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Research on Obtaining Nanostructured Surfaces Efficient in Combating Microbial Biofilm

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Abstract: *Infections that occur after the insertion of biomedical devices are a major problem; potential sources of infection are due to the adhesion of bacteria on the surface of implants, bacteria that form biofilms. In order to combat or to effectively prevent various microbial, which occur in medical procedures, we try to make compounds and materials that prevent the formation or development of microbial biofilm. The aim of this study was to obtain nanostructured surfaces based on magnetite, carboxymethylcellulose and ceftriaxone, as films with anti-infective properties in order to use them in the field of current biomedicine. To obtain nanostructured surfaces with high non-stick potential, the carboxymethylcellulose-functionalized magnetite powder was homogenized with an anti-infective agent, ceftriaxone. From the analysis of the obtained results it was found that the nanostructured surfaces obtained had a strong antimicrobial character infections and can be used successfully in the coating of medical implants, in order to combat the microbial biofilm.*

Keywords: *nanostructured surfaces, microbial biofilm, nanoparticles, magnetite, nanotechnologies*

1. Introduction

Moderate lifestyle, full of toxic foods, genetically modified organisms and overmedication have led to an amazing resistance and ability of bacteria to adapt and resist in the human body.

Bacteria are one of the main infectious threats, due to antibiotic resistance and rapid proliferation. Most of these untreated infections mainly incriminate bacteria such as *E. coli*, *P. aeruginosa* or *S. aureus* and the most severe complications include the formation of biofilm on the surface of implanted devices. Any environment in which bacteria are present and which has a liquid flow is prone to appearance of biofilms [1]. The biofilm is represented by an agglomeration of bacteria that communicate and collaborate with each other in a compact community [2] and may result either from perioperative procedures (introduction and adhesion of microbes during surgery) or postoperative procedures (microbial infection that occurs during hospitalization) [3]. It has a complex three-dimensional structure consisting of microorganisms encapsulated in a polymeric matrix composed of polysaccharides, proteins and DNA [4], being omnipresent in nature and comprising 90% or more of all naturally occurring micro-organisms. The formation of biofilms is accelerated by factors such as: the bacterial defense mechanism, the right area for colonization and the extraordinary way in which bacteria grow and multiply. The matrix acts as a physical barrier against drugs and provides shelter and protection for the survival of microorganisms. Inside a biofilm there may be a single species of bacteria or an agglomeration of many other bacteriocin species [5]. About 80% of pathogenic bacteria are formed when medical devices are inserted inside the body such as: orthodontic prostheses, contact lenses, cardio-vascular valves, urinary catheters, pacemakers, breast implants, etc. Bacteria can also change the *p*H of their environment to facilitate the formation of biofilm [6], and biofilm may be widely used in technologies to improve water quality and biodegradable waste route [7]. The alarming rates of microbial resistance and the health risks of this problem highlight the need for new antimicrobial drugs. Many of the antibacterial surfaces are effective only in the presence of an aqueous solution and may be less effective in killing bacteria that

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grow in the air in the absence of a liquid medium. Consequently, instead of killing bacteria chemically, several studies have explored alternative physical methods through the mechanism of killing the contact between the bacterium and the surface [8]. In an attempt to overcome these problems, new or less common techniques have been developed that have the same goal: the effectiveness of the fight against infections.

In this context, the study aimed to obtain nanostructured surfaces based on magnetite (Fe_3O_4) functionalized with carboxymethylcellulose (Fe_3O_4@CMC) and loaded with ceftriaxone (Fe_3O_4@ CMC/CEFT). Interest in nanotechnologies and nanometric materials, especially magnetic nanoparticles (NMPs), has greatly increased in recent times [9, 10].

