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Research paper

Functionalized halloysite nanotubes: Efficient carrier systems for antifungine drugs

Marina Massaro[a], Ambra Campofelice[a,b], Carmelo Giuseppe Colletti[a], Giuseppe Lazzara[b], Renato Noto[a], Serena Riela[a,*]

[a] Dipartimento STEBICEF, Sez. Chimica, Università degli Studi di Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy
[b] Dipartimento di Fisica e Chimica, Università degli Studi di Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy

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ABSTRACT

Halloysite-cyclodextrin hybrid was employed as carrier for sustained release of clotrimazole for vaginal or buccal treatment of Candidiasis. The nanocarrier was obtained by functionalization of halloysite surface with cyclodextrin moieties by means of microwave irradiation, with the final goal to obtain a scaffold for the covalent linkage of cysteamine hydrochloride. The interaction between clotrimazole and the pristine components, namely cyclodextrin and halloysite, was thoroughly investigated by several techniques such as DSC, TGA, UV–vis spectroscopy and some adsorption studies were, also, carried out. The release of the antifungine molecule was finally investigated in a medium that imitates the physiological conditions.

1. Introduction

Over the past two decades urogenital infections have become a major public health concern affecting pre-menopausal women worldwide (Kennedy and Sobel, 2010). The most common recurring infection is due to opportunistic fungal pathogen responsible of Candidiasis. Specifically, Candidiasis is caused by the invasion of the tissues by a microbiota naturally occurring in the humans, in particular on the skin, mouth, throat, stomach, colon, rectum and vagina. The fungus that caused Candidiasis may belong to 150 different species and among them the most involved are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*. This disease often occurs in immunocompromised individuals, such as people subjected to treatment with certain medications, for example antibiotics, or such as people with pathological states, such as diabetes, AIDS or cancer. It was found that more than 25% of the world's population suffers of a form of mycoses (Wady et al., 2012).

Clotrimazole is one of the most important drugs used for the treatment of Candidiasis both oral and vaginal (Esposito et al., 2013). Generally, this drug is administered by means of several dosage forms such as ovules and cream for vaginal treatment or inserts, lotion and solutions for the oral one. Unfortunately, clotrimazole suffers from low aqueous solubility (~ 0.5 mg/L) and a short plasma half-life (3–6 h) (Hrabálek et al., 2006; Loftsson and Hreinsdôttir, 2006; Bachhav and Patravale, 2009; Esposito et al., 2013; Ravani et al., 2013), which, in combination with hepatic toxicity and neurologic disorders (Yong et al., 2007), make the pharmacological application of CLT very difficult. Therefore, the development of new delivery systems for this drug is the major concern as far as is concerned the preparation of novel formulations for Candidosis treatment. In the years some studies have been focused on the development of systems able to overcome the CLT low solubility, improving its bioavailability. Clotrimazole molecules were successfully incorporated in mucoadhesive gels, liposomes and niosomes (Ning et al., 2005), microemulsions (Hashem et al., 2011), microemulsion-based gels (Bachhav and Patravale, 2009) and inclusion complexes with β-cyclodextrin (Prabagar et al., 2007).

Halloysite nanotubes (Hal) are alumino-silicate clay with a predominantly hollow tubular structure in the submicron range. Compared to other nanoparticles such as organic carbon nanotubes, this kind of inorganic tube is naturally occurring, cheap, abundantly available, eco (Bellani et al., 2016) and bio-compatible (Fakhrullina et al., 2015; Kryuchkova et al., 2016). This last aspect is supported by the evidence that halloysite is efficiently removed from an organism with macrophages (Lvov et al., 2016a) that makes halloysite as a good candidate for drug carrier and delivery.

Chemically, Hal are constituted by siloxane groups on the external surface, while the aluminol groups are located in the inner lumen (Lvov et al., 2016a).

The most attractive feature of halloysite is its inner lumen with a diameter capable of entrapping chemical agents (Lvov et al., 2016b). The use of halloysite as nano-container for drug loading and release was firstly introduced by Price, Gaber and Lvov, who used the nanotube as

* Corresponding author.
E-mail address: serena.riela@unipa.it (S. Riela).

