Nest-like $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ microspheres with hierarchical porous structure for drug delivery

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Abstract

Recent years a surge has been seen in magnetic nanoparticles applications in several areas, particularly in biomedical field. The promising features of the iron oxide based magnetic nanoparticles make them an ideal tool for MRI contrast agents, hyperthermia, and as drug delivery systems (DDS). The present paper describes the design and synthesis of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanostructured meso-macroporous spherical aggregates by sol-gel method via spray drying technique. The obtained spherical aggregates have micrometric size, which let them to be carried by the bloodstream to a specific site where the drug is going to be release. The obtained hierarchical porous structure combined with the interconnected mesoporosity allow the body fluids to be transport through the aggregates; and the macroporosity allows the load of large molecules, like peptides. Furthermore, the structural and morphological characterization of the obtained $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates were carried out using X-ray diffraction and field emission scanning electron microscopy.

Keywords: Nest-like morphology, hierarchical porous structure, drug delivery, barium hexaferrite.

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1. Introduction

Recent years a surge has been seen in magnetic nanoparticles applications in several areas such as microelectronics, optoelectronics, physics, chemistry, biology, and materials science, but particularly in biomedical field [1-10]. Several sorts of magnetic nanoparticles have been widely investigated for biomedical applications, among which iron oxide-based magnetic nanoparticles are very promising candidates due to their unique features like biocompatibility, large surface area and superparamagnetic behavior that make them an ideal tool for cell separation, magnetic resonance imaging (MRI) [11-12], cancer treatment by hyperthermia [13-15] drug delivery systems (DDS) [16, 17]. In all these applications it is necessary to maintain the nanostructure of the individual particles in order to preserve the superparamagnetic behavior. This work is focusing on the design and synthesis of meso-macroporous aggregates made from barium hexagonal ferrites ($\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$) to be applied as DDS. The motivation scheme above mentioned is because of the need to create a DDS that can deliver anticancer drugs at specific sites in a spatiotemporal manner, namely, at particular times and rates. A variety of methods have been reported in the literature on the synthesis of magnetic nanoparticles, such as the chemical co-precipitation, the hydrolysis, the thermal decomposition and the sol-gel technique [18]. We carried out the synthesis of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanostructured meso-macroporous spherical aggregates (hereinafter called $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates) by the sol-gel method combined with spray drying technique. Sol-gel

processing has many advantages, it is an easy and inexpensive method and very pure products are obtained. Size and shape of the particles can be easily controlled. Moreover, the spray drying process has been successfully used to produce porous materials with a spherical shape and a controlled agglomerate size. Great effort is also devoted to characterization, understanding, and improvement of the structural properties of the nanostructured materials. In this work, the design of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates has been developed using self-assembly techniques with surfactant Tween-20 as structure directing agent, and polystyrene (PS) templates. This combination of additives is used in order to obtain the hierarchical meso-macroporous structure. A 2f-factorial experimental design was applied to this research in order to obtain the best synthesis and processing conditions that ensure the formation of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates that allow the load of specific peptides based anticancer drugs.

2. Materials and experimental procedure

Chemical reagents used for the synthesis of barium hexagonal ferrites were reagent-grade chemicals that were used without further purification: iron (III) nitrate nonahydrate ($\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$), barium carbonate (BaCO_3), ammonium hydroxide (NH_4OH) and Tween-20 ($\text{C}_{58}\text{H}_{114}\text{O}_{26}$) as surfactant. Chemicals used for the synthesis of PS spheres were styrene (monomer, $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$) and ammonium persulfate ($(\text{NH}_4)_2\text{S}_2\text{O}_8$). All reagents were provided by Aldrich. Deionized water was used for all the experiments.

2.1 Polystyrene (PS) synthesis

Polystyrene spheres (0.2 microns mean size) were used as pore forming agent (template) in order to obtain macroporous-nanostructured aggregates. The PS spheres were synthesized by our working group. Briefly, the monodisperse PS spheres were synthesized via polymerization. Previously, the styrene monomer was washed with a 1 M sodium hydroxide (NaOH) solution. It was used with a 0.125-wt% ratio for monomer/water. Reaction was carried out under temperature and constant stirring, 60 °C and 300 rpm, respectively. The whole process was taken in 24 hours.

2.2 Design of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates.

A 2^6 -factorial experimental design was used in order to design the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates. The design allowed to evaluate the effect of parameters such as the inlet air pressure (P, Kg/cm²) and inlet temperature (T, °C) into the spray dryer equipment as well as the template concentration (%) in order to evaluate the pore volume and size of the aggregates obtained in the spray drying process. Table 1 shows the above factors to evaluate the effect on the pore volume and size of the porous nanostructured aggregates. In the 23-factorial design each factor has two levels: low (-) and high (+). Then a set of eight experiments was performed.

