Fe_3O_4@C_{18}-CARVONA PENTRU PREVENIREA FORMĂRII BIOFILMULUI DE *CANDIDA TROPICALIS*

Fe_3O_4@C_{18}-CARVONE TO PREVENT *CANDIDA TROPICALIS* BIOFILM DEVELOPMENT

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During recent years there is an increased interest in magnetite nanoparticles for their wide use in biomedical applications, as prevention of microbial colonization and targeted drug delivery systems. They could stabilize the volatile active components of the essential oils improving their antimicrobial activity. Here we report a newly prepared nano-bio-active coated surface for improved antimicrobial activity of classical wound dressings. Our results demonstrate that the reported nano-modified wound care textiles exhibit a great anti-fungal biofilm activity. These properties recommend the recently fabricated nano-bio-active coatings for the design of new antimicrobial medical surfaces.

În ultimii ani, există un interes crescut pentru utilizarea nanoparticulelor de magnetită pe scară largă pentru aplicatii biomedicale, cum ar fi prevenirea colonizării microbiene şi dezvoltarea de sisteme de eliberare țintită a medicamentelor. Acestea ar putea stabiliza componentele active volatile ale uleiurilor esențiale îmbunătățind activitatea lor antimicrobiană. Acest studiu raportează obținerea unei noi suprafețe nano-bio-active, utilizată pentru îmbunătățirea activității antimicrobiene a pansamentelor clasice. Rezultatele noastre demonstrează că pansamentele textile nanomodificate prezintă o mare activitate împotriva biofilmelor fungice. Aceste proprietăți recomandă acoperirea nano-bio-activă pentru proiectarea de noi suprafețe antimicrobiene utilizate în scop medical.

Keywords: *hydroxyapatite, XRD, FTIR, pyromorphite*

1. Introduction

Interest in biomedical applications of magnetite nanoparticles has increased noticeably in the last years [1-8], being studied for targeted drug delivery [9], hyperthermia [10,11], magnetic resonance imaging [12,13], inhibition of microbial colonization [14], stabilization of essential oils [15] or antitumoral treatments with [16] or without [17] the application of any external magnetic field. Our recently published papers report that magnetite nanoparticles significantly enhanced the antimicrobial effect of kanamycin sulfate against Gram positive (*S. aureus*) and Gram negative (*E. coli*) bacterial strains, of beta-lactam antibiotics against *P. aeruginosa* and of non-betalactam antibiotics against *S aureus.* The nanosystem also exhibiting a low cytotoxic activity against eukaryotic cells at active concentrations [18], acting probably by modulating its uptake into the bacterial cell, facilitating the antibiotic penetration in order to reach the bacterial target [19]. Anghel *et al*., [20] recently report successfully fabrication of novel nanostructured phyto-bioactive coated rayon/polyester wound dressing surface refractory to *Candida albicans* adhesion, colonization and biofilm formation, based on functionalized magnetite nanoparticles and essential oils.

In this context magnetite nanoparticles are strong candidates for developing novel antimicrobial and antibiofilm strategies.

Candida tropicalis, the close relative of *C. albicans* is one of the more common *Candida* species causing human diseases in tropical countries. The frequency of invasive disease varies by geographical area causing 3-66% of candidaemia. For example in India, *C. tropicalis* is the most common cause of nosocomial candidaemia, ranging between 67–90% of *Candida* infections [21]. *C. tropicalis* is a particularly virulent pathogen in immunocompromised hosts commonly with hematogenous seeding to peripheral organs. Some studies revealed that *C. tropicalis* can be more invasive than *C. albicans* in the human intestine infections; particularly in patients with malignancies [22].*C. tropicalis* is one of the most frequently encountered fungal pathogens in wound infections. Predisposing factors to cutaneous wound infections include minor trauma, pre-existing

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skin disease, poor hygiene, inadequate wound care and, rarely, impaired host immunity [23].

