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The Effect of Rapid Expansion of Supercritical Solution (RESS) Parameter on Sub-Micron Ibuprofen Particle Forming

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Abstract

Rapid expansion of supercritical solution (RESS) is the most common method of pharmaceutical particle forming approaches using supercritical fluids. The RESS method is a technology which produces a small solid product with a very narrow particle size distribution, organic solvent-free particles. This process is also simple and easy to control the operating parameters in comparison with other methods based on supercritical techniques. In this study, Ibuprofen, anon steroidal anti-inflammatory drugs (NSAID), has been micronized by RESS; the size and morphology effects of three different RESS parameters including extraction temperatures, extraction pressures and expansion nozzle temperatures have been investigated and optimized by response surface method. The particle size distribution has been measured by Light diffraction scattering (LDS) method. SEM has been used to analyze the surface structure, DSC and FTIR for thermal and chemical structure analysis. The obtained results are average particle sizes below 1 μm decreased significantly compared to the initial particle size and the optimal operating conditions are identified, enabled the pilot-scale studies and industrial operation.

Keywords: Ibuprofen; Rapid expansion of supercritical solution (RESS); Response surface methodology; Supercritical fluid

Introduction

In the pharmaceutical industry, the large numbers of drugs are insoluble or poorly soluble in water, so it leads to a low bioavailability which is one of the mainproblems in processing new applications [1]. One of solutions is the reduction in particle size (increase in surface area), which leads to an improvement of the dissolution behaviour. There were several conventional techniques utilized for particle size reduction such as grinding, milling, spray-drying and high-pressure homogenization. However, the disadvantages of these techniques are thermal and chemical degradations of products, large amounts of solvent use, high energy requirements and broad particle size distributions (PSDs). New methods which can overcome these drawbacks are supercritical fluid technologies and The Rapid Expansion of Supercritical Solution (RESS) is the most popular among them [2]. RESS produces fine particles with narrow PSDs while being safe with environment and human health [3]. Although all the parameters affect particle size, nozzle and its characterization have a critical role in RESS process. Hezave AZ [4] and F. Esmaeilzadeh [5] studied the effect of nozzle diameter on particle size of creatine monohydrate and diclofenac. Kayrak [1] carried out a survey of the influence of spraying distance from nozzle to the collection surface on the size of ibuprofen particles. Z. Huang, [6] N. Yildiz [7] , A. Keshavars [8] researched the effect of extraction temperature on the average particle sizes of aspirin, salicylic acid raloxifene, cholesterol and lidocaine. Ibuprofen particle size was studied at different nozzle temperature by Z. Fatemeh [9]. A. Z. Hezave [4], F. Esmaeilzadeh [5], H. R. Satvati [10]; N. Yildiz [7] researched the effect of extraction pressure on sizes of creatine monohydrate, diclofenac, cholesterol and salicylic acid respectively.

Design of experiment (DOE) is an established tool in the pharmaceutical industry for the investigation of complex processes and to study a number of variables and their interactions. Several studies have investigated RESS parameters using an experimental design method. Despite the large number of reports, experimental design has not been used to evaluate the influence of variables in the case of Ibuprofen particle forming. The aim of this study was to evaluate the effect of process parameters on particle characteristics using the Rapid expansion of supercritical solution method, and compare the effect of these parameters on the size distribution. The particle mean size were the response functions (empirical models) of the three factors including extraction temperature, extraction pressure and nozzle temperature that have an effect on particle properties. The methodology applied in this work leads to a mathematical model which describes the effects of process variables on the studied response, and therefore the response behaviour can be predicted over the whole experimental domain.

Experimental

Material

Ibuprofen 99.7% is supplied by Aldrich Sigma in white powder form. CO_2 (>99.9%) originates from Singapore. Nonionic surfactant, polyoxyethylene sorbitan monooleate (Tween 80), originates from Aldrich Sigma.

Experimental Apparatus

The gaseous CO_2 from a cylinder capsule was cooled to make liquid CO_2. The liquid CO_2 was pressurized to the extraction pressure by a high pressure pump and then fed into an extraction vessel (100 ml), which contained dry powder ibuprofen. The extraction vessel was placed the temperature- controlled chamber of supercritical fluid extractor and the paddle to support the material dissolution. The RESS system was operated in 120 minutes with 100 mg ibuprofen for each experiment. Supercritical solution was expanded rapidly through a nozzle, where it

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was heated to avoid clogging, into ambient environment at atmospheric pressure to obtain small particle. CO_2 returned to gaseous form quickly and separated from the product.

