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Hybrid inorganic/organic nanomaterial for controlled cephalosporins release

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ABSTRACT

The dynamics of cephalosporins controlled release from a new hybrid inorganic/organic nanomaterial was investigated. Magnetic Fe_3O_4 nanoparticles were synthesized using the sol-gel method, while a hybrid nanostructured Fe_3O_4/oleic acid – core/shell – material was prepared under microwave conditions and further characterized by High Resolution Transmission Electron Microscopy. The dimensions of Fe_3O_4/oleic acid nanoparticles were in the 5-20 nm range. After drying at 105 ^oC for 24 hours, the hybrid nanomaterial was dispersed in $CHCl_3$ and then various cephalosporins were deposited on the magnetic nanofluid in a concentration of 0,3%. The controlled release properties of the nanostructured core/shell material were studied by means of conductometric and UV-VIS techniques. In all cases, at large time values (more than 4000 seconds), the cephalosporin concentration was much below the solubility plateau for the pure active compound, demonstrating that the adsorption on a hybrid nanostructurated material is a valuable procedure to attain controlled delivery of these compounds in the dispersion medium.

Keywords: *cephalosporins, hybrid organic/inorganic, controlled release, ferrofluid, nanomaterial*

1. Introduction

A more and more intensive and dynamic research field nowadays is that one dealing with the huge application potential of various nanostructured materials, ranging from micromagnets and high density magnetic storage devices [1] to materials with improved peculiar mechanical properties [2], metal colloids [3,4], and nano-biotecnology. Despite, the tremendous effort devoted to possible applications of nanostructured materials in medicine and pharmacology, this research field is still in its infancy. Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and novel physical, chemical and biological properties of materials at the nanometric scale [6]. It has potential impact on the prevention, early and reliable diagnosis and treatment of diseases [7],[9]. Prediction of the physico-chemical, pharmacological and toxicological properties is crucial to implement nanomaterials in therapy and diagnosis [8]. Therefore, a very important research area deals with identification of those parameters that could correlate the intrinsic structure of the nanomaterial to its biopharmaceutical and therapeutic properties. For instance, in the case of some nanotubes, certain properties can be correlated to and deduced from the eccentric connectivity index [8]. Pharmaceutical nanotechnology focuses on formulating therapeutically active agents [10] in biocompatible nanoforms such as nanoparticles, nanocapsules and conjugates. The lack of control of

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drug release [11], [12] from conventional drug formulations in response to physiological requirements have led to development of controlled drug delivery systems [13]. These systems offer many advantages representing an improved and more safety and efficient therapeutic alternative, either by providing targeted drug delivery or conferring a better bioavailability, extended period of drug efficacy and improved stability of therapeutic agents against chemical/enzymatic degradation [14]. Another major benefit of nano-drug delivery systems results from the possibility to reduce the oral administered dose especially for those drugs, such as the current anti-inflammatory medication, known to produce many harmful side-effects. In conventional drug delivery, drug concentration in the blood stream will increase, peak and then drop as the drug is metabolized and eliminated, whereas the cycle is repeated for each drug dose. In nano-drug delivery systems [15], [19], controlled drug release allows for maintaining drug concentration within the therapeutic window for prolonged periods of time. The present work is focused on the preparation of a new drug delivery nanosystem and testing it in controlled release of cephalosporins. This work comes in completion of other results previously reported by our research group [20]-[23]. The new drug delivery nanosystem was prepared by adsorbing various cephalosporins on magnetic Fe_3O_4/oleic acid – core/shell – nanoparticles. The system shown effective controlled drug delivery properties by considerable slowing down the rate of cephalosporins release.

2. Experimental section

2.1. Design of core/shell/adsorption-shell interaction. The studied cephalosporin molecules are presented in Fig. 1-4 as projection structures and perspective representations, with a color gradient charge distribution and the value of the partial charge displayed at each atom. These results were obtained using the MINDO method and optimization by the conjugate gradients method.

