

# Mesoporous Silica Nanospheres Functionalized by TiO<sub>2</sub> as a Photoactive Antibacterial Agent

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## Abstract

In this contribution we present comparative study on synthesis, bio-characterization and antibacterial properties of mesoporous silica nanospheres modified by titanium dioxide. Mesoporous silica nanospheres functionalized by titania were studied as light activated antibacterial agents. The analysis of the antibacterial effects on *E. coli* ATCC 25922 shows strong enhancement during the visible and ultraviolet light irradiation in respect to the commercial catalyst and sample free from the nanomaterials. In darkness the mesoporous silica/titania nanostructures revealed low antibacterial activity dependent on the stirring intensity of the suspension containing nanomaterials and bacteria. The nanomaterials toxicity was determined on the amount of lactate dehydrogenase released from mouse fibroblast cells L929 with LDH assay. Sample was characterized in details by means of high resolution transmission electron microscopy (HR-TEM), Raman spectroscopy, XRD and BET Isotherm.

**Keywords:** Mesoporous silica nanospheres; Mesoporous silica nanotubes; Titanium dioxide; Photocatalyst; Antibacterial

## Introduction

In recently decade scientists concentrated their attention on the environmental and health care issues. One of this field is for photocatalytic water purification by degradation of the chemical and hazardous biological compounds. Conventional methods of water disinfection and protection from hazardous organic compounds are not effective in the longer term and eliminate only alive form of micro-organisms. Application of the efficient photocatalytic nanomaterials, with high antibacterial performance is potentially future generation method of water purification from organic and biological threats. Recently many scientist put high attention on the synthesis and application of silver nanoparticles [1] and nanocomposites of silver and silica [2,3]. Several reviews suggest use of the various mesoporous silica nanomaterials as a matrix for guest molecules [4,5] as drug delivery [6,7], enzyme immobilization [8], gene transfection [9], titania [10]. Due to highly organized porosity, huge surface area, high pore volume, controlled shape, size and wall thickness has been considered as a perfect carrier for transporting the antibacterial and antifungal agents. As these agents can be used antibacterial drugs or photocatalysts they have recently emerged as an attractive alternative technology for bacterial and fungal disinfection. Mesoporous silica nanomaterials can also serve as a host for titania [11,12]. Titania in anatase structure is a well known photocatalyst, widely studied due to its availability, photoactivity and low cost [13]. This photoinduced phenomenon is affected by its quantum size. Increase in reaction yield in photocatalytic activity increases as the diameter of the TiO<sub>2</sub> particles becomes smaller especially below 10 nm [14]. This observation was attributed to the suppression of radiation less transfer and the concurrent enhancement of the activities of the charge carriers. Titania, at the same time acts as antimicrobial agent in presence of light [15]. Nanoparticles of titania are also widely studied for their synthesis, properties and their antibacterial and photocatalytic properties, respectively [16,17]. It was shown that the photocatalytic efficiency further substantially increases when metal nanoparticles are coupled with titania particles. It was reported that the addition of noble metals in TiO<sub>2</sub> may enhance the overall

photocatalytic efficiency [18-21]. Composite structures of titania with Ag nanoparticles are studied for their photocatalytic activity and have shown the enhanced photodegradation of organic molecules [22-24].

This article describes a simple synthesis methodology of mesoporous silica nanospheres functionalized by TiO<sub>2</sub> with enhanced bactericidal efficiency and photocatalytic properties. The detailed studies on spherical mesoporous structures have been performed. Furthermore, the correlation between cytotoxicity and the antibacterial activity of the samples has been revealed.

## Materials and Methods

### Materials

Silica (tetraethyl orthosilicate - TEOS) and titania precursor (Titanium(IV) butoxide - TBT) was purchased from Sigma-Aldrich. Ammonium solution, ethanol and n-propanol were provided from Chempure (Poland, Piekary Śląskie) and from Polskie Odczynniki Chemiczne - POCH S.A. (Poland, Gliwice).

