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ORIGINAL ARTICLE

The study on the preparation process of PEG pellets by vibration nozzle method

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Abstract
Background: Uniform size beads can be easily produced by vibration nozzle method. *Objective*: In this article, the pellets of polyethylene glycol are prepared by a vibration nozzle machine. Thickness of nozzle wall, rotation speed of stirrer, and voltage of excitation are discussed in this article. *Results and Discussion*: A nozzle wall of thickness ≤0.1 mm is applied to decrease the adherence of jet. The stirring device with 20 rotations/min on the upper side of condensed column is used to disperse unsolidified polyethylene glycol pellets. The effect of parameters including vibration frequency *f*, jet velocity *v*, and voltage of excitation *V* on the average diameter *d* and standard deviation SD% are investigated by response surface methodology and Weber equation. A very good linear regression between *d* and *v/f* is presented under optimum *V* (in this article *V* = 3.0 V). Both high *v* and low SD% can also be obtained by optimum *V*

Key words: Nozzle wall, poly ethylene glycol pellets, preparation process, response surface methodology, stirring device, the voltage of excitation, vibration nozzle method, Weber equation

Introduction

The pellets of traditional Chinese medicine have been widely used in clinics in China. Compared with traditional dosage forms, the pellets feature beautiful external form, good fluidity, stable release, accurate dosage, easy absorption and convenient usage. The pellets could be prepared by the method of bed coating, extrusion spheronization, centrifugal granulation, fluid bed granulation, and so on. The sphere size and size distribution are reproducible but often poorly controllable.

Devices based on vibration nozzle processes usually have high work rates and easy to produce particles with monodisperse size distributions. Microspheres or microcapsules in a diameter range of about 30–8000 μm could be obtained by vibration nozzle processes[1]. A wide range of shell materials, such as cosmetic waxes, agar, alginate[2], polymer beads for combinatorical synthesis, pharmaceutics encapsulated in wax, and inorganic microspheres as catalyst carriers, are usable with this highly scalable process. To reproduce in large quantities, a multinozzle system for the encapsulation and immobilization of microorganisms, enzymes, or cells is presented[3]. Experiments using multiple-nozzle synthetic red stone plate are easy and feasible[4]. The stream could be disrupted into uniform droplets by mechanical vibration or ultrasonic transducer. Uniform poly(D, L-lactide-co-glycolide) (PLG) spheres with average diameters from 1 to 500 μm are fabricated by combining acoustic excitation and an annular, nonsolvent carrier stream[5]. Uniform double-walled microspheres with controllable size and shell thickness have been developed by multiple concentric nozzles to produce a smooth coaxial jet comprising an annular shell and core material, which is acoustically excited to break up into uniform core–shell droplets[6].

The effect of conditions on vibration nozzle processes include the flow rate of stream, the frequency of vibration, and the physical characteristics of stream such as viscosity, density, and surface tension. These parameters have been discussed by Rayleigh theory and Weber equation. However, other factors are hardly analyzed. In this study,

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the pellets of poly ethylene glycol (PEG) are prepared by a vibration nozzle machine. The design of nozzle is discussed and the rotation speed of stirring device is evaluated. Furthermore, the effect of parameters involving the power of vibration on the average diameter and standard deviation is investigated by response surface methodology (RSM) and Weber equation.

Materials and apparatus

Materials

Poly ethylene glycol 4000 was purchased from Beijing Haidian Huiyou Refined Chemical Plant. (Beijing city, P R China) Dimethyl silicone oil 201 was provided by Shandong Dayi Chemical Plant (Beijing city, P R China).

Preparation of PEG pellets

A schematic representation of the production system is shown in Figure 1. A 0.6 mm of jet is used. A melt PEG (80°C) is driven through nozzle by micro gear pump. Uniform droplets are obtained by controlling vibration disturbances of magnetic vibrator. PEG pellets are formed after the uniform droplets enter into cold dimethyl silicone oil 201. The blender in coagulation column is used to avoid the pellet conglutination. Along with the flowing of condensed solution, PEG pellets are separated and dimethyl silicone oil passed through the filtrate net into the oil tank being refrigerated and recycled.