Increased virulence of *C. tropicalis* isolates is due mainly to secreted aspartyl proteinase 5 and 9 (SAP5 and SAP9), which are secreted on the surface of *C. tropicalis* fungal cell walls before invading tissues during disseminated infections and invading macrophages after phagocytosis of yeast cells [24]. Most of nosocomial *C. tropicalis* isolates exhibit resistance to azole drugs (fluconazole and voriconazole) leading to very high morbidity and mortality rates in intensive care units [25]. Furthermore, recent studies revealed that use of azoles in both clinical and agricultural settings should be restricted, since many soil *C. tropicalis* isolates exhibit reduced susceptibility to azole drugs [26], most of the resistant strains being genetically related with clinical or community acquired isolates [25].

Because of its metabolic versatility and resistance, novel therapeutic approaches are needed. Using alternative compounds, as natural essential oils and extracts have proved to be one efficient option in avoiding antifungal drugs, but still maintaining an increased anti-*Candida* efficiency.

The aim of present study was to optimize the antimicrobial properties of the classical textile wound dressings surface by coating it with a nanostructured system based on functionalized magnetic nanoparticles and carvone, the major active compound found in *Anethum graveolens* essential oil, previously proven to exhibit an increased anti-microbial effect [27], in order to reduce the fungal adherence and biofilm formation.

2. Materials and methods

All chemicals were used as received $FeCl_3$, $FeSO_4 \cdot 7H_2O$, NH_4OH (25%), carvone and CH_3OH were purchased from Sigma-Aldrich ChemieGmbh (Munich, Germany).

Magnetite nanostructure was prepared and characterized according to paper [17]. Aqueous solutions of Fe^{2+} and Fe^{3+} were separately prepared by dissolving the respective amounts of $FeSO_4 \cdot 7H_2O$ and $FeCl_3$ in de-ionized water. An aqueous solution containing 8 mL NH_4OH (25%) and 500 µg stearic acid (pH 13) was also prepared by dissolving the corresponding amount of NH_4OH and stearic acid (C_{18}) in de-ionized water. Fe^{2+} and Fe^{3+} solution was dropped into the NH_4OH/C_{18} solution with vigorous stirring. At the end of addition, a brownish-black precipitate was formed ($Fe_3O_4@C_{18}$). The whole solution was vigorously stirred at the room temperature.

Functionalized magnetite nanoparticles ($Fe_3O_4@C_{18}$) (100 mg) was solubilized in 2 mL of $CHCl_3$ and 100 µL of carvone (C) was added and mixed until complete evaporation of chloroform. This step was repeated three times for the uniform loading of carvone (C) in the functionalized magnetite nanoparticles ($Fe_3O_4@C_{18}/C$). $Fe_3O_4@C_{18}/C$ was solubilized with chloroform by a ratio $Fe_3O_4@C_{18}/C:CHCl_3$ = 1 mg/mL. Sterile textile wound dressing pieces (1 × 1 cm) were introduced in $Fe_3O_4@C_{18}/C:CHCl_3$ for achieving the nanophytoactive layer. Coated wound dressing pieces have been instant dried at room temperature. The rapid drying was facilitated by the convenient volatility of chloroform [20].

The transmission electron microscopy (TEM) images were obtained on finely powdered samples using a Tecnai™ G2 F30 S-TWIN high-resolution transmission electron microscopy from FEI (FEI Company, Hillsboro,OR, USA). The microscope was operated in transmission mode at 300 kV with TEM point resolution of 2 Å and line resolution of 1 Å. The finely micronutrient powders was dispersed into pure ethanol and ultrasonicated for 15 min. After that the diluted sample was put onto a holey carbon-coated copper grid and left to dry before it was analyzed through TEM.

Biofilm formation was analyzed in 6 multi-well plates (Nunc), using a static model for monospecific biofilms development. Classical textile wound dressings (WDs) and nano-active coated wound dressings were distributed in 6 well plates (one per well). Two mL of *C. tropicalis* inoculum with standardized density [28] were added in each well, to completely cover the wound dressings pieces. Samples were incubated for 24 h at 37°C. Biofilms formation was assessed after 24 h, 48 h and 72 h by viable count assay and Scanning Electron Microscopy (SEM) analysis.