### Synthesis of silica nanospheres with mesoporous shell (mSiO<sub>2</sub>)

1.5 mL of the tetraethyl orthosilicate (TEOS) and 50.0 mL of

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the ethanol (EtOH) were mixed together in a reactor and refluxed associated with magnetic stirring. After receiving and maintaining temperature  $55^\circ\text{C}$ , 2.5 mL of ammonium ( $\text{NH}_3\cdot\text{H}_2\text{O}$ ) was added. After 24 h the suspension was centrifuged at 8,000 rpm for 20 min and the sediment was washed with ethanol and centrifuged again.

Further to create a mesoporous external layer on the as-produced silica spheres, mixture of 160 mg hexadecyl(trimethyl)azanium bromide (CTAB); 0.48 ml  $\text{NH}_3\cdot\text{H}_2\text{O}$ ; 25 mL EtOH; 30 mL  $\text{H}_2\text{O}$  and silica nanospheres was prepared, according to the procedure describe previously [10]. After 30 min of stirring, 0.28 mL TEOS was added and the mixture was stirred for a further 24 h. The suspension was then centrifuged at 8,000 rpm for 10 min. In the next step the silica nanospheres were thoroughly washed with ethanol. In order to remove the surfactant the sample was annealed in air at  $600^\circ\text{C}$  for 3 h.

### Functionalization of mesoporous silica nanospheres by titania ( $\text{mSiO}_2/\text{TiO}_2$ )

Supporting of titania in the mesoporous silica spheres has been realized dispersing through sonication 100 mg of silica nanostructures in 1 ml of the concentrated TBT. Further suspension was sonicated for 3 hours in anhydrous conditions at  $45^\circ\text{C}$ . Then, the suspension was diluted with propanol and centrifuged (8000 rpm for 10 minutes) to separate not bounded titanium dioxide precursor. In order to remove the excess of TBT the sample was washed several times with propanol. After the purification step nanostructures filled with TBT were treated with ethanol to hydrolyze precursor to the titanium dioxide. Finally, the sample was evaporated and heated in air flow in  $600^\circ\text{C}$  for 4 hours to transform the titanium dioxide into the anatase phase.

### Determination of the antibacterial activity

To examine the bactericidal titania/silica nanospheres and commercial catalyst was introduced during the colony forming units (CFU) of *E. coli* ATCC 25922. *E. coli* were pre-cultivated in enrichment nutrient broth (cat no PS 110, BIOCORP, Poland) for 24 h at  $37^\circ\text{C}$ . Glass beakers of 0.1 L were used as 5  $\mu\text{L}$  of the bacterial solution was pipetted into the reactors and illuminated from above with UVA (4 x20 W Philips, with wavelength range 400 – 315 nm) or Vis light (4x18W, Philips, TL-D 18W/33-640). Experiments without irradiation were also done. Dispersed nanocomposites with bacteria were stirred with speed up from 0 to 250 rpm. Control experiments were conducted in pure distilled water. All experiments were carried out at  $37^\circ\text{C}$  for 45 minutes. Samples were taken every 15 minutes. Serial dilutions in NaCl solution (0.9%) were prepared and each of them was used to inoculate of Plate Count Agar from BTL (cat no PS 110, BIOCORP, Poland). The plates were incubated for 24h at  $37^\circ\text{C}$  and the colony-forming units (CFUs) were calculated. The experiments were verified three times.

### The in vitro cytotoxicity test

Suspension of  $\text{mSiO}_2/\text{TiO}_2$  in phosphate buffered saline (PBS) were prepared and added to cell growth medium at six final concentrations (100  $\mu\text{g}/\text{ml}$ , 50  $\mu\text{g}/\text{ml}$ , 25  $\mu\text{g}/\text{ml}$ , 12.5  $\mu\text{g}/\text{ml}$ , 6.25  $\mu\text{g}/\text{ml}$ , 3.125  $\mu\text{g}/\text{ml}$ ). The mouse fibroblast cell line (L929, ECACC) was plated in 96-well culture plates (PAA) at an initial density of  $1 \times 10^4$  cells/well, and incubated at  $37^\circ\text{C}$  in humidified 5%  $\text{CO}_2$  atmosphere in 100  $\mu\text{L}$  of culture medium [Dulbecco's Modified Eagle Medium, High Glucose (DMEM, PAA, Austria) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Thermo Scientific), 0,4% penicillin- streptomycin (Sigma) and L-glutamine (2mM, Sigma)]. After 24 hours of incubation, the culture medium was removed and suspensions of  $\text{mSiO}_2\text{-TiO}_2$  were added. The activity of lactate dehydrogenase (LDH) in the medium

