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Optimization of Injection from IDM Injector into Tissue Simulant by Respond Surface Method

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Abstract

Jet injectors employ high-velocity liquid jets that directly penetrate into human skin and deposit drugs in the dermal or subdermal region. It is sometimes called needle-free jet injector. Although, jet injectors have been marketed for many years, little knowledge about the interactions and dispersion of the liquid jets in the skin layer tissue skin has been revealed. Previously our research work, a new injector device which was constructed by impact driven method (IDM) or call that “IDM injector” and characteristic of jets were investigated. In this study, the optimal conditions of jet generating for more dispersion in tissue simulants are investigated by using Response Surface Method (RSM). In the experiment, polyacrylamide gel is tissue stimulant and three main factorials generate jets as the travelling distance, fluid volume and reservoir pressure. The optimization and relationships between the main factorials and one response variables being dispersion area were explored by the RSM with central composite design (CCD) of experiment design method. The results from the RSM analysis indicate that the travelling distance and fluid volume have the most significant effect on dispersion area, while the reservoir pressure is least significant. The coefficient of determination (R^2) of the mathematical model is 0.9569. The optimal conditions for maximum dispersion area is obtained from the travelling distance of 5.26 mm, fluid volume of 0.18 ml and reservoir pressure of 11.90 bar. Deviation of the predicted values and experimental values is almost identical with low percentage bias of dispersion area of 1.94 %. Therefore, the mathematical model have developed adequately describing ranges of the experimental parameters study and provide a statistically accurate prediction of optimum dispersion area of injection into polyacrylamide gels.

***Keywords*:**IDM injector, Polyacrylamide gels, Response Surface Method, Optimization.

1. Introduction

High speed liquid jets have been successfully applied to many appropriate technologies or applications, such as cutting, automobile, combustion, and medical engineering. Recently, in medical engineering, researchers have been attempting to use high speed liquid jets in a device called a “jet injector.” This medical device employs a high speed liquid jet to replace the needle in a hypodermic syringe and is sometimes called “needle free jet injection.” A high-speed intact jet penetrates into the epidermis and disperses into the targeted tissue. Currently, jet injectors are generally powered by gas, compressed spring, and electromagnet.

However, there are still some controversial areas and disadvantages of the jet injector. In a comparison between two alternative jet injector devices and a standard device, one study showed that jet injector devices were associated with higher levels of pain and more local reactions. Moreover, there was blood contamination in the head of the injector after injection [1] because the device generates a liquid jet at high velocity and its impact results in blood being splashed back from the patients. This blood contamination is the reason for the infection or disease between administrations of the drug [2].

The main advantages of jet injectors are that these injectors are easy to use and readily accepted by children. A large number of medications can be injected in a short time, with a very small hole (approximately one-hundred micrometres) after injection, and jet injectors are widely used with a variety of traditional drug models [3,4].

Especially, results from several studies indicate that jet injection leads to a higher drug activation rate than those of the needle and syringe because jet injection disperses more widely into the tissue, probably due to the high pressure driving the medication liquid more thoroughly. This wider dispersion was discovered and confirmed through the study of Baxter et al. [5,6].

From our previously work, a new concept of the generation method of high speed liquid jet for jet injectors is “impact driven method” or IDM, which is expected to provide a more accurate timing and proper level of impact peak pressure at the early stage of penetration in the jet injector. Hence, better control, no splash back, and less pain should be accomplished. The prototype device is designed, assembled, and tested. All fundamental characteristics of the prototype, such as the jet velocity, jet power, impact peak pressure, and penetration, are tested and analysed. Moreover, preliminary tests on the penetration mechanisms in polyacrylamide gels are visualized and compared with a commercial jet injector by using a high speed video camera [7].After that,IDM jet injector was conducted to investigate the penetration of jet by using ejection into the polyacrylamide gels. The result showed that, the jet introductory penetrated by first pulse and repetitive penetration follow by the second pulse to enhance the jet liquid dispersion [8].

The purpose of this research is to determine optimal condition for three main factorials of injection into the polyacrylamide gels to obtain maximum dispersion area of injection. Therefore, Response Surface Method (RSM) is employed to evaluate the optimal factorial values as the travelling distance, fluid volume and reservoir pressure (as in Fig. 1). This builds the empirical model of relationship of the factorials and dispersion area.

