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Halloysite nanotubes as a carrier for the uptake of selected pharmaceuticals

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ABSTRACT

Halloysite is a clay mineral similar to kaolinite and can be found in soils and weathered rocks in different particle shapes and hydration states. Due to misfit between the SiO_4 tetrahedral sheets and $Al(OH)_6$ octahedral sheets, it may form tubular structure with the SiO_4 tetrahedral sheets on the outer surfaces. The isomorphous substitution resulted in substantial cation exchange capacity (CEC). In this study, we tested the uptake of selected pharmaceutical compounds (PCs) by halloysite nanotubes (HNTs) under different physico-chemical conditions. The uptake capacity of these PCs were slightly lower than the CEC values of the HNTs, while the stoichiometric relation between the amounts of PC uptake and desorption of exchangeable cations supported cation exchange as the major mechanism for the uptake of PCs by the HNTs. The uptake of PCs was on the external surfaces of HNTs, whilst the surface area was not a limiting factor for the uptake of PCs. The finding from this study could extend the application of HNTs as a carrier for ionizable pharmaceuticals.

1. Introduction

Halloysite clay minerals are ubiquitous in soils and weathered rocks where they occur in a variety of particle shapes and hydration states [1]. Adsorption of Na^+ at the level of 2–3 meq/100 g at pH 3 indicated the presence of some permanent negative charge arising from ionic substitution [2]. As such it was studied for its potential application of adsorptive removal of heavy metals from solution [3]. And, its applications were extended to the removal of cationic color dyes from solution with adsorption capacities of 65, 84, 100, and 114 mg/g for neutral red, methylene blue (MB), malachite green, and methyl violet, respectively [4–7]. The colloidal stability decreased drastically and the MB-adsorbed halloysite settled out completely within 30 min while the original aqueous suspension of halloysite nanotubes remained stable for months [5]. This quick flocculation suggested potential applications of halloysite for water treatments.

In addition, studies were also conducted on the uptake of pharmaceutical compounds (PCs) by halloysite, mostly for the purposes of drug delivery. As a microtubular drug delivery system its intercalated space is unlikely to be available for drug loading, because its dehydrated state was not readily reversible, except perhaps to very small hydrophilic molecules [8]. The overall adsorption process of 5-aminosalicylic acid (5-ASA) onto halloysite was explained as the result of two separate processes with an initial rapid adsorption on the external halloysite surface followed by slow adsorption inside the phyllosilicate pores [9]. Adsorption of 5-ASA resulted in dehydration of halloysite as evidenced by the disappearance of the 10 Å peak and appearance of a 7 Å peak in the XRD patterns [10]. Entrapment of tetracycline (TC) was achieved under vacuum condition by mixing dry halloysite powder with TC dissolved in water or ethanol, and the release of TC was monitoring under dialysis conditions with up to 70% TC release achieved in the first 10 h [11]. Adsorption of TC on halloysite/$CoFe_2O_4$ magnetic composites reached a capacity of 33 mg/g based on the Langmuir model [12]. Upload of ibuprofen (IBU) with 2 g of halloysite and 2 g IBU in the presence of 20 mL ethanol over 24 h was mainly into the lumen and partially on the external surfaces of the halloysite with the loaded IBU present as nanocrystal and amorphous state [13]. Surface functionalization of halloysite by 3-aminopropyl

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triethoxysilane (APTES) induced a strong affinity for IBU through electrostatic attractions between the carboxyl groups of IBU and the aminopropyl groups of the grafted APTES [13]. Multicomponent halloysite nanotubes (HNTs) were evaluated as a platform to assist and direct the delivery of anticancer drug doxorubicin [14].

However, in these studies [9,11] either the drug adsorption capacity, or the actual amounts of drug uptake for subsequent release experiments were not provided. Moreover, the mechanism of drug uptake on halloysite was not elucidated. In this study, we choose two antibiotics TC and ciprofloxacin (CIP) and two antihistamine medicines chlorpheniramine (CPM) and diphenhydramine (DPH) to study their interactions with HNTs. Together with our previous studies on interactions between these drugs and platy-like clay minerals, such as kaolinite and montmorillonite, we anticipate to shed some light on structural controls on the uptake of PCs on clay minerals in order to better elucidate mechanisms of the fate and transport of the PCs in the environment and to explore potential use of HNTs as a carrier for drug delivery.

