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Application of Experimental Design for Modelization and Optimization of Sol-Gel Synthesis of Bioactive Glass

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***Abstract*: The characteristics of bioactive glasses developed in ternary (SiO_2, CaO, P_2O_5) system using tetraethyl orthosilicate (TEOS, $Si(OC_2H_5)_4$), Calcium Nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$) and triethyl phosphate (TEP, $OP(OC_2H_5)_3$) as precursors of SiO_2, CaO and P_2O_5, respectively, by means of sol-gel route depends on several factors namely the temperature, stirring speed, concentration of acid catalyst, basic catalyst and volume of alcohol. In order to control these factors effects and their interactions on the synthesis of bioactive glass, an experimental design was defined to model the preparation of this product according to a methodological experimental design. Central Composite Design (CCD) for five variables was chosen, and design variables were as followed: Temperature, Stirring speed, Concentration of the acid catalyst, addition time of the base, amount of alcohol. The model founded describes the variation of the measured response ' gel time ' based on the factors affecting the synthesis.**

Keywords: Biomaterials, Bioactive Glass , Sol Gel, Gelation , Experimental Design.

1. INTRODUCTION

Biomaterial was defined, in 1986 at the European Society for Biomaterials Consensus Conference, as "a non-viable material used in a medical device intended to interact with biological systems", [1]. A bioactive glass is defined as a ceramic used as a biomaterial, which the function of biomaterials is to replace diseased or damaged tissues. There are many applications for biomaterials; actually, the most important is in implants, bioactive materials have the ability to bond directly with bone.

Hench and Andersson defined a bioactive material as followed:[2] "A bioactive material is one that elicits a specific biological response at the interface of the material, which results in the formation of a bond between tissues and the material".

Bioactive glasses develop on their surface a biologically active hydroxy carbonate apatite (HCA) layer which bonds with collagen fibrils. The HCA phase that forms on bioactive implants is equivalent chemically and structurally to the mineral phase of bone. It is that equivalence which is responsible for interfacial bonding. [2], [3], [4].

The first and most studied bioactive glass is Bioglass® 45S5 and was developed at the University of Florida by Hench. Bioglass® 45S5 has the following composition (in wt %): 45% SiO_2, 24.5% Na_2O, 24.4% CaO, and 6% P_2O_5. [5]

The chemical composition of Bioactive glasses is based in ternary and quaternary system (SiO_2-CaO-P_2O_5) and (SiO_2-CaO-Na_2O-P_2O_5) respectively. Glasses are based on silica (SiO_2), calcium oxide (CaO), sodium oxide (Na_2O), and phosphoric anhydride (P_2O_5) which may be added to other components for obtaining better chemical stability and desired properties.[6]

Generally, bioactive glasses can be made using two synthesis methods: the sol–gel synthesis and the traditional melt-quench. The process gives us excellent control of product purity and composition for the simple reason that we start with pure materials, it uses relatively low temperatures and it can create very fine powders. [6], [7]

Generally, sol–gel-derived glass, with its inherent mesoporosity, provides larger surface area and consequently more rapid degradation rate than melt-derived glass of similar composition [11],[12],[13].

It is convention to use the term "sol–gel", a "sol" is Colloidal particles or molecules are suspended in a liquid or solution, and the sol is mixed with another liquid, which causes formation of a continuous 3D network, a "gel".

The basic principle of the sol-gel process is thus the following: a basic precursor solution in liquid phase is transformed into a solid by a set of chemical reactions (1),(2),(3), (hydrolysis and condensation), usually at room temperature, where the term chemistry "soft".[11]

The basic chemical principle behind sol-gel processing of silica-based materials is the transformation of Si-OR- and Si-OH- containing species to siloxane compounds by condensation reactions. To obtain a stable gel, the number of siloxane bonds (Si-O-Si) has to be maximized and consequently the number of silanol (Si-OH) and alkoxo (Si-OR) groups has to be minimized. The reactions are written below in (1), (2), (3).