From specialized literature [11-15], it is known that magnetic nanoparticles, especially magnetite (Fe_3O_4), are advanced materials of real interest in the biomedical field due to low toxicity, high chemical stability, ease of preparation by simple, inexpensive methods. Magnetic particles with nanometric dimensions have interesting new properties that can be attributed either to the extrinsic properties of individual particles, such as finite size, or to the surface effects and coupling between particles [16-18].

Magnetic iron oxide nanoparticles (magnetite or maghemite) are considered to be good adsorbents due to their large specific surface area, which gives them a high adsorption capacity of various pollutants, can be produced in large quantities and at low cost, can be regenerated and reused, and the application of an electromagnetic field allow the separation of water from nanoparticles with adsorbed metal ions [19].

In the medical fields, the integration of nanotechnology is expanding exponentially, especially in terms of drug-free control, which aims to target the drug where necessary, with minimal side effects and a low dose of effectively targeted drug. The unique physico-chemical, optical and biological properties that nanoparticles possess can be easily used in the desired applications [20]. Studies have also [21, 22], shown that biomimetic nanoparticles are a promising approach in treating infections, as they have been shown to have the potential to act as targets for more toxins produced by bacteria and are considered true molecular traps for microbial compounds with harmful effects in the environment. host and in recent years, many methods for obtaining nanoparticles with biomedical applications have been improved.

The choice of the most suitable method for the synthesis of magnetite nanoparticles, depending on the final purpose, is a very important step that influences the size and shape of particles, size distribution, surface chemistry and magnetic properties. In order to guide the function of a magnetite nanomaterial to have a specific biological effect, nanoparticles are usually functionalized to achieve the proposed purpose.

Nanoparticles functionalized with natural and synthetic antimicrobial substances significantly increase the effect of the bioactive drug by controlled release and delivery to the target site [23] (Figure 1).

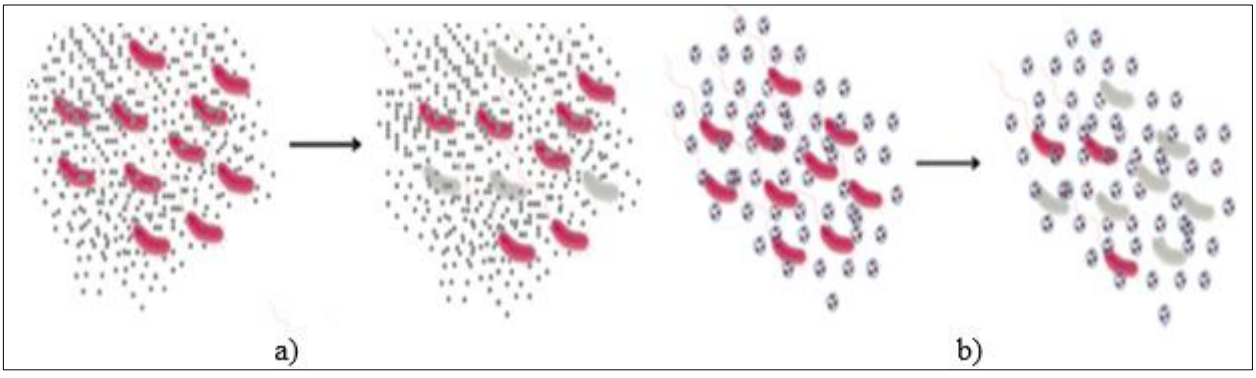

Figure 1. Enhanced antimicrobial effect of functionalized magnetic nanoparticles compared to antimicrobial drug [24]: a) Effect of conventional antibiotic on bactericidal cultures; b) The effect of functionalized magnetic nanoparticles

In case a) a severe death of bacteria is observed (few bacteria being affected), and in case b) it is observed that they significantly increase the effect of the bioactive drug, streamlining the action of the antibiotic. Water-soluble magnetite nanoparticles have significantly improved the activity of antibiotics currently used and have great potential for use as carrier systems for antimicrobials. A recent study shows that magnetites are able to increase, ensure the controlled release of the drug and significantly improve the effectiveness of antimicrobial agents. In recent years, the number of magnetite nanoparticle types has increased considerably [25, 26]. There is a wide variety of particles available for both commercial and research purposes, which makes it difficult to provide an answer to the question of whether magnetite nanoparticles are toxic.