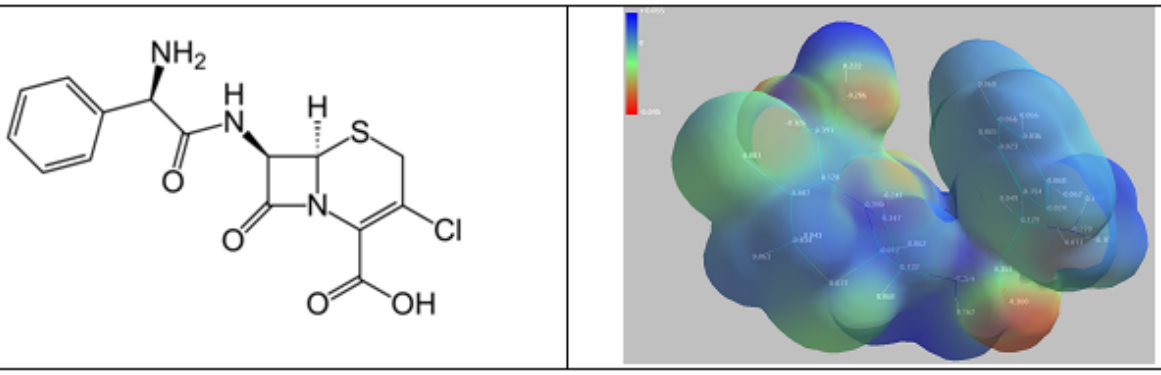


Fig. 1 Cephaclor

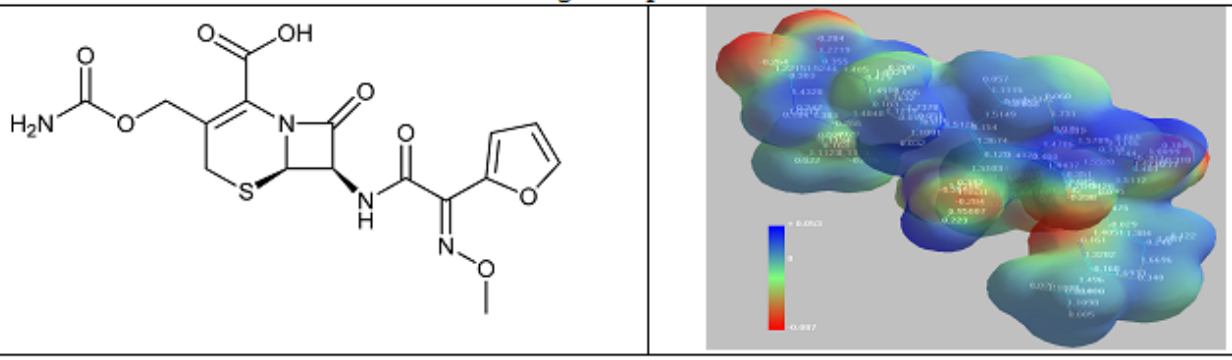


Fig. 2 Cefuroxime