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$$\equiv Si{-}OR + H_2O \leftrightarrow \equiv Si{-}OH + ROH \quad (1)$$

Hydrolysis

Esterification

$$\equiv Si{-}OR + HO{-}Si\equiv \leftrightarrow \equiv Si{-}O{-}Si\equiv + ROH \quad (2)$$

Alcohol condensation

Alcoholysis

$$\equiv Si{-}OH + HO{-}Si\equiv \leftrightarrow \equiv Si{-}O{-}Si\equiv + H_2O$$

Water condensation

The most common precursors are aqueous soluti (3) of silicates ("water glass") Hydrolysis n alkoxides, $Si(OR)_4$, mostly tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS).

The most important parameters influencing hydrolysis and condensation[11] are : the kind of precursor(s), the pH (OH^- or H^+ catalysis), or other catalysts, the alkoxo group to water ratio for alkoxide precursors, the kind of solvent, the presence of electrolytes, and the temperature.

In the sol gel process of bioglass synthesis, many factors such as temperature, stirring speed, concentration of acid catalyst, basic catalyst and volume of alcohol influence the process efficiency. The process efficiency may be increased by the optimization of these factors. In conventional multifactor experiments, optimization is usually carried out by varying a single factor while keeping all the other factors fixed at a specific set of conditions. This method is time consuming, requires large number of experiments.

These limitations of a classical method can be eliminated by optimizing all the affecting parameters collectively by statistical experimental design such as response surface methodology (RSM). [12]

RSM is a collection of mathematical and statistical techniques useful for developing, improving and optimizing the process and can be used to evaluate the relative significance of several affecting factors even in the presence of complex interactions. The main objective of RSM is to determine the optimum operational conditions for the system or to determine a domain that satisfies the operating specifications. The application of statistical experimental design techniques in sol-gel process can result in limited gelation time, defined amount of catalyst, reduced process variability and improved product yields.

The purpose of this paper is to optimize and model the synthesis of bioglass using sol gel route by searching a possible optimum in the response surface.

In this work the relationship between the gelation time and five quantitative variables, Temperature, Stirring speed, Concentration of the acid catalyst, Addition time of the base, Amount of alcohol, are determined by a parabolic model for a set of experiments according to a fractional central composite design (CCD).

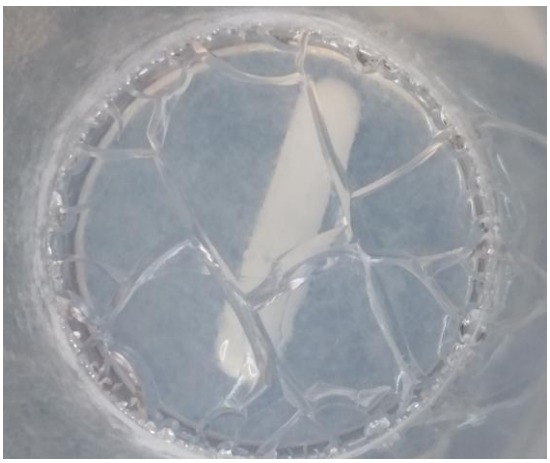
The Statistical calculations are done by using JMP (John's Macintosh Project) software. [13]