A large number of in vitro toxicological investigations did not show any adverse side effects; however, long-term in vivo studies need to be performed to improve the applications of magnetite nanoparticles [27].

2. Materials and methods

2.1 Materials

The following materials were required to perform the proposed study:

- to obtain magnetite nanoparticles 2 solutions were prepared:
  - Solution 1: 3 g of $FeCl_3$, 4.8 g of $FeSO_4$ and 600 mm of distilled water;
  - Solution 2: 50 mg of carboxymethylcellulose (CMC), 25.3 mm of NH_3 (ammonia) - concentration 25% -28% and 600 mm of distilled water;
- 50 mg Ceftriaxone (antibiotic);
- 2 mm of Chloroform.

The co-precipitation method was used to obtain magnetic nanoparticles (The basis of this liquid phase synthesis is the known LaMer mechanism [28] in which: a somewhat monodisperse phase occurs and the concentration of a component must be increased beyond the saturation point).

In order to obtain the magnetic nanoparticles functionalized with carboxymethylcellulose (CMC) and loaded with Ceftriaxone (CEFT), two solutions presented in Figure 2 were prepared.

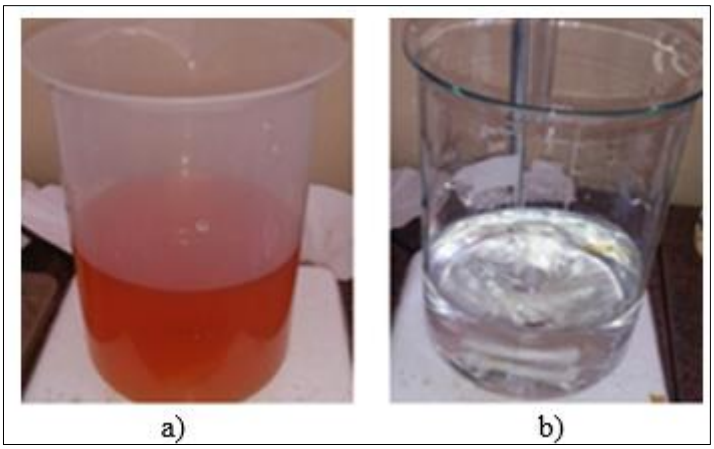

Figure 2. a) Solution 1 of $FeCl_3$, $FeSO_4$ and 600 mL of distilled water;
b) Solution 2 of Carboxymethylcellulose, NH_3 and 600 mL of distilled water

For solution 1, 3 g of $FeCl_3$, 4.8 g of $FeSO_4$ in 600 mL of distilled water were added to a Berzelius beaker.

This is an important solution, as it is where the precursors are. For solution 2, 0.5 g of carboxymethyl-cellulose, 25.3 mL of NH_3 in 600 mL of distilled water were added to a Berzelius beaker.

Solution 1 is important because it represents the basic medium where nanoparticles will form.

After obtaining these solutions, the contents of solution 1 were dripped over the contents of solution 2 using a drip system based on a glass funnel, and after the final solution was obtained, a magnet was placed under it to help the separation (Figure 3).

