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Magnetic scaffold for drug targeting: evaluation of cephalosporins controlled release profile

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ABSTRACT

The great problem associated with drug administration is the inability to target a specific area of the body. To reach an acceptable therapeutic level, large doses of the drug must be administered. Only a part of the dose will actually reach the intended disease. Magnetic targeting simplifies drug administration procedures, increases the concentration of the drug at target sites and decreases the concentration of the drug at non-target sites. This study was focused to evaluate the controlled release profile of cephalosporins from magnetic diethylaminoethyl-cellulose hybrid material (magnetic scaffold). Dissolution behavior of these magnetic scaffolds was evaluated using a modified HPLC system. It was found that in all cases, at large time values, the cephalosporin's concentration was much below the solubility plateau for the pure active compound, demonstrating that the adsorption on the surface of magnetic scaffolds is a valuable procedure to attain controlled release.

Keywords: *magnetic drug targeting, drug delivery, cephalosporins, hybrid materials, cellulose, magnetic scaffolds*

1. Introduction

The idea behind magnetic drug targeting is that magnetic drug carrier (nano)particles [1,2] can be attracted to and retained at a specific site in the body using an external magnetic field source [3]. Magnetic drug targeting is unique in that it represents not just one specific area, but a variety of disciplines ranging from basic materials science to bioscience [4]. The development of hybrid materials [5], nanostructures [6], metal nanoparticles [7,8,9] or nanocomposites [10,11,12] for the delivery of therapeutic agents [13] has introduced new opportunities for the improvement of medical treatment [14] and drug delivery [15]. Magnetic nanoparticles [16,17] have an important application such as magnetic drug delivery or nano-carriers [18] for the treatment of various types of diseases [19]. There is an increasing interest in inventing new magnetic nanoparticles [20] because of their wide applications [21]. Hybrid nanomaterials exhibit unique electronic, optical, and catalytic properties due to their size, morphology and large surface area [22,23]. Cephalosporins [24] are antibiotics with a structure and activity similar to penicillins [25]. They are resistant to penicillinase, but susceptible to cephalosporinases. They have a large action spectrum, including Gram-positive (*Staphylococcus sp., Streptococcus sp., Corynebaterium diphteriae*) and Gram-negative (*Neisseria gonnorhoeae, Haemophilus influenzae, Escherichia coli, Proteus sp., Klebsiella* sp.)

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microorganisms. In this context, our aim was to study the controlled release profile of Cephalosporins from magnetic DEAE-Cellulose monitored by HPLC system.

2. Experimental section

2.1. Magnetite/Diethylaminoethyl-Cellulose/Antibiotics: preparation and characterization. Cephalosporins were chosen from the commercially available class of β-lactams antibiotics: Cefuroxime, Cefotaxime, Cefoperazone, Ceftriaxone, Cefepime. Magnetic scaffold was prepared and characterized according to our previous study, as follows: diethylaminoethyl-cellulose (DEAE-C) was added in aqueous solution of NaOH (2%) and then Fe^{2+} and Fe^{3+} (in 1:2 molar ratio) were dissolved in ultrapure water and were added drop-wise under constant stirring at 25 °C. The DEAE-C/Fe_3O_4 (magnetic scaffold) was separated by applying a magnetic field, and washed several times with water and then with ethanol. The hybrid materials were finally dried at 50° (DEAE-C_{50}) and 100 °C (DEAE-C_{100}). After drying in oven at 50° and 100°C for 24 h, the magnetic magnetic scaffolds were dispersed in minimum quantity of ultra-pure water and then the cephalosporins were added. The mixture was grounded for 10 min. It was dried to 40°C for 6 h. The concentration of deposited cephalosporins was 10 %. Scanning electron micrographs of fibrillated Fe_3O_4/DEAE-cellulose presented no considerably phenomena about the morphology in comparison with untreated DEAE-cellulose according to our previous study [26]. To point out the deposition of cephalosporins on the surface of magnetic scaffolds, FT-IR spectra were performed. Many peaks in the "fingerprint" region between 1600 and 1200 cm^{-1} were observed, as well as changes in the bands area. The "fingerprint" region of the reference and magnetic scaffolds/cephalosporins spectra shows clear differences after deposition of cephalosporins.