2. MATERIAL AND METHOD

A. *Sol–gel synthesis*

Sol–gel glasses were synthesized starting from tetraethyl orthosilicate (TEOS, $Si(OC_2H_5)_4$, Sigma Aldrich), Calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$, Sigma Aldrich) and triethyl phosphate (TEP, $C_6H_{15}O_4P$, Sigma Aldrich) as sources of SiO_2, CaO and P_2O_5 respectively. First, TEOS was added under stirring to a aqueous solution of chloride acid (HCl, 37%, Sigma–Aldrich), and ethanol (EtOH, 99.8% Sigma-Aldrich) respecting the molar ratio of (TEOS+TEP) /H2O was 1:4, the molar ratio of H_2O/EtOH was 1:1 and the amount of water was divided into acid and basic water respecting the ratio (0.8:0.2). After 30 min, TEP was added to the obtained solution. And then Calcium nitrate tetrahydrate solution was added after 30 min under stirring. All reactants were introduced in a container for hydrolysis and polycondensation and kept in different temperature and stirring speeds. After 1 hour of hydrolysis time, an aqueous basic Amonium solution was added to complete hydrolysis and starting gelation. Gelation time is defined as difference time between base addition time and gel formation.

The samples were left to gel at room temperature. The obtained gels appear transparent homogeneous and colorless us shown in the picture 1. Finally, gels were treated at 120°C for 1 day and then 750°C for 3 hours.



Picture 1: The obtained gel after gelation is completed

B. *Statistical analysis*

Modelization and optimization of the synthesis of bioglass using sol gel route is attained by using the RSM. A central composite design is used to study the empirical relationships between the response 'gel time' and five variables, Temperature, Stirring speed, Concentration of acid catalyst, Addition time of base, Amount of alcohol. Table 1 indicates the levels attributed to each variable.

International Journal of Engineering Research & Technology (IJERT)
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TABLE 1. THE CENTRAL COMPOSITE DESIGN PRESENTED ACCORDING TO THE STANDARD ORDER.

Order	Coded variables values				
Logical run	X_1	X_2	X_3	X_4	X_5
1	-	-	-	-	+
2	-	-	-	+	-
3	-	-	+	-	-
4	-	-	+	+	+
5	-	+	-	-	-
6	-	+	-	+	+
7	-	+	+	-	+
8	-	+	+	+	-
9	+	-	-	-	-
10	+	-	-	+	+
11	+	-	+	-	+
12	+	-	+	+	-
13	+	+	-	-	+
14	+	+	-	+	-
15	+	+	+	-	-
16	+	+	+	+	+
17	-1,3408	0	0	-	-
18	1,3408	0	0	-	-
19	0	-1,3408	0	-	+
20	0	1,3408	0	-	+
21	0	0	-1,3408	+	-
22	0	0	1,3408	+	-
23	0	0	0	+	+
24	0	0	0	+	+

1) Mathematical model

Sol gel process system behaves according to the following quadratic equation:

$$\eta = \beta_0 + \sum_{j=1}^{5} \beta_j X_J + \sum_{j=1}^{5} \sum_{j'=1, j \neq j'}^{5} \beta_{jj'} X_J X_{J'} + \sum_{j=1}^{3} \beta_{jj} X_j^2 \quad (4)$$

Where: theoretical response function; X_j: coded variables of the system; β_0, β_j, $\beta_{jj'}$ and β_{jj} : true model coefficients. The observed response y_i for the i^{th} experiment is $y_i = \eta_i + e_i$ (e_i: error).

i) The central composite design

Twenty four experiments are used to estimate the model coefficients. The corresponding five variables central composite design is given in Table 2. The variables are coded according to the following equation:

$$X_i = \frac{x_i - x_0}{\Delta x_i} \quad (5)$$

Where X_i is the dimension less value of an independent variable, x_i is the real value of an independent variable, x_0 is the value of x_i at the center point and Δx_i is the step range.

The 24 experiments can be divided into three groups as follows:

$N_F = 2^{5-1} = 16$ fractional factorial experiments carried out at the corners of the cube;

Na=2×3 = 6 axial experiments carried out on the axes at a distance of ±α from the center. The distance is calculated so as to obtain orthogonally so a five central composite design is orthogonal if: α = 1.3408

N_0 experiments are carried out at the center of the experimental domain. In our case, the N_0 value was fixed at 2 so as to obtain orthogonally properties.

ii) Validation of the model

The analysis of variance (ANOVA) is used to carry out the validation of the model. The model is considered adequate if the variance due to regression is significantly different from the total variance.