Experimental design

The study of the influence of operating parameters on particle properties was based on an experimental design. Three variables were evaluated in term of their effect on the particle characteristics. These variables were: (Z_1) extraction temperature of extraction chamber, (Z_2) extraction pressure and (Z_3) nozzle temperature of the expansion chamber. The response functions were chosen is the mean size of particle (Y). Regression analysis of the data was carried out within a statistical design package ('Design-Expert' version 7.0.0, Stat Ease, Inc,) using a quadratic model with interactions:

$$Y = b_0 + \sum_i b_i X_i + \sum_j b_j X_i X_j \quad (1)$$

With i,j=1, 2, 3

Where Y is the estimated response, Xi is the scaled independent process variable (−1=low level, 0=central level and +1=high level) and the coefficients b_0, b_i, b_{ii}, b_{ij} characterise respectively the constant, the linear and quadratic effects of the variable X_i and the interactions between X_i and X_j. To define these coefficients, it is required a star point at two level in every variable X_i (+α=1.414 and -α=-1.414).

The complete model is based on the simultaneous variation of three factors at two levels implying the running of 18 trials including 4 ones at center points. Each point of experiment was repeated three times and the average was used for the statistic. The ranges of investigated parameters are extraction temperature (35-55°C), extraction pressure (90 -150 bar) and nozzle temperature (80-100°C)

Analysis

Differential scanning calorimetric (DSC) supplied information about physical properties (melting point and enthalpy of fusion) of unprocessed and RESS-processed ibuprofen. The sample (~1,5mg per run) was heated in an aluminum standard pan under a nitrogen gas flow of 20ml/min with heating rate of 5°C/min.

Light diffraction scattering (LDS) was used to determine the particle size and size distribution of the raw and processed particles. Solvent was the combine of ibuprofen saturated solution in distilled water and Tween 80 0.1% v/v, being sonicated for 30 minutes before performing the analysis.

Scanning Electron Microscope (SEM) was used to analyze the size and morphology of particles. The sample was sonicated for 3 minutes in the same solvent of LDS, and then few droplets were added on the SEM stub.

The FT-IR spectra of unprocessed and processed ibuprofen were taken to obtain information on the change of chemical structure after RESS processing.

Results and Discussion

DSC

Similar DSC curves were observed for the unprocessed material and the ibuprofen particles produced by RESS. On the basic of the DSC measurements, it was confirmed that the processed ibuprofen is still in a crystalline state. However the melting point of the product (74.28°C) was lower compared with the unprocessed (75.67°C). The result indicated a slight reduction in the degree of crystallinity of ibuprofen after processing with RESS. These data correspond with the results published by Hezave [11] and Mansouri [12] (Figures1 and 2).

FT-IR

It can be seen from Figure 3 that FT-IR spectra between unprocessed and processed ibuprofen do not show any significant differences. The assignment of bands were as follows: 1558.87 va 1507.33 cm^{-1} (C=C bond in benzene ring), 3090.2– 3018.75 cm^{-1} (=C-H bond in benzene ring), 1117 cm^{-1} (-O- stretching vibrations), 1379.52 cm^{-1} (-CH_3 stretching vibrations), 1720.6 cm^{-1} (C=O stretching vibrations), 2869.68–2921.68 cm^{-1} and 1364,19 cm^{-1}(-CH- stretching vibrations), 1461.27 cm^{-1}(-CH_2 stretching vibrations).

SEM and LDS

The particle size of the original ibuprofen was around 70 μm as

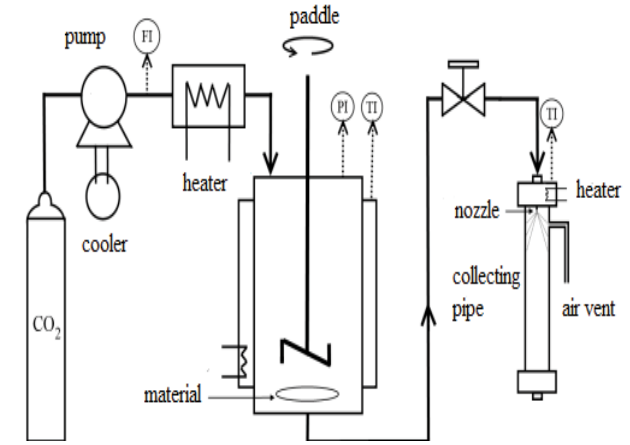

Figure 1: Schematic diagram of the RESS apparatus.

