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Short Communication

Application of orthogonal experimental design in synthesis of mesoporous bioactive glass

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ABSTRACT

An orthogonal experimental design method combining with quantitive analysis of small-angle X-ray scattering (SAXS) pattern was applied to optimize the synthesis of bioactive glasses with highly ordered mesoporous structure (MBGs). The quantitive analysis of SAXS pattern allows a quantified evaluation of the ordering of the mesoporous structure, which makes it possible to tailoring the mesoporous structure of the MBGs with complex component by a traditional orthogonal experimental design method. The number of trials for preparing MBGs can be greatly reduced and the primary factors affecting the formation of mesoporous structure and the properties of MBGs can be easily found out by this orthogonal experimental design method. MBGs containing SiO_2, CaO, Fe_2O_3 were prepared as an example to present the way to obtain optimized ordered mesoporous structure. It confirmed that Fe_2O_3 was the primary factor influencing the mesoporous structure of the MBGs. The ordering of the mesopores increased in the first and then decreased with the increase of F127 content.

1. Introduction

Since the first report of 45S5 [1], MBGs have exhibited more superior bone-forming bioactivities in vitro than solid bioactive glasses (BGs) [2], and have been proposed potential materials for making implants with local drug delivery function [3–5]. The ordered mesoporous structure within MBGs could be obtained by using nonionic block copolymers as structure-directing agents and through an evaporation-induced self-assembly (EISA) process. Synthesis of MBGs containing ions is becoming a frontier research of biomaterialists because it has been confirmed that the addition of some ions into solid BGs can improve the properties of BGs or enable them to have additional functions [6–8]. For instance, the addition of MgO in BGs has been confirmed inducing formation of whitelockite-like phase in the formed biomimetic layer on BGs, thus affecting cell behavior on the scaffold surface and bonding to natural tissues [9–11]. In another report, an ordered mesoporous calcium–magnesium silicate showed better bioactivity than calcium–magnesium silicate [12]. BGs scaffolds containing silver showed important local antibacterial property [13,14]. Inducing Zn^{2+} and Sr^{2+} into BGs can improve the bioactive property significantly [15–17]. MBGs incorporated with Co^{2+} showed enhanced vascular endothelial growth factor secretion, HIF-1α expression and bone related gene expression of human bone marrow stromal cells [18]. However, because MBGs are complicated multicomponent systems, the species and contents of components composed of MBGs can strongly influence the formation of ordered mesoporous structure. For example, a decrease of a specific area and a progressive change of the mesoporous structure was observed when silver was added into a SiO_2–CaO–P_2O_5 ternary system [19]. To prepare a highly ordered mesoporous structure, vast quantities of experiments could be necessary. In a typical case, in order to synthesize a MBG containing SiO_2, CaO, P_2O_5 and Na_2O with a triblock copolymer template F127, five factors in total, taking account of three levels of each factor, 243 (3^5) trials are necessary, which could be a tedious task difficult to be carried out.

The orthogonal experimental design method is a highly efficient way capable of dealing with multifactor experiments and screening optimum levels by using the orthogonal design table. Before making an orthogonal design table, reasonable and representative levels of all factors are determined at first according to theories or a few experimnents. And then experiments represent all the level groups of the experimental factors are performed. Positive and negative factors and their impact degrees (ID) to the objective of production are revealed by calculating the experimental results, e.g. conversion and yield. The possible optimum level can be concluded according to the impact of the factors. At last, a confirmatory experiment is performed following the concluded optimum level. For example, for an experiment with four factors and four

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levels of each factor, an orthogonal design table $L_{16}(4^4)$ could be used, and the experiment program only contains 16 level groups, reflecting the overall situation of the comprehensive experiment containing 256 level groups in all. Thus it is much easier to find out the optimum level group.

This paper is aiming at designing an efficient way to find out the primary factors influencing the formation of MBGs and determine the optimum synthesis formula of the MBGs with complicated multicomponent. We speculate that this aim could be easily realized through the combination of an orthogonal experimental design method and the quantitive analysis of SAXS patterns. MBGs containing SiO_2, CaO, Fe_2O_3 were synthesized through an EISA process and as an example to present the way to obtain an optimized ordered mesoporous structure.

2. Experimental

2.1. Materials

Most raw materials, tetraethyl orthosilicate (TEOS), calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$), ferric nitrate nonahydrate ($Fe(NO_3)_3{\cdot}9H_2O$), nitric acid (HNO_3, 16M), anhydrous ethanol (EtOH), purchased from Sinopharm Chemical Reagent Co., Ltd., were all of analytical grade and used directly without further purification. Nonionic triblock copolymer $PEO_{106}PPO_{70}PEO_{106}$ (F127, PEO is poly(ethylene oxide), PPO is poly(propylene oxide)) was purchased from Sigma–Aldrich. Deionized water was obtained from Millipore water purification system.

Table 1
The factors and levels of the 16 MBGs formulas.

