ACS Sustainable Chemistry & Engineering

Research Article

pubs.acs.org/journal/ascecg

A Mathematical Programming Approach for the Optimal Synthesis of Nanofibers through an Electrospinning Process

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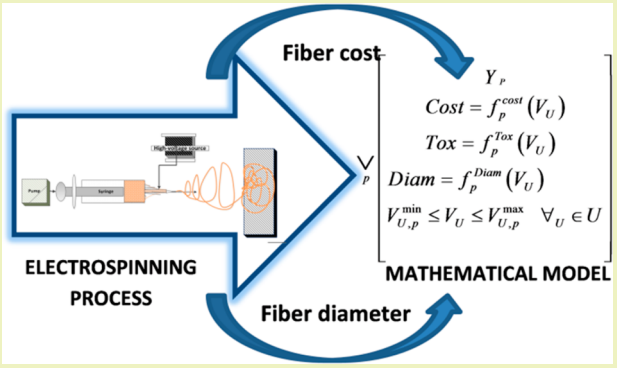
ABSTRACT: This paper presents a general mathematical programming formulation to determine the optimal operating conditions to synthesize nanofibers through an electrospinning process at minimum cost. Several relationships based on experimental data for different polymers to determine the nanofiber diameter and costs are proposed. Also, a general optimization approach is proposed to trade off the relationships between cost and nanofiber diameter. A case study including the specific relationships for three polymers and five operating conditions is presented. The proposed approach is general, and it can be applied to different cases.



KEYWORDS: *Optimization, Electrospinning, Nanofibers, Minimum cost and diameter, Disjunctive programming*

INTRODUCTION

Recently, the optimal synthesis of nanofibers has been the subject of several research efforts. This is because nanofibers have a high potential to be used in biomedical applications due to their high surface area with respect to their volume and microporous structure.[1−10] Besides that, a recent market research report from *BCC Research* shows that nanofibers are currently the fastest growing segment of the nanotechnology market. Their market value was $151.5 million in 2012, and the forecast is $570.2 billion in 2017. Currently, there are several techniques available for the synthesis of nanofibers (i.e., electrospinning, self-assembly, melt spinning, template synthesis, electroblowing, and phase separation). Of these, electrospinning is the most widely studied technique and also is the most promising for tissue engineering applications.[11−25] In the electrospinning process (Figure 1), a polymer solution is pumped at a constant rate through a syringe with a small-diameter needle that is connected to a high-voltage source, and an electric field is created between the needle and the metallic collecting plate. The solvent is evaporated before reaching the collector, and the final collected product is a mat composed of interconnected fibers. The morphology and fiber diameters produced by electrospinning are key parameters for potential biomedical applications.[26,27] Different parameters influence the electrospinning process to yield nanofibers from polymer solutions,[26,28−32] and several studies have focused on analyzing the effect of these parameters. In this regard, Thompson et al.[33] found that the volumetric charge density, distance from nozzle to collector, initial jet/orifice radius, relaxation time, and viscosity have the most significant effect on the jet radius and therefore the final fiber diameter, whereas other parameters such as initial polymer concentration, solution density, electric potential, perturbation frequency, and solvent vapor pressure have moderate effects. Tiwari et al.[12] evaluated the effect of viscosity in the electrospinning process. Heikkilä et al.[15] utilized an orthogonal experimental design in the electrospinning process using Polyamide-6; the analyzed parameters were polymer grade, viscosity of solution, salt content, solvent grade, voltage, distance, nozzle size, and feeding pressure of solution. In this study, the viscosity of the solution was the main parameter influencing the fiber diameters, while the salt content and strength of the electric field had strong effects. Maleki et al.[21] implemented a genetic algorithm for analyzing the electrospinning process to determine the optimum nanofiber diameter; in this approach, the initial polymer concentration, jet radius, electrical potential, relaxation time, initial elongation, viscosity, and distance between nozzle and collector were analyzed. Sencadas et al.[28] evaluated the parameters in the electrospinning process to synthesize nanofibers from chitosan. Kong et al.[26] determined the interaction between some parameters in the electrospinning process. Torres-Giner et al.[29] studied the effect of molecular weight, polymer concentration, TFA/DCM ratio of solvents, and distance between the nozzle tip and the collector on the morphology

Received: September 18, 2013
Revised: November 27, 2013
Published: December 8, 2013

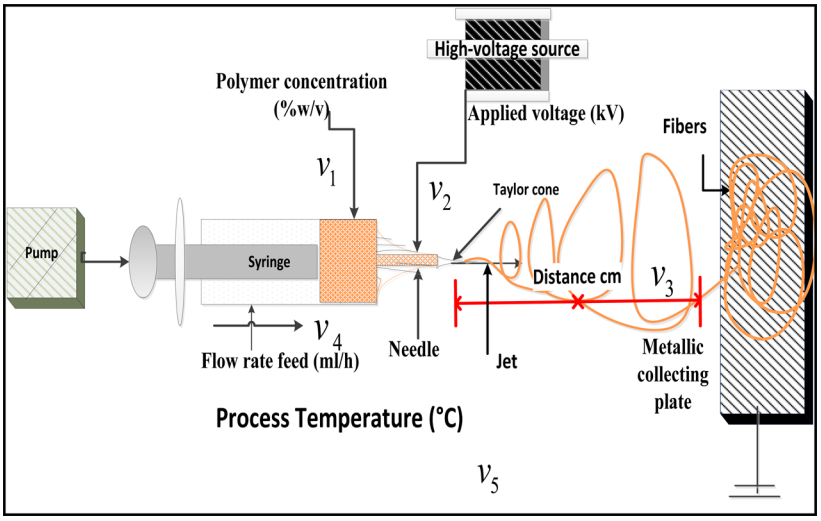


Figure 1. Schematic representation of the electrospinning process.

and diameter of electrospun nanofibers from chitosan solutions. Son et al.[30] investigated the effect of viscosity and water content on chitosan/polyvinyl alcohol (PVA) nanofiber synthesis. Park et al.[31] examined the resulting polyvinylacetate (PVAc) nanofibers under different conditions.