was determined using a commercially available kit CytoTox96 Non-Radioactive Cytotoxicity Assay (Promega, WI, USA) according to the manufacturer's instructions. The LDH leakage assay is based on the measurement of lactate dehydrogenase activity in the extracellular medium. The loss of intracellular LDH and its release into the culture medium is an indicator of irreversible cell death due to cell membrane damage. The untreated cells were used as the control (positive and negative). In the 24 hour of incubation cells with nanomaterials, 10  $\mu\text{L}$  Lysis Solution was added and incubated for further 45 minutes in a humidified chamber at  $37^\circ\text{C}$ , 5%  $\text{CO}_2$ . Next, the plate was centrifuged at  $250\times\text{g}$  for 4 minutes. In order to obtain a cell-free supernatant, and aliquots of the supernatant were then transferred into fresh 96-well flat-bottom plates. The reconstituted Substrate Mix (50  $\mu\text{L}$ ) was added to each well, and incubated at room temperature for 30 minutes, covered with foil for light protection. Finally, 50  $\mu\text{L}$  Stop Solution was added to each well, and the absorbance was measured at 490 nm (with 620 nm background correction) using a spectrophotometric microplate reader (Sunrise Reader, Tecan, Switzerland). The readings were acquired from three independent experiments (each conducted in triplicate) using cells from different passages (2-10). Results were normalized to the control cells, and the percentage of necrotic cells was calculated using the following formula: % cytotoxicity = [(experimental LDH release – control / maximum LDH release – control)]  $\times$  100%.

The influence of the studied nanostructures on the mitochondrial activity of the mouse fibroblast cells was assessed using WST-1 test (Roche Applied Science, Mannheim, Germany). The cell proliferation WST-1 test is based on the reduction of the tetrazolium salt WST-1 to a soluble red-colored formazan by mitochondrial dehydrogenases of metabolically active cells. The amount of formazan dye formed directly correlates with the number of metabolically active cells. For the present study mouse fibroblast cell line L929 was seeded into a 96-well plate at density of  $5 \times 10^4$ /well, and then cultured in a humidified incubator with 5%  $\text{CO}_2$  at  $37^\circ\text{C}$ . The cell culture medium (Dulbecco's modified eagle's medium D-MEM) was supplemented with 10% of fetal bovine serum (FBS) and 1% streptomycin/penicillin. After 24 hours incubation, L929 cells were exposed to the studied nanostructures in increasing concentrations, i.e. 0 and then 3.125; 6.25; 12.5; 25.0; 50.0; 100.0  $\mu\text{g}/\text{ml}$ . Further cells with nanomaterials were incubated for 48 hours. After the incubation period with the studied nanostructures, WST-1 reagent was added for 2 hours, and the absorbance was measured using a micro plate spectrophotometer at 450 nm wavelength. The absorbance values were hence analyzed (calculating the average value from three wells per each experimental point in the case of the studied nanomaterials and from nine wells in the case of free medium PBS) to determine cell proliferation compared to control wells.

### Characterization techniques

TEM images were collected using an FEI Tecnai G<sup>2</sup> F20 S Twin with an accelerating voltage of 200 kV and x-ray dispersion spectroscopy (EDX) was employed. Specific surface area of the samples was measured through adsorption  $\text{N}_2$  isotherm using the (interpreted with the Brunauer-Emmett-Teller or BET model) Quadrosorb SI (Quantachrome Instruments). Crystallographic phase identification was performed using X,Pert philips PRO X-ray diffractometer (X,Pert PRO Philips diffractometer, CoKa radiation).