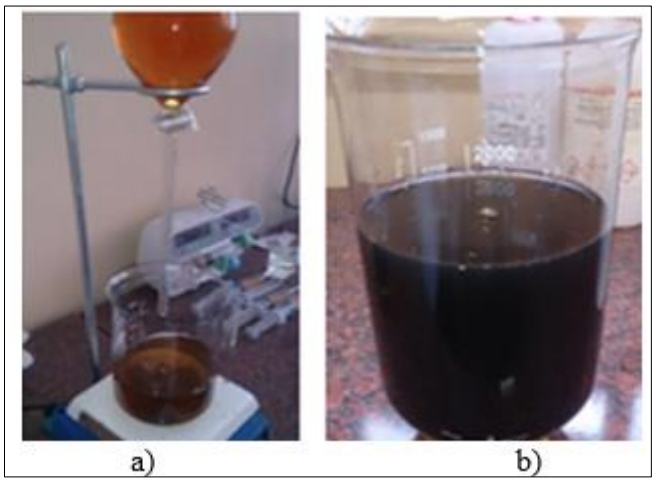

Figure 3. a) The dripping stage; b) Magnetic separation stage

After magnetic separation, the solution was washed three times with distilled water, allowed to dry at room temperature and then ground. After grinding, some of the functionalized magnetite powder was taken for analysis. 950 mg of magnetite was mixed with 50 mg of Ceftriaxone.

For a better mixing and homogenization of the two powders, add 2m of Chloroform (add milliliter by milliliter), then grind the obtained paste until the sample becomes dry. The powder thus obtained was placed in eppendorphs for analysis. The material obtained can be deposited in thin films based on magnetite nanoparticles functionalized with carboxymethylcellulose and mixed with antibiotic by various deposition techniques (eg MAPLE technique). The quality of the film depends on the method and conditions of deposition, as well as on the heat treatment after deposition.

2.2. Methods

The analysis of the obtained materials was performed by specific methods of solving the approached problem.

X-ray Diffraction (XRD)

The crystallinity investigation of the synthesized magnetite nanopowder was performed using the diffraction technique, using an Empyrean model diffractometer (PANalytical, The Netherlands).

Experimental determinations were made at room temperature, using a Cu electrode and K1 type radiation, which has a wavelength $\lambda = 1.540598$ Å. The diffractometer consists of a 2 × Ge hybrid monochromator (2 2 0) for copper and a PIXcel3D detector. Analyzes were performed using Bragg-Brentano geometry ("theta-2theta") for angle values between 10^o and 80^o (every 2 degrees with a step size of 0.04) and a sampling frequency time of 3s [29-31].

Scanning Electron Microscopy (SEM)

In order to investigate the morphology and size of the obtained nanostructured thin films, the samples were sectioned with a diamond disk, fixed on a slide and placed in the analysis chamber of a scanning electron microscope purchased from FEI (Oregon, USA). United States of America). The obtained images were made by recording the resulting secondary electron beam, with an energy of 30 keV. Scanning electron microscopy was used to study the morphology of Fe_3O_4@CMC powder (CMC-functionalized magnetite powder (carboxymethylcellulose) and Fe_3O_4@CMC/CEFT (CMC-functionalized magnetite powder) and loaded with cef [32-34].

Thermal analysis

The experimental determinations were performed using a Netzsch Jupiter 449^{o}C device.

The measurements were performed in a dynamic air atmosphere 50 mL / min, on a range of thermal values between 30 and 900^{o}C, in an Al_2O_3 crucible, the heating speed of the enclosure being 10^{o}K/min.

Differential scanning calorimetry is a thermal analysis that measures the difference between the amount of heat needed to increase the temperature of a reference sample and the analysis sample. The temperature program for a DSC analysis is designed in such a way that the temperature of the sample holder increases linearly with time. The principle underlying this analysis is that when the analyzed sample undergoes a physical transformation there is a change in heat compared to that of the reference sample [35- 38].

Fourier Transform Infrared Spectroscopy (FT-IR)

To investigate the integrity of the functional groups characteristic of synthesized particles, a small amount of particle suspension was analyzed using a ZnSe crystal of the Nicolet 6700 FT-IR spectrometer, purchased from Thermo Nicolet (Wisconsin, USA).

The measurements were performed at room temperature, 32 scans of the sample being performed between 4000 and 1000 cm^{-1}, at a resolution of 4 cm^{-1}. The recording of the information thus acquired was possible by connecting the spectrometer to a data collection and processing unit, through the Omnic work program (version 8.2 Thermo Nicolet) [39 - 45].