Evaluation of PEG pellets

The diameter of PEG pellet is determined microscopically with a Vernier scale micrometer. The average diameter d and standard deviation SD% are calculated from a sample population of at least 100 pellets randomly selected from the population. The equations of calculation are as follow:

$$d = \frac{\sum_{i=1}^{n} d_i}{n}, \tag{1}$$

$$\mathrm{SD\%} = \frac{\sqrt{\frac{\sum_{i=1}^{n}\left(d_i - \bar{d}\right)^2}{n}}}{\bar{d}}\%. \tag{2}$$

Results and discussion

Preparation theory and design of nozzle

The process of jet breakup is shown in Figure 2. Because of axisymmetric disturbances, a laminar jet breaks up into droplets. The frequency f relates to the jet linear velocity v and the wavelength λ by

$$\lambda = \frac{v}{f}. \tag{3}$$

The volume of the resulting sphere should be equal to the volume of a cylindrical element of the jet, the length of which is defined by the acoustic wavelength λ:

$$\frac{\pi d_{\mathrm{D}}^3}{6} = \frac{\pi d_{\mathrm{s}}^2 \lambda}{4}, \tag{4}$$

where d_{D} is the diameter of droplet and d_{s} the size of undisturbed stream. Generally, these two parameters are, respectively, slightly larger than the average size of

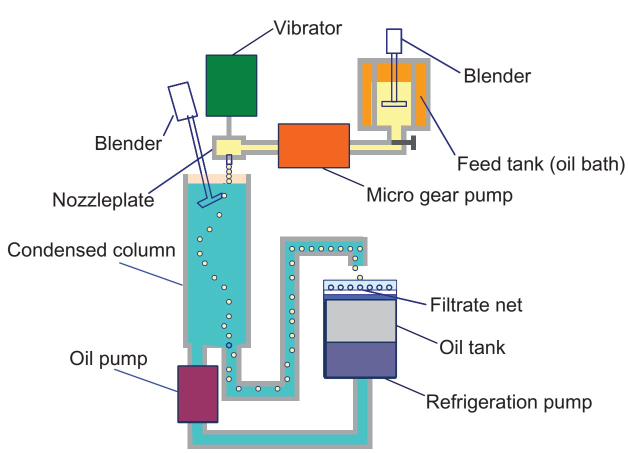

Figure 1. A schematic representation of the production system.

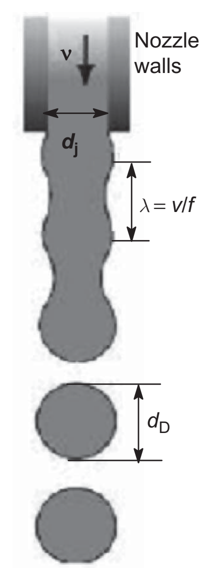

Figure 2. Process of jet breakup.

PEG pellets d and the diameter of the nozzle orifice d_j because of the volume shrinkage of pellets and the pressure reduction of liquid spouting out. Then we can define them as

$$d_D = k_1 d, \tag{5}$$

$$d_s = k_2 d_j, \tag{6}$$

where both k_1 and k_2 are constants and relate to the physical characteristics of the stream.

Moreover, we considered that the thickness of the nozzle wall would influence the value of k_2 especially for high-viscosity solution and low velocity of flow. It is observed from experiments that operation of small frequency and low flow rate are helpful to break up high-viscosity liquid. In this case, it is possible that the bigger droplets but not jet liquid are formed by using more thickness of nozzle wall. In our work, the nozzle wall of thickness ≤0.1 mm (Figure 3) is applied to decrease the adherence of jet.

Equations (7) and (8) are presented as

$$(d)^3 = k\lambda, \tag{7}$$

$$k = \left(\frac{3}{2}\right)\frac{(k_2)^2}{(k_1)^3}(d_j)^2. \tag{8}$$

Assume $(k_2)^2/(k_1)^3 \approx 1$, for 0.6 mm of jet, then the theoretical value of k is 5.4×10^{-7} m^2.