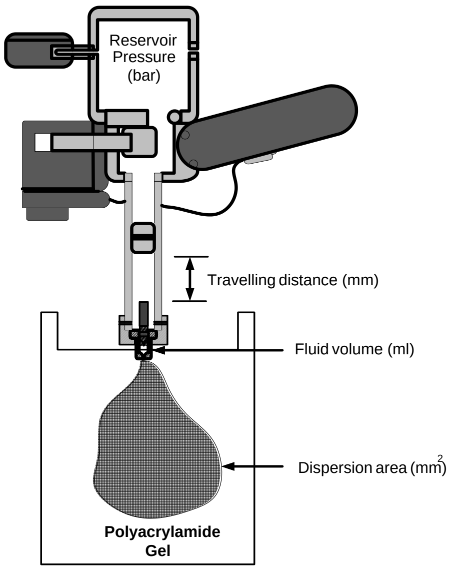

Fig. 1 Condition of experiment from IDM injector

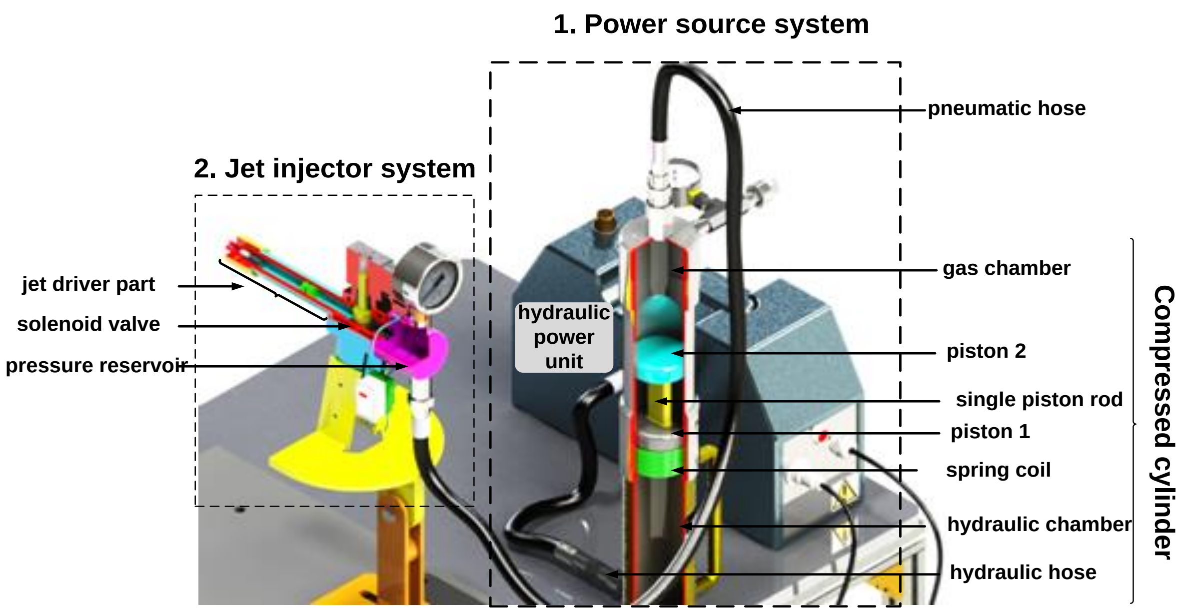

Fig. 2 IDM injector system

2. Materials and methods

2.1 IDM jet injector

In this study, the prototype of an IDM jet injector is designed and constructed. The Momentum Exchange Method (MEM) principle is used in this prototype. The major task of the device is to generate jet pulse and wide ranges of high speed liquid jets. Jet velocities of approximately 150 - 400 m/s and impact peak pressures of approximately 18 to 68 MPa are expected. Nozzle with 0.1 to 0.2 mL of liquid ranged in volume and 0.2 mm of orifice will be used. From the literature reviews, the liquid jet generated at these conditions should be able to penetrate human or animal skin. This prototype consists of two major parts, as shown in Fig. 2, and is described below.