## Results

### Nanomaterials characterization

In Figure 1 the morphology of the mesoporous silica nanostructures

before and after functionalization with the titania is demonstrated. The HR-TEM micrograph of mesoporous silica nanospheres clearly shows that the structure is composed from solid core with outer surface covered by the mesoporous silica shell with an average diameter of 30 nm (Figures 1 a' and a''). The elemental composition of the nanostructure determined by EDX spectroscopy (Figure 1 a'''), shows that nanostructure is composed from silicon and oxygen. TEM images in Figures 1 b' and b'' reveal the presence of the additional structure in the channels of the mesoporous silica shell after filling with titanium dioxide. From the comparison of the TEM images from the figure 1a and 1b see that the TiO<sub>2</sub> is deposited on the external side of the mesoporous silica shell in the form of thin darker layer. The thickness of the structure was not significantly changed which means the most of titania is placed inside the pores of the mesoporous silica nanospheres. From the comparison of the EDX spectra before and after the titania modification (Figure 1 a''' and b''') clearly see the additional peak corresponding to the titanium. According to the EDX mapping the strongest signal (green) corresponding to the titanium comes from the outer surface of the mesoporous silica shell, the results are depicted in Figure c''.

For further verification of the morphological modification, the surface area is measured based on the N<sub>2</sub> adsorption isotherm. Surface area measured with the BET method of the mSiO<sub>2</sub> and mSiO<sub>2</sub>/TiO<sub>2</sub> was 987 g/m<sup>2</sup> and 157g/m<sup>2</sup>, respectively. The significant decrease of the specific surface area is related to the presence of titanium dioxide in the channels and external space of mSiO<sub>2</sub>/TiO<sub>2</sub>.

Figure 2 shows the X-ray diffraction (XRD) patterns of mSiO<sub>2</sub>/TiO<sub>2</sub> in which the majority of the diffraction peaks can be indexed to the pure tetragonal anatase phase (ICDD #00-021-1272) of highly UV-light active titania. In the range of 15 to 30 degrees, the broad peak corresponds to silica. The peaks marked in the spectrum corroborates the high efficiency in the fabrication of mesoporous silica nanotubes with titanium dioxide.

### Cytotoxicity study

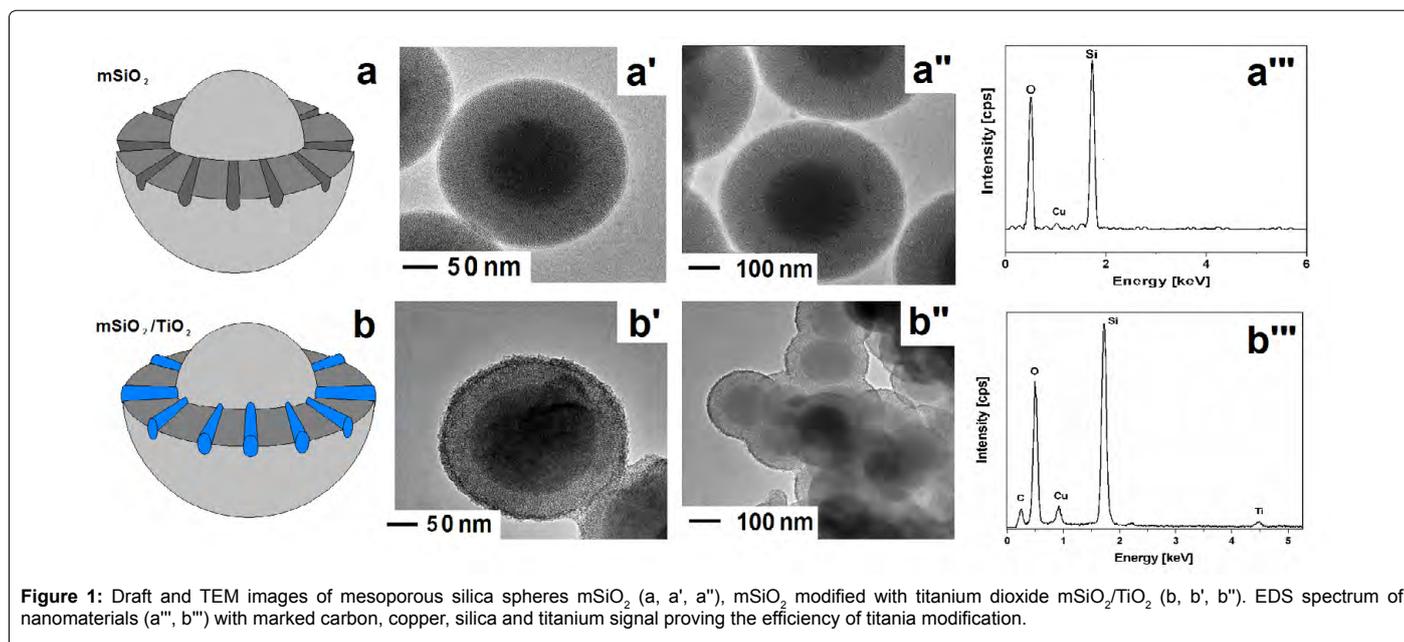
Cytotoxic potential of mSiO<sub>2</sub>/TiO<sub>2</sub> tested on L929 fibroblasts