On other hand, solvent selection is essential in determining the critical minimum solution concentration to allow the transition from electrospraying to electrospinning, thereby significantly affecting the solution spinnability and the morphology of the electrospun fibers.[13,14] In this regard, Luo et al.[13] studied 28 solvents diversely positioned on the Teas graph for the solubility and electrospinnability of polymethylsilsesquioxane (PMSQ) solutions; they showed that solvents of high solubility do not necessarily produce good solutions for electrospinning. Similarly, there are some reports about the use of empirical modeling for the study of electrospinning parameters.[18,19,24,32,34] In this way, Comlekci[18] studied the static electric field force effect considerations in the electrospinning process. He et al.[19] obtained a relationship for the electric current and solution flow rate. Yördem et al.[24] utilized the response surface methodology to design experiments involving the solution concentration, voltage, and collector distance in the synthesis of polyacrylonitrile nanofibers. Kong et al.[34] developed an empirical model using a fractional factorial experimental design over a constrained region. This allowed establishing a quantitative relationship between fiber diameter and certain electrospinning parameters of Hylon VII (i.e., starch concentration, applied voltage, spinning distance, and feed rate), and then Roso et al.[32] used the same methodology to investigate the polymethylmethacrylate-co-methacrylic acid nanofibers.

Therefore, based on the previous analyses, it should be noted that it is important to determine the relationships of the involved variables in the electrospinning process to yield nanofibers. These relationships can be very useful to produce nanofibers with specific characteristics. Notice that several options or combinations of variables can yield desirable characteristics of nanofibers. However, none of the previously reported approaches has considered the use of formal optimization approaches to determine the combination of parameters that allows yielding nanofibers with desirable characteristics and at the same time at the minimum possible cost. Therefore, in this paper, there is proposed a formal mathematical programming model to determine the combination of parameters (i.e., concentration, voltage, distance between electrodes, injection velocity, and temperature) that yield polymer nanofibers with desirable diameters at minimum cost. This model formulation is based on experimental results for the electrospinning process.

PROPOSED MODEL FORMULATION

Mathematical programming has been widely used in the optimization of processes.[35] This has the advantage that it allows for manipulation of many variables and constraints to determine the optimal solution of a given problem. Particularly, disjunctive programming formulations allow for easy representation of complex combinatorial problems, and these formulations have been proven in several engineering applications (see for examples Ponce-Ortega et al.[36−39]) This way, in the present paper, a general disjunctive programming formulation is proposed to determine the minimum cost associated with electrospun nanofiber production with specific characteristics. This disjunctive formulation must select the type of polymer used (p) and the value for the variables (V) that includes concentration, voltage, distance between electrodes, injection velocity and temperature to determine the required nanofiber diameter (Diam) and satisfying specific constraints for the manipulated variables (V). This formulation includes relationships for each polymer for the cost ($f_p^{\text{cost}}(V_U)$), diameter ($f_p^{\text{Diam}}(V_U)$), and toxicity ($f_p^{\text{Tox}}(V_U)$) as a function of the manipulated variables (V). The proposed disjunctive formulation is stated as follows

$$\bigvee_p \begin{bmatrix} Y_p \\ \text{cost} = f_p^{\text{cost}}(V_U) \\ \text{Tox} = f_p^{\text{Tox}}(V_U) \\ \text{Diam} = f_p^{\text{Diam}}(V_U) \\ V_{U,p}^{\min} \le V_U \le V_{U,p}^{\max} \quad \forall_U \in U \end{bmatrix}$$

In previous formulation, Y_p is a Boolean variable that is true when the polymer p is selected as the optimum one, and for this case, the corresponding relationships for the cost and

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

diameter are applied. In the case when the Boolean variable Y_p is false, the relationships are not considered. It should be noticed that for each polymer there are specific relationships for the diameter and cost as well as limits for the involved variables. In addition, only one polymer must be selected as the optimal one. Then, previous disjunctive formulation must be reformulated as a set of algebraic relationships to be implemented as a formal mathematical programming formulation.[40] The following reformulation is proposed in this paper. First, the Boolean variables (Y_p) are transformed in binary variables (y_p). When the Boolean variable Y_p is true (i.e., the polymer is selected as the optimum one), then the corresponding binary variable y_p is 1, and when the Boolean variable Y_p is false (i.e., the corresponding polymer is not selected), the corresponding binary variable y_p is zero. Then, the reformulation is stated as follows.

Only one polymer must be selected (i.e., only one binary variable y_p must be equal one)

$$\sum_P y_p = 1 \tag{1}$$

Then, the relationships to determine the cost (cost) for nanofibers must be stated only for the polymer p selected to be the optimum as follows

$$\text{cost} \le f_p^{\text{cost}}(V_U) + M^{\text{Cost}}(1 - y_p), \quad \forall\, p \in P \tag{2}$$

$$\text{cost} \ge f_p^{\text{cost}}(V_U) - M^{\text{Cost}}(1 - y_p), \quad \forall\, p \in P \tag{3}$$

where M^{Cost} is a big M parameter used to activate the corresponding cost. This way, when polymer p is selected, the binary variable y_p is one and the last term of relationships 2 and 3 is zero. This means that the associated cost must be calculated according to the relationship for the polymer p ($f_p^{\text{Cost}}(V_U)$).On the other hand, when the polymer is not selected, the binary variable y_p is zero and the last term of relationships 2 and 3 are M^{Cost} and $-M^{\text{Cost}}$, respectively. Notice that for this case these terms (M^{Cost} and $-M^{\text{Cost}}$) relax relationships 2 and 3; this means that the cost is not calculated using the corresponding function for this polymer.

The toxicity (Tox) for the production of nanofibers considering the polymer and solvent is considered as a measure of the environmental impact. This effect must be stated only for the polymer p selected to be the optimum one as follows

$$\text{Tox} \le f_p^{\text{Tox}}(V_U) + M^{\text{Tox}}(1 - y_p), \quad \forall\, p \in P \tag{4}$$

$$\text{Tox} \ge f_p^{\text{Tox}}(V_U) - M^{\text{Tox}}(1 - y_p), \quad \forall\, p \in P \tag{5}$$

where M^{Tox} is a big M parameter used to activate the corresponding toxicity. This way, when the polymer p is selected, then the binary variable y_p is one and the last term of relationships 4 and 5 is zero. This means that the associated toxicity must be calculated according to the relationship for the polymer p ($f_p^{\text{Tox}}(V_U)$). For determining the toxicity relationships, Probit functions can be properly used.

