tank
2. Controller valve
3. Pressure gauge
4. Cooling system
5. HPLC pump
6. Pre-heater
7 & 8. Solute loaded columns
9. Pressure gauge
10. TIC
11. Electrical bath
12. Pressure reducing valve
13. Precipitation chamber
14. Venting valve

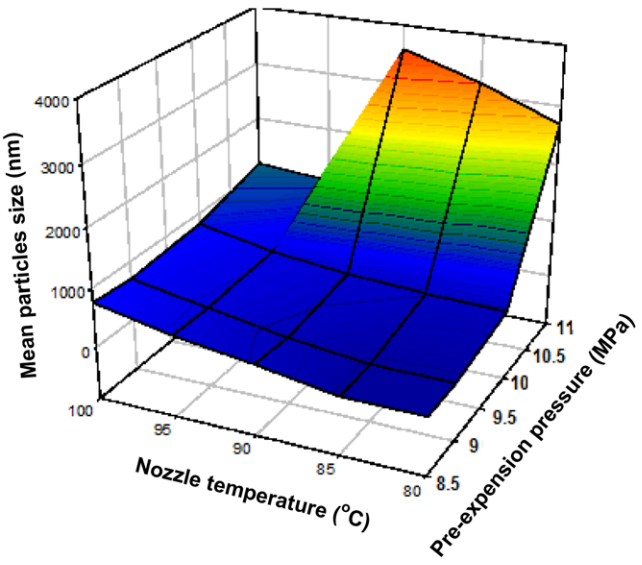

Fig. 2. The size distribution of particles as a function of pre-expansion pressure (MPa) and nozzle temperature (C).

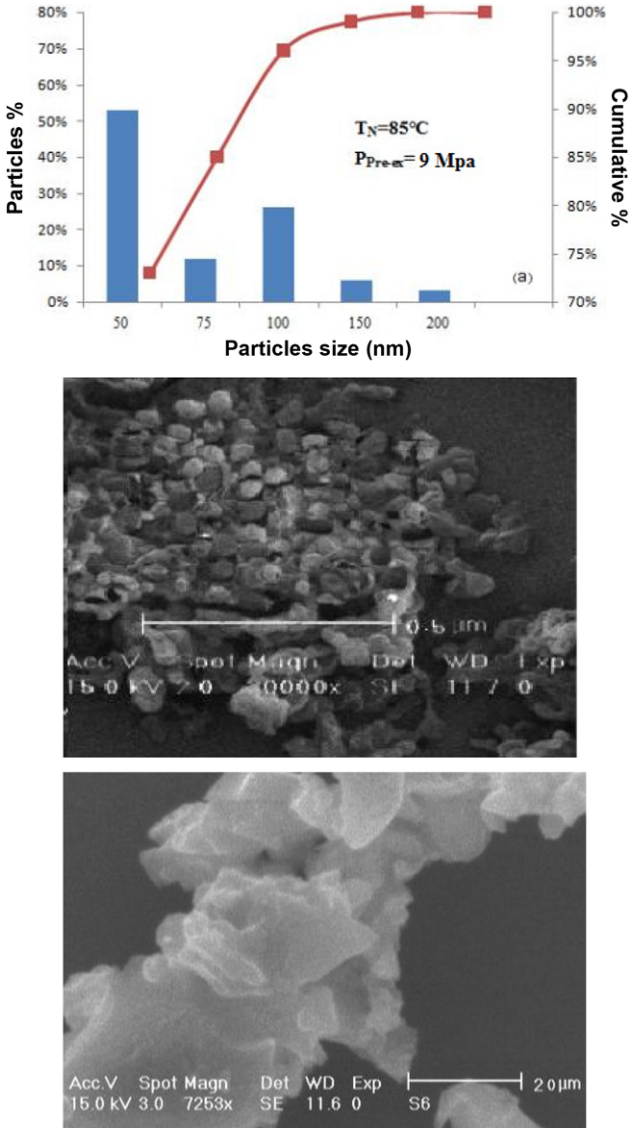

Fig. 3. (a) SEM image and Particle size analyzer results for the sample processed in nozzle temperature 85 °C and pre-expansion pressure 9 MPa, (b) SEM image of unprocessed sample.