After 24, 48, 72 h incubation period has expired, wound dressings were gently washed with sterile PBS (phosphate buffered saline), for not disturbing the biofilm, and fixed by immersing each sample in cold methanol for 5 seconds. After fixation, samples were allowed to air dry and SEM analysis was performed on a HITACHI S2600N electron microscope in secondary electrons fascicle, on samples covered with a thin silver layer.

Viable cell counts (VCCs) analysis of microorganisms grown in biofilms was assessed following an adapted protocol, previously described [27]. Briefly, after 24 h incubation the culture medium was removed and the pieces of wound dressing washed with sterile PBS, in order to remove unattached bacteria. Wound dressing samples were placed in fresh medium and inoculated for other additional 24 h, 48 h and 72 h. After the incubation period wound dressing pieces were gently washed with sterile PBS to remove the non-adherent cells and placed in 1.5 mL microcentrifuge tubes containing 750 µL PBS. Samples were vigorously mixed by vortexing for 30 seconds and sonicated for 10 seconds in order to disperse biofilm cells into the suspension. Serial ten-fold dilutions were achieved and plated on Sabouraud Chloramphenicol Agar for viable cell

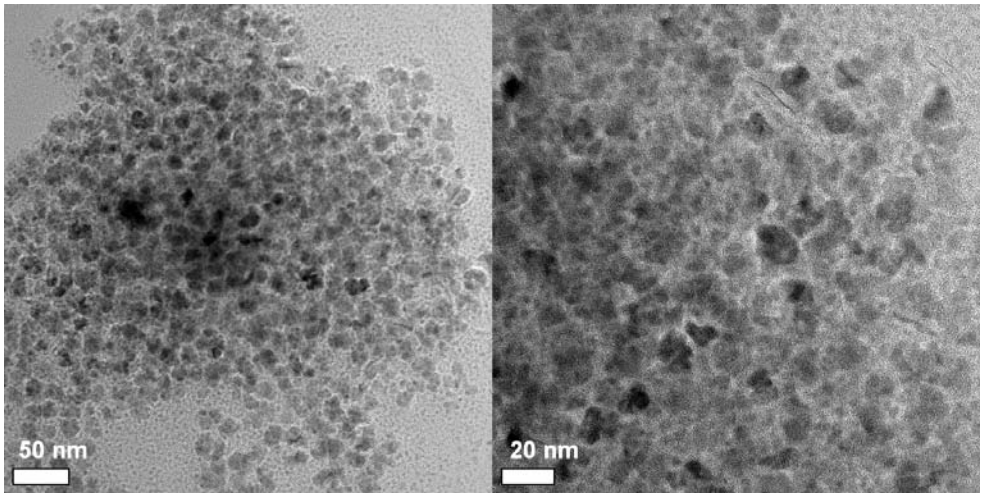

Fig. 1 - TEM images of Fe_3O_4@C_{18} / *Imagini TEM ale Fe_3O_4@C_{18}.*

counts assay. Experiments were performed in triplicate and repeated on three separate occasions.

3. Results

Here we report a newly optimized nano-bio-active coated wound dressing surface with an enhanced anti–fungal biofilm effect.

Previous paper report the characterization of the Fe_3O_4@C_{18} as follow [17]: the crystalline properties of the prepared nanoparticles was investigated by XRD. The sample has the characteristics of bulk magnetite crystallite phase (Fe_3O_4). The selected area electron diffraction (SAED) pattern proved the presence of Fe_3O_4 as the single crystalline phase, the most intense planes being: (220), (311), (222), (400), (511) and (440). The FT-IR analysis identified the organic coating agent (C_{18}), on the surface of the magnetite nanoparticles. Two sharp bands at 2915 and 2848 cm^{-1} were attributed to the asymmetric CH_2 stretching and the symmetric CH_2 stretching, respectively. The 1440 cm^{-1} band is assigned to the antisymmetric CH_3 deformation vibration.

The peak recorded at about 1701 cm^{-1} at FT-IR spectra of the nanoparticles show the C=O stretching vibration of fatty acids. The ATD curves of the sample exhibit strong exothermic peaks between ~200°C and 400°C associated with C_{18} burns. During the shell decomposition carbon based residues are formed, their burns being visualized at temperatures higher than 450°C, the most important peak being at ~535°C. Based on the thermogravimeric curve of the sample, the content of fatty acid salt was 38.75% [17].