Experiment	Factor						Average diameter (μm)	Pore volume (cm³/g)	Specific surface area
	A Pressure (P, Kg/cm²)		B Inlet temperature (T, °C)		C Template concentration (% PS)				
	Low (-)	High (+)	Low (-)	High (+)	Low (-)	High (+)			
	1.5	2	180	200	30	50			
1	1.5		180		30		1.69	0.0743	14.94
2	1.5		200		30		1.73	0.0639	13.26
3	2.0		180		30		1.71	0.1686	20.42
4	2.0		200		30		1.58	0.0238	16.11
5	1.5		180		50		1.50	0.0463	13.61
6	1.5		200		50		1.64	0.0085	10.86
7	2.0		180		50		1.72	0.1015	7.210
8	2.0		200		50		1.73	0.0143	18.92

Table 1 Variation levels of the studied parameters and conditions, and the obtained values of the response variables: aggregate average diameter, mesopore volume and specific surface area for the prepared $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates.

1. táblázat A vizsgált paraméterek, a vizsgálati körülmények változékonysága, és a kifejlesztett $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ termék jellemzői: átlagos szemecske átmérő, mezopórus térfogat és fajlagos felület.

2.3 Synthesis of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates

$\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates were synthesized by sol-gel method via spray drying (Mini-Spray Dryer ADL31 Yamato). The former reagents for the synthesis of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ [$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (21 mM) + BaCO_3 (1.5 mM)] were dissolved in an aqueous solution with constant stirring for 30 min. At the same time, but separately, Tween-20 (2g/l) was dispersed in deionized water under the same conditions. Both solutions were mixed and kept again under constant stirring for 30 min. The pH value for the obtained suspension was fixed at pH 8, in accordance with a previous study. The mixture was kept under magnetic stirring for 6 h. Next, the solution was mixed homogeneously with PS spheres suspension according to the 23-factorial design and kept under magnetic stirring for 1 hour. The resulting suspension was fed to the spray dryer using the experimental design variables. The obtained aggregates were calcined at 700 °C.

2.4 Characterization

X-ray diffraction (XRD, SIEMENS D-5000) with a Cu K α radiation (45 KV, 30 mA) was used to determine the crystal structure. Scans were taken from 10° to 80° (2 θ) with a constant step width of 0.02°. Scanning electron microscopy was carried out to analyze the microstructural characterization and morphology of the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$. The SEM images were recorded in a field-emission scanning electron microscope JEOL JSM-7600. N₂ adsorption/desorption isotherms at 77 K were recorded on a Quantachrome instrument. Prior to analysis, samples (0.14 - 0.38 g) were filled in a tube under N₂ atmosphere and then outgassed for 4 h at 100 °C. In addition, the mesopore size distribution was measured by the Barrett-Joyner-Halenda (BJH) technique. The magnetic behavior of the sample calcined at 700°C was carried out at room temperature applying a constant magnetic field of 5000 Oe. The hysteresis loop was recorded in a vibrating sample magnetometer (VSM LDJ 9600). From the hysteresis loop the values for the magnetic saturation (M_s), remnant magnetization (M_r) and coercivity (H_c) were obtained.

3. Results and discussion

Table 1 shows the overall of 8 experiments carried out when used a 23-factorial design and the obtained values for the pore volume and main agglomerates size for all the experiments. Therefore, having an effect about the pore volume and size of the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates. Average diameters of the obtained aggregates after the spray drying process and calcined at 700 °C ranged from 1.50 to 1.73 μm. Superparamagnetic iron oxide nanostructured particles ranging from 2.9 nm up to 3.5 μm have been synthesized by various authors. Most of applications are size-dependent. We have chosen to synthesize $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates of micron size in order to increase the payload on the DDS, assuring the stability of the aggregates during its transport in the bloodstream. Moreover, we have taken in account that the larger aggregate obtained here is capable of being injected even in the capillaries (measuring around 5 to 10 micrometers).

ANOVA								
Factor	Degrees of freedom (DF)	Aggregate average diameter			Mesopore Volume			F _T
		Sum os squares (SS)	Mean square (MS)	Distribution F(F ₀)-value	Sum of squares (SS)	Mean square (MS)	Distribution F(F ₀)-value	
A	1	0.49	0.0150	5.74	-0.79	0.063	8.66	5.32
B	1	0.39	0.0095	3.63	-0.50	0.168	3.98	
AB	1	-0.35	0.0076	2.93	0.35	0.023	1.74	
C	1	-0.05	0.0001	0.05	0.46	0.049	2.98	
AC	1	0.15	0.0014	0.53	-0.65	0.008	5.81	
BC	1	0.31	0.0060	2.29	-0.66	0.101	6.02	
ABC	1	0.17	0.0018	0.69	0.59	0.014	4.79	
ERROR	8	0.041	0.0026		0.073	0.0046		
TOTAL	15	0.083			0.227			

Table 2 Analysis of variance of aggregate average diameter and mesopore volume for the prepared $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates
2. táblázat A kifejlesztett $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ termék átlagos szemcse átmérőjének és mezopórus térfogatának változékonysági vizsgálata.