'JMP' software [13] is performed for regression and graphical analysis of data obtained. The optimum of studied parameters (Temperature, Stirring speed, Concentration of acid catalyst, Addition time of base, Amount of alcohol) is obtained by analyzing the response surface contour plots.

3. RESULT AND DISCUSSION

The most important parameters, which affect the gel time, are Temperature, Stirring speed, Concentration of acid catalyst, Addition time of base, Amount of alcohol. In order to study the combined effect of these factors, experiments are performed for different combinations of the physical parameters using statistically designed experiments. The Concentration of acid catalyst studied was between 0.0083 and 0.022M. The Addition time of base was between 10.74 and 44.26 min. The Amount of alcohol was between 8.376 and 16.82 ml. The temperature was varied between 25 and 50°C. The Stirring speed was varied between 400 and 600 rpm (table 2).

TABLE 2. NATURAL AND CODED VARIABLES

Natural variables (x_j)	Coded variables X_1, X_2, X_3, X_4, X_5				
	-1,3408	-1	0	1	1,3408
x_1=Concentration of the acid catalyst(M)	8,3 *10-3	0,01	0,015	0,02	0,022
x_2= Amount of alcohol(ml)	8,376	9,45	12,6	15,75	16,82
x_3= Addition time of base (min)	10,74	15	27,5	40	44,26
x_4= Temperature(°C)		25		50	
x_5= Stirring speed(rpm)		400		600	

The main effects of each of the parameter on gel time are given in Fig.1. It shows that the gel time depend on all parameters, in the first order gel time highly increases with increasing time adding base, this time correspond on hydrolysis, it means that gel time highly increases when hydrolysis reaction is completed, ammonia catalyze the condensation reaction. On the

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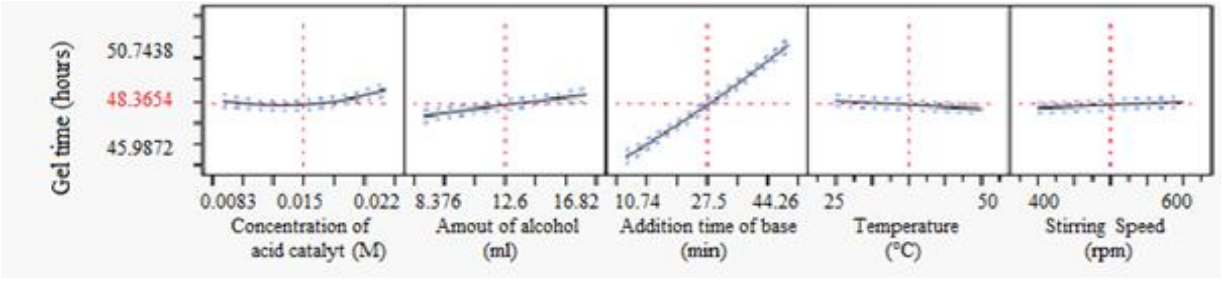

Fig 1. Main effects plot of parameters for gel time

other hand, gel time increases with increasing concentration of acid catalyst and the amount of alcohol (solvent), it means that acid catalyst and alcohol are effectives and hydrolysis is facilitated in the presence of homogenizing agents which are especially beneficial in promoting the hydrolysis of silanes and most rapid and complete when catalyst are employed. Then temperature and stirring speed affected gel time, temperature effect was negative but stirring speed effect was positive.

Table 3 shows the experimental results of gel time for the 24 experiments.