2.2. HPLC release control. The cephalosporin's controlled release dynamics from the magnetic hybrid material was studied using an Agilent 1100 series high pressure liquid chromatograph. All the reagents used in the experimental work were of analytical grade. HPLC release control were performed with a modified Agilent 1100 series high-performance liquid chromatography (Agilent Technologies, Palo Alto, USA) equipped with quaternary pump, vacuum degasser, UV-VIS detector (Figure 1). Chromatographic software HP ChemStation was used for data collection and processing. The samples were introduced in the working apparatus, thermostated at 25°C, under controlled and continuous stirring. In order to avoid migration of the magnetic hybrid material through the system, the sample (40 mg of hybrid support along with the deposited active compound) was placed in a filter paper sample basket of small porosity. Ultra-pure water was used as mobile phase with a flow rate of 3 mL/min. The obtained results are plotted in Figure 2.

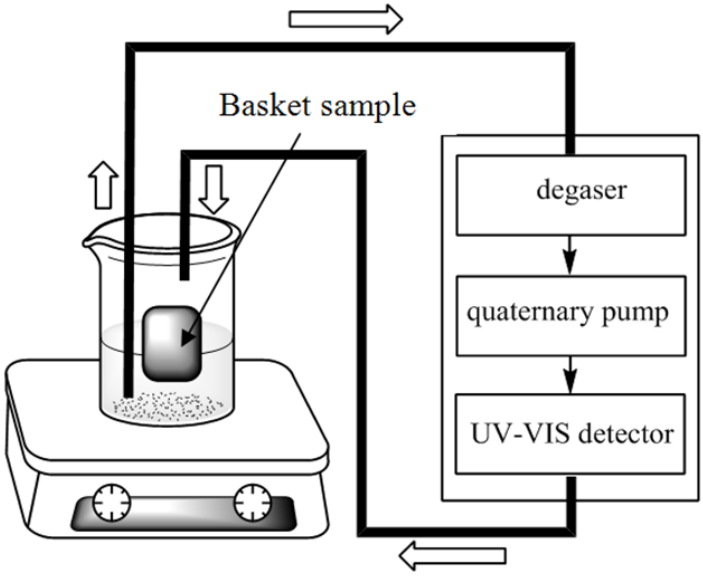

Figure 1: Modified HPLC system for release control

3. Results section

For all studied cephalosporins, the same quantity that was first used to determine the corresponding solubility limit of each compound was subsequently deposited on the magnetic scaffolds (DEAE-C_{50} and DEAE-C_{100}).