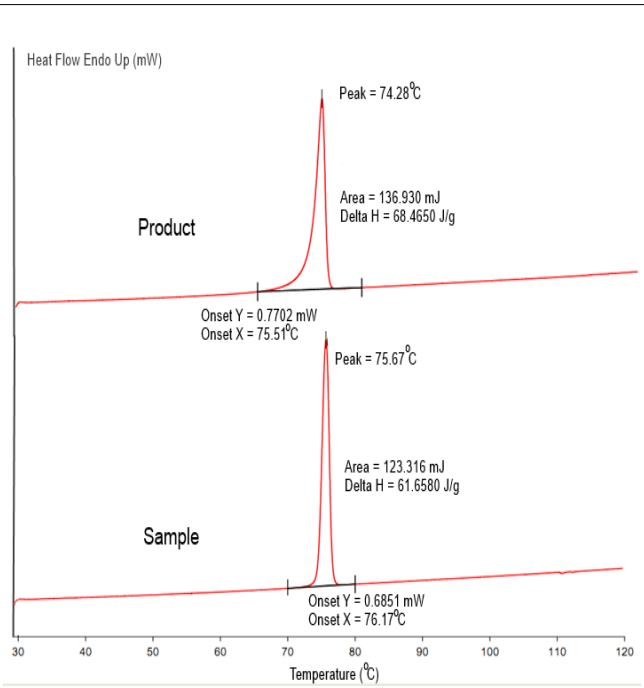

Figure 2: DSC analysis of ibuprofen before and after RESS processing.

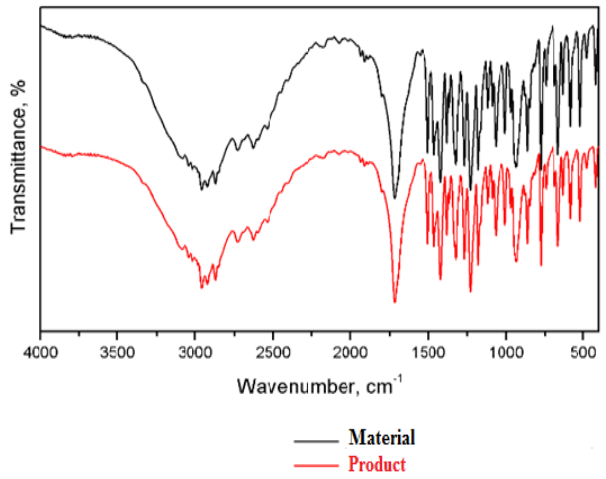

Figure 3: Comparison of ibuprofen FTIR spectra before and after RESS processing.

shown in Figure 4. After RESS processing, the particle size reduced significantly although the product was agglomerated. The SEM images revealed that the degree of aggregation was reduced after sonication. The similar results were found in researches of Kayrak [1] and Charoenchaitrakool [13].

The differences in size of ibuprofen before and after RESS process were also shown by LDS. The obtained results proved that the particle size of products was very small with the narrow PSDs, which was much smaller than that of the original sample.

Experimental design

To evaluate the influence of the considered variables on the measured responses, a mathematical model (Eq. (1)) was postulated with coefficients to be estimated. The he average particle sizes of products were the subject of a mathematical modelling (Figure 5).

The average particle size of products was measured by LDS and shown in Table 1.

The regression equation of objective function, which was mean particle size of ibuprofen, was integrated as following equation:

$$y = 5.55 + 0.59x_2 + 0.54x_3 - 0.88x_1^2 - 1.23x_2^2 - 1.39x_3^2$$

with y: average particle size, x_1: extraction temperature, x_2: extraction pressure, x_3: nozzle temperature

The effect of extraction temperature

According to the regression and the diagram (Figure 6), the mean particle size was seen to increase as the temperature increase from 35°C; reach the highest point at 45°C and then decrease till 55°C. The result might be explained as follows.

Increasing the extraction temperature led to a decrease inthe density of CO_2 and a concurrent increase in the solute'ssublimation pressure. The decrease of the solvent densitycaused a decrease of the solvent strength, which was the reason for the lower supersaturation and nucleation rate. Therefore, the particles might preferably grow to become larger. On the other hand, aconcurrent increase in the solute's vapor pressure was responsiblefor an increase in the ibuprofen solubility, which led to smaller particles. The net effect ofthese two competing factors resulted in the slight influence of extraction temperature. This result is suiTable with research of Z. Huang[6].