In this study TEM analysis was performed to confirm the nanometric scale of prepared Fe_3O_4@C_{18}. Dimension of the structure not exceeding 10 nm and their spherical shape was confirmed by TEM analysis (Fig. 1).

The results of the viable cell counts (VCCs) assay of fungal cells embedded into the experimental biofilms developed on the treated surfaces, prove that the modified wound dressings exhibit an enhanced anti-adherence and anti-biofilm effect, against the versatile *C. tropicalis* (Fig. 2). The nano-modified wound dressing surfaces does not allow *C. tropicalis* biofilm formation, acting since the very beginning step of biofilm formation. Both early and mature biofilm formation phases were significantly impaired when the modified wound dressings were used. Furthermore, the effect of nano-modified bio-active wound care materials seems to be highly stable during time, since its activity is maintained for at least three days (Fig. 2).

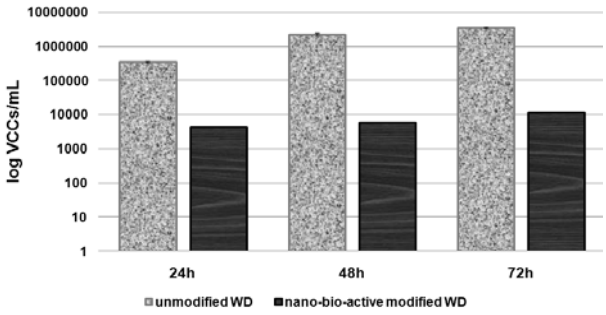

Fig. 2 - Graphic representation of *C. tropicalis* biofilm formation on classical and nano-bio-active modified wound dressing (WD), after different exposure times/ *Reprezentarea grafică a formării biofilmului de C. tropicalis pe pansamente textile (WD) clasice şi nano-bio-activ modificate, la diferiți timpi de expunere.*

VCCs were also confirmed by SEM analysis. Microscopic examination of the biofilms revealed that *C. tropicalis* monospecific biofilm formation is significantly impaired on nano-coated wound dressing fibers. Biofilm formation is significantly reduced starting with the initial stage, after 24h of development (Fig. 3-a_1 and b_1), *Candida* being unable to grow and initiate normal

biofilm structures on modified WD (fig. 3-b_1). This antibiofilm effect is enhanced during time, after 48h of incubation the attached *Candida* cells are not able to produce mature biofilms (fig. 3-a_2 and b_2). After 72 h incubation only few isolate cells can be observed on the surface of the modified WD fibers (fig.-3 a_3 and b_3), fungal colonies or aggregates are not observed in nano-coated wound dressings.

These results demonstrate that newly produced nano-bio-coated WDs can be effective not only in the initial steps of biofilm formation, which includes adherence and micro-colonies forming, but also in the development of mature biofilms.

4. Conclusions

Nanotechnology has been largely used for different biomedical applications, including drug delivery, antimicrobial therapy, stabilizing system, optimization of medical textiles and fibers. Our previous work reported that nanosystems can be used as efficient stabilizers for less stable natural antimicrobial compounds as vegetal extracts.

C. tropicalis strains involved in biofilm-associated wound infections are often resistant to traditional antifungal drugs; therefore alternative ways for reducing their persistence are needed. Carvone-based nano-coatings significantly reduced microbial adherence and fungal mature