Finally, the relationships to determine the diameter for the electrospun nanofibers depend on the type of polymer and these are stated as follows

$$\text{Diam} \le f_p^{\text{Diam}}(V_U) + M^{\text{Diam}}(1 - y_p), \quad \forall\, p \in P \tag{6}$$

$$\text{Diam} \ge f_p^{\text{Diam}}(V_U) - M^{\text{Diam}}(1 - y_p), \quad \forall\, p \in P \tag{7}$$

where M^{Diam} is a big M parameter used to relax previous relationships. The explanation for these relationships for the diameter of electrospun nanofibers is similar to that for nanofibers cost. This is, when the polymer is selected, y_p is one, and then the right-hand side of relationships 6 and 7 is zero. This way, previous relationships are activated for that polymer. In the opposite case, when the polymer is not selected, the binary variable y_p is zero; therefore, the big M parameter, M^{Diam}, relaxes the relationships for this polymer.

Notice in the disjunction that the limits for the variables involved depend on the type of polymer selected, and because the type of polymer is an optimization variable, this is modeled as follows. First, there are upper (V_U^{up}) and lower (V_U^{lo}) limits for the involved variables U; however, these limits are optimization variables that are determined depending on whether the polymer is selected or not. This is stated as follows

$$V_u^{\text{lo}} \le V_u \le V_u^{\text{up}}, \quad \forall\, u \in U \tag{8}$$

where these lower and upper bounds are determined as follows

$$V_u^{\text{lo}} = \sum_p V_{\text{p,u}}^{\min}\, y_p, \quad \forall\, u \in U \tag{9}$$

$$V_u^{\text{up}} = \sum_p V_{\text{p,u}}^{\max}\, y_p, \quad \forall\, u \in U \tag{10}$$

In previous relationships, $V_{\text{p,U}}^{\min}$ and $V_{\text{p,U}}^{\max}$ are lower and upper limits for the variable U associated to the polymer p. Notice that the variables V_U^{lo} and V_U^{up} are equal to the polymer selected because for this case the binary variable is active.

This model is general, and it can be used for any number of polymers and different variables. The only requirement is to determine the relationships for the cost and diameter through a set of correlations from experimental data. Also notice that this can be a mixed integer linear or nonlinear programming problem depending on whether these relationships are linear or nonlinear. The model was coded in the software GAMS,[41] and a case study is presented in next section.

CASE STUDY

In this work, three polymers were evaluated (collagen, gelatin, and chitosan). These polymers were selected because their biomedical applications have been continuously increasing due to their excellent biocompatibility and biodegradability characteristics.[1,2,4,7,10,11,25,27,28] The biomedical applications of these polymers are related to a large surface area-to-mass ratio, and this is achieved with diameters on the order of 500 nm and below.[42] The relationship between nanofiber diameter and electrospinning parameters is represented by eq 11

$$\text{Diam} = f_p^{\text{Diam}}(v_1, v_2, v_3, v_4, v_5) \tag{11}$$

where Diam is the average electrospun nanofibers diameter (nm), and v_1, v_2, v_3, v_4, and v_5 are the optimization variables U considered in this case. They are described in Table 1.

On the basis of the experimental data previously reported and for the synthesis of electrospun collagen, gelatin, and chitosan nanofibers,[2,4,5,7,10,11,25,27,28] a regression was performed using the Statgraphics software to establish a quantitative relationship between fiber diameter and spinning parameters for each polymer. By multiple regression analysis, a polynomial equation was found; it shows a relationship between the dependent variable (diameter) and independent variables (initial polymer concentration (% w/v), applied

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

Table 1. Electrospinning Optimization Variables of Nanofibers for the Case Study Presented

independent variable	electrospinning parameter
v_1	polymer concentration (% w/v)
v_2	applied voltage (kV)
v_3	distance (cm)
v_4	flow rate feed (mL/h)
v_5	temperature (°C)

voltage (kV), distance between the needle tip to the collector (cm), flow rate feed (mL/h), and temperature (°C)). This equation is established after a series of regressions obtaining a 99% confidence interval. This polynomial equation is introduced into the mathematical model to represent the dependence of the fiber diameter versus electrospinning parameters.

First, for collagen, the relationship for the diameter is given as follows

$$\begin{aligned}\text{Diam} = {} & -3736.98 + 12.65v_1^3 - 173.84v_1^2 + 694.29v_1 \\ & + 143.202v_2 - 16.21v_3^2 + 286.731v_3 - 497.904v_4 \\ & - 0.01v_1^3v_2^2 + 2.23v_3^2v_4 + v_1^2v_5 \end{aligned} \quad (12)$$

The correlational coefficient (R^2) for the experimental and calculated values obtained from the response surface equation is 0.975. This value indicates a good correlation between process and solution parameters and nanofibers diameter. Table 2 shows the intervals for each variable in eq 12.

Table 2. Interval for Variables for Collagen Nanofibers Used in Eq 12

variable	V^{min}	V^{max}
v_1	1.3	9.9
v_2	14.5	22.5
v_3	11	20
v_4	0.1	8
v_5	23	26

For gelatin, the correlations for the diameter are shown in eq 13, and the corresponding limits for the variables involved are shown in Table 3. The correlational coefficient for relationship

Table 3. Intervals of Variables for Gelatin Nanofibers Used in Eq 13

variable	V^{min}	V^{max}
v_1	1.5	30
v_2	10	25
v_3	10	14.5
v_4	0.1	1
v_5	19	27

13 (R^2) between the experimental and calculated values obtained from the response surface equation is 0.898, indicating a good correlation between process and solution parameters and nanofiber diameter.

$$\begin{aligned}\text{Diam} = {} & -7647.83 + 0.07v_1^3 - 3.35v_1^2 + 46.19v_1 - 3.66v_2^2 \\ & + 153.0v_2 - 47.07v_3^2 + 1048.3v_3 - 465.71v_4^3 \\ & + 1203.88v_4^2 + v_1v_4^2 + v_1v_5 \end{aligned} \quad (13)$$

For chitosan, the relationship for the diameter is given in eq 14, and the confidential intervals for the involved variables are given in Table 4.

$$\begin{aligned}\text{Diam} = {} & 1089.67 - 0.45v_1^2 + 32.26v_1 - 0.94v_2^2 + 31.29v_2 \\ & + 4.19v_3^2 - 180.26v_3 - 180.89v_4^2 + 478.72v_4 \\ & + v_1v_5 \end{aligned} \quad (14)$$

Table 4. Intervals of Variables for Chitosan Nanofibers Used in Eq 14

variable	V^{min}	V^{max}
v_1	4.5	10
v_2	14	34
v_3	10	30
v_4	0.05	1.4
v_5	20	102

The correlational coefficient (R^2) between the experimental and calculated values in eq 14 for chitosan is almost 1.00. This value indicates a good correlation between process and solution parameters and nanofiber diameter. Notice that the value of R^2 for the case of gelatin is lower than that for chitosan and collagen, which are nearly one. One way to improve the value of R^2 for gelatin would to increase the degree of the polynomial equation; however, this could originate significant computational problems. In addition, for the preliminary analysis proposed in this case study, this value of R^2 is considered acceptable. The intervals for each variable shown in Tables 2, 3, and 4 were calculated using the Statgraphics software using estimations from polynomial equations. These values are valid for the obtained equations.