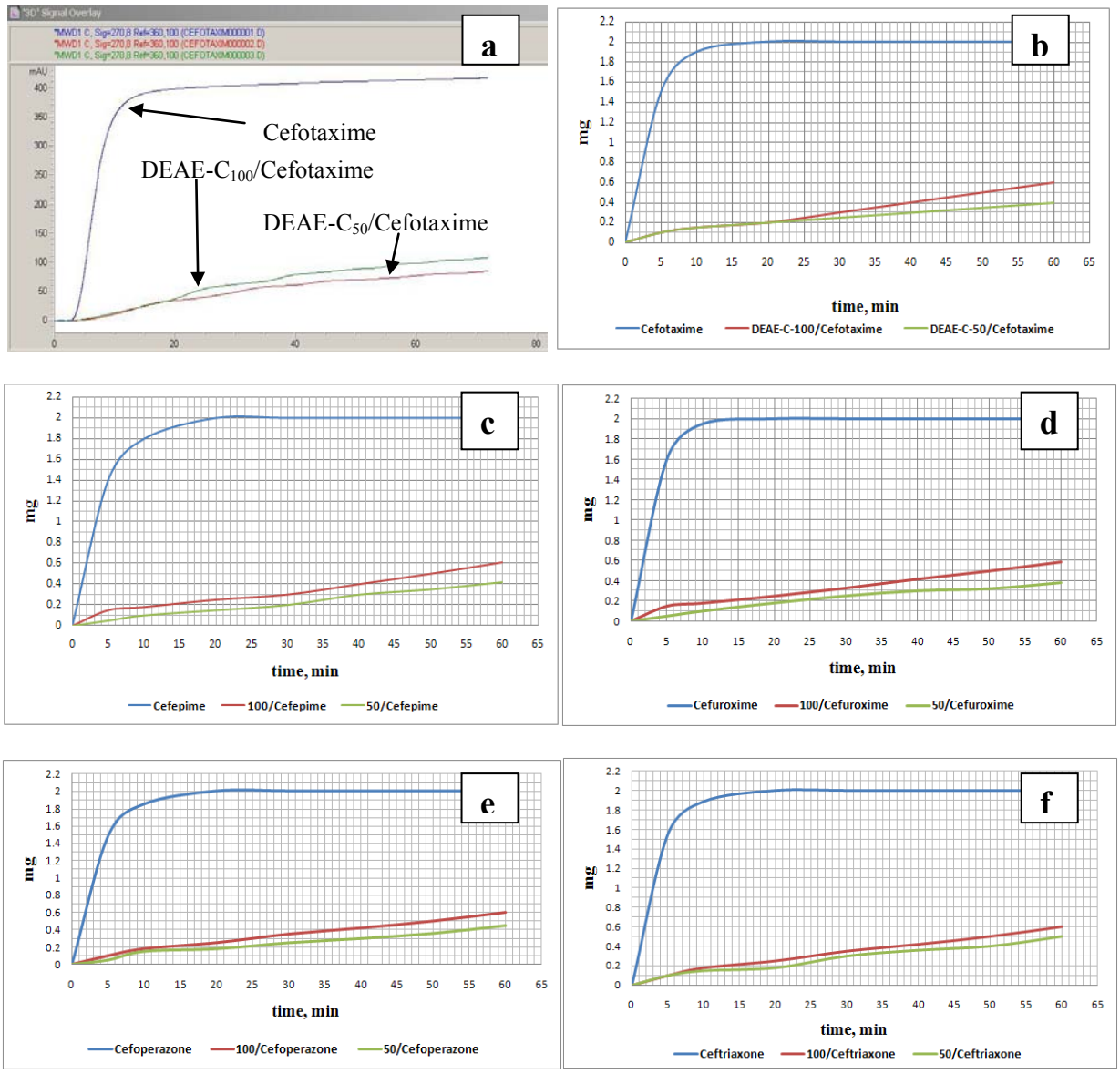

Figure 2: Release control profile of Cephalosporin's: (a) Overlays of HPLC chromatograms of Cefotaxime, Fe_3O_4/DEAE-Celullose$_{50}$/Cefotaxime and Fe_3O_4/DEAE-Celullose$_{100}$/Cefotaxime; (b) Cefotaxime, (c) Cefepime, (d) Cefuroxime, (e) Cefoperazone, (f) Ceftriaxone: amount of cephalosporin's released from magnetic scaffolds in one hour.

In Figure 2(a) the overlays HPLC chromatogram of pure Cefotaxime, DEAE-C_{50}/Cefotaxime and DEAE-C_{100}/Cefotaxime were plotted. It was observed that at times over 1 h the water solubility plateau for the Cefotaxime was not reached, clearly indicating that the cephalosporin is gradually released in aqueous medium from the magnetic scaffold support. In figure 2 (a-f) the quantification of amounts released for all pure cephalosporins, DEAE-C_{50}/Cephalosporins and DEAE-C_{100}/Cephalosporins were plotted. In all cases, the maximum pure active compound concentration

was reached after less than 10 min, being followed by a plateau that indicates that the solubility limit corresponding to the complete dissolution of each active compound was attained. The complete release of the active compound from the magnetic materials is expected to reveal a similar concentration-time profile. The controlled release properties of the prepared DEAE-C_{50} and DEAE-C_{100} were high lightened by the fact that the active compound concentration was much below its solubility limit after 1 h, in every experiment. A period of approximately 10 hours is necessary for the complete release of the active compound from the support. In all experiments, on the mg *vs*. time curve, two or three distinct regions of different slope were observed. Some changes in the release process can explain the passage from one region to another. Such changes were presumed to be due to the formation of multiple adsorption shells in the synthetic process. Firstly, the solvation process affects the outermost shell and continues with the other multiple adsorption shells. Therefore, the successive release of different adsorption shells starting with the outermost shell of the whole magnetic scaffolds/successive adsorption shells and moving to its interior can explain the appearance of several regions of different slope. Slight changes in the intermolecular forces are concomitant with the successive dissolution of the multiple adsorption shells, the adsorption shell being gradually closer to the outer surface of the magnetite/diethylaminoethyl-cellulose magnetic hybrid materials.