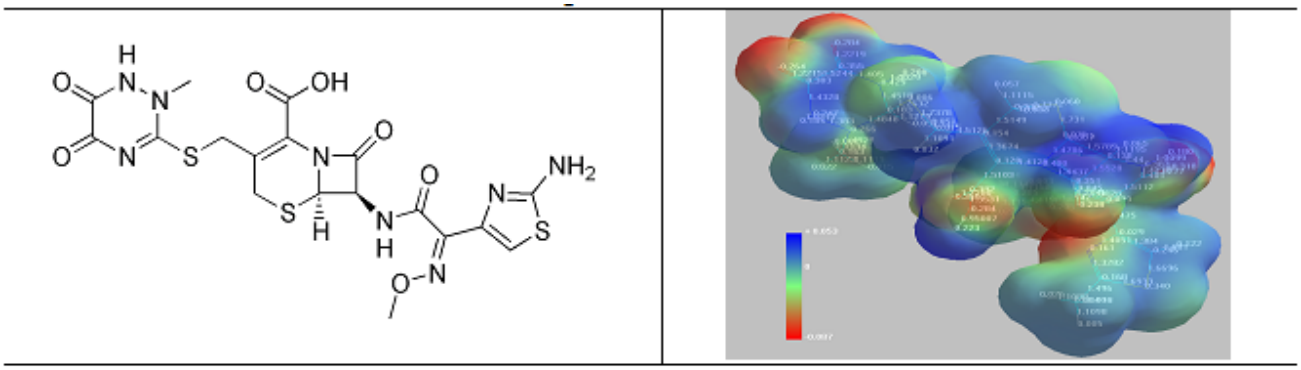


Fig. 3 Ceftriaxone

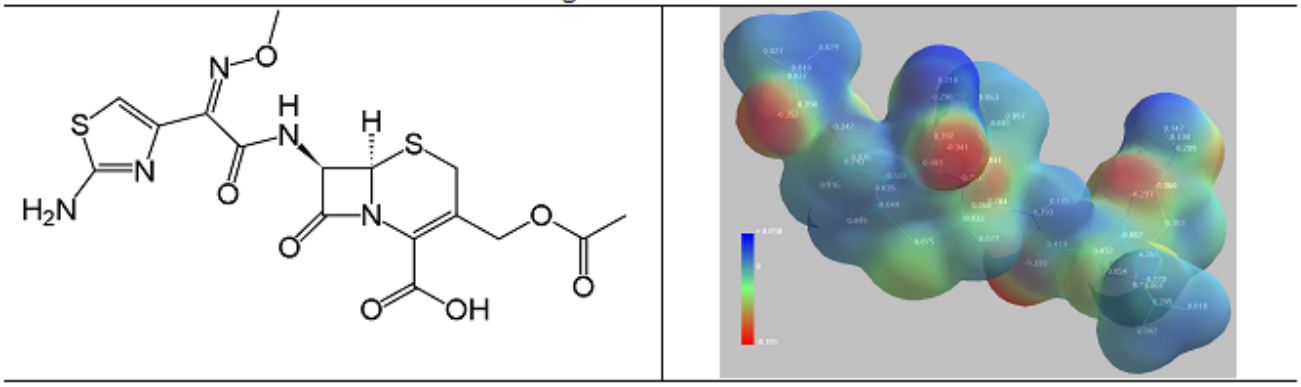
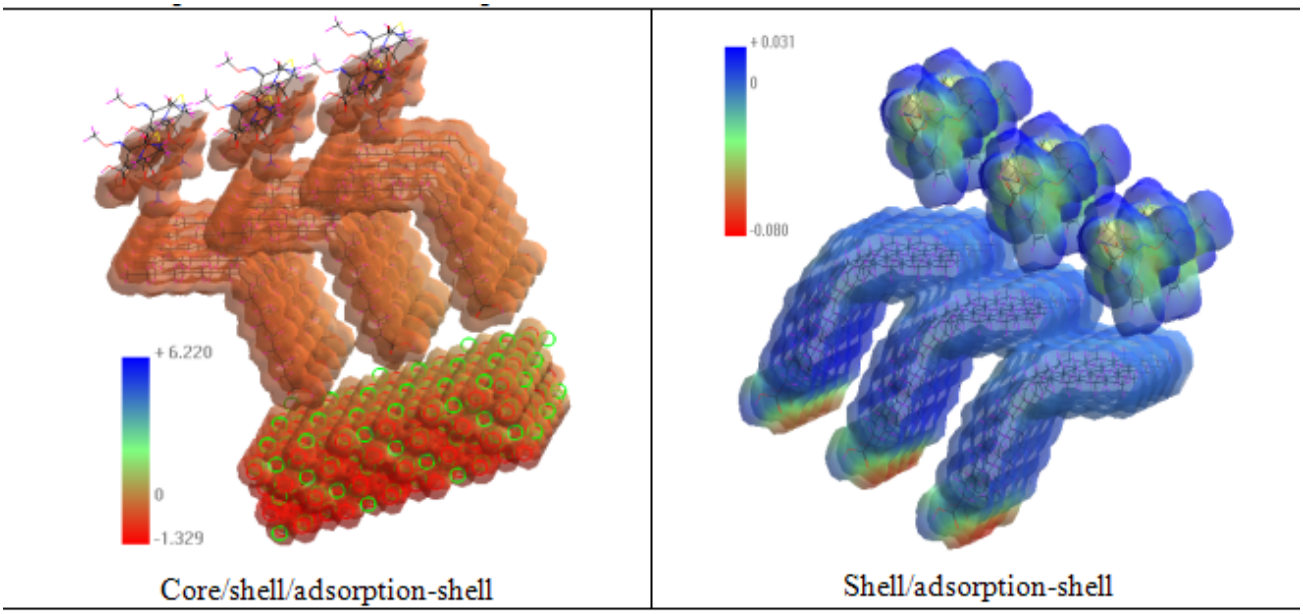