To estimate the cost of 1 mg of electrospun nanofibers produced through the electrospinning process, the following equation was used

$$\text{TotCost} = \text{cost}^{\text{polymer}} + \text{cost}^{\text{solvent}} + \text{cost}^{\text{electricity}} \quad (15)$$

where TotCost is the total production cost of 1 mg of nanofibers, $\text{Cost}^{\text{polymer}}$ is the cost associated to the polymer used in the production of 1 mg of nanofibers, $\text{Cost}^{\text{solvent}}$ is the cost of solvent used, and $\text{Cost}^{\text{electricity}}$ is the cost associated to the electricity consumed for the production of 1 mg of nanofibers with the specific characteristics indicated.

To determine the cost for the polymer used ($\text{Cost}^{\text{polymer}}$), eq 16 is applied

$$\text{cost}^{\text{polymer}} = \text{UC}^{\text{polymer}} m^{\text{polymer}} \quad (16)$$

where m^{polymer} is the volume of the polymer required to yield 1 mg of electrospun nanofibers, and $\text{UC}^{\text{polymer}}$ is the unit cost for the polymer.

To calculate the cost of solvent used ($\text{Cost}^{\text{solvent}}$), eq 17 is used

$$\text{cost}^{\text{solvent}} = \text{UC}^{\text{solvent}} V_{\text{solution}} \quad (17)$$

where V_{solution} is the total volume used in milliliters, and $\text{UC}^{\text{solvent}}$ is the cost per milliliter of solvent used in the synthesis of 1 mg of nanofibers. Table 5 shows the unit costs associated with the considered polymers and their corresponding solvent.

The electricity consumed during the production of electrospun nanofibers represents a cost, which is calculated using eq

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

Table 5. Cost of Polymer and Solvent for Each Polymer Considered in the Case Study

polymer	solvent	polymer (cost/mg)	solvent (cost/mL)
collagen	1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)	$50.31	$5.29
gelatin	acetic acid	$0.0012	$0.1091
chitosan	trifluoroacetic acid	$0.0018	$0.3580

18 and considers the electricity expenses of dissolution, injection pump, and electrospinning.

$$\text{cost}^{\text{electricity}} = \text{cost}^{\text{electricity}}_{\text{pump}} + \text{cost}^{\text{electricity}}_{\text{electrospinning}} + \text{cost}^{\text{electricity}}_{\text{applied voltage}} \quad (18)$$

Therefore, in this case, the electricity total cost is calculated as follows

$$\text{cost}^{\text{electricity}} = \text{UEC}\, P_{\text{pump}} t + \text{UEC}\, P_{\text{electrospinning}} t + \text{UEC}\, 24 \nu_2 t \quad (19)$$

where P_{pump} is the power of the pump, $P_{\text{electrospinning}}$ is the power of electrospinning, 24 ν_2 is the power per kV applied to the polymeric solution, t is the time of electrospinning process, and UEC is the cost of electricity per kilowatt h. Table 6 shows the power and unit electricity costs for the pump, electrospinning, and applied voltage.

Table 6. Power and Electricity Cost for the Equipment Used in Electrospinning Process

equipment	power	electricity cost (kW h)
pump	0.040 kW	$0.06
electrospinning	5.30 kW	$0.06
applied voltage	$24\nu_2$	$0.06

Notice that t is the time at which the total polymeric solution is syringed, and this is calculated as follows

$$t = \frac{V_{\text{solution}}}{\nu_4} \quad (20)$$

where V_{solution} is the total volume of the polymeric solution and this is calculated with the following relationship

$$V_{\text{solution}} = \frac{100 m^{\text{polymer}}}{\nu_1} \quad (21)$$

and combining eqs 20 and 21

$$t = \frac{100 m^{\text{polymer}}}{\nu_1 \nu_4} \quad (22)$$

Then, substituting the unit values reported in Table 6 and combining previous equations, the following expression is obtained for the electricity cost associated to the electrospinning process to yield one milligram of nanofiber:

$$\text{cost}^{\text{electricity}} = 0.040\ \text{UEC}\frac{100 m^{\text{polymer}}}{\nu_1 \nu_4} + 5.30\ \text{UEC}\frac{100 m^{\text{polymer}}}{\nu_1 \nu_4} + 24\ \text{UEC}\frac{100 \nu_2 m^{\text{polymer}}}{\nu_1 \nu_4} \quad (23)$$

Then, the total production cost per milligram of nanofiber is calculated as follows

$$\text{TotCost} = \text{UC}^{\text{polymer}} m^{\text{polymer}} + \text{UC}^{\text{solvent}} V_{\text{solution}} + \text{UEC}\, P_{\text{pump}} t + \text{UEC}\, P_{\text{electrospinning}} t + \text{UEC}\, 24 \nu_2 t \quad (24)$$

Substituting eqs 21 and 22 and the data from Table 6 into eq 24, the following expression is obtained for the total cost per milligram of nanofibers

Table 7. Experimental Data for Electrospun Collagen Nanofibers[4,5]

concentration (% m/v)	voltage (kV)	distance (cm)	injection (mL/h)	solvent	temperature (°C)	diameter (nm)
15	15	15	1	HFIP	25	295
15	15	15	1	HFIP	25	225
7	12	13	0.6	HFIP	25	70
12	12	13	0.6	HFIP	25	170
2	12	13	0.8	HFIP	25	80
8.3	15	10	0.8	HFIP	25	490
8	15	10	0.8	HFIP	25	800
15	15	10	0.3	HFIP	25	210
29	17	12	0.3	HFIP	25	840
10	18	10	0.3	HFIP	25	103
6	18	10	0.3	HFIP	25	77
8	18	10	0.3	HFIP	25	93
12	13	12	0.2	HFIP	25	184
15	16	12	0.2	HFIP	25	312
23	24	12	0.2	HFIP	25	485
5	12.5	12	0.8	HFIP	20.3	100
7.5	10.5	12	0.8	HFIP	19.9	140
10	10	12	0.8	HFIP	19.5	240
12.5	10	12	0.8	HFIP	20.3	340
8	22	10	0.2	HFIP	26	291