4. Conclusions

The capability of magnetic cellulose hybrid material for local delivery of antibiotics increases their utility in biomedical applications. The drugs were successfully incorporated and released from micro fibrous scaffolds without structural integrity loss or change in functionality according to our previous study [26]. The *in vitro* drug release properties of both magnetic scaffolds were investigated. It was observed that the cephalosporins loaded onto magnetic scaffolds presented a slow initial burst during the first 5 minutes followed by a rather constant and low release profile over the subsequent period of 55 minutes. The cephalosporins without magnetic scaffolds showed a sharp initial burst during the first 5 minutes. The whole release period of pure cephalosporins could last up to 10 minutes, in comparison with the magnetic scaffolds drugs that even after 1 hour did not reach the maximum release. At high levels of magnetic scaffold dehydration, the drug interaction with the support is weaker. These distinct behaviors make the hybrid structure material promising for new drug release materials.

5. References

[1]Asadpour J., Optoelectronics and Adv. Mat.–Rapid Com., Some topological polynomial indices of nanostructures, 5, 7, 769, **2011**

[2]Stancu M., Ruxanda G., Ciuparu D., Dinescu A., Purification of multiwall carbon nanotubes obtained by AC arc discharge method, Optoelectronics and Adv. Mat.–Rapid Com., 5, 8, P. 846, **2011**

[3]Avile´ S M. O., Ebner A. D., Ritter J. A., Ferromagnetic seeding for the magnetic targeting of drugs and radiation in capillary beds, J. of Mag. And Mag. Mat., 310, 131 (2007)

[4]Ungureanu C., Ionita D., Badea N., Demetrescu I., From nanoscale engineering to biomedical application - characterization of pulse electrodeposited biomimetic antibacterial coating on Ti_6Al_4Zr, Digest J. of Nanomat. and Biostruct., 6, 3, 1273, **2011**

[5] Xi-Lin Wang, Yu-Zhen Zhao, Yong-Jie, Zhao, Shan-Shan Liu, He-Ping Zhou, Fabrication of bst nano-ceramics by two-step sintering, Digest J. of Nanomat. and Biostruct., 6, 3, 953, **2011**

[6]Asadpour J., Mojarad R., Safikhani L., Computing some topological indices of nano structures, Digest J. of Nanomat. and Biostruct., 6, 3, 937, **2011**