Power source system

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The hydraulic power unit for the fluid in a 2 liter tank is driven by a 350 W motor through the hydraulic hose into the compressed cylinder by a controller. The cylinder is divided into two chambers (i.e., hydraulic chamber and gas chamber) by a single piston rod, and both ends are connected to the piston. The hydraulic chamber obtains a high pressure from hydraulic fluid pumping, which pushes piston 1 and stretches the spring coil together. At the same time, the volume of the gas chamber is decreased to create a high pressure that the top of the gas chamber is connected to a pneumatic hose for transferring the high pressure into a pressure reservoir of the jet injector. Moreover, the pressure reservoir can be adjusted to decrease the pressure by extending the volume of the gas chamber in which the move back of piston 2 due to spring recoils and the fluid is back pulled into the hydraulic pump unit.

Jet injector system

From Fig. 2, the jet injector system can be divided into three parts, i.e., the pressure reservoir, solenoid valve, and jet driver. In general, the operating concept is quite similar to the common gas gun. The pressure reservoir is connected to the gas chamber from the power source system; therefore, a high pressure gas is ready in the reservoir. A quick opening solenoid valve is used as the trigger device. Once it is switched to open, the high pressure gas will quickly flow into the launcher or jet driver. The projectile, which is loaded at the beginning of the launch tube, will be launched to impact the plunger rod according to the MEM principle. Then, the plunger rod will expel the liquid contained in the nozzle cavity through a tiny orifice as a high speed liquid jet.

2.2 Visualization of the penetration mechanism

Motion analysis setup

To gain a better understanding of the dynamics of jet behaviours occurring during jet ejection, high-speed photography is performed (Photron APXRS motion analyzer). Liquid jets are ejected into 20% polyacrylamide gels (E=0.22 MPa), which was previously prepared. The gel is backlit with a white light source to allow the images to be captured at a frame rate of 10,000 fps. The penetration mechanisms are determined in IDM injector [8].

Polyacrylamide gels

In this study, polyacrylamide gel (20% acrylamide) is used as a tissue stimulant. The jet penetration mechanism is investigated in this polyacrylamide gel. The gel is produced by the addition of initiators (10% ammonium persulfate (APS) and tetramethylethylenediamine (TEMED)) to a 40% (w/v) acrylamide solution (Bio-rad Laboratories, Hercules, CA). In the experiment, ‘‘acrylamide’’ indicates a mixture of both acrylamide and bisacrylamide in a ratio of 37.5:1. The mechanical properties of the gels are varied by simply changing the mass/volume percentage of acrylamide in each gel. Acrylamide solution (40% (w/v)) is mixed with DI water to create solutions possessing various acrylamide concentrations in the range of 20% w/v, which are contained in transparent bottles with volumes of 35 ml. Next, the gels are polymerised by the addition of 10% APS and TEMED to the acrylamide solution. The volumes of APS solution and TEMED solution used for the polymerisation are 300 µl and 60 µl, respectively [9].

2.3 Response Surface Method

Response surface methodology, or RSM, is a collection of mathematical and statistical techniques that are useful for the modeling and analysis of problems, which a response of interest is influenced by several variables and the objective is to optimize this response[10]. For injection of IDM injector, the dispersion area of jet injection into polyacrylamide gel is function of the levels of three factorials, which are travelling distance (A), fluid volume (B) and reservoir pressure (C) as Fig 1. It can be replaced form of Eq. 1.

$$y = f(A, B, C) \tag{1}$$

The central composite design or CCD for fitting is a second-order model. This is the most popular class of design used for fitting these models[10]. Generally, the CCD consists of a 2^k factorial (or fractional factorial of resolution) with point runs, axial or star runs, and center runs. The CCD for k=3 factors are travelling distance, fluid volume and reservoir pressure which yield is dispersion area which is replaced by box in Fig. 3. The low and high values will be assigned to the limits of the factorial part of the design, i.e., the low and high levels will be coded -1 and +1 in the table 1. In the on-screen picture of the CCD, the factorial portion is represented by the solid sphere points forming a box. The star (axial) points are located at the end of the arrows that come from the center point.