revealed their neutral cellular influence (Figure 3). Up to concentration of 50 µg/mL no marked toxic effects were determined. The cells viability determined on mitochondrial activity (WST1 assay – blue bar) range from 100% to 90% of live cells. At highest nanomaterial concentration (100 µg/mL) cells viability decrease to 70%. Cytotoxic effect of mesoporous silica/titania nanospheres determined by activity of lactate dehydrogenase (LDH assay – green bar). Increasing nanomaterials concentration increases cytotoxicity up to 10% with 100 µg/mL nanomaterials.

### Antibacterial activity of the mSiO<sub>2</sub>/TiO<sub>2</sub>

Results of the antibacterial activity of the mSiO<sub>2</sub>/TiO<sub>2</sub> against *Escherichia coli* (Figure 4) clearly show their more effective growth inhibition compared to commercial TiO<sub>2</sub>-P25. The daily growth rates highly depend on the light conditions, and are strongly enhanced by the visible light. The mesoporous silica titania nanocomposites completely inhibit bacterial activity under UV light treatment and almost entirely kill bacteria under visible light (irradiated for 45 min). Figure 4a shows the time course of mSiO<sub>2</sub>/TiO<sub>2</sub> nanocomposites bactericidal activity against *E. coli* under visible light for 45 min, respectively. As a comparison, disinfection of *E. coli* without any disinfectants was also investigated (marked H<sub>2</sub>O). The pure water (H<sub>2</sub>O) shows no significant inhibition of the bacterial growth. The mSiO<sub>2</sub>/TiO<sub>2</sub> nanocomposites exhibit antibacterial action under visible light irradiation, 68% of *E. coli* are killed after 45 min, respectively (Figure 4a). From Figure 4b, it can be seen that under UV light irradiation the composites show further enhancement of their performance in the inactivation of *E. coli*. Almost 100% of *E. coli* are killed in 15 min upon UV light irradiation, while without the photocatalyst a time frame of 45 minutes is required. Figures 4a and 4b show bactericidal activity of mSiO<sub>2</sub>/TiO<sub>2</sub> and nanocomposites compared to the commercial catalyst under UV light and visible light irradiation, respectively. As shown in figures 4 commercial catalyst inactivates only 35% of *E. coli* after 45 min under visible light and 100% of the bacteria exposed to UV irradiation for 40 min.

In Figure 4c one can observe that the mesoporous titania silica nanospheres shows antibacterial activity also in darkness. In studied



**Figure 1:** Draft and TEM images of mesoporous silica spheres mSiO<sub>2</sub> (a, a', a''), mSiO<sub>2</sub> modified with titanium dioxide mSiO<sub>2</sub>/TiO<sub>2</sub> (b, b', b''). EDS spectrum of nanomaterials (a''', b''') with marked carbon, copper, silica and titanium signal proving the efficiency of titania modification.