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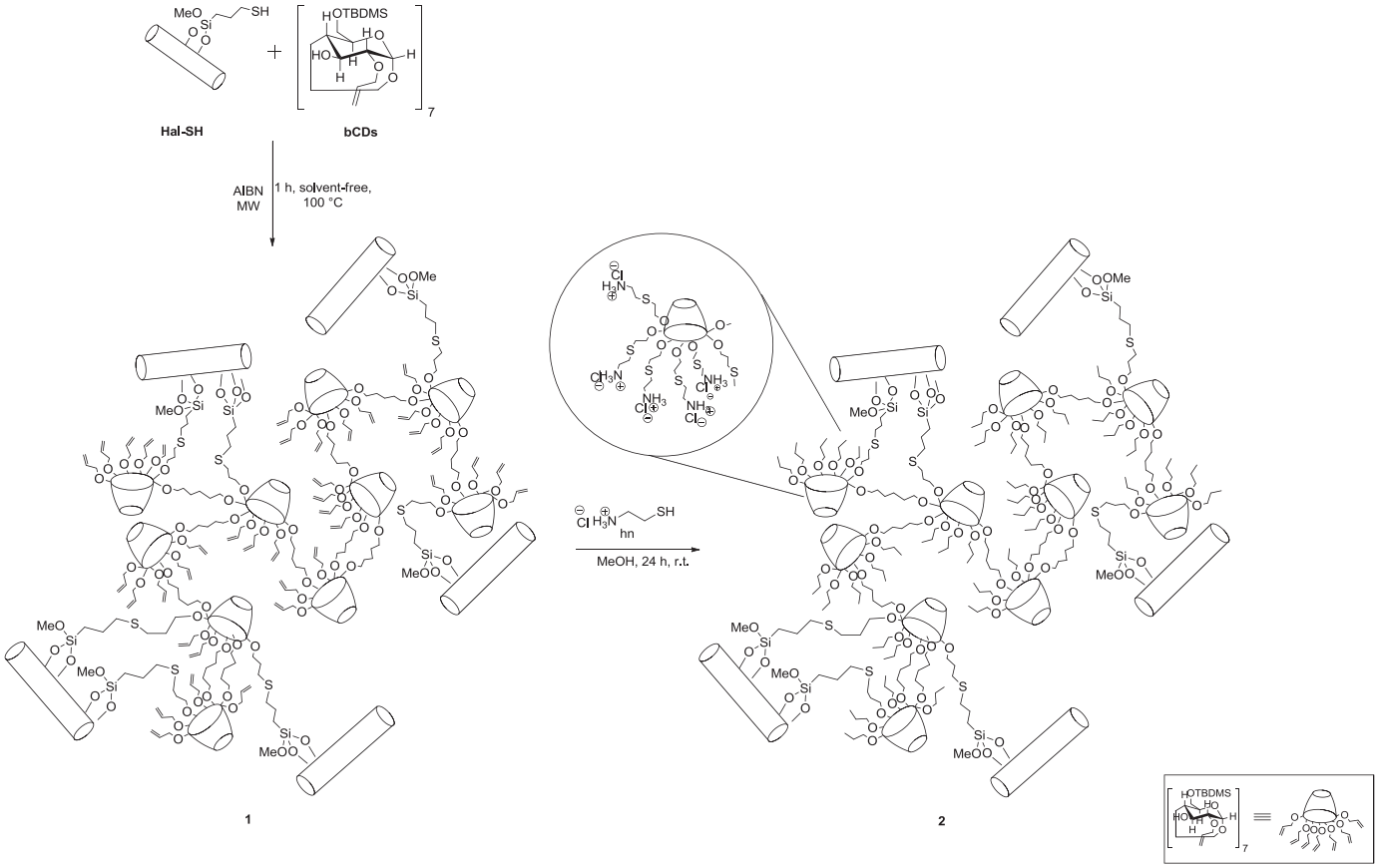

Scheme 1. Schematic representation of the synthesis of compound **2**.

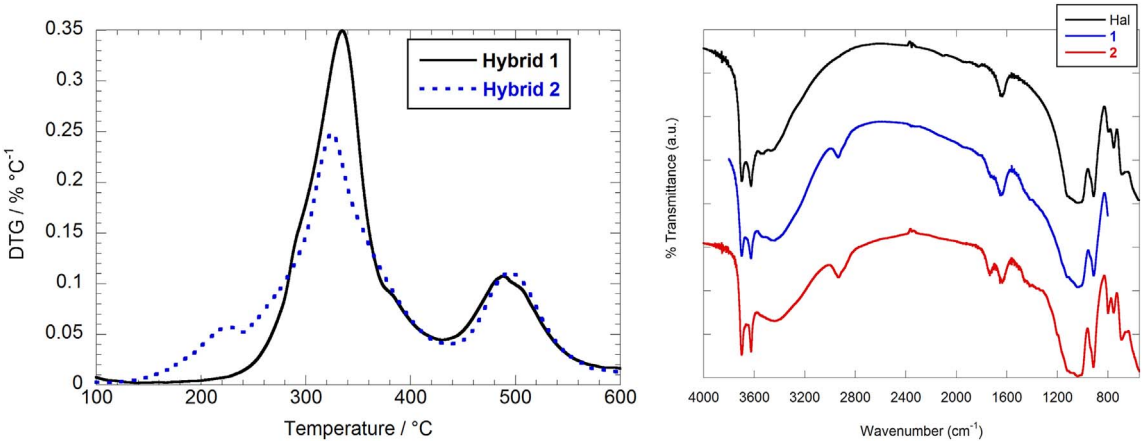

Fig. 1. a) DTG of compound **1** and compound **2**; b) FT-IR spectra of pristine Hal, compound **1** and compound **2**.

carrier for several drugs (Price et al., 2001). Successively, Veerabadran et al. (2007) reported that halloysite can load and release dexamethasone and furosemide in controlled manner.

Furthermore, thanks to the peculiar chemical composition, the surfaces of halloysite can be easily functionalized by covalent grafting of silane groups (Yuan et al., 2015; Massaro et al., 2017c), that increases Hal application fields. The covalent modification of the Hal surface is most commonly achieved by grafting silanes via condensation between hydrolyzed silanes and the surface hydroxyl groups of the Hal located on the edges or on external surface defects (Yuan et al., 2008; Peng et al., 2012; Bischoff et al., 2015). Functionalized Hal have been used as filler for polymer (Biddeci et al., 2016) or hydrogel matrices (Fan et al., 2013; Rizzo et al., 2017), drug carrier (Tan et al., 2013, 2014; Liu et al., 2016; Tully et al., 2016; Lazzara et al., 2017; Rawtani et al., 2017; Wu et al., 2017) and delivery (Massaro et al., 2016a; Yendluri et al., 2017), catalyst support (Massaro et al., 2016b, 2017b; Rostamzadeh et al., 2017; Sahiner and Sengel, 2017) as well as absorbents (Peng et al., 2015; Massaro et al., 2017a).

Herein we report a novel drug carrier system based on functionalized Hal containing clotrimazole drug. The grafting of cyclodextrin on Hal external surface endowed to synthesize an organic/inorganic hybrid nanofiller with high encapsulation capacity towards the drug.

2. Materials and methods

Thiol-functionalized Hal and heptakis-6-(*tert*-butyldimethylsilyl) 2-