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$BaO{\cdot}6Fe_2O_3$ as DDS using tetracycline as model drug

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Abstract: - This paper focuses on the loading and release studies of tetracycline as model drug from spherical aggregates of micron size (approx. 1.2 μm in diameter) of barium hexaferrite ($BaO{\cdot}6Fe_2O_3$) synthetized from wet chemical sol-gel method via spray drying. $BaO{\cdot}6Fe_2O_3$ aggregates were characterized using x-ray diffraction and scanning electron microscopy. The load capacity of $BaO{\cdot}6Fe_2O_3$ systems was reached at 40 minutes after contact with tetracycline drug. Release of tetracycline was confirm from *E. coli* bacterial death when $BaO{\cdot}6Fe_2O_3$ particles were in contact with the bacteria.

Keywords: - *Barium Hexaferrite, Drug Delivery System, Sol-Gel Method, Tetracycline.*

I. INTRODUCTION

In recent decades, the biomedical field has a great scientific leap; a variety of materials (for example, dendrimer, micelles, emulsions, liposomes, nanoparticle systems) [1] have been investigated as contrast agents in magnetic resonance imaging (MRI), hyperthermia and drug delivery systems (DDS). Nanostructured magnetic materials are considered advanced materials for biomedical applications. Because of the prominent properties of these materials, treatments related to cancer treatment by conventional methods have been reduced; for example, the DDS are able to release the drug at a target site in a spatiotemporal manner while the concentration and number of doses of the drug is reduced. A growing interest for the use of magnetic materials based on iron oxide as DDS has been observed. In this paper loading capacity and release of tetracycline from nanostructured barium hexaferrite systems ($BaO{\cdot}6Fe_2O_3$) synthesized by the sol-gel and spray drying method was investigated.

II. EXPERIMENTAL

$BaO{\cdot}6Fe_2O_3$ synthesis

Nanostructured magnetic spherical aggregates of barium hexaferrite ($BaO{\cdot}6Fe_2O_3$) were synthesized by molecular self-assembly by chemical sol-gel method and spray drying. In brief, salts of iron (III) nitrate nonahydrate $Fe(NO_3)_3 9H_2O$ (Sigma-Aldrich) and barium carbonate $BaCO_3$ (Sigma-Aldrich) were dissolved in deionized water by magnetic stirring (300 rpm) for 30 min. in a molar ratio of 1:12. A second suspension formed by surfactant Tween20 (Merck) was dispersed in deionized water for 30 min. at 300 rpm. Both suspensions were mixed again by constant magnetic stirring for 6 hours. The pH of the resulting mixture was adjusted to pH 8 using ammonium hydroxide NH_4OH. Then, the resulting mixture was fed a tubular drying chamber of a Mini Spray Dryer (Yamato, ADL31) through a flow of hot air as carrier gas. The process of spray drying was initiated by the generation of droplets from the colloidal suspension followed by the atomization of the liquid at a temperature T = 175 °C and a pressure P = 1.5 kg/cm^2, resulting in the production of powders compounds of solid particles. Then the powder was collected by a cyclone and subjected to heat treatment of 800 °C at a heating rate of 3 °C/min for 2 hours for further characterization. Finally, the loading and release capability from the $BaO{\cdot}6Fe_2O_3$ systems was tested using antibiotic tetracycline as model drug.

$BaO{\cdot}6Fe_2O_3$ Characterization

The powders heat treated at 800 °C after the process of spray drying were characterized using x-ray diffraction on a Bruker model D8 Advance using radiation Cu Kα (45 kV, 30 mA) and scanning electron microscopy field emission (FESEM) using a microscope JEOL JSM-7600F.