The experimental results are shown on Fig. 2 that presents the effects of the nozzle temperature and pre-expansion pressure on mean particle size.

Fig. 3 shows a sample of Ibuprofen particles which is processed using pre-expansion pressure of 9 MPa and nozzle temperature of 85 °C. It is compared with an unprocessed Ibuprofen sample.

3. Mathematical Method and Optimization

To achieve a better conception of nozzle temperature and pre-expansion pressure parallel effects on particles size, a two-variable equation was fitted to the experimental data. This equation can be used to:

1) Understand the relationship between particle size and process variables (T_N, P_{pex}), keeping other process parameters constant

2) Optimization of the RESS process conditions

3) Prediction of the size distribution of particles.

Considering these goals and with respect to the special effects of nozzle temperature and pre-expansion pressure on particles size, we employed a 2-D Sp-line (s(x, y)) data patch method to fit our experimental data [36-38]. A 2-D Sp-line is a continuous representation of a surface. Each patch within the surface at index (i, j) is described by a polynomial that can be generally expressed using Eq. (2) [39-41].

$$S_{ij}(x, y)=\Sigma_i^n \Sigma_j^m s_i(x)s_j(y), \quad m=8, n=8 \tag{2}$$

Each $s_i(x)$ and $s_j(y)$ are one-dimensional, cubic function with 8 coefficients, that represent the nozzle temperature and pre-expansion pressure effects on the particles size. The complete form of $s_{ij}(x, y)$ function and the schematic representation of the 2-D Sp-line are presented in Appendix 1.

The approach proposed here yields a 15 parametric polynomial where the highest order term (i.e., the coefficient multiplying x^3y^3) is forced to zero [42-44]. In this paper, all the Sp-line coefficients (k_{ij}, α_{ij} and β_{ij}) were computed by solving the equations system in MATLAB [45]. We put all the experimental points into this equation and calculated the particle size to prove the accuracy of the mathematical model. Calculated results showed a very good agreement (within ±8%) with the experimental data as shown in Fig. 4.

Since the main purpose of RESS processes is producing fine particles (micro and nano meters), it is of interest to predict what pre-expansion pressure and nozzle temperature would be needed exactly, to produce a desired powder sample with the target mean particles size. Mean particle sizes for about 600 more operational conditions were also computed at the experimental range of nozzle temperature and pre-expansion pressure. The results are presented in Fig. 5.

A comparison between Figs. 2 and 5, confirms that the dependence of mean particle size on the pre-expansion pressure and nozzle temperature in the interpolated and experimental results is in good agreement. We optimized the Sp-line equation in order to find the nozzle temperature and pre-expansion pressure that result in the minimum value of mean particle size. Results showed that the minimum particle size (40 nm) can be gained in the pre-expansion pressure of 8.6 MPa and the nozzle temperature of 82 °C. To prove the

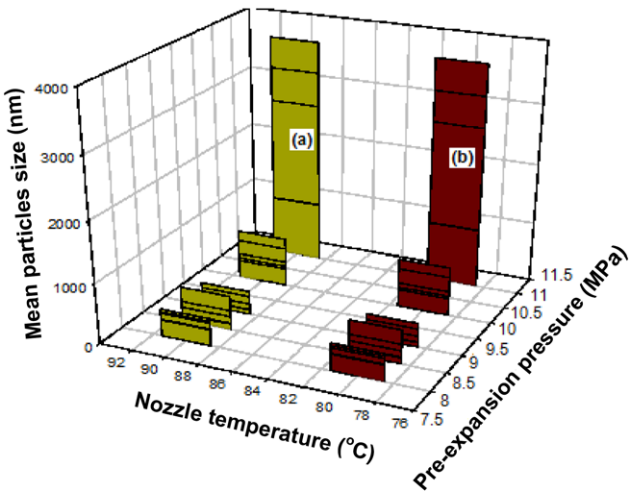

Fig. 4. Comparison between experimental (a) and calculated (b) experimental data.