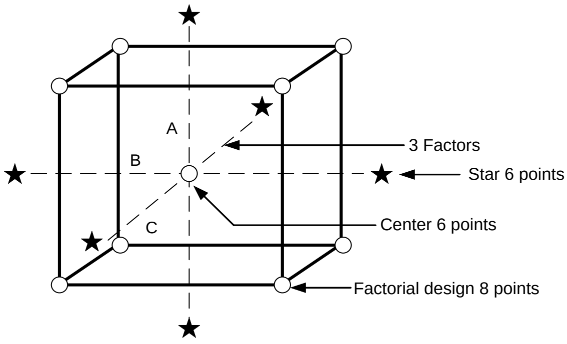

Fig. 3 Center composite design for 3 factors

In this study commercial software (Design-Expert 10.01) was employed for experimentally statistical analysis which the response surface methodology (RSM) was provided. The factorial is aimed at optimization. The responses, designated by the factorial, are the dispersion area from nozzle orifice diameter of 0.2 mm, which show in the Fig. 1 (this call that yield which replace by “Y”). Three main factorials corresponding to main factor were chosen. . Their names and levels can be seen in Table 1 following.

Table 1 Processing parameters involved in central composite design

Code	Name	-2 (-α)	-1	0	1	2 (α)
A	Travelling distance (mm)	1.3	4	8	12	14.7
B	Fluid volume (ml)	0.066	0.1	0.15	0.2	0.23
C	Reservoir pressure (bar)	1.3	4	8	12	14.7
Y	Dispersion (mm^2)					

3. Results and discussion

In order to describe the response surfaces, a five-level, three-factorial central composite design (CCD) was adopted in this study. The three independent variables and their levels for the 20 experiments (a-t) in the CCD study are shown in Table 2. The three columns on the left of the design layout identify the experimental runs. This software will randomize the order, so condition runs will probably not match the layout. The design layout contains the completed design in run order showing the actual factor levels. When has completed the experiment and the responses enter into total yield results. Which CCD experimental design gather the results from the experiments, are shown in Table 2.

After the computations are complete, the program displays the results inwhich, the central composite design provides too few unique design points to determine all of the terms in the cubic model. It's set up only for the quadratic model (or some subset), which are the significance of adding the quadratic (squared) terms to the mean, block, linear and two factorial interaction terms already in the model.

In this work, the objective is to optimize the dispersion area and conduct regression and the analysis of variables. The statistical significance of the model was evaluated by ANOVA. It is shown that the regression is statistically significant at a 95% confidence level ($P < 0.05$). The ANOVA was also performed to test the effect of linear, quadratic and interaction terms on the predicted responses. A stepwise regression procedure was performed using the backward elimination method in order to exclude non-significant interaction terms from the initial response surface model. The fit quality of model was expressed by the multiple correlation coefficients (R^2). The statistical significance of each parameter was determined via P-values. According to Myers and Montgomery [11], smaller P-values identify the effective parameters.

Table 2 Design layout and experimental results

Run	A Travelling distance (mm)	B Fluid volume (ml)	C Reservoir pressure (bar)	Y Dispersion area (mm^2)
a	12	0.2	4	176.12
b	12	0.1	4	60.20
c	4	0.1	4	50.91
d	1.3	0.15	8	98.38
e	8	0.15	8	107.25
f	4	0.2	4	65.63
g	8	0.15	8	130
h	4	0.1	12	120
i	8	0.23	8	128
j	12	0.1	12	67.58
k	8	0.15	8	70.46
l	8	0.15	14.7	99.29
m	8	0.066	8	85.03
n	12	0.2	12	70.40
o	14.7	0.15	8	72.74
p	4	0.2	12	190.38
q	8	0.15	8	66.94
r	8	0.15	8	87.42
s	8	0.15	8	130.11
t	8	0.15	1.3	60.03

Table 3 shows the ANOVA and regression analysis’ results for the dispersion area. The terms without statistical significance were eliminated from the full quadratic model. The reduced model for dispersion content gives R^2 and adjusted R^2 values of 95.69% and 93.00%, respectively presenting the significance of the model. The response surface and contour plots can be used to show the individual and cumulative effect of the variables on the responses. These graphical representations for models are plotted as a function of two variables, while keeping other variables at central level.