Fig. 4 Cefotaxime

Due to its polar structure, oleic acid was chosen to attach the active compound to the nanostructured support; the polar moiety –COOH interacts with the core. The non-polar hydrocarbon chain forms the outer layer (shell) of the nanoparticle. Due to the *cis* configuration of the double bond, the bent structure of the oleic acid allows a better spatial orientation of the hydrocarbon moieties and an extended interaction with the more polar active compounds. It is also prone to formation of a charge transfer complex with the active compound.



Core/shell/adsorption-shell Shell/adsorption-shell

Fig. 5 Design of core/shell/adsorption-shell interaction

Molecular mechanics model of active compounds revealed that in addition to their high polarity, they also exhibit a significant non-polar surface that allows a good interaction with the nanostructured support. In Fig. 5 the core/shell/adsorption-shell interaction model is presented. It implies fixation of the active compound adsorption-shell on the oleic acid shell by dipole-induced

dipole and van der Waals bonds and that of the oleic acid shell on the Fe_3O_4 core by dipole-dipole and hydrogen bonds (assuming that some polar –OH groups in the initial ferric hydroxide were retained on the surface of the nanoparticle). The core/shell/adsorption-shell interaction model shows that the active substance forms a secondary layer whose polarity is determined mostly by the polarity of the active substance and by its orientation towards the initial oleic acid shell.

2.2. Synthesis and characterization of core/shell/adsorption-shell. The Massart method, was used for Fe_3O_4 nanoparticles synthesis. Fe_3O_4/oleic acid – core/shell nanoparticles – were prepared by microwave assisted synthesis. Thus, a mixture of Fe_3O_4 nanoparticles and oleic acid was subjected to a microwave field for 10 minutes. High resolution transmission electron microscopy was used as a primary characterization method for Fe_3O_4/oleic acid – core/shell – dimension [20]-[23]. Dimensions of resulted core/shell magnetic nanoparticles were in the range between 5-20 nm [20]-[23]**.** After drying in an oven at 105°C for 24 hours, and subsequent dispersion of the core/shell nanoparticles in $CHCl_3$, various cephalosporins were added. The concentration of deposited cephalosporins was 0.3 % [20]-[23]. FT-IR spectroscopic measurements were performed using a Thermo-Nicolet 6700 spectrometer operating in the wave number range 650– 4000cm^{-1} with a resolution of 4 cm^{-1} for both Fe_3O_4 and Fe_3O_4/oleic acid nanoparticles, as well as for Fe_3O_4/oleic acid/cephalosporins.

2.3. Controlled cephalosporins release from the hybrid organic/inorganic nanomaterial monitored by conductometric method. The cephalosporin controlled release dynamics from the core/shell/adsorption shell nanoparticles was conductometrically studied using a Denver Instruments 220 conductometer. An OIML standard of KCl with a conductivity of 1408 μS/cm was used for calibration. The analytical instrument was coupled with a PC by a RS232 interface, the data acquisition being performed at 0.5 seconds, with mediation at each 10 experimental points. Data processing was performed in Microsoft Excel, with a spline interpolation. The samples were introduces in the working apparatus, thermostated at 25°C, under controlled and continuous stirring. The experimental results (conductivity *vs* time) are presented in Figure 8.