Lord Rayleigh[7] was the first of numerous scientists to analyze the instability of capillary jets and give the equation of optimal wavelength λ_{opt} with the fastest growing disturbance for inviscid fluids. Weber[8] extended the analysis by including the effect of viscosity μ into the analysis. The λ_{opt} for breakup is given by (ρ, density; σ, surface tension)

$$\lambda_{opt} = 4.44 d_j \left(1 + \frac{3\mu}{\sqrt{d_j \rho \sigma}}\right). \tag{9}$$

For PEG 4000, at 80°C, $\mu = 147 \times 10^{-3}$ Pa·s, $\sigma = 38.5 \times 10^{-3}$ N/m, $\rho = 1.125 \times 10^3$ kg/m^3, the λ_{opt} calculated by Equation (9) is 9.95×10^{-3} m for 0.6 mm jet.

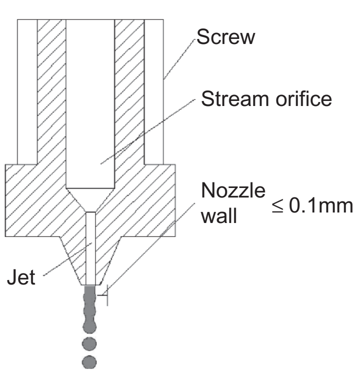

Figure 3. Structure of nozzle.

Operation of stirring device

It is found from Figure 1 that the stirring device on the upper side of condensed column is used to disperse PEG droplets that are not being completely solidified. Tangential velocity of stirring should be greater than drop speed of PEG droplet. Assume that droplets are falling into dimethyl silicone oil one by one. Equation (10) is developed to estimate the minimum rotation speed ω_{min} (rotations/min):

$$\omega_{min} \pi D = \frac{V_{P,max}}{(4/3)\pi d_{min}^3} d_{min}, \tag{10}$$

where D is the effective diameter of blender, $V_{P,max}$ the maximal flux of melt PEG. D = 38.6 mm is educed for diameter of paddle 40 mm because axis of stirrer and spouting stream lie at an angle of about 15°. d_{min} = 1.6 mm is calculated by Equation (7) with minus experimental $\lambda = 7.87 \times 10^{-3}$ m (v = 12 mL/min, f = 90 Hz). Above values and $V_{P,max}$ = 21 mL/min are joined into Equation (10) and ω_{min} is approximately 16 rotations/min. For safety, 20 rotations/min is applied in this study. Higher rotation speed which increases the possibility of collapsing droplets should not be selected.

The action of stirring on the size distribution is shown in Figure 4. A very narrow size distribution is obtained with stirring dispersion. Without agitating, two peak size distributions and higher SD% appear. Furthermore, we can know from Figure 5 that spherical value of PEG pellets (d_{min}/d_{max} value) is lower than 1.1. It is demonstrated that uniform size of PEG pellets could be produced by our apparatus.

Discussion of average diameter of PEG pellets

RSM offered statistical design of experimental tools, such as central composite design (CCD), which are often used to optimize process performance in pharmacy[9], food[10], and so on. Table 1 displays the experimental data according to the three factors and three levels of CCD. V is the voltage of excitation and could be used to express the power of vibration. The regression equation of $(R1)^3$ is as follows:

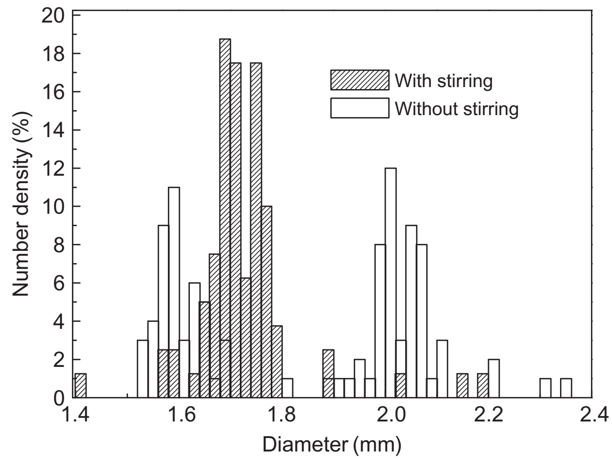

Figure 4. Size distribution of PEG pellets (v = 12 mL/min, f = 70 Hz, V = 2.5 V). With stirring, d = 1.74 mm and SD% = 5.9%. Without stirring, d = 1.83 mm and SD% = 12.5%.