Statistical analysis of variance (ANOVA) was conducted in order to establish which factors aforementioned affected the aggregate size and the mesopore volume of the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$. According to the ANOVA in Table 2 which analyzes the average aggregate diameter, the only factor that has a significant effect on the aggregate size is pressure. While a minimum effect may be given for the temperature or by the combination of the pressure-temperature and temperature-temperature. On the other hand, the ANOVA analysis shows that the factor that have a significant effect on the mesopore volume is the pressure alone, in addition to the pressure-temperature and the temperature-temperature interaction.

The X-ray diffraction (XRD) pattern of the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates is shown in Fig. 1a. In a previous study we carried out a thermal analysis in order to determine the optimal temperature to which the pursued hexagonal phase was obtained. The study was performed from 500 up to 1200 °C. Here, we present only XRD pattern of the sample calcined at 700 °C. Scans were made from 10° to 80° (2 θ) with a constant step width of 0.02°. The XRD pattern presents three phases, which were identified by using the following Open Database Crystallography, COD cards: the hexaferrite- $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ hexagonal (H), COD card No. 1008841; the monoferrite- BaFe_2O_4 orthorhombic (O), COD card No. 4107896; and the magnetite- Fe_2O_3 Hexagonal (F), COD card No. 9015964. The relative intensity of the BaFe_2O_4 peaks was found to decrease with increasing the temperature. Fig. 1b and Fig. 1c shows representative images of scanning electron microscopy (SEM). The images were taken by secondary electrons (SE) at 5.0 KV. It is seen that porous-nanostructured aggregates are made from $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ with a spherical shape. The aggregates were ~1.7 μm average of diameter. A magnification at 15 000 X is presented in the insert of Fig. 1b and Fig. 1c, where the macroporosity of the nanostructured aggregates of $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ is clearly seen, as a result of the pyrolysis from the PS spheres after being calcined at 700 °C. Moreover, it is seen that a homogeneous-spherical morphology with a 200 nm average macropore size has been formed. Therefore, they fall in the classification of macroporous materials according to the IUPAC. As mentioned earlier, due to the 2³-factorial design, a set of eight experiments was performed. All samples had a similar structure and

morphology, therefore, only the representative images for each of the polystyrene concentrations, 30 and 50-wt%, respectively, are shown. Sample in Fig. 1b was synthesized with an inlet temperature at 200 °C and a pressure at 2 Kg/cm² corresponding to the parameters on the spray drying, and a concentration of polystyrene spheres of 50-wt%. Sample in Fig. 1c was synthesized with an inlet temperature at 180 °C and a pressure at 1.5 Kg/cm² corresponding to the parameters on the spray drying, and a concentration of polystyrene spheres of 30-wt%. The main difference between images of Fig. 1b and Fig. 1c is the pore distribution. A variety of different morphologies have been reported on the literature. For instance, Kikuo Okuyama and coworkers [19] have reported completely spherical dense particles, small rough spherical dense particles, highly rough spherical dense particles, hollow particles, doughnut particles, porous particles, encapsulated particles, mixed particles and hairy particles. Oka Chiemi and coworkers have reported the synthesis of core-shell composite particles [10], and other morphologies such as nanowires, nanorods, nanoworms, nanotubes and so on have been reported in the literature. We have obtained meso-macroporous $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanostructured aggregates with a spherical shape. An advantage of the spherical-shape particles is their practical importance owing to their rheological properties as compared with other morphologies. For example, when on vessels, the flow of the spherical-shape nanoparticles on bloodstream is improved. The morphology of the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanoparticles is elongated fiber-like crosslinked forming a nest-like structure.

Fig. 2 shows the adsorption/desorption isotherms for the samples calcined at 700 °C having template concentrations of 30 and 50 wt%, respectively. Sample in Fig. 2a was synthesized with an inlet temperature at 200 °C and a pressure at 2 Kg/cm² corresponding to the parameters on the spray drying, and a concentration of polystyrene spheres of 50-wt%. Sample in Fig. 2b was synthesized with an inlet temperature at 180 °C and a pressure at 1.5 Kg/cm² corresponding to the parameters on the spray drying, and a concentration of polystyrene spheres of 30-wt%. According to BET classification, the isotherms correspond to a typical type II isotherm. The specific surface areas from the $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates range from 7.21 to 20.42 m²/g.