2.4. Controlled cephalosporins release from hybrid organic/inorganic nanomaterial monitored by UV-VIS spectrometry.

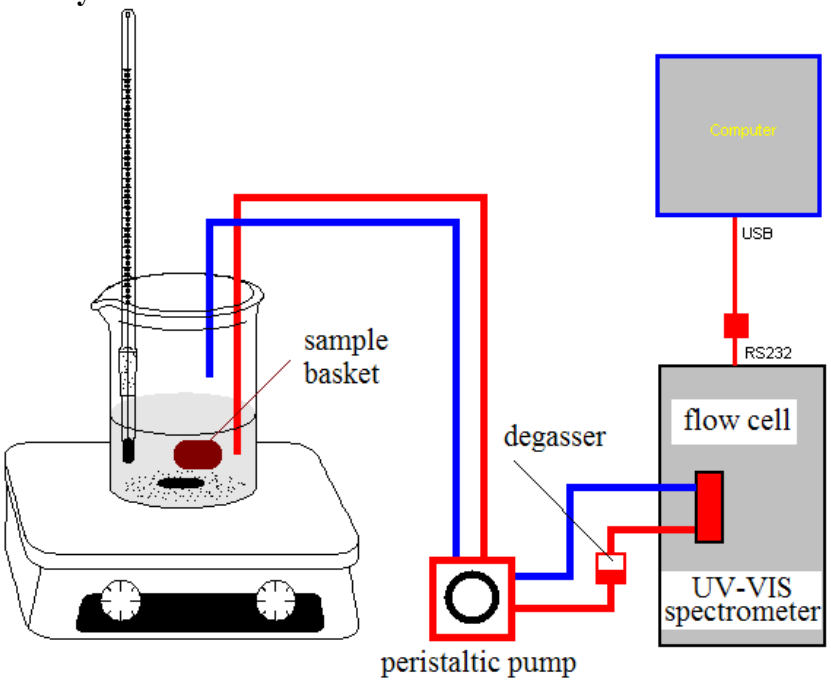


Figure 6. Experimental equipment for controlled release monitoring by UV-VIS spectrometry

The experiments were conducted using a spectofotometer coupled with a PC by a RS232 inferface, the data acquisition being performed at 1 second, with mediation at each 7 experimental points. Data processing was performed in Microsoft Excel, with a spline interpolation. The samples were introduces in the working apparatus, thermostated at 25°C, under controlled and continuous stirring. In order to avoid migration of the hybrid nanomaterial through the system, the sample (40

mg nanostructurated support along with the deposited active compound) was placed in a sample bascket of small porosity filter paper. The work flow was maintained with a peristaltic pump at 150 mL/min. The obtained results (in absorbance units *vs* time) are plotted in Figure 9.

3. Results section

Figure 7 presents the FT-IR spectra of Fe_3O_4/oleic acid and Fe_3O_4/oleic acid/cephalosporins nanoparticles. The successful modification of the Fe_3O_4/oleic acid nanoparticles by cephalosporins was undoubtedly confirmed by appearance of new bands between 1350 and 1650 cm-1. In Figures 8 and 9, the red-marked curves correspond to the pure active compound while the blue ones to the hybrid core/shell/adsorption-shell nanomaterial**.** It can be observed that at times over 4000 seconds the water solubility plateau for the pure compound was not reached, clearly indicating that the cephalosporins are gradually released in aqueous medium from the nanostructured support on which they were previously adsorbed.