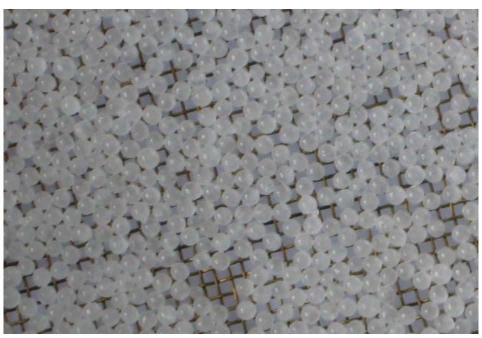

Figure 5. Light micrograph of PEG pellets by vibration and stirring.

Table 1. Experimental data according to three factors and three levels of CCD.

Run	Factor 1 A:v (mL/L)	Factor 2 B:f (Hz)	Factor 3 C:V (V)	Response 1 R1:d (mm)	Response 2 R2:SD (%)
1	15	90	2.5	1.671	8.96
2	15	80	2.5	1.739	5.89
3	15	80	2.0	1.675	11.4
4	12	90	3.0	1.571	7.18
5	12	70	3.0	1.813	6.25
6	18	90	3.0	1.753	5.47
7	15	80	3.0	1.708	6.93
8	12	80	2.5	1.645	6.29
9	18	70	2.0	1.846	7.14
10	18	90	2.0	1.773	9.36
11	15	70	2.5	1.841	5.62
12	12	90	2.0	1.650	8.59
13	12	70	2.0	1.704	2.60
14	18	70	3.0	1.921	3.66
15	18	80	2.5	1.795	7.53

Table 2. Results of ANOVA.

Response	$(R1)^3$		$\sqrt{R^2}$	
Source	F-value	P-value (Prob>F)	F-value	P-value (Prob>F)
Model	38.42	<0.0001	4.52	0.0107
A-v	145.57	<0.0001	0.35	0.5628
B-f	144.43	<0.0001	12.4	0.0039
C-V	5.65	0.0388	3.60	0.0801
AB	0.059	0.8123	0.84	0.3765
AC	0.20	0.6674	8.00	0.0142
BC	28.86	0.0003	2.16	0.1650
A^2	0.011	0.9302		
B^2	16.91	0.0021		
C^2	3.21	0.1036		

$$\begin{aligned} d^3 &= 17.57 + 0.09873v - 0.5913f + 8.923V \\ &+ 4.937\times10^{-4} vf + 0.017933vV - 0.6528fV \\ &+ 1.183\times10^{-3} v^2 + 4.261\times10^{-3} f^2 - 0.7423V^2. \end{aligned} \tag{11}$$

Results of ANOVA are listed in Table 2. It is found from Table 2 that the model F-value of 39.42 implies the model is significant and the average diameter could be predicted by RSM. Values of 'Prob > F' less than 0.0500 indicate model terms are significant. In this case A, B, BC, and B^2 are significant model terms. It is demonstrated that v, f, and the interaction of f and V have higher impact on average diameter. Moreover, peculiarly large values of V give a very small effect on the average diameter (Figure 6b and c).

The three-dimensional (3D) figures of $(R1)^3$ response surface are shown in Figure 6. From Figure 6a, we can know that d^3 increases with the increase of v and the decrease of f. Especially, the area of higher v and lower f is approximately a plane and its contours are straight lines. Comparing with v and f, peculiarly large values of V give a very small effect on the average diameter (Figure 6b and c). It is illustrated that Equation (7) could be used under large λ and V.

To validate the above results, the effect of V on the relationship between d and (v/f) is presented in Figure 7 and regression results are listed in Table 3. It is detected that the data of 12 mL/min could not join with regression in case of V = 2.0 and 2.5 V (Figure 7a and b). When V reaches 3.0, a very good linear regression is obtained except for the first data (Figure 7c). Moreover, with the increase of V, both the parameter of linear regression R^2 and the slope of line k increase (Table 3). The experimental value of k = 4.78 × 10^{-7} m (V = 3.0 V) nearly approaches the theoretical value of k = 5.4 × 10^{-7} m. It is using higher power of vibration that $(d)^3$ is linear with λ because of jet completely being breaking up.