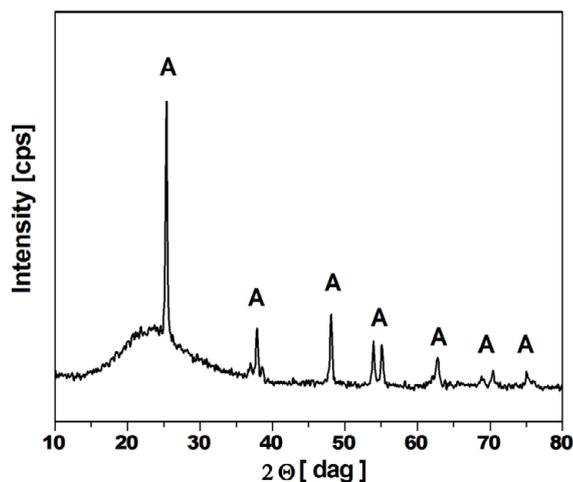


Figure 2: XRD patterns of mSiO<sub>2</sub>/TiO<sub>2</sub> nanocomposites with marked main peaks from anatase and silica.

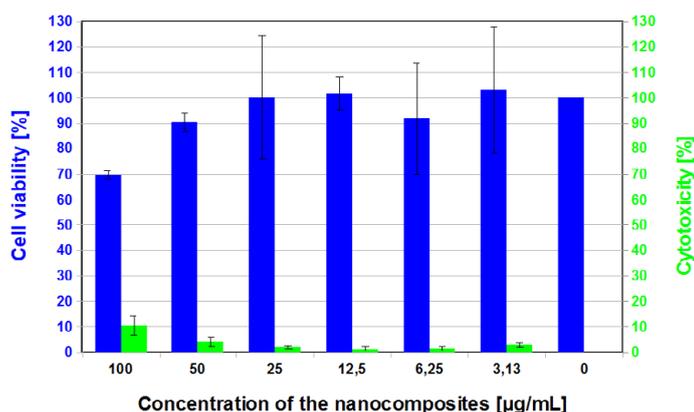


Figure 3: Mitochondrial activity (WST1 - blue columns) and cytotoxicity (LDH - green columns) to L929 mouse fibroblast of mesoporous silica nanospheres (mSiO<sub>2</sub>/TiO<sub>2</sub>) supported with the titania at the concentrations from 3.125 µg/mL to 100.0 µg/mL.

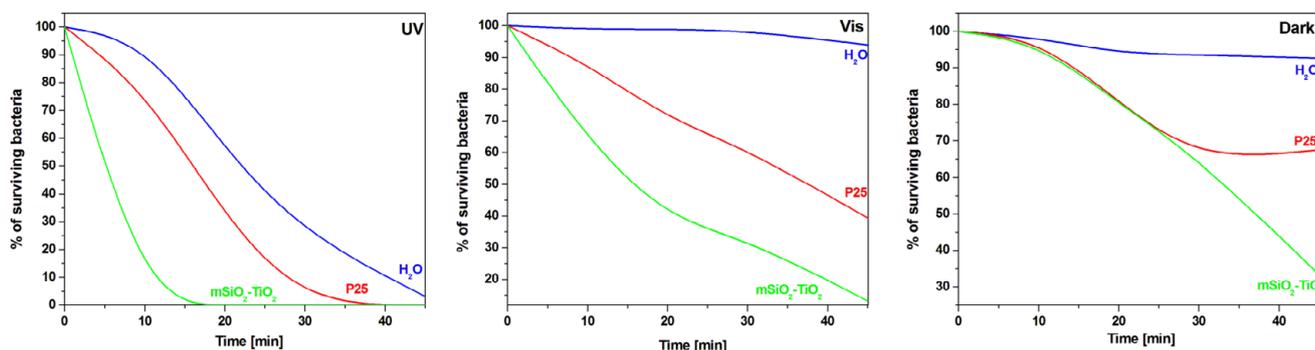


Figure 4: Diagram of the antibacterial activity of mSiO<sub>2</sub>/TiO<sub>2</sub> nanospheres and commercial catalyst (P25) under darkness (a), visible (b) and ultraviolet light (c) as well as a blank comparator (H<sub>2</sub>O) as reference samples tested against *Escherichia coli*. (ATCC 25922).