The Effect of extraction pressure

Extraction pressure had a considerable effect on ibuprofen particle size. The mean particle size increased dramatically as the pressure increased from 90 bar; reached a peak at 120 bar and then decreased slightly till 150°C. The possible explanation might be that the rise extraction pressure led to the growth of ibuprofen solubility, which resulted in the increase of higher supersaturations in the fluid upon expansion. Perhaps at high aspirin concentrations, the particle growth might be dominant. Therefore large particles could be obtained. Similar results havealso been reportedfor lidocaine by J.-T. Kim [14]. However, when pressure climbed to a certain level, the nucleation process was the deciding factor. So, the particle might become to decrease in size. Similar results can be referred in A. Z. Hezave [4] , A. Z. Hezave [5], H. R. Satvati [7] and N. Yildiz [10] researches for creatine monohydrate, diclofenac, cholesterol and salicylic acid respectively

The effect of nozzle temperature

In all runs, the nozzle temperature was kept higher than the

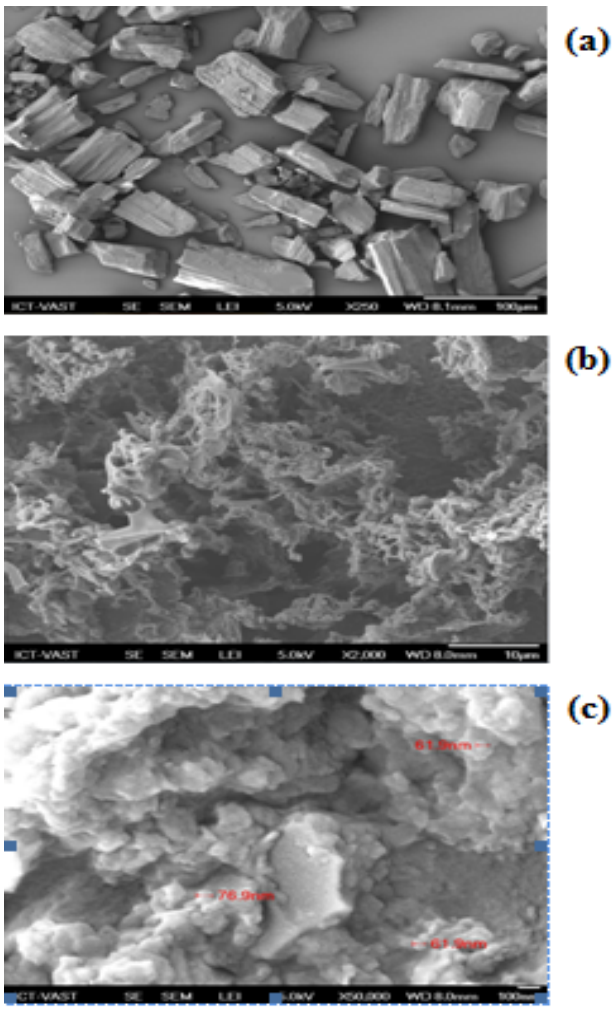

Figure 4: Typical SEM of (a) original and (b) Run 15 without sonication (c) Run 15 with 3 mins of sonication in solvent.

Figure 3: Comparison of ibuprofen FTIR spectra before and after RESS processing.