3. Results and discussions

This chapter highlights the results obtained from the analysis of the samples prepared by the methods described in the chapter Materials and methods.

X-ray Diffraction (XRD)

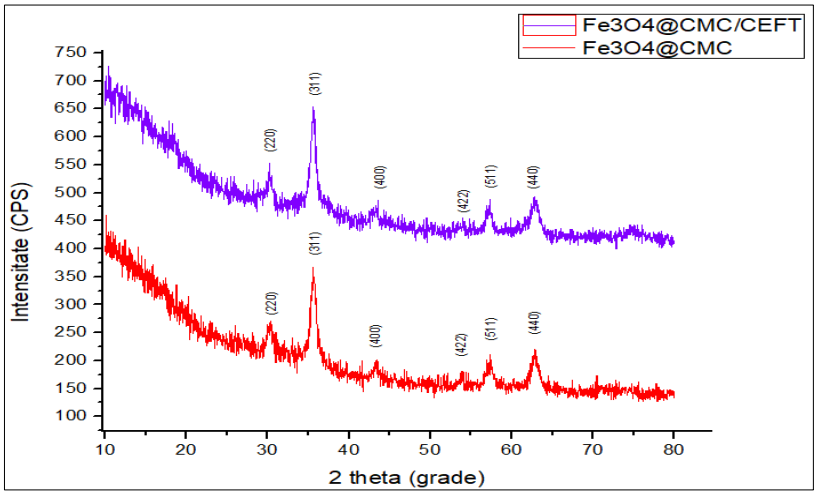

Figure 4. Diffractogram recorded for powders of:
Fe_3O_4@CMC (red) and Fe_3O_4@CMC/CEFT (purple)

By X-ray diffraction analysis we investigated the crystallinity of the powders obtained in the case of Fe_3O_4@CMC and Fe_3O_4@CMC/CEFT. The presence of diffraction maxima gives us data on the degree of crystallinity of the sample. The diffraction maxima characteristic of the diffractoframe below at the values of the angle 2θ is:

• In the case of Fe_3O_4@CMC, the following diffraction maxima are recorded: 30.26^{0}, 35.54^{0}, 43.60^{0}, 53.92^{0}, 57.28^{0}, 62.76^{0}.

• In the case of Fe_3O_4@CMC/CEFT, the following diffraction maxima are recorded: 30.34^{0}, 35.54^{0}, 43.39^{0}, 53.82^{0}, 57.35^{0}, 62.81^{0}.

All interferences can be indexed using the ASTM sheets and the specialist data consulted (JCPDS sheet number 19-0629 corresponding to magnetite). The results obtained from XRD correspond to the diffraction planes (220), (311), (400), (422), (511), (440) of the cubic crystallographic system.

In conclusion, the obtained diffractogram demonstrates the correspondence with the diffraction interferences characteristic of magnetite.

Scanning Electron Microscopy (SEM)