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

Table 8. Experimental Data for Electrospun Gelatin Nanofibers[2,5,10]

concentration (% m/v)	voltage (kV)	distance (cm)	injection (mL/h)	solvent	temperature (°C)	diameter (nm)
8	19	15	4.8	acetic acid	25	100
8	21	20	4.8	formic acid	26	600
7.5	13	13	1	formic acid	25	330
3	15	14	1	formic acid	25	100
2	15	14	1	HFIP	25	115
8	15	14	1	HFIP	25	612
10	20	13	0.8	HFIP	25	500
8	17	8	1.2	acetic acid	25	460
8.3	10	15	1	acetic acid	25	420
8.3	10	15	3	acetic acid	25	520
8.3	10	15	5	acetic acid	25	500
8.3	10	15	8	acetic acid	25	550
6	25	12.5	4.8	formic acid	25	310
5	13	14	1.2	formic acid	26	100

Table 9. Experimental Data for Electrospun Chitosan Nanofibers[7,11,25,27,28]

concentration (% m/v)	voltage (kV)	distance (cm)	injection (mL/h)	solvent	temperature (°C)	diameter (nm)
3	14	12	1	acetic acid	25	250
6	20	13	0.8	HFIP/TFA	25	300
10	20	13	0.8	HFIP/TFA	25	500
4	15	10	0.2	acetic acid	25	275
4	30	15	0.5	acetic acid	80	60
7	40	10	1.2	acetic acid	22	130
7	17	16	1.6	acetic acid	22	200
2	25	10	0.2	acetic acid	23	100
5	19	29	0.6	TFA	25	140

$$\text{TotCost} = \text{UC}^{\text{polymer}} m^{\text{polymer}} + \text{UC}^{\text{solvent}} \frac{100 m^{\text{polymer}}}{v_1} + 0.040\ \text{UEC} \frac{100 m^{\text{polymer}}}{v_1 v_4} + 5.30\ \text{UEC} \frac{100 m^{\text{polymer}}}{v_1 v_4} + 24\ \text{UEC} \frac{100 v_2 m^{\text{polymer}}}{v_1 v_4} \quad (25)$$

For the case of collagen nanofibers, substituting the data of Table 5 and assuming no leaks for every milligram of nanofiber obtained, 1 mg of polymer feedstock will be used. Therefore, m^{polymer} is equal to one, and eq 25 is stated as follows

$$\text{TotCost} = 50.31 + \frac{529.23}{v_1} + \frac{32.24}{v_1 v_4} + \frac{144 v_2}{v_1 v_4} \quad (26)$$

Similarly, the total production cost for gelatin nanofibers is represented by the following equation

$$\text{TotCost} = 0.0012 + \frac{10.91}{v_1} + \frac{32.24}{v_1 v_4} + \frac{144 v_2}{v_1 v_4} \quad (27)$$

Finally, the total production cost of chitosan nanofibers is represented by the following equation

$$\text{TotCost} = 0.0018 + \frac{35.80}{v_1} + \frac{32.24}{v_1 v_4} + \frac{144 v_2}{v_1 v_4} \quad (28)$$

It should be noticed that in eqs 26, 27, and 28 used to determine the cost, the term distance (v_3) is not present; however, it is included in the correlations to determine the diameters. Additionally, the distance is directly related to the concentration and rate of injection variables included in the equations of cost. Thus, the distance is intrinsically present in other variables.

For this case study, the solvent concentrations are very low, and also, the solvent is trapped in the camera of the electrospinning and avoids any significant environmental impact. Therefore, in this case, the toxicity is not considered as an important factor.

RESULTS AND DISCUSSION

In this section, first is presented an analysis for the interactions between the involved variables in the nanofibers production using the electrospinning process, and then the optimization results are presented and discussed.

Interaction between the Involved Variables. Tables 7, 8, and 9 show the experimental data used for the synthesis of collagen, gelatin, and chitosan electrospun nanofibers, respectively, as well as the final fiber diameter obtained. Table 8 shows the different solvents used to obtain electrospun gelatin nanofibers; however, the one considered was the cheapest one that corresponds to acetic acid. In Table 9, the data used for the trifluoroacetic acid (TFA) were included with the aim of experiment a different solvent for each polymer, and TFA was used because it is cheaper than 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP).

Collagen Nanofibers. Figure 2 shows the influence of electrospinning parameters on collagen nanofibers. The most important parameter affecting the diameter is the concentration. It can be observed in Figure 2a and c that higher concentration and voltage yield smaller nanofiber diameter. Whereas, when the distance decreases and the injection velocity increases, the nanofiber diameter increases. Notice in Figure 2b and d that nanofibers diameter increases when the distance decreases. Smaller fibers diameters are obtained at longer