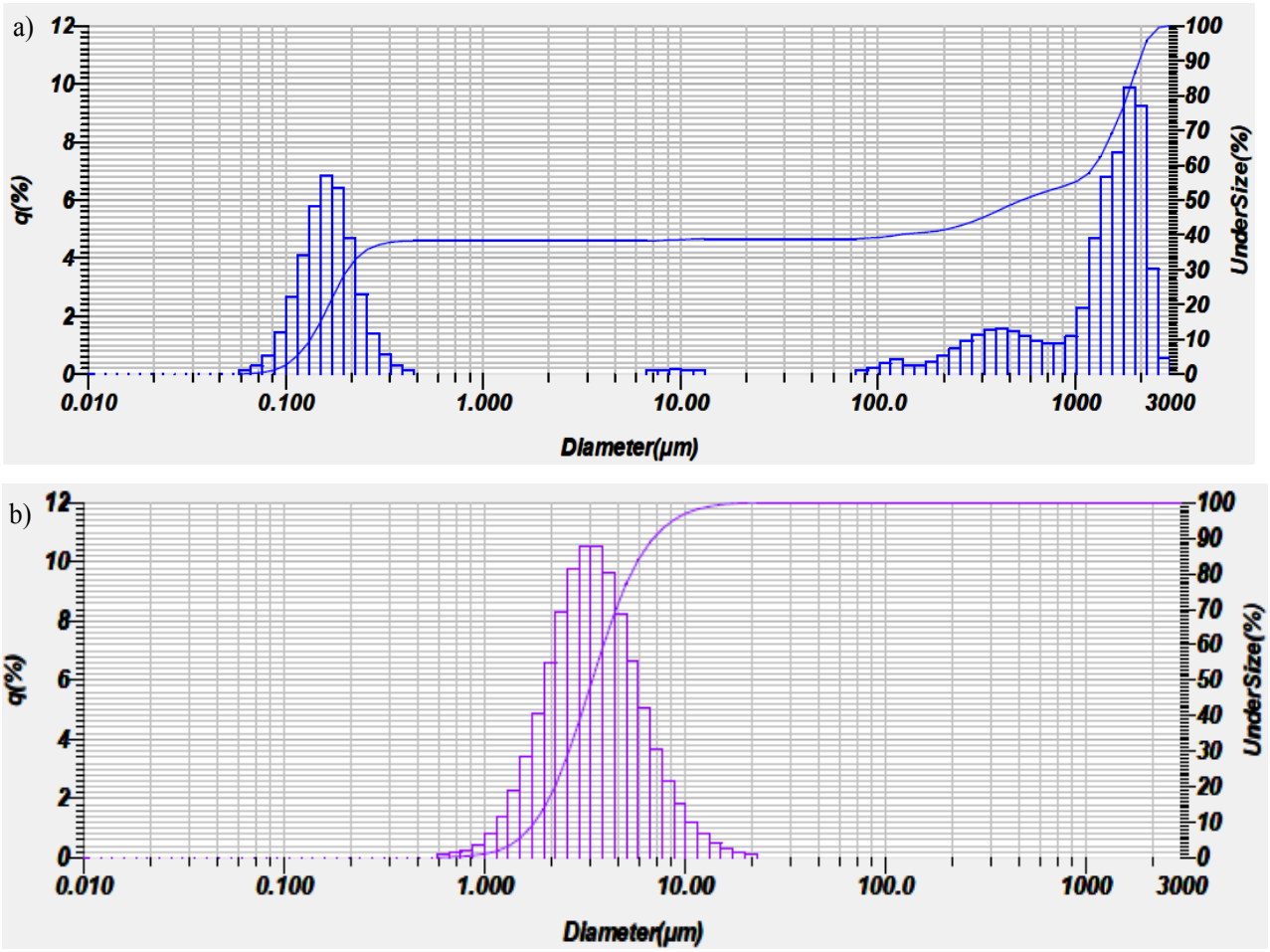

Figure 5: LDS analysis of ibuprofen before (a) and after RESS processing (b).

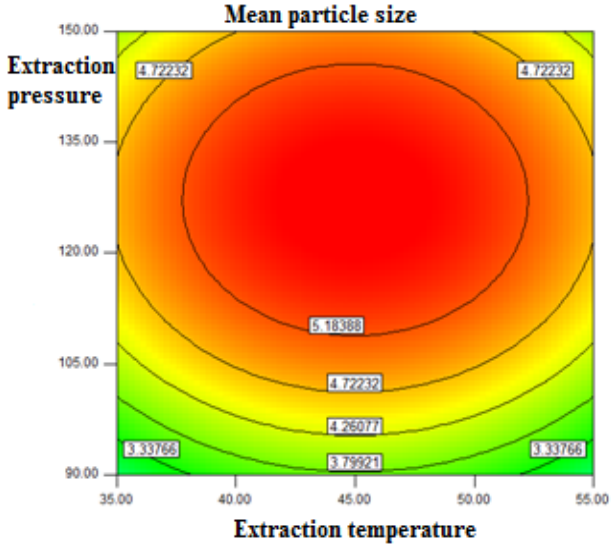

Figure 6: The effects of extraction temperature and extraction pressure on particle size at nozzle temperature 90 °C.

extraction temperature to prevent the early precipitationof ibuprofen solute along the expansion line.The pattern of extraction pressure was similar for nozzle temperature. The mean particle size increased as the nozzle temperature rose significantly in the range of 80°C-90°C. When the temperature continued to climb from 90°C to 100°C, the particle size of product reduced gradually. The reason for this phenomenon might be the high supercritical solution concentration andnumerous nucleus collisions that led to large clustersformation.However, when the nozzle temperature reached to 90°C, the nucleation rate might increase, so the particle size declined. This result is suiTable with research of Zahibi F.[9].