TABLE 3. THE EXPERIMENTAL DATA FOR GEL TIME (GT) ACCORDING TO CENTRAL COMPOSITE DESIGN

	Reponse Gt (hours)		
Logical run	Gt Experimental	Gt predicted	Standard error
1	33.33	32.615340616	0.5007153959
2	26.67	26.003252581	0.5007153959
3	70	69.334838327	0.5007153959
4	55	55.444500945	0.3435376332
5	31.67	31.02879431	0.5007153959
6	30	30.468456927	0.3435376332
7	80	79.912847683	0.5007153959
8	75	74.864935718	0.5007153959
9	28.33	28.14385226	0.5007153959
10	31.67	31.584403555	0.3435376332
11	76.67	75.929798887	0.5007153959
12	65	65.41898909	0.5007153959
13	41.67	42.112945073	0.5007153959
14	36.67	35.95375487	0.5007153959
15	71.67	72.063447362	0.5007153959
16	78.33	78.823998656	0.3435376332
17	51.67	52.972152698	0.918551206
18	50	49.796975044	0.918551206
19	48.33	49.779818901	0.918551206
20	58.33	57.979248841	0.918551206
21	21.67	23.048351173	0.918551206
22	75	74.720716569	0.918551206
23	46.67	45.589319958	1.1720982432
24	45.83	45.589319958	1.1720982432

The graph represented in Fig 2 shows the correlation between the model established and the values found experimentally, it's shown that the model established represent good the experience, so there is no statistically significant difference between values found by the experience and those calculated by the model and this is demonstrate by very high values of coefficient of determination (R^2=0.9986).

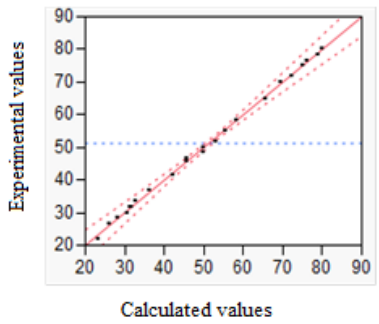

Fig 2 .Observed values of gel time function of the expected values

Using the experimental results, the regression model equations (second-order polynomial) was developed and given in (6). Apart from the linear parameter's effect for the response, the RSM also gives an insight into the quadratic and interaction parameter's effect. These analyses are done by means of Fisher's 'F' test and Student 't' test. The Fisher's 'F' test is used to determine the significance of each of the interaction among the variables, which in turns may indicate the patterns of the interactions among the variables. In general, the larger the magnitude of F, the smaller the value of P, the more significant is the corresponding coefficient term.

The regression coefficient, F and P values for all the linear, quadratic and interaction parameter's effects are given in table 4.

International Journal of Engineering Research & Technology (IJERT)
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Vol. 5 Issue 06, June-2016

TABLE 4. ESTIMATED REGRESSION COEFFICIENTS AND CORRESPONDING F AND P VALUES FOR GEL TIME.

Term	Coefficient	Sum of squares	F	P
constant	48.36549	—	—	<0.0001
X_1	1.8973889	66.5318	29.4631	0.0029
X_2	3.7971378	266.4582	117.9989	0.0001
X_3	19.61766	7112.3113	3149.6300	<0.0001
X_4	-2.036223	72.9738	32.3159	0.0023
X_5	1.5050267	39.8662	17.6544	0.0085
X_1*X_1	2.6326436	32.8558	14.5499	0.0124
X_1*X_2	-0.3125	1.5625	0.6919	0.4434
X_2*X_2	-0.1514	0.1087	0.0481	0.8350
X_1*X_3	-0.3125	1.5625	0.6919	0.4434
X_2*X_3	1.145	20.9764	9.2892	0.0285
X_3*X_3	1.0097768	4.8337	2.1406	0.2033
X_1*X_4	1.2276111	27.8508	12.3335	0.0171
X_2*X_4	1.4103622	36.7602	16.2790	0.0100
X_3*X_4	-0.79984	11.8229	5.2357	0.0708
X_1*X_5	1.8538611	63.5142	28.1267	0.0032
X_2*X_5	0.6708878	8.3179	3.6835	0.1130
X_3*X_5	-0.45141	3.7658	1.6677	0.2530
X_4*X_5	-2.244973	88.7030	39.2814	0.0015