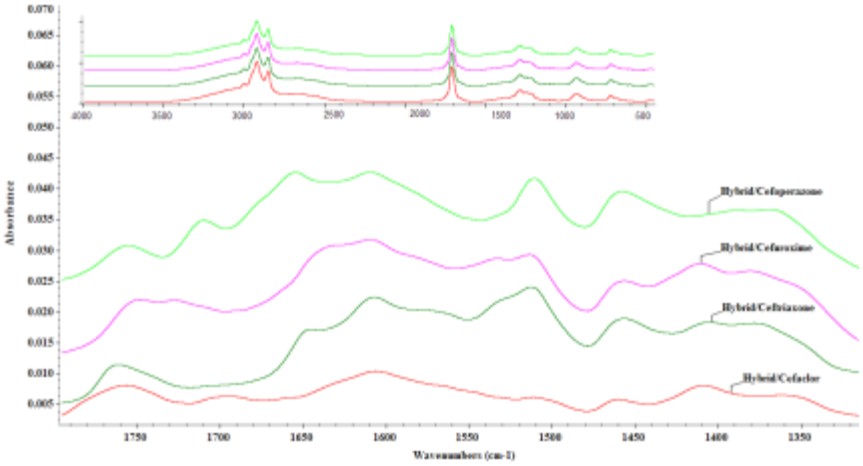


Figure 7: FT–IR spectra of hybrid inorganic/organic nanostructured material

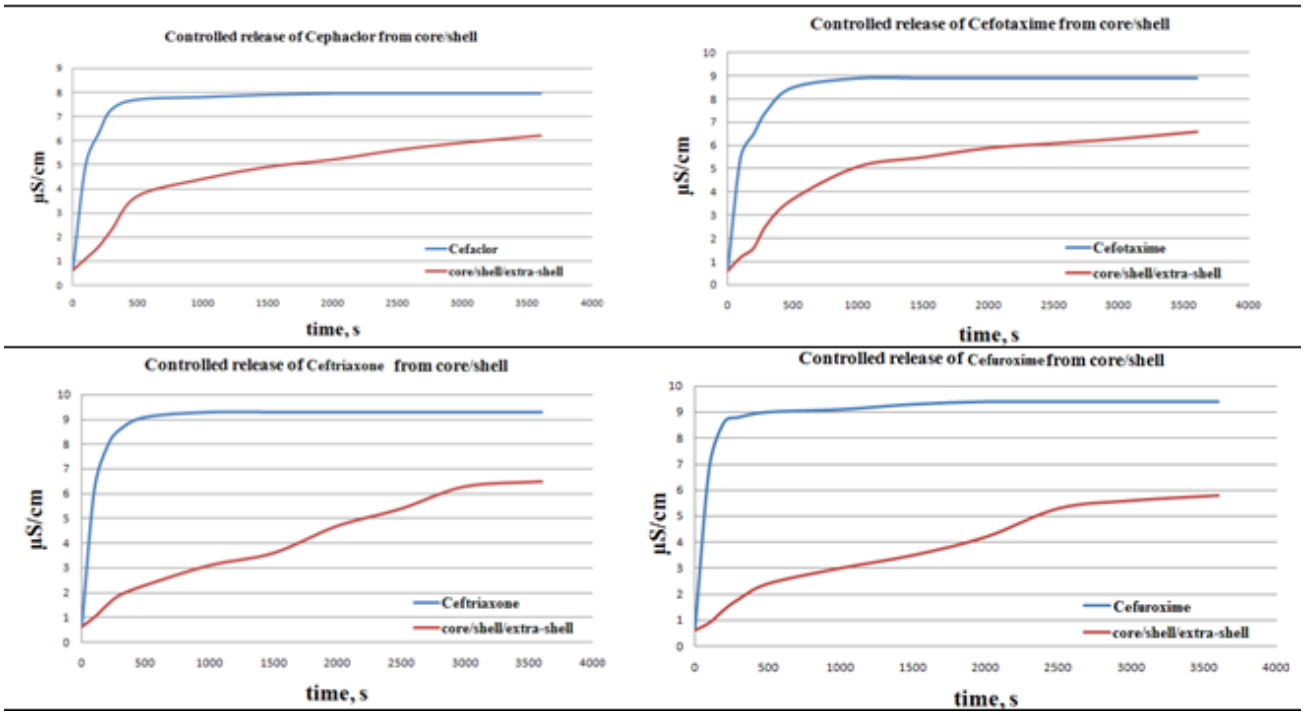


Figure 8. Controlled release of cephalosporins from core/shell/adsorption-shell monitored by conductometric method

