NEW APPLICATIONS OF FeMOF AS DRUG DELIVERY SYSTEM FOR THEOPHYLLINE

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Introduction

Over the past few years, the rapid development of pharmaceutical science has led to the creation of multiple drug delivery platforms. However, search continues for more versatile solutions that will be able to handle many different routes of administration and fulfil additional applications, e.g. as theranostics. One of the promising drug carriers are MOF materials (Metal-Organic-Framework). It is a group of porous solids built of metallic clusters and organic connections between them, so-called linkers. The formation of coordination bonds between building blocks allows obtaining three-dimensional structures with well-developed surface and extremely large internal space. As a result, MOFs are able to encapsulate drugs and its controlled release [1]. Additionally, G. Wyszogrodzka and coworkers proved that MOF materials could be used in inhalation treatment of tuberculosis [2]. On the basis of the studies, FeMIL-100 MOF material was chosen as a matrix suitable for the inhalation route of administration. The aim of this study was initial evaluation of the properties of FeMIL-100 as a drug carrier of theophylline in terms of its functionality, i.e. drug loading, kinetics of release and biological effect on epithelial human cells.

Materials and Methods

Synthesis and characterization

FeMIL-100 was synthesized according to the procedure described by Guesh et al [3]. The obtained material was examined by PXRD and FTIR techniques.

Preparation of composite

In the first step, 300 mg of Fe-MIL-100 was activated under vacuum at 110°C. After 6 hours of activation, the saturated solution of theophylline in what solution was injected into the glass vial and mixed together with MOF material for 24 hours. After that, the solvent was removed by what treatment. Obtained composite was washed three times with distilled water and dried at room temperature overnight.

Drug release

The drug release was carried out in Franz cells. Gamble's solution (pH=7,4) was used as the medium, simulating lung environment. 5 mg of the composite was placed in the membrane. After 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 24 and 48 hours, an aliquot of 0,1 ml was withdrawn and replaced with the same volume of fresh dissolution medium.

Cell study

Epithelial human cells (A549, ATTC, USA) were cultured in F-12 medium (ATTC, USA) supplemented with 10% foetal bovine serum (ATTC, USA). Murine macrophages (RAW, ATTC, USA) were maintained in Dulbecco's Modified Eagle Medium (DMEM, Sigma Aldrich, USA). The cells were cultured in optimal condition at 37° C, 5% CO_2, and 95% humidity. After passage 3rd, cells were seeded at a density of 5 x 10^3 cells per well (200 µl/well), kept under culture conditions and allowed to adherent. The biocompatibility of the MOF was analysed after 1 and 3 days of the culture with the use of PrestoBlue™ assay (Invitrogen, USA). The level of ROS generation was determined using DCF-DA probe. Depending on the assay, the intensity of the signal of fluorescence or luminescence was measured on the microplate reader POLARstar Omega (BMG Labtech, Germany). Cells morphology was controlled using optical microscope. For all tests, three independent repetitions of each measurement were performed. All data are given as mean ± standard error of mean (SEM).

Results and Discussion

In this study, FeMIL-100 was chosen as a new potential drug carrier for theophylline. PXRD and IR measurements confirmed that drug was placed inside the structure [FIG. 1]. The drug dissolution studies showed the extended release of theophylline. Based on in vitro study, FeMIL-100 is not toxic for epithelial human cells [FIG. 2]. The ROS level was elevated after 1-day incubation but after 3 days it returned to the value characteristic of the control group [FIG. 2]. This effect may be connected with shock for cells after water solution of MOF was added but it did not influence the viability of cells.

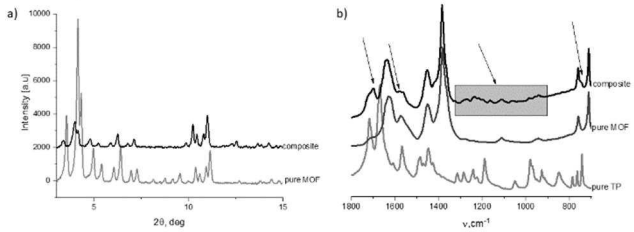

FIG. 1. a) PXRD patterns of FeMIL-100 after and before encapsulation; b) IR spectra in framework vibration region of pure theophylline (TP), pure MOF and composite.

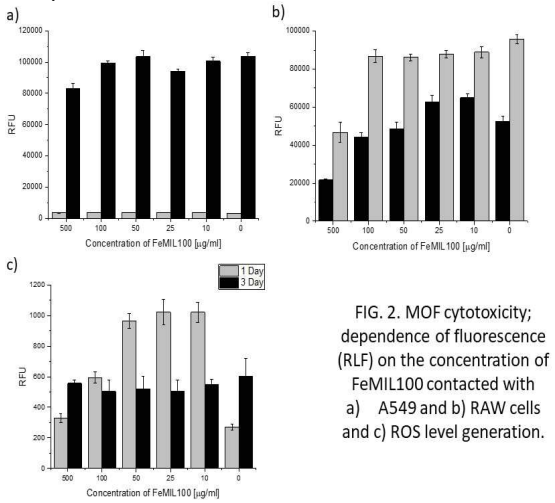

FIG. 2. MOF cytotoxicity; dependence of fluorescence (RLF) on the concentration of FeMIL100 contacted with a) A549 and b) RAW cells and c) ROS level generation.

Conclusions

Based on data gathered from the viability test it is proven that the FeMIL-100 is not cytotoxic and is not negatively influencing the growth of cells. Moreover, it is a potential carrier for theophylline and it is suitable for potential inhalation treatment.

References

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