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CONTROLED RELEASE STUDY OF AZTREONAM FROM MCM-41 MESOPOROUS MATERIAL

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The present study is focused on the synthesis of the Aztreonam loaded MCM-41 based materials and testing of the release profile of Aztreonam from these materials. Based on these results it can conclude that these materials are potential tools towards achieving more efficient release of the drug in the human body, thus minimizing the dosage needed for the desired antibacterial effect. Based on the delivery curve, a fast release is observed in the first 3h followed by a very slow release. The degree of aztreonam recovery is less than 60% at 18h.

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1. Introduction

The field of controlled drug release/delivery has become important nowadays because it allows us to reduce the dosage required in order to achieve the desired inhibitory effect and to maximize the efficiency of the existing antibiotics [1]. Controlled drug delivery systems based on MCM-41 are extensively used, current application includes delivery of non-steroids anti-inflammatory drugs – NSAID, antibiotics, antihypertensive drugs, citostatics, etc. [2].

Aztreonam [3-6] is a synthetic antibiotic from the beta-lactam class [3], monocyclic, with the nucleus based on a simpler monobactam isolated from Chromobacterium violaceum. It was FDA approved for the first time in 1986. It is resistant to some beta-lactamases, but it is inactivated by extended-spectrum beta-lactamases.

Aztreonam has a similar action in many ways to the one of penicillin [3]. It inhibits mucopeptide synthesis in the bacterial cell wall, thereby blocking peptidoglycan crosslinking. Aztreonam is bactericidal but less so than some of the cephalosporins. Aztreonam has strong activity against susceptible gram-negative bacteria, including *Pseudomonas Aeruginosa* [3] . It has no useful activity against gram-positive bacteria or anaerobes. It is known to be effective against a wide range of bacteria including *Citrobacter* [7], *Enterobacter* [5], *E. coli* [8], *Haemophilus* [9] and others. Aztreonam is often used in patients who are penicillin allergic or who cannot tolerate aminoglycosides [3].

Due to the fact that the bactericidal activity of Aztreonam is not as important as that of other cephalosporins, the dosage must be increased in order to produce the desired effect, in order to compensate for digestive losses due to decomposition of the product before it can get a chance to reach the blood stream. In order to prevent such occurrences, controlled drug delivery experiments can be a way to achieve this goal.

MCM-41 materials have been used in the last years for various applications, among which microwave assisted catalysis [10], catalyzed hydrolysis [11], materials with low power microwave heating [12] super-capacitor devices [13], nanosensors [14] or studies for positron annihilation

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[15]. From among the possible means of drug delivery, MCM-41 type materials are a good way of delivery, given the robust mechanical features of this material, the tunable networks of mesopores, and the possibility for further improvement of the materials by addition of functional groups anchored on the surface. MCM-41 was intensively used as candidate for controlled release of different bio-active substances. To our knowledge it was never used as a controlled release candidate for aztreonam. Therefore in the present article the release profile of aztreonam from MCM-41 mesopores, as a possible tool for an improved delivery for aztreonam in the human body was studied.

2. Materials and methods

Aztreonam was purchased from Sigma Aldrich, analytical standard purity, and was used as such without further purification. Cetyl trimethyl ammonium bromide (CTAB) was purchased from FLUKA, reagent grade, tetraethylorthosilicate (TEOS), Ethylic alcohol, Ammonium hydroxide solution 25%, were purchased from Sigma Aldrich, reagent grade.

For all the experiments, 0.5g CTAB were dissolved in 96 ml of distilled water, under heavy magnetic stirring. After the solution turned clear, 34ml of ethylic alcohol were added and 10ml of ammonium hydroxide solution. After 5 minutes of intense stirring, 2ml of TEOS were added and the reaction was left to stir for 3 hours at room temperature. The final product was recovered by filtration and dried overnight at room temperature, and heated at 550°C with 5°C/min, than left at the temperature for 11 hours.

The method for the synthesis of MCM-41 is the one used by H.I. Melendez-Ortiz [16] with minor modifications. After the white powder has cooled, it was characterized by IR spectroscopy and Transmission Electron Microscopy - TEM in order to confirm that the MCM-41 hexagonal mesopore structure was achieved. The loading with Aztreonam was done at room temperature. 100mg of MCM-41 materials were ground together with 30mg of Aztreonam to a fine powder, and afterwards 10ml of ethanol were added in order to induce the diffusion of the antibiotic into the mesoporous channels. The alcohol was removed over-night in order to facilitate a slow diffusion of the antibiotic in the mesopores.