The optimization of Ibuprofen particle formation by RESS process

The optimum condition to obtain the smallest particle diameter is shown in Table 2. There were 2 operating conditions that were able to form the particles below 1 μm. However, the first condition which had extraction temperature 35°C was preferable to select in industry. It was also suiTable with the actual experiment.

Conclusions

The particle size and particle size distribution of ibuprofen was investigated by RESS process. The obtained average particle diameters of product were from 0.7222 μm to 5.8077 μm, which were much

Run	Extraction temperature (°C)	Extraction pressure (bar)	Nozzle temperature (°C)	Mean particle size (μm)
1	35	90	80	0.7222
2	55	90	80	2.1030
3	35	150	80	1.5955
4	55	150	80	1.2511
5	35	90	100	1.3137
6	55	90	100	2.4398
7	35	150	100	3.0495
8	55	150	100	3.4618
9	30.86	120	90	4.6505
10	59.14	120	90	3.14055
11	45	77.58	90	1.6840
12	45	162.42	90	4.7346
13	45	120	75.86	2.2324
14	45	120	104.14	3.5306
15	45	120	90	5.5656
16	45	120	90	4.9153
17	45	120	90	5.76767
18	45	120	90	5.72292

Table 1: Experimental conditions and the results of the mean particles size of the particles produced by RESS process.

Extraction temperature (°C)	Extraction pressure (bar)	Nozzle temperature (°C)	Mean particle size (μm)
35	90	80	0.922
55	90	80	0.922

Table 2: Results of the optimization.

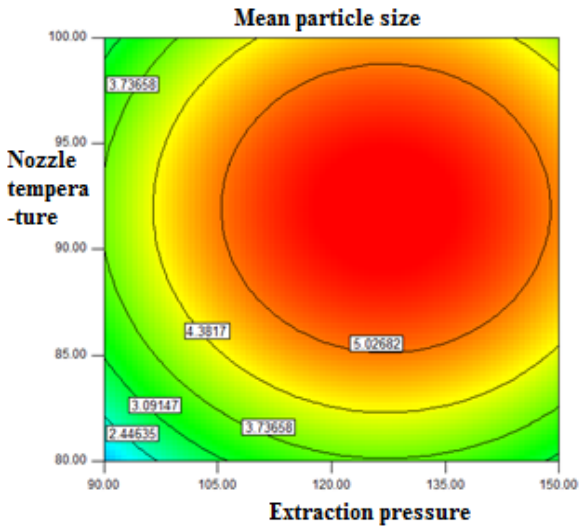

Figure 7: The effects of extraction pressure and nozzle temperature on particle size at extraction temperature 45°C.

smaller than that of material. The processed ibuprofen also had narrow PSDs compared with unprocessed one. The original and processed ibuprofen was analyzed by DSC and FTIR. No significant change was defined in structure of ibuprofen during the process. The effects of process parameters such as extraction temperature, extraction pressure and nozzle temperature were researched on ibuprofen particle size. Response surface methodology (RSM) was successfully applied for optimization of particle size design parameters by RESS. The optimum values of the variables (extraction temperature 35°C, extraction pressure 90 bar and extraction temperature 35°C) were determined inorder to obtain the smallest median particle diameter. The extraction pressure and nozzle temperature had significantly effects; however, extraction temperature affects slightly on particle size. The mathematical model then can be used for predicting the behaviour which describes the effects of process variables on the products (Figures 7 and 8).

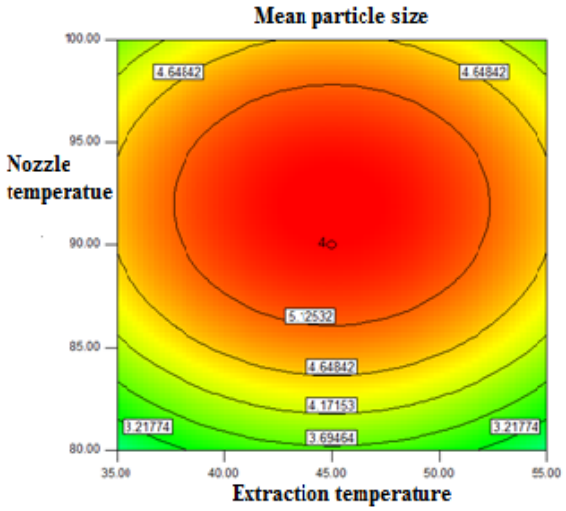

Figure 8: The effects of extraction temperature and nozzle temperature on particle size at extraction pressure 120 bars.

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