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Antimicrobial performance of nanostructured silica–titania sieves loaded with izohidrafural against microbial strains isolated from urinary tract infections

Mustafa Basim M. Al Tameemi [a], Raluca Stan [a, *], Viorel Prisacari [b], Georgeta Voicu [a], Marcela Popa [c], Mariana Carmen Chifiriuc [c], Cristina Ott [a], George Marton [a], Aurelia Meghea [a]

[a] *Faculty of Applied Chemistry and Material Science, Politehnica University of Bucharest, Polizu Street No. 1-7, 011061 Bucharest, Romania*

[b] *"Nicolae Testemitanu" State University of Medicine and Pharmacy, 165, Stefan cel Mare Boulvard, Chisinau, MD 2001, Republic of Moldova*

[c] *Faculty of Biology, Microbiology Immunology Department, University of Bucharest, Aleea Portocalelor No. 1-3, 060101 Bucharest, Romania*

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ABSTRACT

This study aimed to examine the efficiency of novel bioactive nanostructures represented by silica–titania sieves used as carriers for a new antibacterial agent izohidrafural against bacterial strains isolated from nosocomial urinary tract infections, by using biological quantitative assays. Several release trials have been established and compared with **MCM-41** in parallel experiments to achieve the optimum release profile. The obtained systems showed that silica–titania sieves loaded with izohidrafural proved to be the most active material against *Klebsiella pneumoniae* (average minimal inhibitory concentration [MIC] 40.62 μg/mL), desaminase-positive strains (average MIC 2.925 μg/mL), and *Proteus mirabilis* (average MIC 9.37 μg/mL), the last being reported with the highest growth rate in the urinary tract catheters. In contrast, the nonloaded silica–titanium sieves exhibited the highest antimicrobial activity against the Gram-positive cocci. Izohidrafural exhibited the highest antimicrobial efficiency, superior to the common drug nitrofurantoin against most *Escherichia coli* strains, with average MIC of 4.68 μg/mL.

1. Introduction

The infectious diseases are considered as one of the most important health issues around the world because of many challenges posed by the emergency of antibiotic resistant strains [1] and the inability of many classes of antibiotics to reach the intracellular bacterial strains [2,3]. Nosocomial infections afflict one of 10 patients admitted to the hospital. These types of infections might be caused by Gram-negative bacteria, Gram-positive bacteria, and other types of microorganisms [4]. Urinary tract infections (UTIs) are considered as one of the most widespread nosocomial

* Corresponding author.
E-mail addresses: rl_stan2000@yahoo.com, raluca.stan@chimie.upb.ro (R. Stan).

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infections [5], they are representing also one of the most common pathology encountered in community with a prevalence varying from 0.7% in community-acquired infections to 24% among health care–associated infections, and these numbers vary depending on the geographical area [6]. The most prevalent microorganism involved in the etiology of UTI is *Escherichia coli*, followed by *Klebsiella pneumoniae*, *Proteus* sp., *Enterobacter* sp., *Pseudomonas* sp., *Enterococcus* sp., and *Staphylococcus* sp. [7,8].

In the past few years, an increasing trend in the antibiotic resistance in these isolates has been observed. Resistance to most available antibiotics in hospital-acquired UTIs is currently more than 20%, and the increasing isolation rates of multidrug, extended-drug, and pan-drug–resistant bacterial strains are urging the development of novel antimicrobial agents and strategies [9]. Retention of the antibiotic in the therapeutic level without increasing the drug dosages represents the point of challenge in many research works while seeking to specific drug administration in the living body. Nowadays, with the evolution of nanotechnology, high performance of drug delivery can be achieved through controlling the release profile with certain nanoscaled drug delivery systems. The suitable systems for the antibiotic agents can be achieved by using antimicrobial nanoparticles or nanosized drug carriers for delivering these antibiotics [1].