However, using V = 3.5 V a very bad linear regression is presented (Figure 7d). It is illustrated that d could not be evaluated by Equation (7) under extra-high V. High V predicts high power of vibration and also implies big

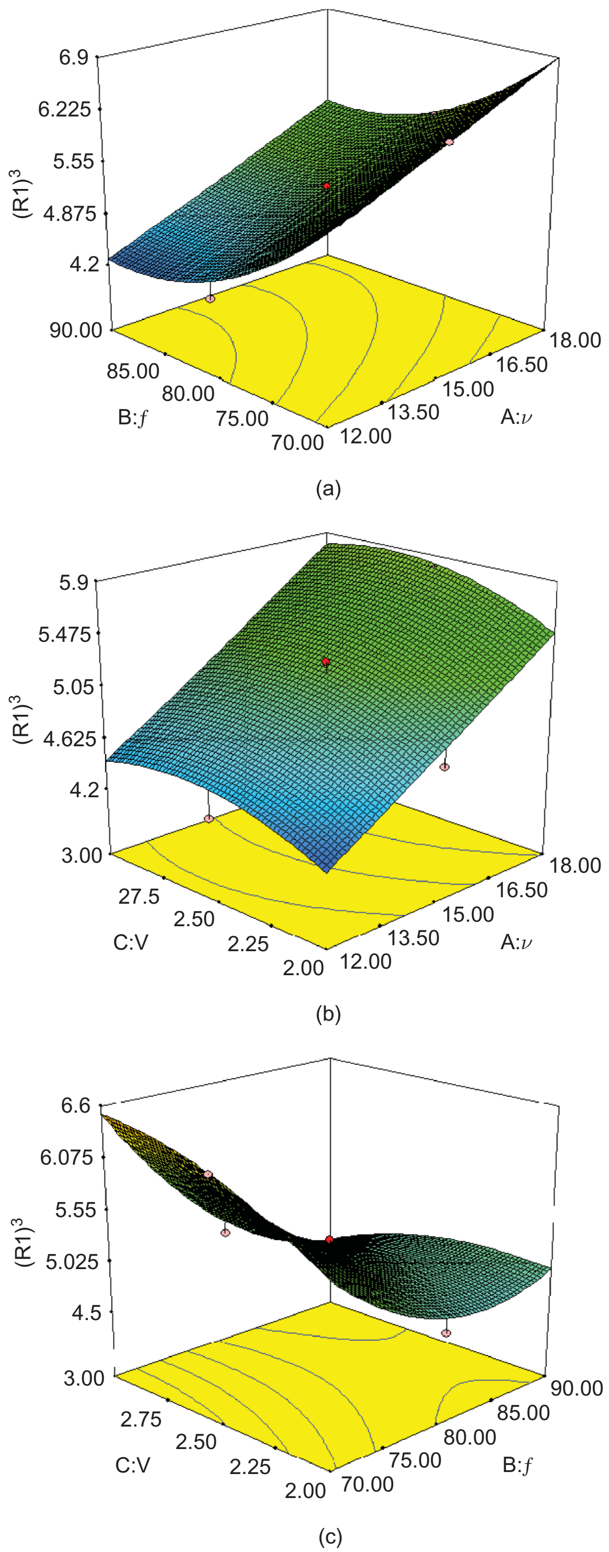

Figure 6. Three-dimensional figures of $(R1)^3$ response surface.

amplitude of vibration which may lead to operation not being finished if high f is compelled because this time needs small amplitude of vibration. Thereby, extra-high V leads to unstable operation.

Table 3. The effect of V on regression results by Equation (7).

V (V)	k ($\times 10^{-7}$ m)	R^2
2.0	3.52	0.8733
2.5	4.12	0.9512
3.0	4.78	0.9934
3.5	3.11	0.7893

These experimental results indicate that V is an important factor for theoretical calculation of average diameter. Experimental data perfectly accord with theoretical equations under optimum V (V = 3.0 V).

Figure 8 and Table 4 present the effect of v on regression results by Equation (7) under V = 3.0 V. Operations of 60–110 Hz are investigated under v = 18 mL/min and v = 21 mL/min. Good linear regressions appear by the above working condition. It is found that k slightly decreases with increase in v. Under high v, the long and thin jet appeared, which suggests small k_2 (Equation 6) and then lower k. Of course, jet of extra-high v could not be broken up effectively.