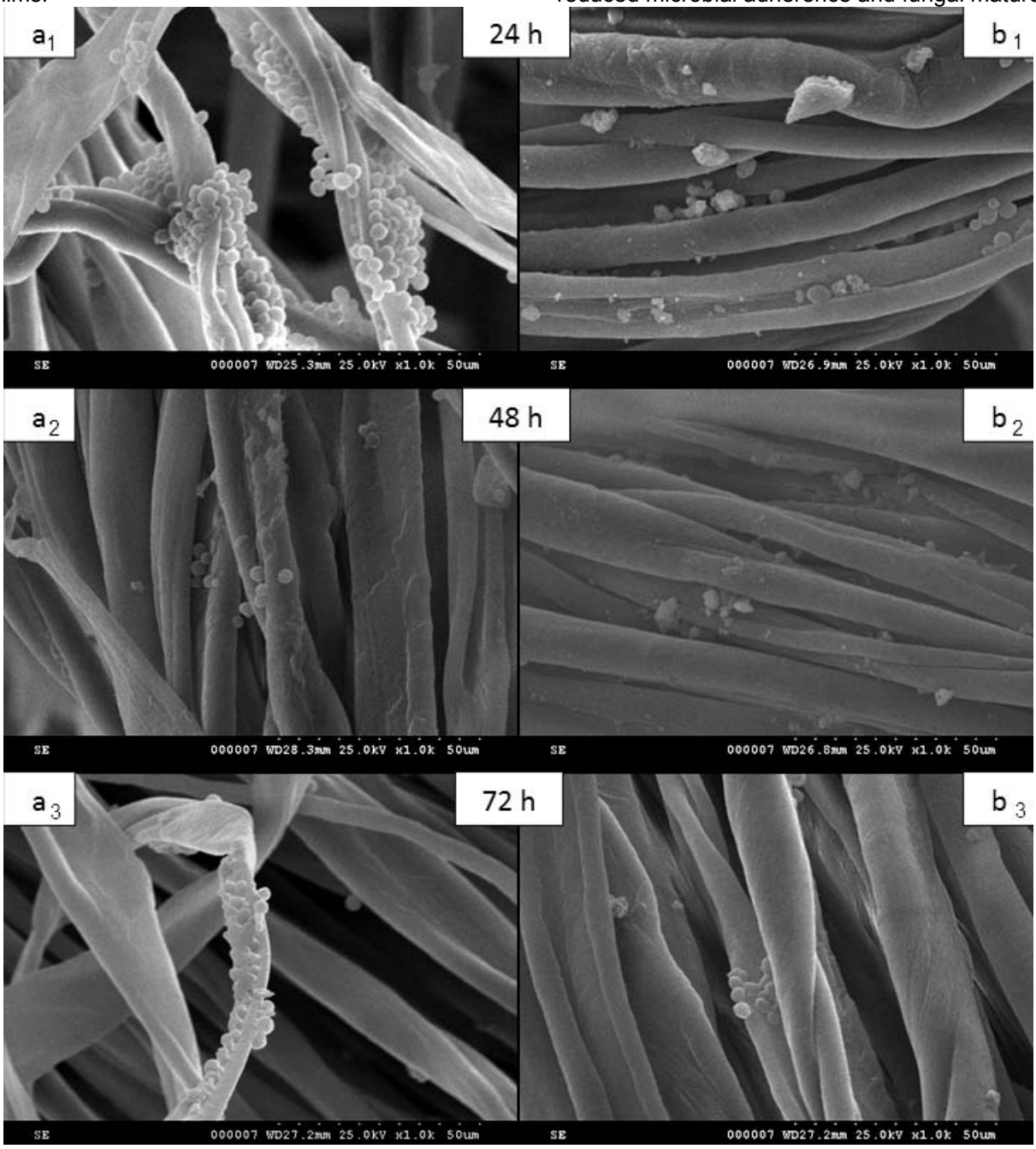

Fig. 3 - SEM micrographs revealing *C. tropicalis* biofilm development after 24 (a_1 and b_1), 48 (a_2 and b_2)and 72h (a_3 and b_3) incubation on classical (a) and nano-bio-active modified (b) wound dressings / *Micrografii SEM evidențiind dezvoltarea biofilmului de C. tropicalis după 24 (a_1 şi b_1), 48 (a_2 şi b_2) şi 72h (a_3 şi b_3) de ore de la incubare pe pansamente textile clasice (a) şi nano-bio-activ modificate (b).*

biofilm formation on the traditional textile wound dressings, the most often used materials in wounds care, the bio-active function of the reported surface proving to be stable for 72 h. Therefore, the novel nano-phyto-active coating may be successfully used to improve the resistance to colonization of the wound dressings, providing them with optimal properties for long-term wounds care.

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