Loading and release study of tetracycline

The load capacity of $BaO{\cdot}6Fe_2O_3$ systems were determined by placing 1 mg of $BaO{\cdot}6Fe_2O_3$ powder in contact with a standard solution of tetracycline (10 mg/mL) in constant magnetic stirring. Tetracycline is a broad-spectrum antibiotic used to treat a number of bacterial infections, which acts by inhibiting protein synthesis. An aliquot of the tetracycline solution containing particles $BaO{\cdot}6Fe_2O_3$ was taken at 5 minute intervals, first allowing the precipitation of powders $BaO{\cdot}6Fe_2O_3$. Then we analyzed the changes in optical density (OD) of the tetracycline solution using a UV-vis spectrophotometer (Cary 50 Probe spectrum, UV-vis spectra). The decrease in OD values indicated that the tetracycline was adsorbed on $BaO{\cdot}6Fe_2O_3$ particles. The

optical density measurements were taken until observing stabilization in the OD reading. Thus, indicating the maximum load of tetracycline on $BaO{\cdot}6Fe_2O_3$ particles. To perform the release studies of tetracycline from $BaO{\cdot}6Fe_2O_3$ systems we continued as indicate below. A hoe of the *XL1-Blue strain of Escherichia coli (Stratagene) [recA1, endA1, gyrA96, thi-1, hsdR17, supE44, lac19ZDM15, Tn10 cam (TCRs)]* which was distributed on LB agar solid was taken and it incubated overnight at 37 °C. Then a young colony was selected and inoculated into 2 mL of LB liquid medium incubating at 37 °C overnight at 150 rpm. Then 49 mL of LB liquid were placed in a 250 mL Erlenmeyer flask, it was added 1 mL of pre-inoculum and the $BaO{\cdot}6Fe_2O_3$ particles charged with tetracycline. A first reading of optical density was taken at OD_{600}, which is the OD at time zero. The medium was incubated at 37 °C at 150 rpm (LAB-LINE®, incubator shaker) and at predetermined times 1 mL aliquots were taken to measure the OD_{600} until stabilization in the OD_{600} values. For reference in the interpretation of results, two controls were prepared. The first composed solely of LB liquid medium plus pre-inoculated. The second composed from LB liquid, pre-inoculum plus uncharged $BaO{\cdot}6Fe_2O_3$ particles. For both controls was carried out the same procedure as the test.

III. RESULTS AND DISCUSSION

The pattern of x-ray diffraction for the sample calcined at 800 °C shown in Figure 1 indicates that the sample thus obtained is composed of a mixture are crystalline phases; mostly barium hexaferrite $BaFe_{12}O_{19}$ with a hexagonal structure, together with hematite Fe_2O_3 having an hexagonal structure and to a lesser amount barium monoferrite $BaFe_2O_4$ with an orthorhombic structure. Several authors [3-10] have reported the synthesis of $BaFe_{12}O_{19}$ at different temperatures in which coexist a mixture similar to the phases obtained in this research or the presence of one or more different phases to those shown here. The difference in the presence of the different phases as well as the weight ratio of the phases present can be influenced by factors such as the synthesis method, type of precursor salts and their molar ratio, temperature and residence time heat treatment, among others. In general, an increase in the calcination temperature leads to increased sample crystallization and greater purity of the $BaFe_{12}O_{19}$ phase as has been shown elsewhere. However, although higher temperatures can be obtained $BaFe_{12}O_{19}$ higher purity, higher temperatures produce larger particle size resulting in obtaining a hard magnetic material with magnetic properties unsuitable for biomedical applications in which a superparamagnetic behavior is required because this does not retain magnetism after removal of the magnetic field [11-14].

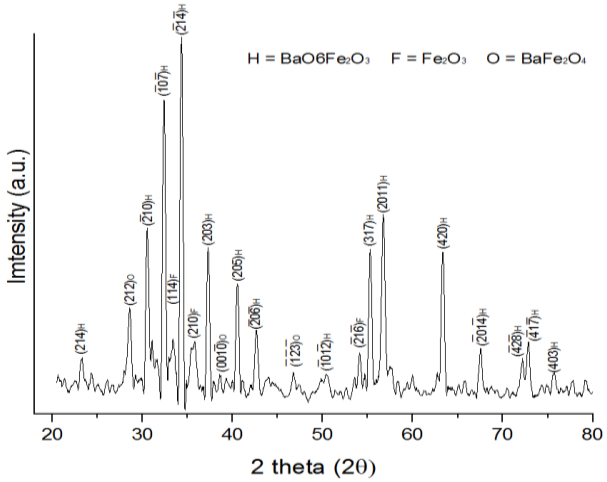

Fig. 1 X-ray diffraction pattern for a sample calcined at 800 °C. The XRD pattern shows the presence of three crystalline phases: H = $BaO{\cdot}6Fe_2O_3$, F = Fe_2O_3 and O = $BaFe_2O_4$.