Discussion of standard deviation of PEG pellets

The regression equation of standard deviation average of PEG pellets is as follows:

$$\sqrt{\mathrm{SD\%}} = -14.80 + 0.6857v + 0.1409f + 4.528V - 2.854\times 10^{-3} vf - 0.1763vV - 0.02751fV. \quad (12)$$

From Table 2, we can see that the model is significant and B and AC are significant model terms. Values of 'Prob > F' greater than 0.1000 indicate the model terms are not significant. It is indicated that f and interaction of v and V have higher effect on SD%.

The 3D figures of $\sqrt{R^2}$ response surface are laid out in Figure 9. The least of $\sqrt{\mathrm{SD\%}}$ (Figure 9a) emerges under $\lambda = 10.1\times 10^{-3}$ m (v = 12 mL/min, f = 70 Hz) which is close to $\lambda_{opt} = 9.71\times 10^{-3}$ m by Weber equation from Section Preparation Theory and Design of Nozzle. It is demonstrated that Weber equation could be applied for PEG 4000 system. Also, $\lambda = 9.83\times 10^{-3}$ m (v = 15 mL/min, f = 90 Hz) is very near to λ_{opt} but $\sqrt{\mathrm{SD\%}}$ is relatively larger.

Moreover, it was obviously found from Figure 9a and 9c that $\sqrt{\mathrm{SD\%}}$ increases with increase in f. It is known that high f companying low amplitude of vibration may induce insufficient breakup of jet and improve SD%. Furthermore, for Figure 9b, $\sqrt{\mathrm{SD\%}}$ increases with increasing v under low V (V = 2.0 V), opposite results happen under high V (V = 3.0 V). It is shown that uniform pellets can be obtained under high v when jet is adequately broken up. From Figure 10a we can see that SD% values of v = 18 mL/min and v = 21 mL/min by V = 3.0 V are relatively low especially under low f of

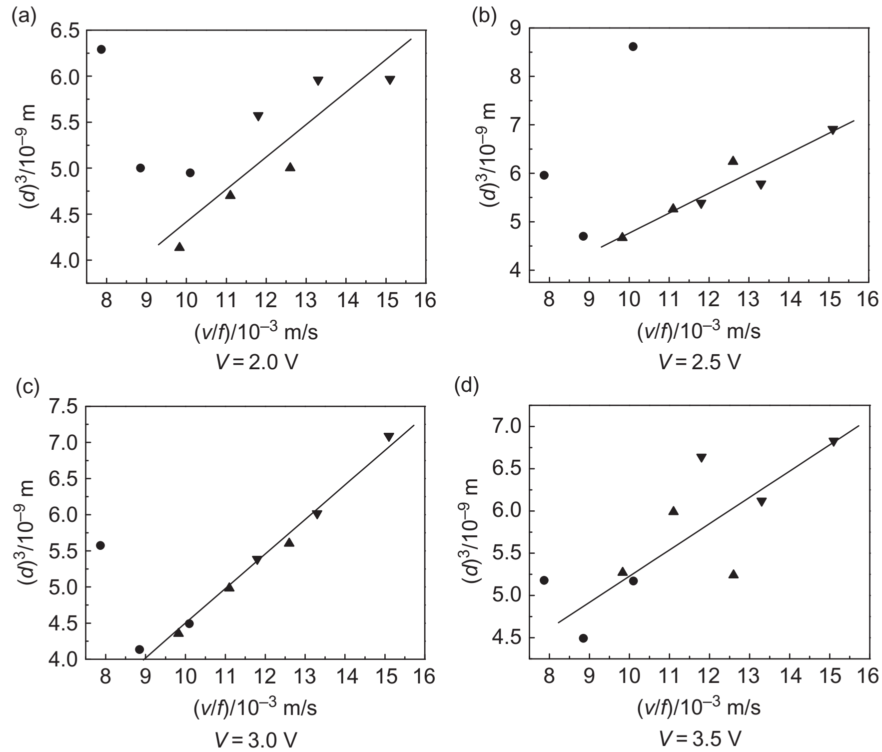

Figure 7. Effect of *V* on the relationship between *d* and (v/f). ● 12 mL/min, ▲ 15 mL/min, ▼ 18 mL/min. (a,b) Linear regression by 15 mL/min and 18 mL/min; (c,d) Linear regression removing the first data.