[7]Banerjee J., Narendhirakannan R.T, Biosynthesis of silver nanoparticles from syzygium cumini (l.) seed extract and evaluation of their in vitro antioxidant activities, Digest J. of Nanomat. and Biostruct., 6, 3, 961, **2011**
[8] Andeani J. K., Kazemi H., Mohsenzadeh S., Safavi A., Biosynthesis of gold nanoparticles using dried flowers extract of achillea wilhelmsii plant, Digest J. of Nanomat. and Biostruct., 6, 3, 1011, **2011**
[9]Satyavani K., Ramanathan T., Gurudeeba S., Green synthesis of silver nanoparticles by using stem derived callus extract of bitter apple (citrullus colocynthis), Digest J. of Nanomat. and Biostruct., 6, 3, 1019, **2011**
[10]Slav A., Optical characterization of TiO_2-Ge nanocomposite films obtained by reactive magnetron sputtering, Digest J. of Nanomat. and Biostruct. 6, 3, 915, **2011**
[11]Popovici R. F., Mihai C.T., Seftel E.M., Rotinberg P., Popovici,V. E., Voicu A., Interactions of the mesoporous silica-captopril nanocomposites with some metabolic processes in monkey kidney vero cells, Digest J. of Nanomat. and Biostruct. 6, 3, 999, **2011**
[12]Alexa I. F., Popovici R. F., Ignat M., Popovici E., V. Voicu A., Digest J. of Nanomat. and Biostruct., 6, 3, 1091, **2011**
[13]Mahmoodi M., Khosroshahi M. E., Atyabi F., Early experimental results of thrombolysis using controlled release of tissue plasminogen activator encapsulated by plga/cs nanoparticles delivered by pulse 532 nm laser, Digest J. of Nanomat. and Biostruct., 6, 3, 889, **2011**
[14]Vlad S., Ciobanu C., Gradinaru R. V., Gradinaru L. M., Nistor A., Antibacterial evaluation of some polyurethane membranes modified by zinc oxide nanoparticles, Digest J. of Nanomat. and Biostruct., 6, 3, 921, **2011**
[15]Neamtu J., Verga N., Magnetic Nanoparticles for Magneto-Resonance Imaging and Targeted Drug Delivery, Digest J. of Nanomat. and Biostruct., 6, 3, 969, **2011**
[16]Saviuc C., Grumezescu A.M., Holban A., Bleotu C., Chifiriuc C., Balaure P., Lazar V., Phenotypical studies of raw and nanosystem embedded Eugenia carryophyllata buds essential oil antibacterial activity on Pseudomonas aeruginosa and Staphylococcus aureus strains, Biointerface Res. in App. Chem., 1, 3, 111, **2011**
[17]Saviuc C., Grumezescu A. M., Holban A., Chifiriuc C., Mihaiescu D., Lazar V., Hybrid nanostructurated material for biomedical applications, Biointerface Res. in App. Chem., 1, 2, 064, **2011**
[18] Ming-Jenn Chen,Yen-Yi Chu, Pei-Heng Lai, Ya-Min Cheng, Yi-Chiang Hsu, Experimental results of colorectal cancer chemoprevention by curcuminoids loaded nano-carrier drug delivery system increased in vitro biocompatibility, Digest J. of Nanomat. and Biostruct., 6, 3, 1187, **2011**
[19]Fatahian S., Shahbazi D., Pouladian M., Yousefi M. H., Amiri Gh. R., Shahi Z., Shahabadi M,, Jahanbakhsh H., Preparation and magnetic properties investigation of Fe_3O_4 nanoparticles ^{99m}Tc labeled and Fe_3O_4 nanoparticles DMSA coated, Digest J. of Nanomat. and Biostruct., 6, 3, 1161, **2011**
[20]Grumezescu A. M., Mihaiescu D. E., Mogoşanu D. E., Chifiriuc M. C., Lazăr V., Călugărescu I., Trăistaru V., *In vitro* assay of the antimicrobial activity of Fe_3O_4 and $CoFe_2O_4$ / oleic acid – core/shell on clinical isolates of bacterial and fungal strains, Optoelectronics and Adv. Mat.–R. Com., 4, 11, 1798, **2010**
[21]Ghazi M.E., Izadifard M., Bagherzadeh M., Effect of electrolyte temperature on magnetic properties of Ni-Co-Cu alloy nanofilms grown on si substrate by electrodeposition method, Digest J. of Nanomat. and Biostruct., 6, 3, 1167, **2011**
[22]Chirea M., Pereira E. M., Pereira C. M., Silva F., Synthesis of poly-Lysine/Gold nanoparticle films and their electrocatalytic properties, Biointerface Res. in App. Chem., 1, 4, 119, **2011**
[23]Chirea M., Pereira E. M., Pereira C. M., Silva F., DNA Biosensor for the Detection of Actinomycin D, Biointerface Res. in App. Chem., 1, 4, 151, **2011**
[24]Grumezescu A. M., Ilinca E., Chifiriuc C., Mihaiescu D., Balaure P., Traistaru V., Mihaiescu G., Influence of magnetic MWCNTs on the antimicrobial activity of cephalosporins, Biointerface Res. in App. Chem., 1, 4, 139, **2011**
[25]Mihaiescu D.E.., Grumezescu A.M., Mogosanu D.E., Traistaru V., Balaure P.C.., Buteica A.S., Hybrid organic/inorganic nanomaterial for controlled cephalosporins release, Biointerface Res. in App. Chem., 1, 2, 41, **2011**
[26]Grumezescu A. M., Voicu G., Saviuc C., Holban A., Mihaiescu D., Chifiriuc C., Magnetic DEAE-Cellulose/Cephalosporins hybrid material for targeted drug delivery, *Romanian Journal of Materials*, in press