All FT-IR spectra were recorded using a Thermo Nicolet 6700 series spectrometer fitted with ZnSe crystal/microATR accessory. The samples were grinded to a very fine powder before spectra recording. TEM measurements were made using a TecnaiTM G2 F30 S-TWIN type microscope, equipped with a STEM/HAADF detector.

For the determination of the release profile, 50mg of loaded material were placed inside a nacelle made from filter paper and were suspended in 150ml of distilled water. The release profile was recorded continuously using the pump and the UV-Vis detector from a HPLC system. Both the inlet and the outlet of the HPLC system were place inside the beaker, thus providing a continuous loop. The beaker containing the solution was constantly stirred using magnetic stirring. The experiments were repeated three times with no statistically different results. In order to determine the amount of aztreonam released from the matrix, a calibration curve (10-50mg) was used. The same experimental conditions were used, except that in the filter paper were placed different quantities of pure aztreonam. Concerning calibration, from the linear regression, the coefficient of correlation obtained was 0.999 and the regression parameters ($y=b_0+b_1x$) b_0=-131.505 and b_1=130.071.

3. Results and discussion

From the FT-IR spectra (Fig. ***1***), the loading with Aztreonam can be noticed by remarking the set of peaks which are characteristic to the Aztreonam (3297, 1778, 1644, 1187 şi 1043cm^{-1}) and the characteristic peaks for the MCM material (the characteristic peak at 1058cm^{-1} is partially masked by the 1043cm^{-1} from the Aztreonam).

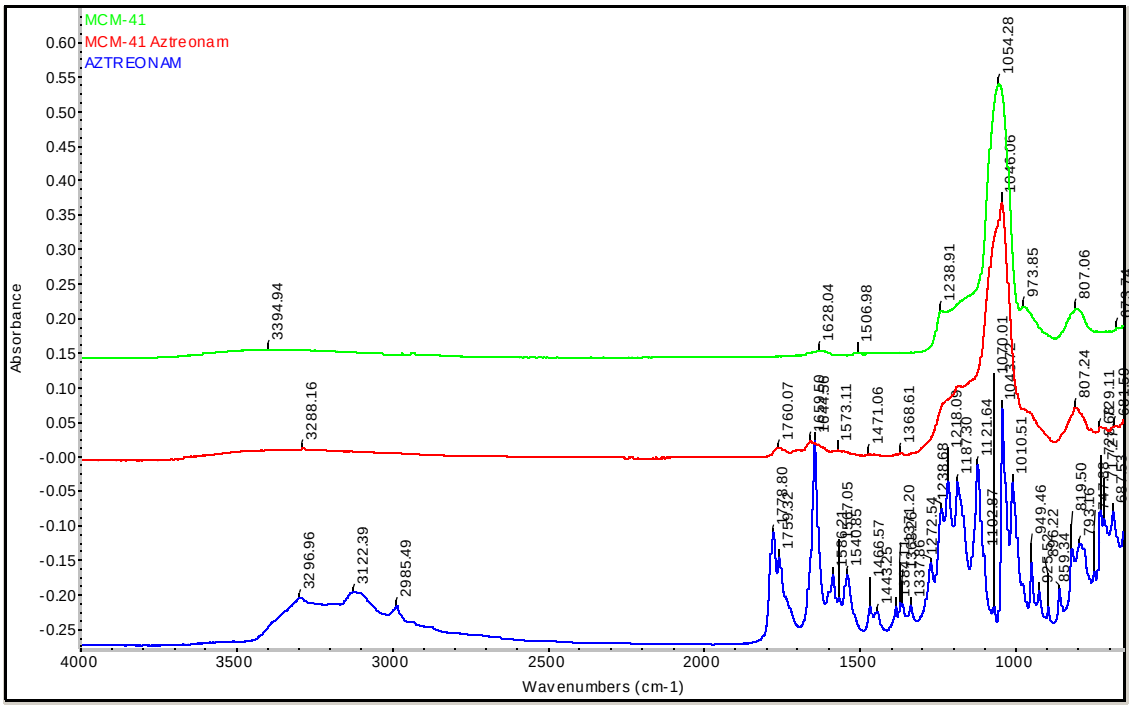

Fig. 1 FT-IR spectra of MCM-41 and aztreonam as references and aztreonam loaded MCM-41

From the high resolution TEM images can be noticed the hexagonal network of mesopores specific to the MCM-41 type material. The mean pore size ranges between 2.8 and 3.2 nm, size which classifies the material in the mesoporous region according to IUPAC [15].