Various types of nanomaterials have been reported as vehicles for antibiotic administration such as carbon nanotubes, gold nanoparticles, and nanostructured silica materials [10,11]. Mesoporous silica materials present a good biocompatibility, and because of the presence of free silanol active groups within their porous structure are able to successfully encapsulate and slow release various types of biologically active compounds and thus antimicrobial agents [10,12,13]. Furthermore, the well-designed mesoporous silica possesses high surface area allowing to accommodate large amounts of antibiotics, tuned pore sizes with narrow distribution determining well-controlled release profile [14,15]. For example, silica xerogel has been reported to be a carrier for gentamicin to increase the intracellular penetration [16]. SBA-15 was also investigated as an antibiotic delivery system for tetracycline [17], and amino-modified SBA-15 was investigated to deliver clarithromycin [18]. Mesoporous silica sieves such as **MCM-41**-type nanocomposites have been widely investigated for delivery of antibiotics. Some **MCM-41**-type composites modified with aluminum used as delivery systems for amikacin, an aminoglycoside antibiotic, were reported to improve retention of the drug with slower release kinetics [10]. These materials were also reported as delivery systems for other kinds of antibiotics such as vancomycin [11] and nitrofurazone [13].

The combination between silica and biocompatible metals or derivatives may be extended from aluminum to other metals with improved biological activity, for example, gold [19] or titanium dioxide. The presence of titanium dioxide into mesoporous silica composites enhances the specific surface, modifies the activity of the silica surface, and provides photocatalytic activity, thus conferring a good disinfectant activity [20].

In this study, we used a new encapsulation support, nanostructured silica-titania sieves which combines the advantages of the silica nanomaterials in terms of microporosity or nanoporosity [21] with their ability to encapsulate antibiotics and prolonged release [18,22]. These advantages have been employed along with titanium dioxide properties in the anatase form, known for its photocatalytic effect and antibacterial activity [23]. By loading suitable antimicrobial into these sieves, we may provide a bioactive cover for the urinary tract catheters. Stickler [24] confirmed that catheters provide ideal conditions for the growth of many bacterial species colonized as biofilm, *Proteus mirabilis* being the most abundant among them.

The recently reported silica–titania sieves were used for encapsulation of a new drug, izohidrafural (izonicotinoilhidrazone aldehyde 5-nitro-2-furan) a stable organic compound from the class of nitrofurane-type antibacterial agents. Izohidrafural (Fig. 1c) has been synthesized from 5-nitrofurfural and isoniazid, characterized, and its biological properties investigated by Prisacari co-authors [25,26]. Izohidrafural proved to be by two to four times more active toward both Gram-negative and Gram-positive types of bacteria and exhibits nine times less toxicity than the parent compound nitrofurazone (Fig. 1a) against a large number of microorganisms responsible for nosocomial infections and longer-term stability [27]. However, no data were provided for comparison of the antimicrobial activity of izohidrafural with the commonly used nitrofurantoin (Fig. 1b) employed for decades as an alternative to sulfamethoxazole and fluoroquinolones for the first-line treatment of uncomplicated UTIs, preserving a high rate of susceptibility among uropathogenic strains and having a favorable adverse-effect profile [28,29].

To establish the influence of titanium dioxide on the silica matrix as a carrier for nitrofurane-derived antibacterials, a parallel encapsulation/release experiment was conducted using **MCM-41** and the same antimicrobial agent, izohidrafural. The secondary goal of this study attempts to elucidate the ability of **MCM-41** to encapsulate and to provide prolonged release of izohidrafural, being reported that the parent compound, nitrofurazone, failed the loading experiment in **MCM-41** [13]. The biological

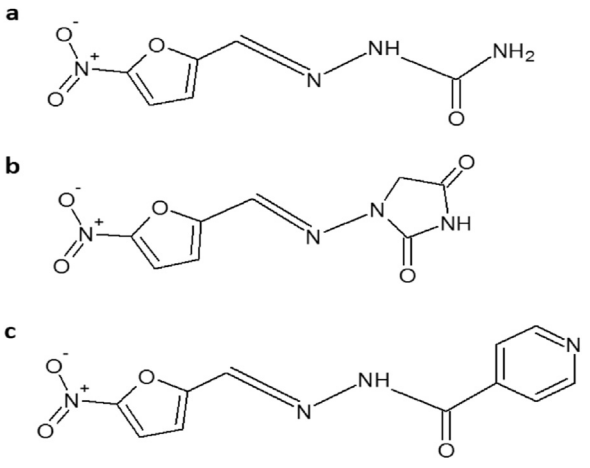

Fig. 1. Chemical structures of (a) nitrofurazone, (b) nitrofurantoin, and (c) izohidrafural.