The regression model for dispersion area (Y), in coded factorials, is expressed by the following quadratic model Eq. (2) below:

$$Y = 98.37+11.73A+20.22B-7.01C-7.18AB - 36.52AC+4.21BC-4.61A^2+4.89B^2-2.52C^2 \quad (2)$$

The results from the RSM analysis indicate that the fluid volume and travelling distance have the most significant effect on dispersion area, while the reservoir pressures are no significant. The coefficient of determination (R^2) of the mathematical model is 0.9569. The optimal conditions of dispersion area, which obtain the travelling distance of 5.26, fluid volume of 0.18 ml and reservoir pressure of 11.90. The experimental values with those of the predicted values are almost identical with low percentage bias of dispersion area of 1.94 % as is shown in Table 4. Therefore, the mathematical model have developed adequately describing ranges of the experimental parameters study and provided a statistically accurate prediction of optimum dispersion area of injection into polyacrylamide gels.

Table 3 Regression and ANOVA analysis on the dispersion area (Y)

R^2	**95.69 %**				
R^2 adjusted	93.00 %				
Source	**DF**	**SS**	**MS**	**F**	**P-Value**
Regression	10	614.82	61.48	35.52	0.00
Residual	16	27.69	1.73		
Lack of Fit	14	26.99	1.93	5.46	0.15
Pure error	2	0.71	0.35		
Total	26	642.51			
Model terms	**Coefficient**		**P-Value**		
Constant	98.37		0.00		
A	11.73		0.00		
B	20.22		0.02		
C	-7.01		0.05		
AB	-7.18		0.02		
AC	-36.52		0.05		
BC	4.12		0.03		
A^2	-4.61		0.05		
B^2	4.89		0.00		
C^2	-2.52		0.00		

Table 4 Comparison between experiment and simulation value within optimal conditions

Code	Optimal Conditions		Dispersion area (mm^2)		Bias
			Experiment	Prediction	
A	Travelling distance	5.26 mm	190.38	194.15	1.94%
B	Fluid volume	0.18 ml			
C	Reservoir pressure	11.90 bar			

The Eq. (2) indicates the main effects of each parameter correlateing positively with dispersion area (Y). The magnitude of coefficients for and travelling distance (A) and fluid volume (B) are larger than the coefficients for and reservoir pressure (C), indicating that these parameters have a more significant effect on the dispersion area. In addition reservoir pressure coupled with travelling distance seems to have an interaction effect on the dispersion area.

In Fig. 4 (a) and (b), it is obvious that this influence is positive and quadratic. Additionally, the interaction effect of travelling distance and fluid volume can be observed. Due to the main effect, the increment of fluid volume conducts to increasing of dispersion area.

Fig. 4 (c) and (d) shows the effect of both travelling distance and reservoir pressure on the dispersion area. It is clear that this interaction term has a quadratic effect on the dispersion area. This phenomenon could partially be explained by the fact that at low levels of travelling distance, a reservoir pressure increase leads the increasing in the dispersion area value together. In our work, this was only observed at high reservoir pressure values. On the other hand, there is a linear increase in dispersion area with an increase in the travelling distance at lower reservoir pressure, as shown in Fig. 4 (c) and (d). Also, Table 3 and Eq. (1) reveal that the interaction effect between reservoir pressure and travelling distance is very significant.

Fig. 4 (e) and (f) illustrates the response graph for dispersion area as a function of the fluid volume and the reservoir pressure. Reservoir pressure significantly influences the dispersion area (see Table 3). This effect is linear, positive and steep. Although the fitted response surface shows a quadratic influence, the linear effect seems to influence predominantly dispersion area, which is in agreement with the P values. The quadratic effect of reservoir pressure is observed only at higher fluid volume. Moreover, the effect of the fluid volume on the dispersion area is fairly low for high values of the reservoir pressure. In addition to main effects, the interaction effect between the fluid volume and the reservoir pressure is considerable. Note that, the dispersion area is found to increase with the simultaneous increase in fluid volume and reservoir pressure.