Figure 2 shows a representative SEM image in which nanostructured spherical aggregates are observed (approx. 1.2 µm in diameter). The insert in the image shows that the aggregates are formed by nanometer-sized particles (< 100 nm)

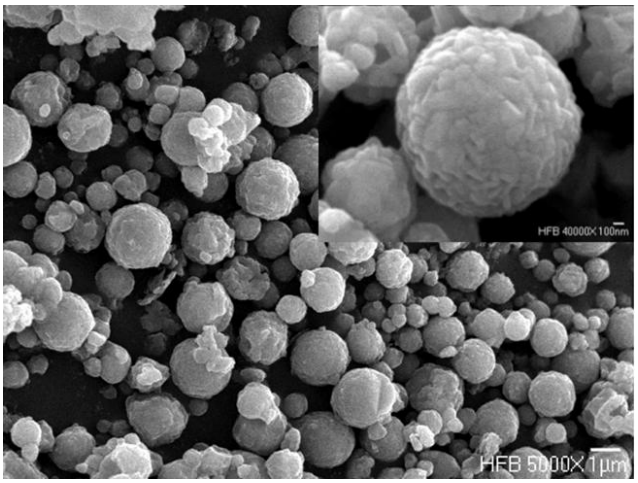

Fig. 2 shows a representative SEM image in which nanostructured spherical aggregates are observed (approx. 1.2 μm in diameter).

The load capacity of $BaO{\cdot}6Fe_2O_3$ powders was observed when analyzing the decrease in the OD values from the tetracycline solution in contact with $BaO{\cdot}6Fe_2O_3$ particles. The tetracycline concentration of 10 mg/mL ensures killing bacteria when in contact. Figure 3 shows the decrease in OD values when the tetracycline solution kept in contact with the $BaO{\cdot}6Fe_2O_3$ particles. This indicates that tetracycline was adsorbed by particles of $BaO{\cdot}6Fe_2O_3$. Furthermore, it can be seen from the graph that at 60 min the $BaO{\cdot}6Fe_2O_3$ particles have adsorbed all possible tetracycline, reaching their saturation.

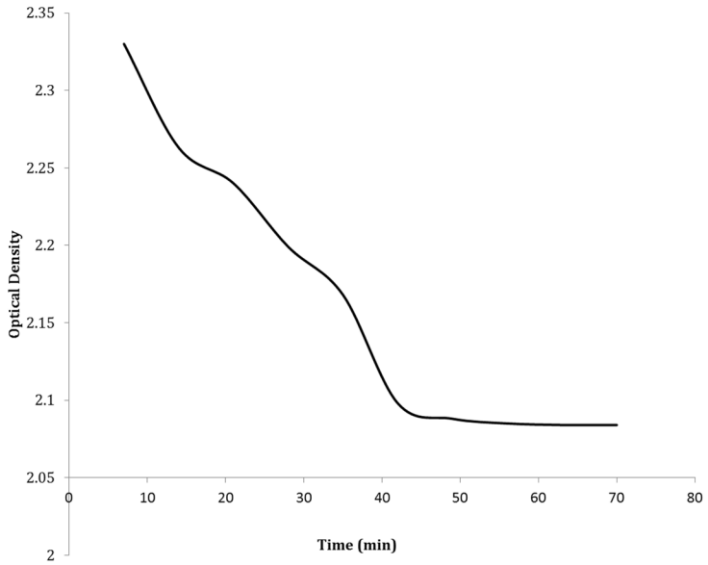

Fig. 3 variation in optical density values indicating the absorption of tetracycline on $BaO{\cdot}6Fe_2O_3$ systems