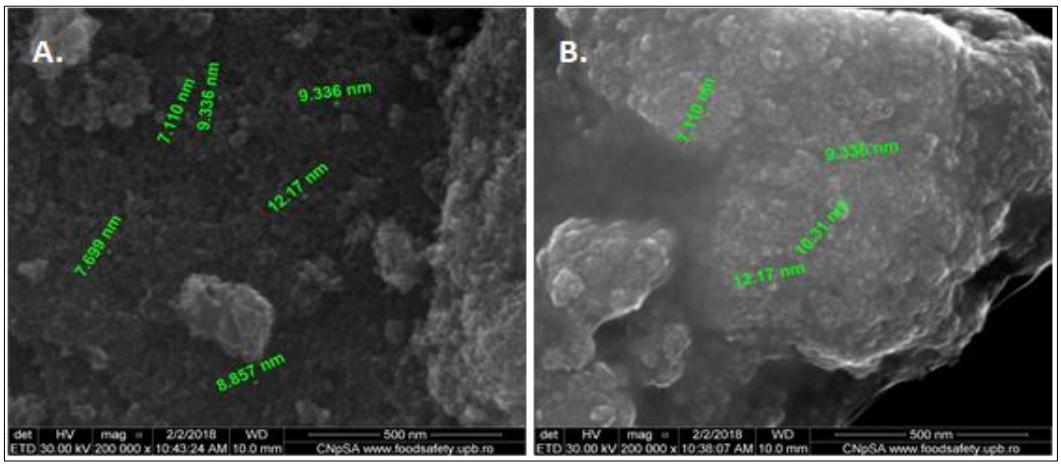

Figure 5. A: Fe_3O_4@CMC; **B:** Fe_3O_4@CMC/CEFT

Comparing the two results from Figure 5, agglomerated particles of different sizes with an asymmetric morphology are observed. The shape of the particles is polyhedral, and the surface is rough, showing roughness.

The agglomeration tendency is due to the high surface energy due to the small particle size and the magnetic attraction forces existing between the particles.

The particle sizes vary between 5 and 9 nm, which confirms that the material obtained has particles at the nanometer scale.

Thermal analysis

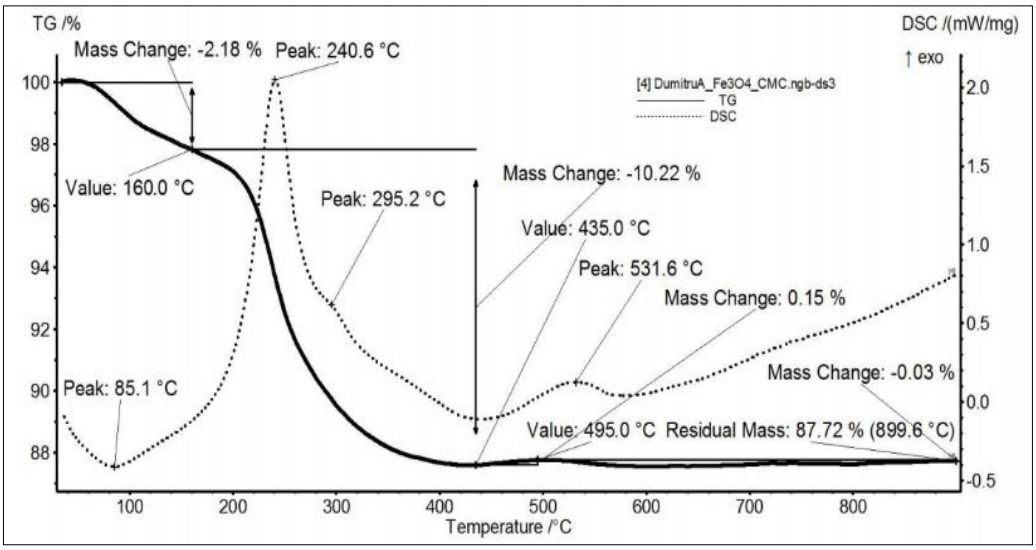

Figure 6. Thermogravimetric analysis performed on Fe_3O_4@CMC

Following the thermogravimetric analysis, the sample loses 2.18% of the mass, in the range RT-160ºC, the process being accompanied by an endothermic effect with a minimum of 85.1ºC. Most likely it is water or solvent molecules left in the sample from the synthesis. The main stage of mass loss takes place between 160ºC - 435ºC (10.22%), on the DSC curve the process being accompanied by a wide, asymmetric exothermic effect, with maximums at 240.6ºC and 295.2ºC. The fact that we have several peaks and the asymmetric shape of the effect leads to the conclusion that we have several overlapping oxidation reactions. In the range 435ºC - 495ºC there is a slight increase in mass (0.15%, due to an oxidation of metal ions). At 531.6ºC we have on the DSC curve an exothermic effect due to the magnetite-hematite phase transformation. The residual mass is 87.72%, reddish-brown.