It is observed that the coefficients for the linear effect of the factors Concentration of acid catalyst, Amount of alcohol, Temperature, Stirring speed are significant (P = 0.0029, P = 0.0001, P = 0.0023, P = 0.0085 respectively). And the linear effect of Addition time of base is highly significant (p<0.0001). However, the interaction parameter's effects which are significant are as follows:

Amount of alcohol─Addition time of base (P = 0.0285), Concentration of acid catalyst─Temperature (P = 0.0171), Amount of alcohol─Temperature (P = 0.0100), Concentration of acid catalyst─Stirring speed (P = 0.0032), Temperature─ Stirring speed (P = 0.0015).

The coefficient of the quadratic effect of Concentration of acid catalyst is significant (P = 0.0124), all the coefficient of the quadratic effect of other variables are not significant Amount of alcohol, and Addition time of base, (P = 0.8350), (P = 0.2033) respectively.

Table 5 shows estimated regression coefficients sorted in ascending order.

TABLE 5. ESTIMATED REGRESSION COEFFICIENTS SORTED IN ASCENDING ORDER

Term	Coefficient	Standard error	t	P	Pareto diagram
X_3	19.61766	0.349557	56.12	<0.0001	
X_2	3.7971378	0.349557	10.86	0.0001	
X_4*X_5	-2.244973	0.358193	-6.27	0.0015	
X_4	-2.036223	0.358193	-5.68	0.0023	
X_1	1.8973889	0.349557	5.43	0.0029	
X_1*X_5	1.8538611	0.349557	5.3	0.0032	
X_5	1.5050267	0.358193	4.2	0.0085	
X_2*X_4	1.4103622	0.349557	1.03	0.01	
X_1*X_1	2.6326436	0.690178	3.81	0.0124	
X_1*X_4	1.2276111	0.349557	3.51	0.0171	
X_2*X_3	1.145	0.375678	3.05	0.0285	
X_3*X_4	-0.79984	0.349557	-2.29	0.0708	
X_2*X_5	0.6708878	0.349557	1.92	0.113	
X_3*X_3	1.0097768	0.690178	1.46	0.2033	
X_3*X_5	-0.45141	0.349557	-1.29	0.253	
X_1*X_2	-0.3125	0.375678	-0.83	0.4434	
X_1*X_3	-0.3125	0.375678	-0.83	0.4434	
X_2*X_2	-0.1514	0.690178	-0.22	0.835	

Consequently, for the level of significance of 95%, the response function model (6) is written as follows:

$$\eta = 48.365 + 1.897\ X_1 + 3.797X_2 + 19.618X_3 - 2.036X_4 + 1.505X_5 + 1.145\ X_2X_3 + 1.227X_1X_4 + 1.410X_2X_4 + 1.854\ X_1X_5 - 2.245\ X_4X_5 + 2.632\ X_1^2 \quad (6)$$

The statistical significance of the ratio of mean square variation due to regression and mean square residual error is tested using ANOVA. ANOVA is a statistical technique that subdivides the total variation in a set of data into component parts associated with specific sources of variation for the model. According to the ANOVA, as shown in Table 6, the $F_{statistics}$ values for all regression are higher. The large value of F indicates that most of the variation in the response can be explained by the regression equation. The associated P value is used to estimate whether $F_{statistics}$ is large enough to indicate statistical significance. A P value lower than 0.05 indicates that the model is considered to be statistically significant. This means that at least one of the terms in the regression equation have a significant correlation with the response variable. The ANOVA table also shows a term for residual error, which measures the amount of variation in the response data left unexplained by the model. The form of the model chosen to explain the relationship between the factors and the response is correct.