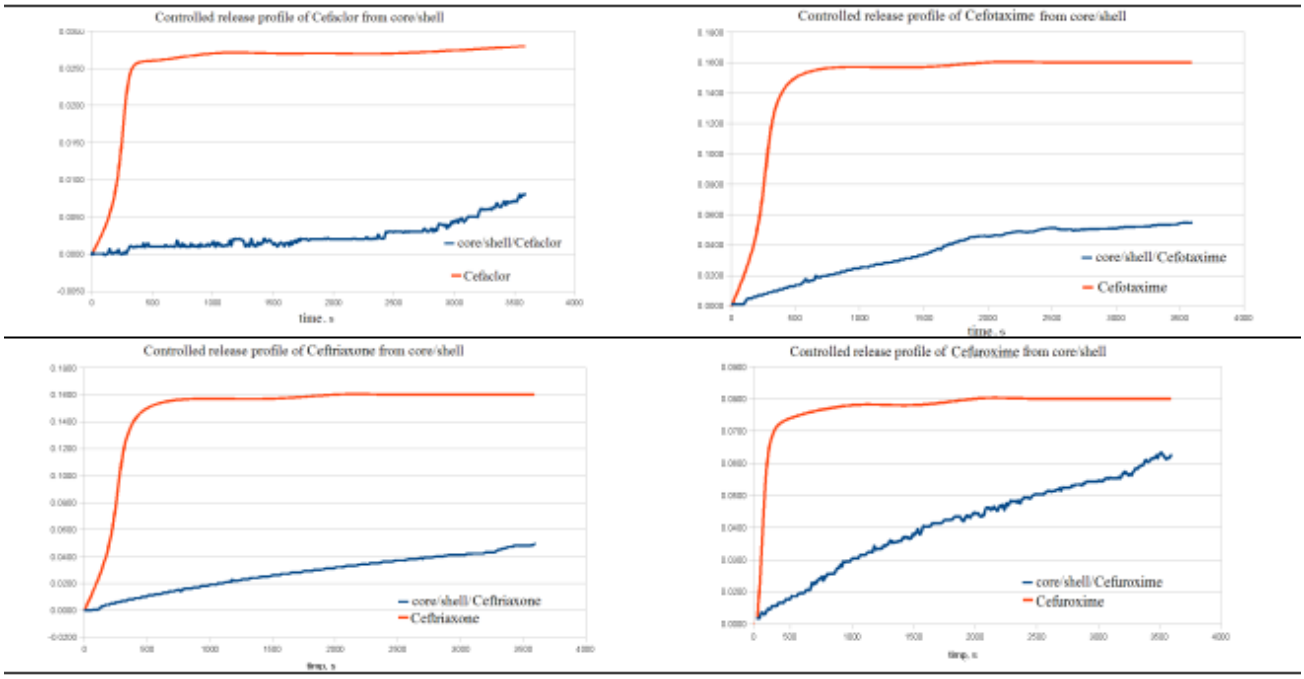


Figure 9. Controlled release of cephalosporins from core/shell/adsorption-shell monitored by UV-VIS spectrometry

4. Conclusions

For all studied active compounds, the same quantity that was first used to determine the corresponding solubility limit of each compound, was subsequently deposited on the hybrid inorganic/organic controlled release nanosystem. In all cases, the maximum pure active compound concentration was reached after less than 300 s, being followed by a plateau that indicates that the solubility limit corresponding to the complete dissolution of each active compound was attained. The same concentration-time profile should be obtained in the case of a complete release of the active compound from the core/shell/adsorption-shell nanostructured system. The performed experiments revealed that after 3600 s, the active compound concentration was much below its solubility limit clearly demonstrating the controlled release properties of the prepared hybrid nanosystem. A complete release of the active compound from the nanostructured support occurs only after a time period of about 10 hours. In all the cases, two or three distinct regions of different slope were observed on the conductivity *vs*. time curve. The passage from one region to another is correlated with some changes in the release process. These changes were ascribed to formation of multiple adsorption shells in the synthetic process. In turn, these multiple adsorption shells are successively solvated starting from the outermost shell. Hence, the appearance of several regions of different slope would indicate the successive release of different adsorption shells starting with the outermost shell of the whole core/shell/successive adsorption shells nanostructured system and moving to its interior. Successive solvation of the multiple adsorption shells is accompanied by slight changes in the intermolecular forces as the adsorption shell gets gradually closer to the outer surface of the hybrid inorganic core/organic shell nanostructured material.

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