Fourier Transform Infrared Spectroscopy (FT-IR)

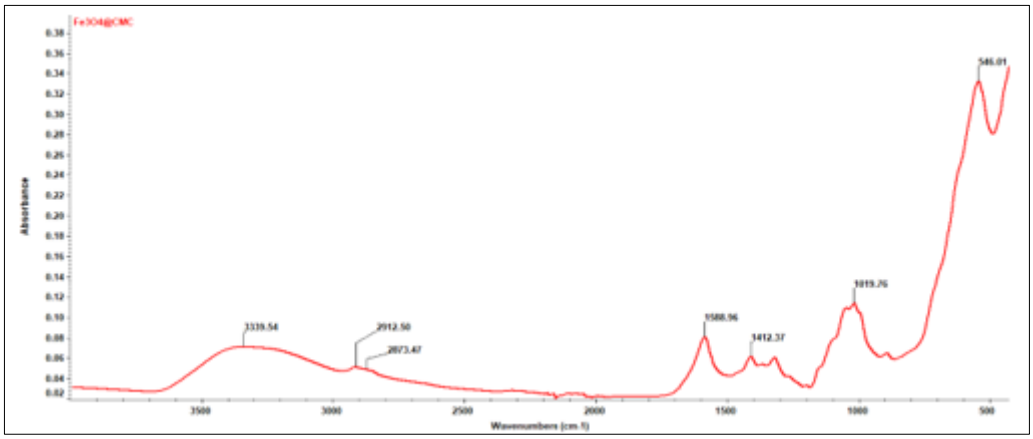

Figure 7. IR spectrum of powder Fe_3O_4@CMC

Following the IR analysis of the Fe_3O_4@CMC powder, important absorption maxima characteristic of the carboxyl (COOH) and methyl (CH_3) and hydroxyl (-OH) functional groups corresponding to carboxymethylcellulose can be observed. According to the resulting data, the absorption maxima corresponding to the wavelengths 1588.96, 1412.37 cm^{-1} represent two different functional groups of carboxymethylcellulose.

The absorption band corresponding to the wavelength 1588.96 cm^{-1} confirms the presence of the COO- group due to the extent of the carboxyl group (COOH). The corresponding wavelength 1412.37 cm^{-1} confirms the presence of the C-H group due to the deformation of the methyl group (CH_3).

The characteristic absorption band 3339.54 cm^{-1} is due to the stretching vibrations of the hydroxyl group (-OH). The bands at 2912.50 cm^{-1} and 2873.47 cm^{-1} are due to C-H stretching vibrations. The absorption band characteristic of the wavelength 1019.76 cm^{-1} is due to the extension of the CH-O-CH_2 group, and the one from 546.01 cm^{-1} is characteristic of pure α-Fe_2O_3 (hematite).

4. Conclusions

The present study showed that magnetite nanoparticles functionalized with antimicrobial substances have good antioxidant properties, biocompatibility and significantly improve the effect of the bioactive drug by controlled release and delivery to the target site.

Due to the properties presented in other specialized studies, for the realization of nanostructured surfaces used in order to control the microbial biofilm we used magnetite nanoparticles, obtained by the co-precipitation method, functionalized with carboxymethylcellulose (CMC). In order to have a high non-stick potential, the carboxymethylcellulose-functionalized magnetite powder was homogenized with an anti-infective agent, ceftriaxone. From the physico-chemical properties analysis of the obtained materials, through the methods XRD, SEM, thermal analysis and FT-IR, it was found that they had a high antimicrobial activity and can be easily used in the desired applications. Due to these characteristics,

synthesized nanostructured surfaces are a competitive candidate for the development of new surfaces or biomedical devices with low costs and high efficiency, helping to combat microbial biofilm.

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