2. Materials and methods

2.1. Materials

The HNTs were purchased from Sigma–Aldrich. An X-ray diffraction analysis revealed relatively pure halloysite with trace amount of quartz and gibbsite (Fig. 1a). Thus, it was used without further pre-treatment. It has an average length of 0.5–1 μm as revealed by an SEM observation (Fig. 1b), an average diameter of 30–70 nm with a tubular internal diameter of 20 nm as seen on TEM (Fig. 1c), a BET surface area of 65 m^2/g, and a pore volume of 1.3 mL/g. Its cation exchange capacity (CEC) was determined by the method of Borden and Giese [15]. The concentrations of exchangeable cations were determined by ICP analyses. The CEC was 115 meq/kg, with major exchangeable cations being Ca^{2+} (78–82 meq/kg); Mg^{2+} (21–22 meq/kg); followed by Na^{+} (10–14 meq/kg); and K^{+} (2–3 meq/kg). The point of zero charge (pzc) of halloysite was <3 [16]. The ICP analyses from the product certificate sheets provided by the vendor showed 269 ppm of Mg, 384 ppm of K, 112 ppm of Na, and 814 ppm of Ca.

The TC in the HCl form (CAS # 64-75-5) was purchased from Calbiochem (Darmstadt, Germany). It has a molecular weight of 480.9 g/mol, pK_{a1}, pK_{a2}, and pK_{a3} values of 3.3, 7.7, 9.7 [17], and $\log K_{ow}$ value of −2.2 to −1.3 [18]. The CIP, also in the HCl form (CAS # 86393-32-0), was purchased from Hangzhou Minsheng Pharmaceutical Group Co. Ltd (China). It has a molecular weight of 367.8 g/mol, pK_{a1} and pK_{a2} values of 6.1 and 8.7 [19]. The CPM (CAS #: 23095-76-3), also called chlorphenamine, and DPH (CAS #: 147-24-0), or 2-(diphenylmethoxy)-N,N-dimethylethanamine, were kindly provided by Wei Li Pharmaceutical Co. Ltd. (Tainan, Taiwan). The CPM has maleate as the balancing anion, a molecular weight of 390.9 g/mol, a water solubility of 1–5 g/100 mL at 21 °C, and a log K_{OW} value of 3.38 [20]. Its two pK_a values (9.2 and 4.0) correspond

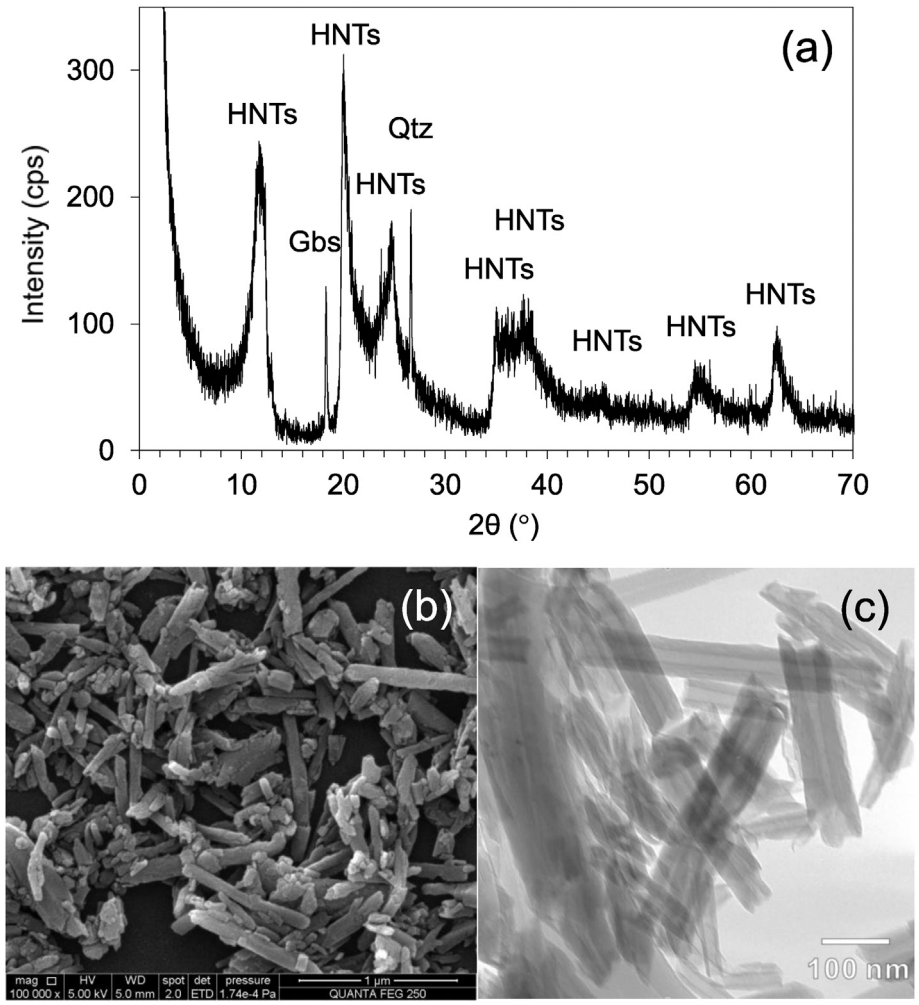

Fig. 1. XRD pattern (a), SEM (b) and TEM (c) images of HNTs. Gbs = gibbsite; Qtz = quartz.