Level *i*	Factors			
	TEOS A/mol	$Ca(NO_3)_2{\cdot}4H_2O$ B/mol	$Fe(NO_3)_3{\cdot}9H_2O$ C/mol	F127 D/g
1	0.012	0.005	0.0015	3.0
2	0.013	0.006	0.0020	3.6
3	0.014	0.007	0.0025	4.2
4	0.015	0.008	0.0030	4.8

2.2. Preparation of MBGs

In this paper, mesoporous SiO_2–CaO–Fe_2O_3 bioactive glasses were synthesized by using nonionic triblock copolymer PEO_{106}-$PPO_{70}PEO_{106}$ (F127) as a structure-directing agent through an evaporation-induced self-assembly (EISA) process according to Zhao's method [2]. In a typical synthesis procedure of MBGs, tetraethyl orthosilicate (TEOS, 2.7 g), $Ca(NO_3)_2{\cdot}4H_2O$ (1.18 g), $Fe(NO_3)_3{\cdot}9H_2O$ (0.8 g; Si/Ca/Fe = 65:25:10, molar ratio), F127 (4.2 g) and 2 M HNO_3 (0.08 g) were dissolved in ethanol (8 g) and stirred at room temperature for 2 h. The resulting sol was put into a drying oven to undergo an EISA process at 40 °C. The dried gel was calcined at 600 °C for 3 h to obtain the final MBGs (denoted 65S25C according to the molar fraction of Si and Ca). The formed MBGs were mechanically grinded into powder.

2.3. Orthogonal experimental design

Mesoporous SiO_2–CaO–Fe_2O_3 BGs specimens with different molar ratios were obtained by varying the masses of tetraethyl orthosilicate (TEOS), $Ca(NO_3)_2{\cdot}4H_2O$ F127 and $Fe(NO_3)_3{\cdot}9H_2O$. Here, an orthogonal experimental design method was applied to discuss the ID of TEOS, $Ca(NO_3)_2{\cdot}4H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$ and F127 to the mesoporous structure of MBGs for selecting the optimium formula. TEOS, $Ca(NO_3)_2{\cdot}4H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$ and F127 were determined as four factors of the orthogonal experiment and each factor had four levels, as shown in Table 1. It was assumed that any two factors did not interact with each other. The orthogonal array of the 16 MBGs samples is shown in Table 2, designed according to the orthogonal design table $L_{16}(4^4)$. The four ordered degree values (OD) of each factor in the same level *i* were summed, and the corresponding average value k_i and range *R* were calculated respectively as follows:

$$K_i = \frac{\sum OD_i}{4} \quad (1)$$

$$R = k_{max} - k_{min} \quad (2)$$

k_i represents the impact of level *i* of each factor to the mesoporous structure of the MBGs (*i* = 1, 2, 3, 4). The higher the k_i is, the better

Table 2
The pore ordered degree evaluation of the 16 MBGs samples.

Exp. number	TEOS A/mol	$Ca(NO_3)_2{\cdot}4H_2O$ B/mol	$Fe(NO_3)3{\cdot}9H_2O$ C/mol	F127 D/g	PO	OD
1	0.012	0.005	0.0015	3.0	3224.88	98.35
2	0.012	0.006	0.0020	3.6	762.11	23.24
3	0.012	0.007	0.0025	4.2	471.70	14.39
4	0.012	0.008	0.0030	4.8	230.90	7.04
5	0.013	0.005	0.0020	4.2	295.65	9.02
6	0.013	0.006	0.0015	4.8	1102.68	33.63
7	0.013	0.007	0.0030	3.0	301.99	9.21
8	0.013	0.008	0.0025	3.6	462.44	14.10
9	0.014	0.005	0.0025	4.8	1084.11	33.06
10	0.014	0.006	0.0030	4.2	479.64	14.63
11	0.014	0.007	0.0015	3.6	3279.07	100.00
12	0.014	0.008	0.0020	3.0	462.93	14.12
13	0.015	0.005	0.0030	3.6	2302.56	70.22
14	0.015	0.006	0.0025	3.0	1215.96	37.08
15	0.015	0.007	0.0020	4.8	1413.93	43.12
16	0.015	0.008	0.0015	4.2	1905.35	58.11
k_1	35.75	52.66	72.52	41.20		
k_2	16.49	27.14	22.37	48.86		
k_3	40.45	41.68	24.66	27.06		
k_4	52.13	23.34	25.27	27.70		
R	35.64	29.32	50.15	21.80		
ID of factors		$Fe(NO_3)_3{\cdot}9H_2O$ > TEOS > $Ca(NO_3)_2{\cdot}4H_2O$ > F127				
Best level of factors		TEOS(0.015), $Ca(NO_3)_2{\cdot}4H_2O$(0.005), $Fe(NO_3)_3{\cdot}9H_2O$(0.0015), F127(3.6)				
Optimum group		TEOS(0.015)-$Ca(NO_3)_2{\cdot}4H_2O$(0.005)-$Fe(NO_3)_3{\cdot}9H_2O$(0.0015)-F127(3.6)				