nanomaterials the inactivation of the bacteria is stronger with the reaction time indicating that toxicity effect of the mSiO<sub>2</sub>/TiO<sub>2</sub> nanocomposite plays important but a limited role in killing *E. coli* during 45 min. The data presented in Figure 5 shows results of the

blank experiments without any irradiation (visible or UV light) at set of different stirring speed of the solution. The blank control experiments exhibit that cytotoxicity of the nanomaterials has low effect on bactericidal activity in the stationary conditions. Less than 10% of *E. coli*

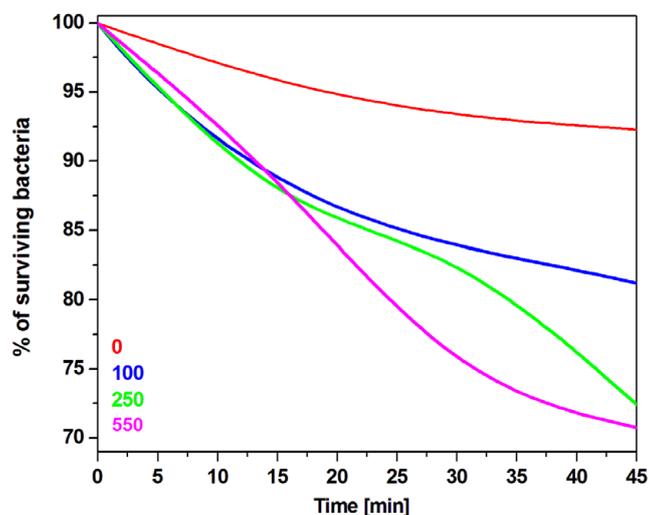


Figure 5: Diagram of the antibacterial performance of the mSiO<sub>2</sub>/TiO<sub>2</sub> nanospheres in a in darkness with different stirring speed, tested on the Escherichia coli.

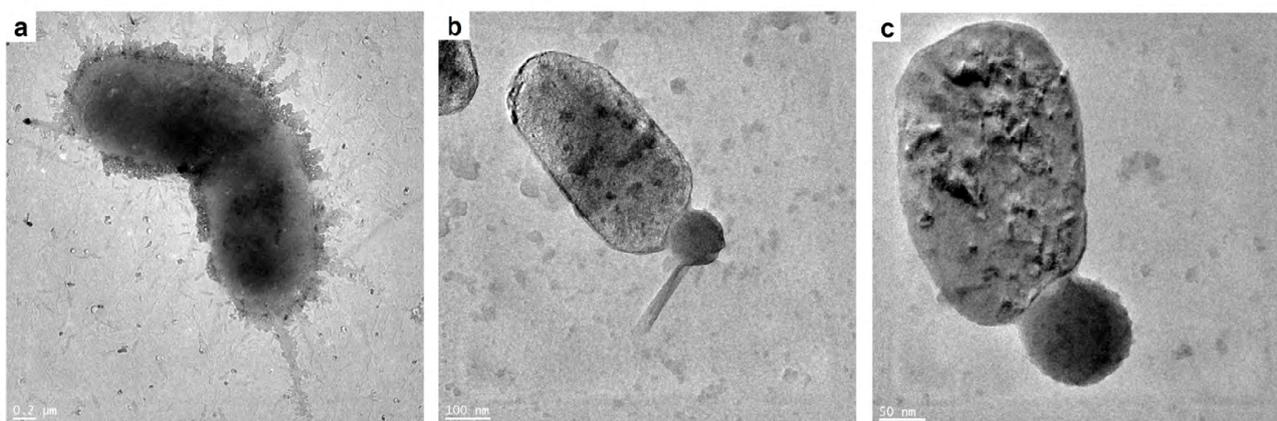


Figure 6: TEM images of the Escherichia Coli (a) bacteria and bacteria with mesoporous nanospheres with titanium dioxide mSiO<sub>2</sub>/TiO<sub>2</sub> (b, c), without irradiation (in darkness).

are killed after 45 min for the mSiO<sub>2</sub>/TiO<sub>2</sub>. During the increase of the stirring speed up to 250 rpm 21% of *E.coli* are killed (after 45 min.) in the presence of mSiO<sub>2</sub>/TiO<sub>2</sub>.