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

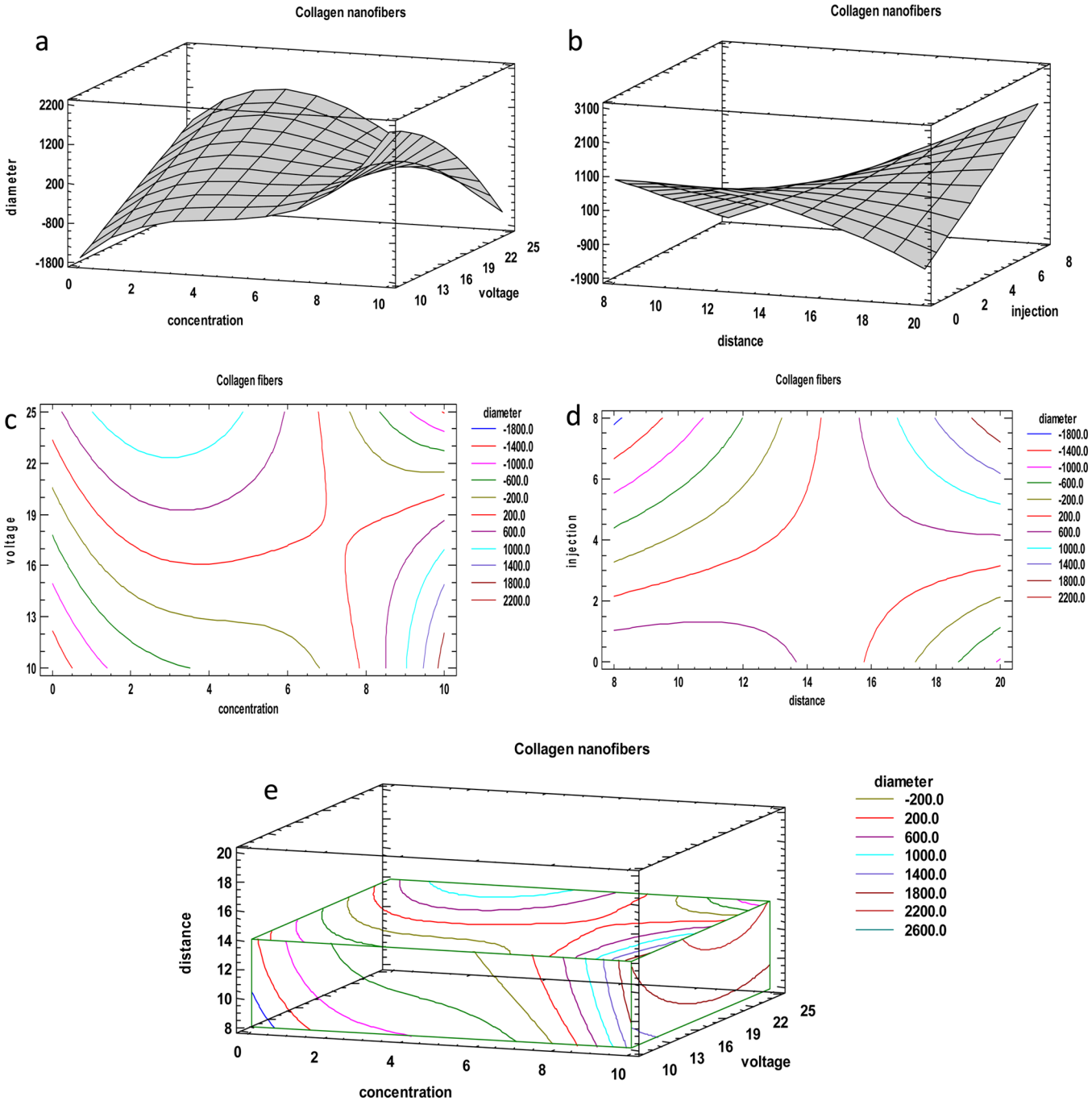


Figure 2. Response surface (a), (b), and (d) and contour plots (c) and (d) of interaction effect of levels of distance and injection ((a) and (c)) and concentration and voltage ((b) and (d)) on nanofiber diameter for collagen.

distance, lower concentration, and higher applied voltage (Figure 2e).

Gelatin Nanofibers. The influence of the different parameters on gelatin nanofiber diameter is shown in Figure 3. Notice that when the concentration and voltage increase the nanofiber diameter obtained also increases (Figure 3a and c), and when the distance decreases and the injection velocity increases, the nanofiber diameter increases. Also, at longer distances, the nanofiber diameter decreases at low injection velocity (Figure 3b and d). Smaller nanofiber diameter is obtained at longer distance, higher concentration, and higher applied voltage (Figure 3e).

Chitosan Nanofibers. Finally, Figure 4 shows the influence of the different parameters on chitosan nanofibers diameter. In this case, the lower concentration and voltage are, the lower the nanofiber diameter is, and when the concentration and voltage increase, the diameter increases (Figure 4a and c). Also, when the distance decreases and the injection velocity increases, the fiber diameter decreases (Figure 4b and d). Smaller nanofiber diameter is obtained at lower applied voltage, distance, and concentration (Figure 4e).

Optimization Results. The optimum results obtained for the different polymers considered are shown in Table 10 (this table shows the results for the three considered polymers, even the optimum one was gelatin). It should be noticed that the

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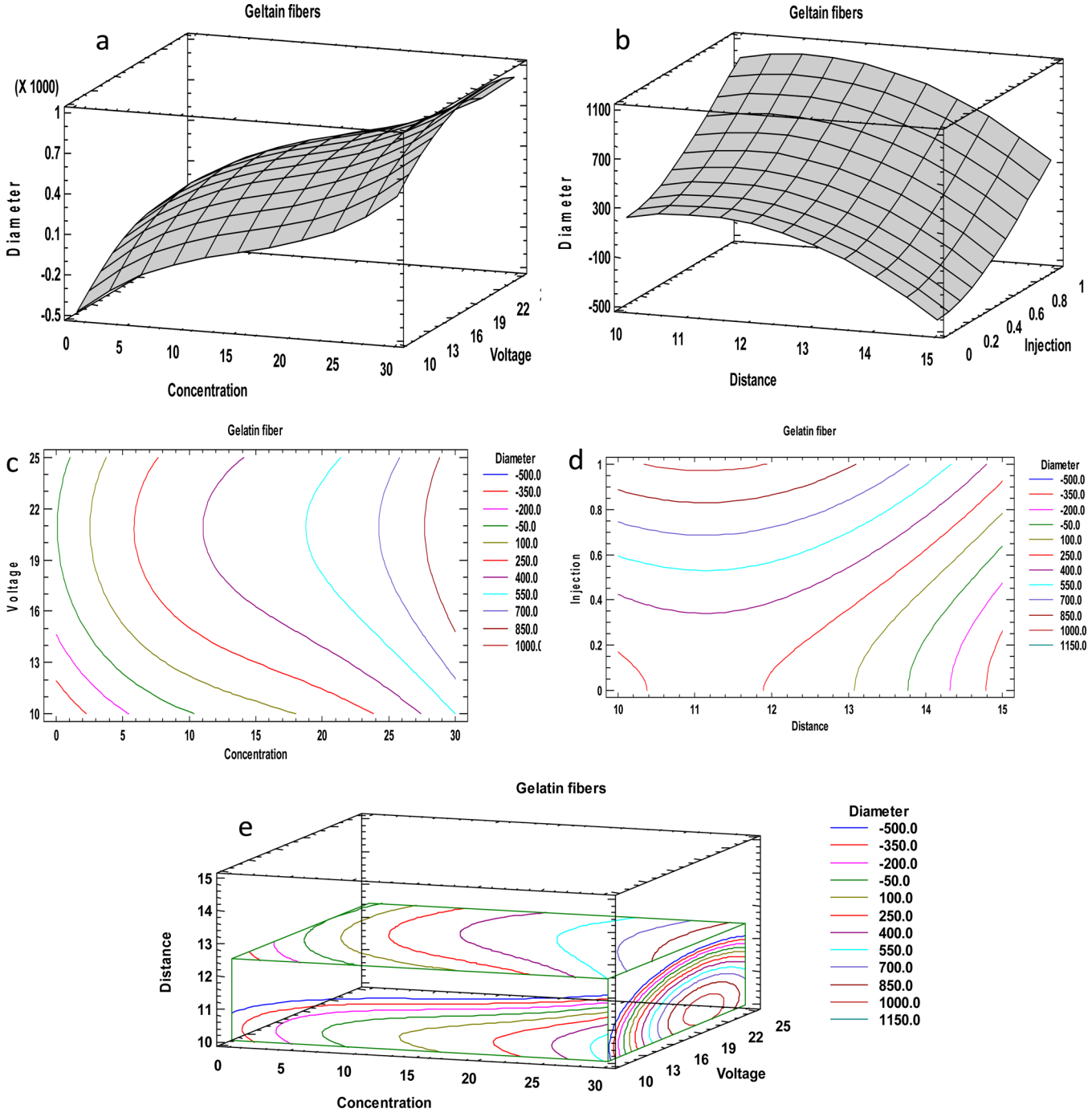