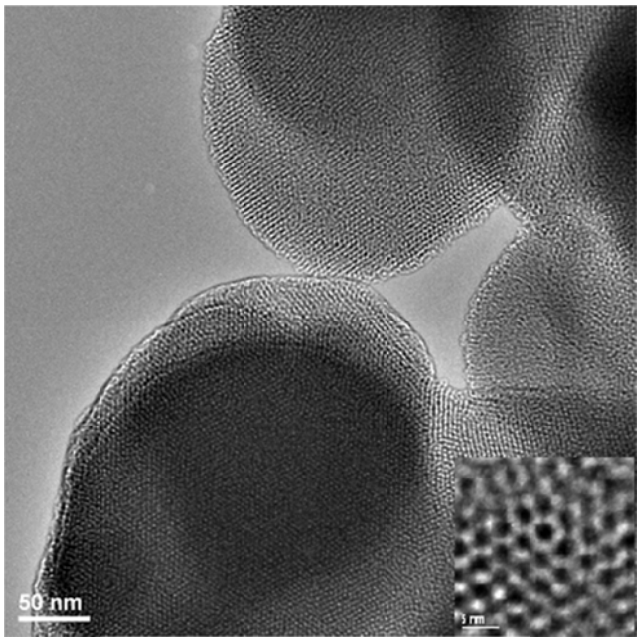

Fig. 2 HR-TEM image of MCM-41 material showing hexagonal porous network

The release profile of Aztreonam from MCM-41 type mesoporous material shows some interesting aspects: the release profile corresponds to a slow release, with a change of delivery rate in the area 100-200 minutes. The amount release is almost constant, the change in slope being due to the excess of aztreonam on the surface groups. The release profile is a convenient one, with a slightly bigger release rate in the first 200 minutes, followed by a slower release, yet incomplete after 1200 minutes, which is conclusive with the assumption of a very slow release profile. In the

first 200 minutes nearly half of the aztreonam was released (8.9mg from the total of 15 mg), the rest following a very slow release profile.

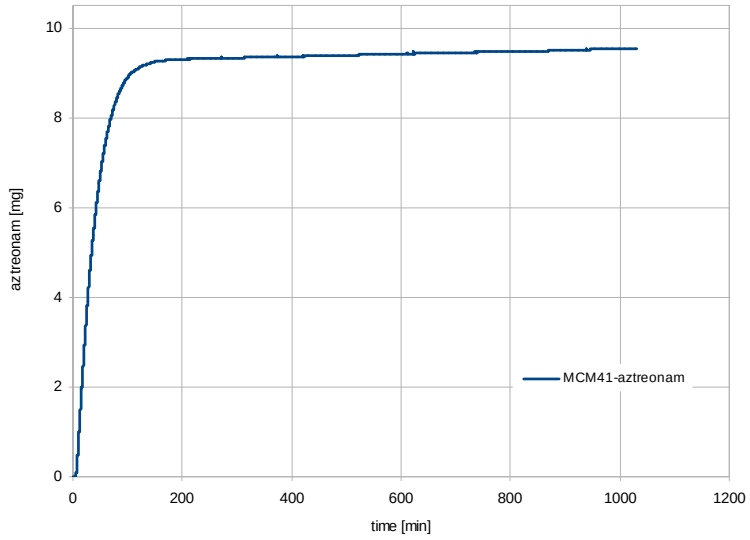

Figure 3 UV release profile of aztreonam loaded MCM-41 material

4. Conclusions

The scope of use of MCM-41 materials in the release of Aztreonam is dual, one being the adjustment of the release rate and the other being the protection of the antibiotic from the action of the gastric acid, in case of oral administration. The average release rate on the first 160 minutes is 3.48 mg/h, and from 160 minutes till 1000 minutes the release rate is drastically reduced to $3x10^{-4}$ mg/h. The amount of antibiotic with a slower release rate, the one most probably stored in the pores, is also well protected to the actions of the gastric acid, the MCM-41 material being immune to acid environments.

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