After the $BaO{\cdot}6Fe_2O_3$ particles were loaded with tetracycline, these were placed in a culture medium for *E. coli* in order to test the release of tetracycline. Figures 4 and 5 show the effect of the $BaO{\cdot}6Fe_2O_3$ particles loaded with tetracycline on growth of bacteria. The decrease in the OD of the culture medium of *E. coli* indicates inhibition and death of the bacteria. In Figure 4, a decrease in OD values were seen when the bacteria was in contact with the $BaO{\cdot}6Fe_2O_3$ particles loaded with tetracycline as well as the uncharged $BaO{\cdot}6Fe_2O_3$ particles. However, the decrease in OD was more remarkable when the bacteria come in contact with $BaO{\cdot}6Fe_2O_3$ particles loaded with tetracycline. Figure 5 shows the growth curve expressed in colony forming units CFU, evaluated as a number of CFU kinetics versus time. The kinetic behavior corresponds to a normal growth reaching a maximum at 40 minutes and decreasing thereafter. This curve is modified in media containing the $BaO{\cdot}6Fe_2O_3$ particles with and without tetracycline. In the presence of particles of $BaO{\cdot}6Fe_2O_3$

the bacteria have a completely different behavior, decreasing the CFU initially to have a minimum 40 minutes and then gradually increase. When in the media containing the $BaO{\cdot}6Fe_2O_3$ nanoparticles loaded with tetracycline, the behavior of the growth curve changes completely, since from the first minutes an effect suggesting inhibition and death of the bacteria is presented suggesting that the release tetracycline is given in a gradual way.

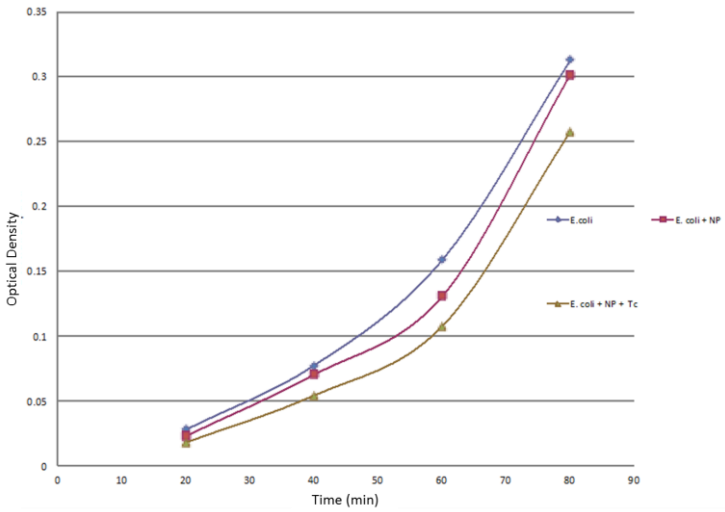

Fig. 4 variation in optical density values due to the effect of the $BaO{\cdot}6Fe_2O_3$ particles loaded with tetracycline on growth of bacteria

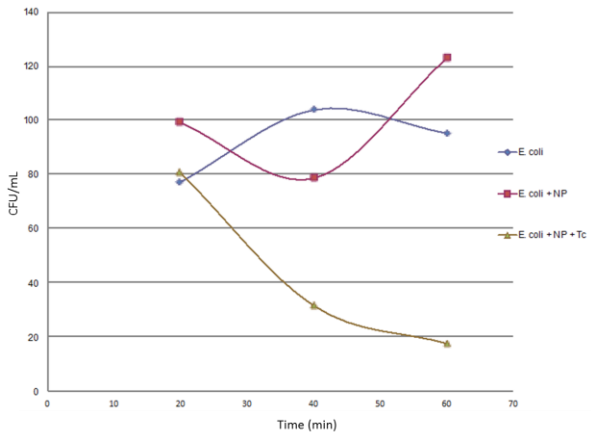

Fig. 5 variation in CFU of *E. coli* due to the effect of $BaO{\cdot}6Fe_2O_3$ particles loaded with tetracycline on growth of bacteria

IV. CONCLUSION

$BaO{\cdot}6Fe_2O_3$ spherical aggregates in micrometer size were successfully synthesized from a chemical wet sol-gel method via spray drying. Loading and release studies of tetracycline as a model drug shows that the $BaO{\cdot}6Fe_2O_3$ systems can be a good candidates as drug delivery systems.

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