Figure 3. Response surface (a), (b), and (d) and contour plots (c) and (d) of interaction effect of levels of distance and injection ((a) and (c)) and concentration and voltage ((b) and (d)) on nanofiber diameter for gelatin.

best economic solution involves the use of gelatin, whereas the use of chitosan provides a solution with a moderate cost but with the minimum diameter. Collagen yields the worst economic scenario with a moderate diameter. For further analysis, the Pareto curve presented in Figure 5 shows the trade-offs between the cost and diameter. This Pareto front represents a set of optimal solutions that compensate the economic and diameter objectives for the nanofiber. That is, the solutions above the curve represent suboptimal solutions, whereas the solutions below the curve are infeasible solutions. This Pareto curve can be very useful to determine the minimum costs and operating conditions to synthesis a nanofiber with a specific diameter. It should be noticed that in this case all the considered polymers are for biomedical applications; these involve tissue engineering, drug delivery, cartilage restoration, bone restoration, and others. For all these biomedical applications, the upper limit for the nanofiber diameter is 500 nm. Therefore, all the nanofibers considered can be used for the indicated application. However, the quality for the nanofiber increases at lower diameter. This is because the ratio of the area-to-volume is higher, and this way the similarity to human cells is closer. Furthermore, it is not possible to indicate that a given diameter is the one indicated for each specific application.

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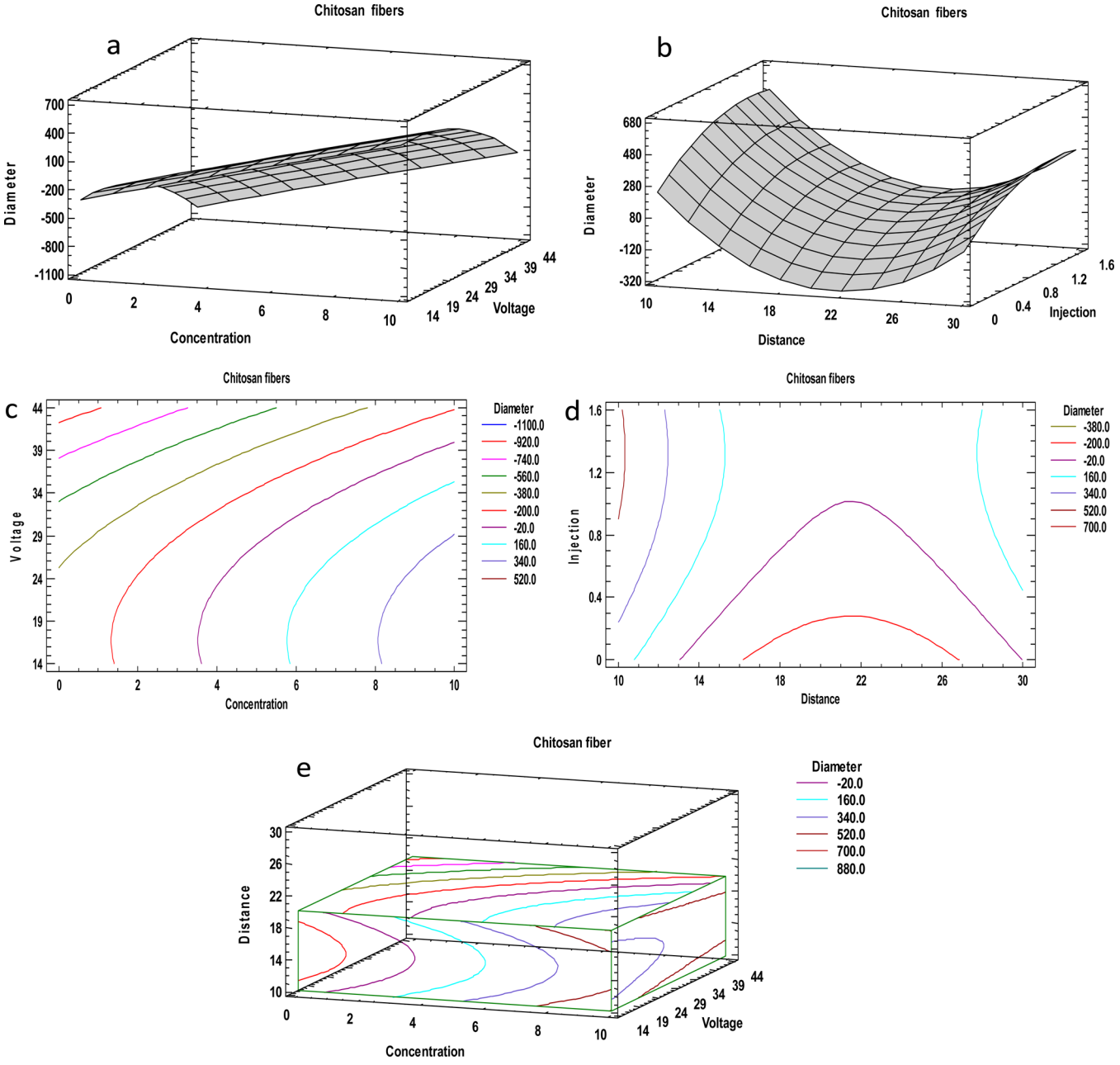

Figure 4. Response surface (a), (b), and (d) and contour plots (c) and (d) of interaction effect of levels of distance and injection ((a) and (c)) and concentration and voltage ((b) and (d)) on nanofiber diameter for chitosan.