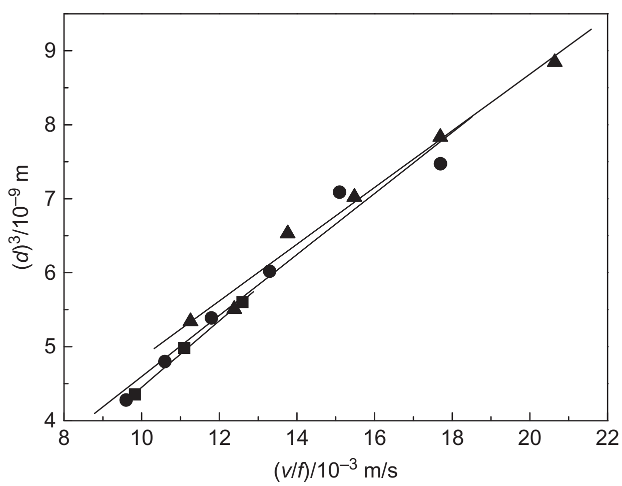

Figure 8. Effect of *v* on the relationship between *d* and (v/f). ■ 15 mL/min, ● 18 mL/min, ▲ 21 mL/min.

60–80 Hz. For example, using $v = 21$ mL/min, for which $\lambda = 17.7 \times 10^{-3}$ m ($f = 70$ Hz, $V = 3.0$ V) bigger than $\lambda_{opt} = 9.95 \times 10^{-3}$ m, very uniform pellets (SD% = 3.1%) are also received.

Otherwise, Figure 10 shows the effect of *v* and *f* on SD% under *V* =vt 3.5 V. It is shown that SD% of $V = 3.5$ is higher (>10%) except under small *f* ($f = 70$ Hz). We know from Section (Discussion of Average Diameter of PEG Pellets) that extra-high *V* induces unstable operation and thus higher SD% value. However, higher amplitude of

Table 4. The effect of *v* on regression results by Equation (7) under $V = 3.0$ V.

v (mL/min)	*k* ($\times 10^{-7}$ m)	R^2
15	4.49	0.9986
18	4.12	0.9828
21	3.38	0.9926

vibration could be satisfied under low *f* thereupon lower SD% is achieved. It is very important that breakup of high-viscosity system is applied by high *V*. At this time, operation with low *f* is suggested. These results are in agreement with the experimental data of our reported paper[2].

Conclusions

Thickness of nozzle wall, rotation speed of stirrer, and power of vibration are discussed in this article. For high-viscosity liquid, the jet with very thinner nozzle wall can be used for reducing the adherence of jet. Although the low agitation velocity (20 rmp) of blender is applied, the obvious decrease in SD% comes forth. The voltage of excitation *V* is the key factor in theory calculation of average diameter *d* and evaluation of standard deviation SD%. High *V* implying high power of vibration helps the breakup of jet. However, extra-high *V* leads to unstable operation. Therefore, it is under optimum *V* (in this study $V = 3.0$ V) that better theory