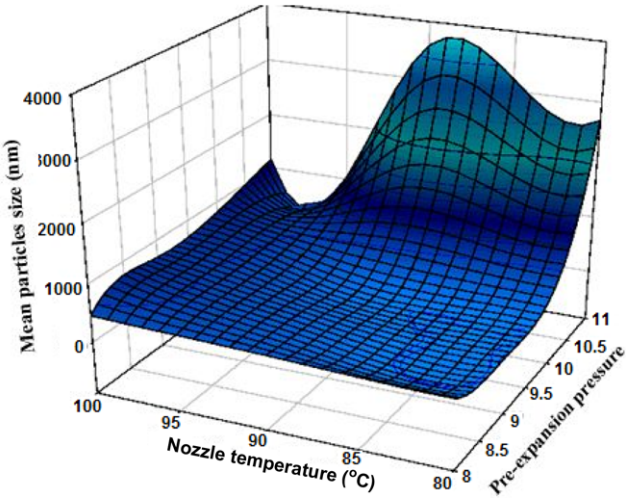

Fig. 5. Calculated values of particles size as a two-dimensional function of pre-expansion pressure (MPa) and nozzle temperature.

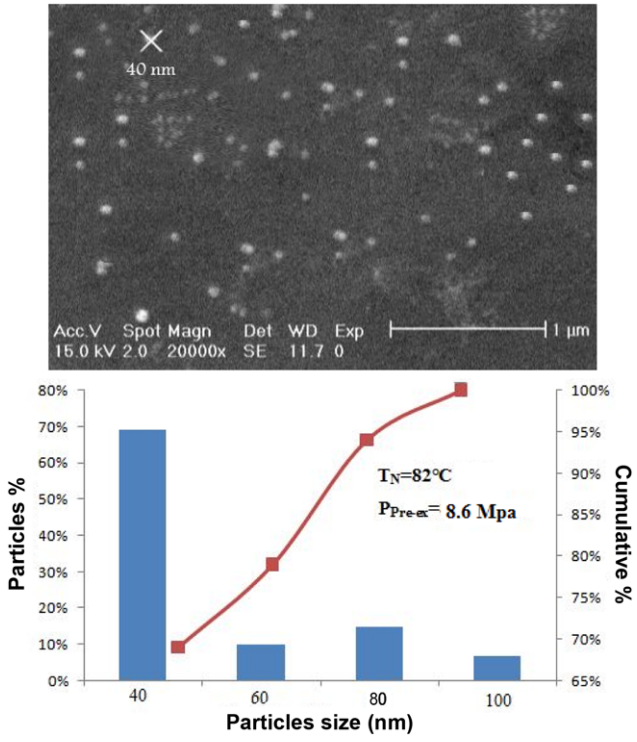

Fig. 6. SEM image and Particle size analyzer result for the sample processed in nozzle temperature 82 °C and pre-expansion pressure 8.6 MPa.

accuracy of the model, an experiment was run under these predicted optimum conditions. The product particles were analyzed by SEM and particle size analyzer system. The results are shown in Fig. 6.

Fig. 7 shows the results of SEM and particle size analyses for another powder which was produced using the pre-expansion temperature of 10.3 MPa and the nozzle temperature of 86 °C. The calculated mean particle size for this sample is 814 nm and the experimental result is 803 nm.

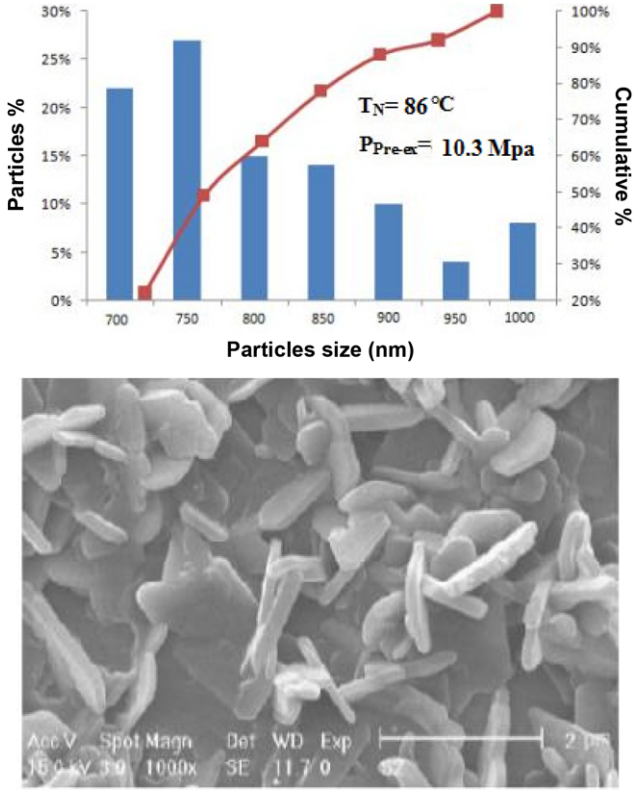

Fig. 7. SEM image and Particle size analyzer result for the sample processed in nozzle temperature 86 °C and pre-expansion pressure 103 MPa.