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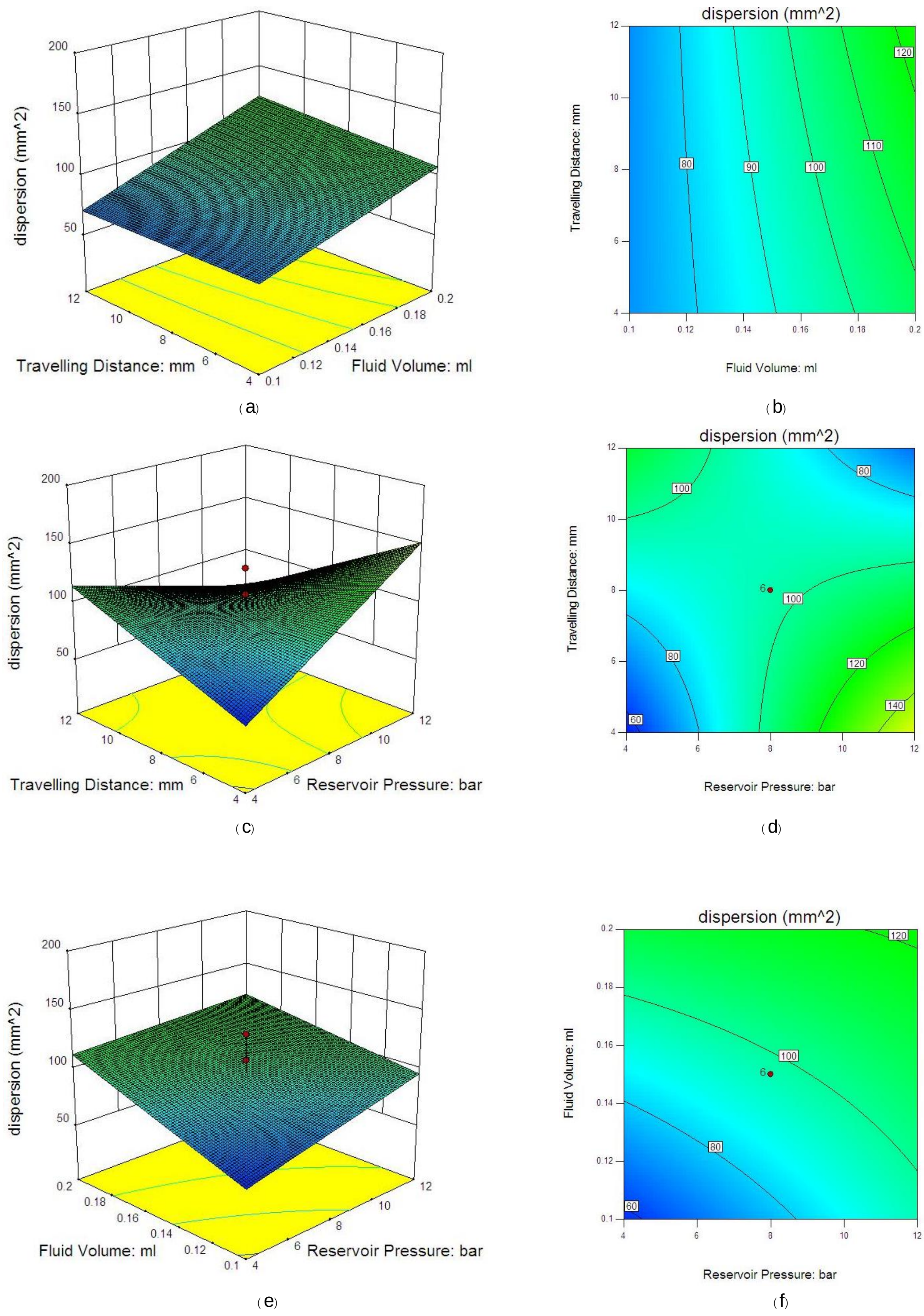

Fig. 4 Show response surface and contour plot of dispersion (mm^2), which (a) and (b) are function of fluid volume and reservoir pressure, (c) and (d) are function of travelling distance, (e) and (f) are function of travelling distance and fluid volume respectively.

4. Conclusions

Response Surface Method (RSM) is method for experiment design to find optimal operating condition of IDM jet injector. The results from the RSM analysis indicate that the fluid volume and travelling distance have the most significant effect on dispersion area. The coefficient of determination (R^2) of the mathematical model is 0.9569. The optimal conditions of dispersion area, which obtain the travelling distance of 5.26 mm, fluid volume of 0.18 ml and reservoir pressure of 11.90 bar. The experimental values with those of the predicted values are almost identical with low percentage bias of dispersion area of 1.94 % . Therefore, the mathematical model have developed adequately describing ranges of the experimental parameters study and provide a statistically accurate prediction of optimum dispersion area of injection into polyacrylamide gels.

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