TABLE 6. REGRESSION VARIANCE ANALYSIS FOR GEL TIME

	Degree of freedom	Sum of squares	Mean square	$F_{statistics}$	P
Model	18	8253.5537	458.531	203.0567	<0.0001
Residual	5	11.2907	2.258	-	
Total	23	8264.8444			

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Further, the ANOVA for Gel time indicates that the second-order polynomial model (4), is highly significant and adequate to represent the actual relation-ship between the response and variables, with very small values $P < 0.0001$ and a high value of coefficient of determination (R^2=0.9986). This implies that 99.86% of sample variation for gel time is explained by the model.

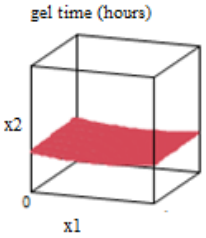

Fig 3. Response surface plot of gel time at fixed values of Addition time of base x_3=13.6975 min, Temperature x_4= 25°C, and Stirring speed x_5= 402 rpm.

The 3D response surface and 2D contour plot are generally the graphical representation of the regression equation. This representation shows the relative effects of any two variables when the remaining variables are kept constant. We will use it to search the optimal values of the process parameters: minimum gel time. Then, the response surface plots and contour plots to estimate the gel time are given in Fig. 3, it shows the interaction effect of Concentration of acide and the Amount of alcohol, at fixed values of Addition time of base x_3=13.6975 min, Temperature x_4= 25°C, and Stirring speed x_5= 402(rpm).

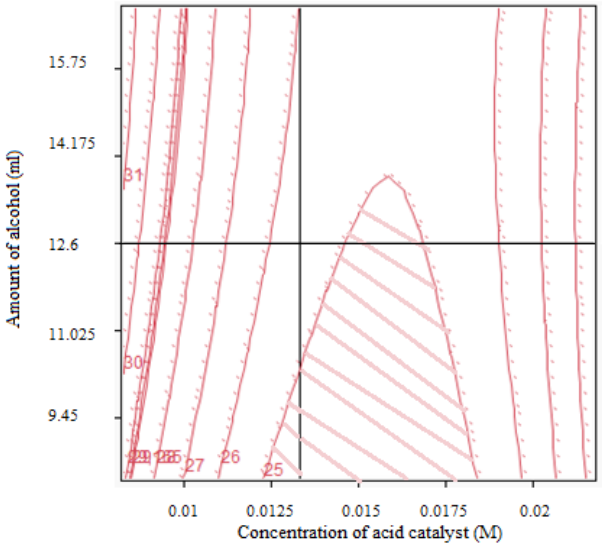

Fig 4 Isoresponse contour plot for gel time at fixed values of Addition time of base x_3=13.6975 min, Temperature x_4= 25°C, and Stirring speed x_5= 402 rpm.

The representation of the gel time response for variables x_1 and x_2 as isoresponse contour plot (fig 4) shows at fixed concentration of acide, the gel time increases when the amount of alcohol increase, and an optimum is observed which correspond to 25 hours for gel time, this optimum is obtained for concentration of acide varied between x_1[0.0125; 0.0175] (M) and amount of alcohol varied between x_2 [9.45; 14.175] (ml).

From these, optimal conditions are obtained to get minimum gel time and are given in Table 7.

TABLE 7. OPTIMAL CONDITIONS TO OBTAIN OPTIMUM GEL TIME

Parameter	optimum values
x_1=Concentration of the acid catalyst	0.0125 - 0.0175
x_2= Amount of alcohol	9,45 - 14,175
x_3= Addition time of base	13,6975
x_4= Temperature	25
x_5= Stirring speed	402

4. CONCLUSION

In this paper, a mathematical model describing sol gel synthesis was fined by statistical experimental design, in this study the response surface methodology (RSM) was used, this allows to defined optimal operating conditions to get bioglass by the way of sol gel in short gel time. The aim of this work was attended using composite central design which the response was gel time and operating conditions were Temperature, Stirring speed, Concentration of the acid catalyst, addition time of the base and amount of alcohol. So to get optimum gel time sol gel synthesis must unroll in optimal conditions previously determined.

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