CONCLUSION

A mathematical model has been used as a novel method for data prediction. This model allows the prediction of the mean diameter of nano Ibuprofen powder produced using the RESS process in an extended range of nozzle temperature and pre-expansion pressure. A 2-D Sp-line equation is matched with experimental data. The model computes the mean particle size as a function of nozzle temperature and pre-expansion pressure with a deviation of less than 8%. Using the model, optimum conditions for production of smallest size particles were found and later confirmed experimentally. Use of this model allows a systematic approach to particle size production and reduces trial and error experiments considerably.

APPENDIX 1

The mathematical derivation of the 15 equations necessary to form a 2D Sp-line is presented here [48,49];

$$S_{i,j}(x,y)={}_0k_{i,j}+{}_1k_{i,j}x+{}_2k_{i,j}y+{}_3k_{i,j}x^2+{}_4k_{i,j}y^2+{}_5k_{i,j}xy+{}_6k_{i,j}x^3+{}_7k_{i,j}y^3 +{}_8k_{i,j}x^2y+{}_9k_{i,j}xy^2+{}_{10}k_{i,j}x^3+{}_{11}k_{i,j}xy^3+{}_{12}k_{i,j}x^2y^2+{}_{13}k_{i,j}x^3y^2+{}_{14}k_{i,j}x^2y^3$$

$$L1(x)=S_{i,j}(x,0)={}_0k_{i,j}+{}_1k_{i,j}x+{}_3k_{i,j}x^2+{}_6k_{i,j}x^3$$

$$L2(y)=S_{i,j}(0,y)={}_0k_{i,j}+{}_2k_{i,j}y+{}_4k_{i,j}y^2+{}_7k_{i,j}y^3$$

$$L3(x)={}_0\alpha_{i+1,j}+{}_1\alpha_{i+1,j}x+{}_2\alpha_{i+1,j}x^2+{}_3\alpha_{i+1,j}x^3=S_{i,j}(x,1)$$

$$L4(y)={}_0\beta_{i,j+1}+{}_1\beta_{i,j+1}y+{}_2\beta_{i,j+1}y^2+{}_3\beta_{i,j+1}y^3=S_{i,j}(1,y)$$

$_4k_{i,j}+_9k_{i,j}+_{12}k_{i,j}+_{13}k_{i,j}=_2\beta_{i,j+1}$

$_7k_{i,j}+_{11}k_{i,j}+_{14}k_{i,j}=_3\beta_{i,j+1}$

$L5(x)=_0\alpha_{i+0.5,j}+_1\alpha_{i+0.5,j}x+_2\alpha_{i+0.5,j}x^2+_3\alpha_{i+0.5,j}x^3=S_{i,j}(x, 0.5)$

$_3k_{i,j}+0.5_8k_{i,j}+(0.5)^2{}_{12}k_{i,j}+(0.5)^3{}_{14}k_{i,j}=_2\alpha_{i+0.5,j}$

$_6k_{i,j}+0.5_{10}k_{i,j}+(0.5)^2{}_{13}k_{i,j}=_3\alpha_{i+0.5,j}$

$L6(y)=_0\beta_{i,j+0.5}+_1\beta_{i,j+0.5}y+_2\beta_{i,j+0.5}y^2+_3\beta_{i,j+0.5}y^3=S_{i,j}(0.5, y)$

$_7k_{i,j}+0.5_{11}k_{i,j}+(0.5)^2{}_{14}k_{i,j}=_2\beta_{i,j+0.5}$

NOMENCLATURE

d : diameter of a species of particles
D.a. : mean particle size
k_{ij} : constant coefficient
n : number of particles of the species d
s : 1-dimensional Sp-line equation

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