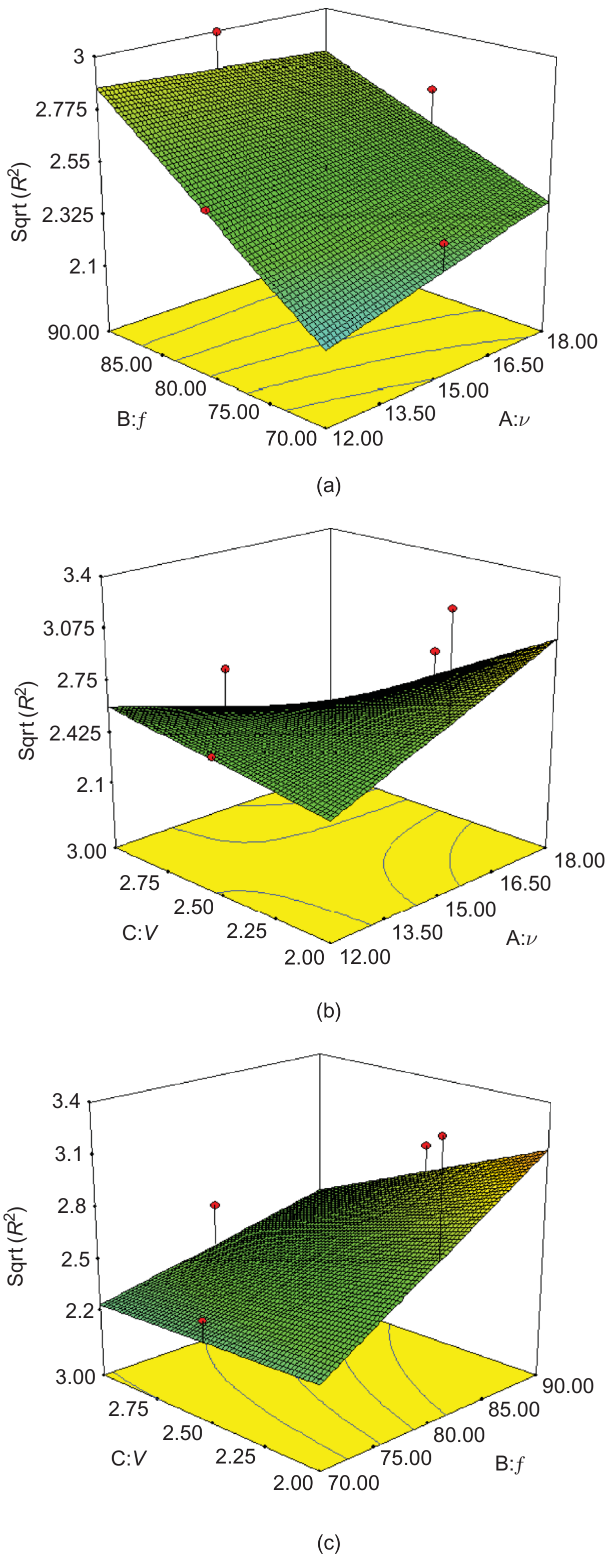

Figure 9. Three-dimensional figures of $(R^2)^3$ response surface.

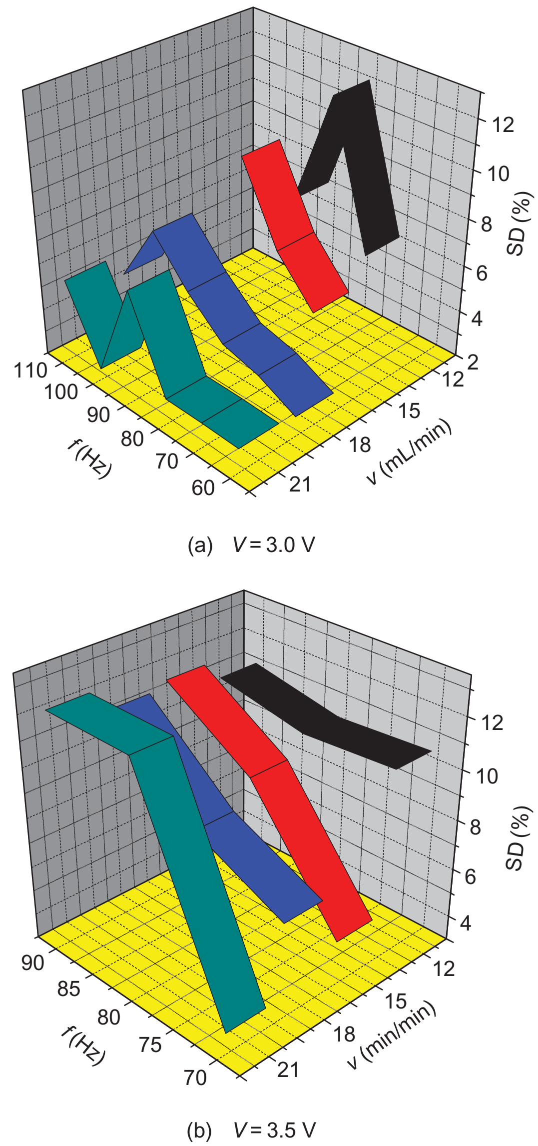

Figure 10. Effect of ν and f on SD% under V = 3.0 and 3.5 V.

calculation of d and lower SD% occur. It is very interesting that both high yield and low SD% can be obtained by optimum V. Of course, further improvements are necessary to research the action of V on vibration nozzle process.

Declaration of interest

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