## Discussion

In this contribution nanocrystalline TiO<sub>2</sub> successfully functionalized mesoporous silica nanospheres through the novel and efficient methodology. TiO<sub>2</sub> precursor supported in silica nanochannels was transformed into crystallized TiO<sub>2</sub> nanoparticles through the high temperature treatment. The obtained nanomaterials also showed the high specific surface area due to the presence of lightweight spherical mesoporous template. This enables the mSiO<sub>2</sub>/TiO<sub>2</sub> to exhibit enhancement of the photocatalytic decomposition of organic pollutant [10] and inhibition of the bacterial growth. This can be attributed to higher specific surface area of this sample, in respect to the commercial catalyst. The surface area dependence on the photocatalytic activity was already widely studied and well described in the state of the art [11,12,25].

The bactericidal activity of the mSiO<sub>2</sub>/TiO<sub>2</sub> nanocomposites, as compared to pure water and the commercial catalyst (control sample), were studied against *E. coli* bacteria in dark conditions, under visible and ultraviolet light irradiation. Nanomaterial exhibited weak antibacterial activity in darkness (in static conditions) which can be correlated to their low toxicity confirmed by LDH test. In order to determinate the true bactericidal effect of mSiO<sub>2</sub>/TiO<sub>2</sub> monitored effect of different stirring speed of the analysed solutions (in darkness). Increasing stirring speed of the solution see significant but mild decrease of the bacteria until reach stirring speed of 500 rpm.

The comparing of the mSiO<sub>2</sub>/TiO<sub>2</sub> antibacterial study in darkness and under irradiation shows that photo induced bactericidal activity of titanium dioxide is the predominant effect. Under visible light mSiO<sub>2</sub>/TiO<sub>2</sub> catalyst efficiency is comparable with pure ultraviolet light. According to King Lun Yeung et al. [26] and Pinggui Wu et al. [27] microorganisms, due to heightened sensitivity, can be inactivated with titanium dioxide nanocomposites in the presence of weak UV and visible light, inducing oxidative lesions to the cell membrane and damaging of

interior DNA molecules, resulting in cells injuries and death. Bacteria increased sensitivity to the visible light and nanomaterial high surface area, may be the explanation of the difference between UV, visible and non-light antibacterial performance.

Further microscopic study on the titania/silica nanospheres with *E. coli* bacteria were performed in order to understand the antibacterial enhancement (Figure 6). The Figure 6 shows clearly that titania/silica nanospheres adsorb on the wall of the bacteria cell membrane. The interaction of the silica nanomaterials with the cell membrane facilitates titanium dioxide penetration inside bacteria thereby enhancing bactericidal photo-antibacterial efficiency.

Further investigation of the titanium dioxide antibacterial activity (confined in the mesoporous silica nanotubes) will include the bacteria gram-negative (eg. *Shigella dysenteriae*, *E coli* - research continuation) and gram-positive (eg. *Staphylococcus aureus*, *Streptococcus pyogenes*) bacteria test group.

In conclusion mesoporous silica nanospheres and mesoporous silica nanotubes modified with nanocrystalline titanium dioxide (anatase phase) placed in the pore were successfully fabricated and used as an photoactivated antibacterial agent. The photocatalyst not only inhibit bacterial growth but also show more efficient antibacterial properties with respect to the controls (water, P25) under visible and ultraviolet light. The comparison of the anti-bacterial efficiency and biocompatibility study of the mSiO<sub>2</sub>/TiO<sub>2</sub> clearly indicates that silica/titania nanospheres exhibits low toxicity and can be proposed as a new generation water cleaning system for the environmental and health protection, due to higher photocatalytic efficiency in the decomposition of the hazardous chemical compounds and micro-organisms.

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