Table 10. Optimization Results

concept/polymer	collagen	gelatin	chitosan
cost ($/mg of nanofibers)	106.956	1.459	6.827
diameter (nm)	400.75	748.29	184.38
concentration (%w/v)	9.900	30.000	10.000
voltage (kV)	22.500	25.000	34.000
distance (cm)	11.000	10.000	10.000
injection (mL/h)	0.100	0.100	0.050
temperature (°C)	26.000	27.000	20.000

Notice in Figure 5 that for the case of collagen nanofibers for diameters lower than ~10 nm, the production cost of nanofibers per milligram is $US 488.97. But for diameters from ~10 to ~400 nm, the production cost per milligram is $US 107.08, whereas for diameters above ~400 nm, the

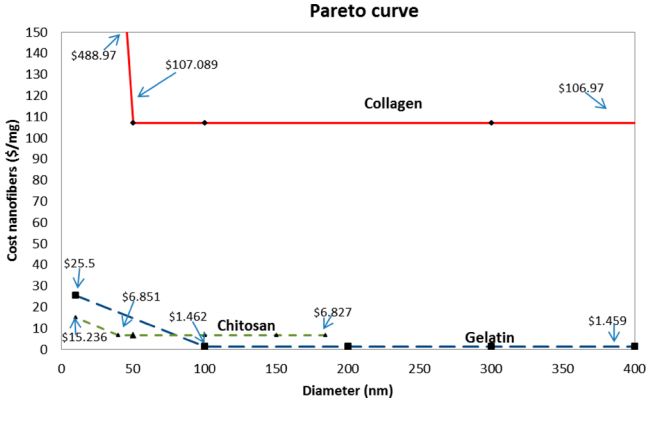

Figure 5. Pareto curve cost vs nanofiber diameter.

dx.doi.org/10.1021/sc400360k | ACS Sustainable Chem. Eng. 2014, 2, 454−464

production cost per milligram is $US 106.96. When the diameters are small, the concentration of polymeric solution tends to be ∼1.3 (% w/v), voltage ∼14.5 kV, distance ∼10 cm, injection velocity ∼0.885 mL/h, and temperature ∼23 °C. However, when the diameter is greater, the concentration tends to be ∼9.9 (% w/v), voltage ∼22.5 kV, injection velocity ∼0.10 mL/h, temperature ∼26 °C, and distance is constant.

With respect to gelatin nanofibers, for diameters below ∼10 nm, the associated cost per milligram is $US 25.5. But for nanofiber diameters between ∼10 to ∼700 nm, the associated cost per milligram of nanofiber is $US 1.46, whereas above ∼700 nm, the cost is $US 1.45. When the diameters are low, the concentration of polymeric solution tends to be ∼2.12 (% w/v), voltage ∼10.5 kV, distance ∼10.5 cm, injection velocity ∼0.79 mL/h, and temperature ∼19 °C. However, when the diameter is higher, the concentration tends to be ∼30 (% w/v), voltage ∼25 kV, injection velocity ∼0.10 mL/h, temperature ∼27 °C, and distance is constant.

For chitosan nanofibers, for diameters lower than ∼50 nm, the production cost per milligram is $US 15.23, for diameters between ∼10 and 180 nm, the cost is $US 6.85, and for diameters greater than ∼180 nm, the cost is $US 6.82. When the diameters are low, the concentration of polymeric solution tends to be ∼4.5 (% w/v), voltage ∼14 kV, distance ∼12 cm, injection velocity ∼0.05 mL/h, and temperature ∼20 °C. However, when the diameter is higher, the concentration tends to ∼10 (% w/v), voltage ∼34 kV, and distance, injection velocity, and temperature are constant.

CONCLUSIONS

This paper proposed a set of relationships to determine the diameter and cost of nanofibers as a function of some independent variables involved in the electrospinning process (i.e., concentration of polymer, voltage, distance between electrodes, injection velocity, and temperature); these relationships are integrated into a disjunctive programming formulation to determine the optimal conditions to yield the desired nanofiber diameter at minimum cost. Notice that the model includes the toxicity that is related to the solvent used depending on the polymer. However, in the case study presented here, this parameter is not considered as an important factor because very low solvent concentrations are used, and it is stuck in the electrospinning camera. Also, a systematic optimization approach is proposed to trade-off the diameter of nanofibers and the associated cost manipulating the operating conditions in the electrospinning process. The proposed model was applied to a case study where the advantages of the proposed approach are highlighted. This approach can be useful to determine the minimum costs and operating conditions to yield a desirable nanofiber diameter. A future work should consider the manipulation of the application of the produced nanofibers as an additional independent variable. Finally, the proposed approach is general, and it can be easily extended to analyze different polymers and other conditions.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge financial support from the Mexican Council for Science and Technology (CONACYT) and Scientific Research Council of the Universidad Michoacana de San Nicolás de Hidalgo.

NOMENCLATURE

Parameters

$m^{polymer}$	volume required of polymer to yield a milligram of nanofibers
M^{cost}	big M parameter used to activate the corresponding cost
$P_{electrospinning}$	power for electrospinning
P_{pump}	power for the pump
$UC^{polymer}$	unit cost for the solvent used in the synthesis of 1 mg of nanofibers
$UC^{solvent}$	cost per milliliter of solvent used in the synthesis of 1 mg of nanofibers
UEC	cost of electricity per kilowatt h, $/kW h
$V_{p,u}^{max}$	upper limit for variable U associated to polymer p
$V_{p,u}^{min}$	lower limit for variable U associated to polymer p
$V_{solution}$	total volume used in milliliters
V_U	values for the involved variables U
V_U^{lo}	lower limits for the involved variables U
V_U^{up}	upper limits for the involved variables U
Y_p	Boolean variable for polymer p

Variables

Cost	cost for the nanofiber production, $/mg of nanofibers
$Cost^{electricity}$	cost associated with electricity consumed for production of 1 mg of nanofibers
$Cost^{polymer}$	cost associated with polymer used in production of 1 mg of nanofibers
$Cost^{solvent}$	cost for solvent used for production of 1 mg of nanofibers
Diam	nanofiber diameter
p	polymer (collagen, gelatin, chitosan)
TotCost	total production cost of 1 mg of nanofibers
Tox	toxicity associated with solvent in the manufacturing process
U	variable (v_1,v_2,v_3,v_4)
v_1	polymer concentration, % w/v
v_2	applied voltage, kV
v_3	distance between electrodes, cm
v_4	flow rate feed, mL/h

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