Fig. 1 Structural and morphological characterization of the BaO-6Fe₂O₃ aggregates calcined at 700 °C showing a) XRD patterns having the phases: hexaferrite-BaO-6Fe₂O₃ hexagonal (H), monoferrite-BaFe₂O₄ orthorhombic (O), and the magnetite-Fe₃O₄ hexagonal (F); and SEM images of the BaO-6Fe₂O₃ with b) 50% of PS spheres and c) 30% of PS spheres.

1. ábra A 700 °C hőmérsékleten kalcinált BaO-6Fe₂O₃ szemcsék szerkezeti és morfológiai jellemzői a) röntgendiffraktogrammal: hexagonális hexaferrit-BaO-6Fe₂O₃ (H), ortorombos monoferrit-BaFe₂O₄ (O), és hexagonális magnetit-Fe₃O₄ (F); és pásztázó elektronmikroszkopos felvételek b) 50% PS gömbökkel és c) 30% PS gömbökkel.

Due to the magnetic properties of the iron oxide-based nanostructured systems, in biomedical applications such as drug delivery systems, these materials can benefit from the application of an external magnetic field in order to delivering and targeting a drug to a specific site of action. In order to maintain the magnetic properties that characterize these materials, which are necessary for such applications, the BaO-6Fe₂O₃ aggregates obtained here were calcined at 700 °C to analyze their magnetic behavior using VSM. Fig. 3 shows the hysteresis loop from which the values of magnetic saturation (M_s), remnant magnetization (M_r) and coercivity (H_c) were calculated. The obtained values were $M_s = 14.24$ emu/g, $M_r =$

5.93 emu/g and $H_c = 194.65$ Oe, respectively, which represent a low semi-hard magnetic behavior in which the nanoparticle aggregates can be still safely used for DDS.

Fig. 2 Adsorption/desorption isotherm plot for the BaO-6Fe₂O₃ aggregates, relative pressure (P/P_0) as a function of N₂ volume adsorbed (cm³/g) at STP.

2. ábra A kifejlesztett BaO-6Fe₂O₃ szemcsék adszorpció/desorpció izotermái.

Fig. 3 Hysteresis loop from the BaO-6Fe₂O₃ aggregates calcined at 700 °C.

3. ábra Hízterézis hurok illusztrációja 700 °C hőmérsékleten kalcinált BaO-6Fe₂O₃ szemcsékhez.

4. Conclusions

Design and synthesis of BaO-6Fe₂O₃ nanostructured meso-macroporous spherical aggregates was possible through a 2³-factorial design by using a sol-gel method via spray drying. A number of three factors were evaluated including the pressure and the inlet temperature corresponding to the spray drying process as

well as the template concentration on the wet chemical synthesis. Evaluation through an analysis of variance (ANOVA) showed that not only the individual factors including the PS concentration and the pressure corresponding to the spray drying process affected the morphology and the size of the meso-macroporous $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ aggregates, but the interaction between the pressure and the inlet temperature as well. Meso-macroporous- $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanostructured spherical-shape aggregates with a diameter of $1.7 \mu\text{m}$ were obtained. The spherical-shape was confirmed by scanning electron microscopy. Characterization of meso-macroporous $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nanostructured systems shows that the formulation used here, as well as parameters involved in the sol-gel method via spray drying can be used as a good approach in order to synthesize effective magnetic nanoparticles conforming micrometric spherical aggregates with meso-macroporous structure for the load of large molecules like peptides to be used as drug delivery systems.

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Torres-Cadenas, S. – Bravo-Patiño, A. – Zarate-Medina, J. – Contreras-García, M. E.: Nest-like $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ microspheres with hierarchical porous structure for drug delivery
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Hierarchikus pórusszerkezetű $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ mikrogömb szemcsék fejlesztése gyógyhatóanyag közvetítéséhez
A mágneses tulajdonságú nano-részecskék alkalmazási lehetőségeinek kutatása fokozódik napjainkban, különösen a gyógyászati területen. A vasoxid bázisú mágnesezhető nano-részecskék ideálisak MRI kontrasztanyagként vagy gyógyhatóanyag továbbítására. A cikk bemutatja a hierarchikus pórusszerkezetű $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ mikrogömb szemcsék fejlesztését szol-gél módszerrel. A kifejlesztett, gömb alakú aggregátum mikro-méretű szemek halmaza, amely a véráramban könnyen mozgatható és ezáltal a gyógyhatóanyag meghatározott helyre továbbítható bennük. A hierarchikus pórusszerkezet az összekapcsolódó mezopórusok révén lehetővé teszi nagyméretű molekulák pl. peptidok szállítását és lehetőséget biztosít a testfolyadékok általi kimosásukra. A kifejlesztett $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ nano-részecskék jellemzőit és hatékonyságát röntgendiffrakciós és pásztázó elektronmikroszkópos vizsgálatok eredményeivel illusztrálják a szerzők.

Kulcsszavak: fészekszerű morfológia, hierarchikus pórus szerkezet, gyógyhatóanyag továbbítás, barium-hexaferrit.